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Cancer Conundrum
The Etiology, Global Trends, and National Response
Ika Nurlaila, Dwi Wahyu Indriati, Dwi Wahyu Indriani,
Asri Sulfianti, Sri Ningsih
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Cancer Conundrum
The Etiology, Global Trends, and National Response



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Cancer Conundrum
The Etiology, Global Trends, and National Response



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PUBLISHER'S FOREWORD

Publisher's Foreword (Pengantar Penerbit)As a scientific publisher, BRIN Publishing is committed to continuously providing high-quality scientific publications. This effort represents BRIN Publishing's duty to contribute to developing superior human resources and educating the nation, as mandated in the preamble of the 1945 Constitution of the Republic of Indonesia.

Cancer remains one of the most formidable public health challenges and the second leading cause of mortality worldwide. Beyond its intricate biological etiology and shifting global epidemiological patterns, the fight against cancer is complicated by profound disparities in healthcare access, diagnostic delays, and variable therapeutic responsiveness, particularly in developing nations such as Indonesia. Cancer Conundrum: The Etiology, Global Trends, and National Response delivers a comprehensive exploration of carcinogenesis mechanisms—including the Warburg effect, cellular hallmarks of cancer, and tumor microenvironment dynamics—alongside conventional and cutting-edge therapeutic platforms such as gene therapy, oncolytic virotherapy, and immunotherapy. By bridging fundamental molecular oncology with Indonesia's national health landscape and clinical strategies,

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this book serves as a vital reference for researchers, healthcare professionals, oncologists, and policymakers committed to transforming cancer management.

We hope that the presence of this book will serve as a valuable reference to broaden insight and knowledge for all readers. Finally, we would like to express our gratitude to all parties who have contributed to the publication of this book.

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FOREWORD

As the Head of the Research Center for Vaccine and Drugs at the National Research and Innovation Agency, it is with great pride and a true sense of honor that I mark this important moment— the launch of our contribution to health sciences: a book titled ***Cancer Conundrum: The Etiology, Global Trends, and National Response.***

I am deeply proud to share that this achievement marks a significant milestone for our center. For the very first time, our dedicated researchers have successfully completed and published a comprehensive book that will have our eyes more wide-open about the most pressing health challenges of all time—cancer.

This book is the result of collaborative synergy among our research scientists: Ika Nurlaila, Dwi Wahyu Indriani, and Asri Sulfianti are from our Research Center for Vaccine and Drugs; Dwi Wahyu Indriati from Department of Health, Faculty of Vocational Studies, Airlangga University; and Sri Ningsih from the Research Center for Pharmaceutical Ingredients and Traditional medicine. Their dedication and expertise have made this achievement possible.

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Cancer Conundrum aims to elucidate the complex causes of cancer, examine the latest global trends, and discuss the national responses necessary to combat this disease effectively. It integrates theoretical insights with recent, widely recognized facts about the respective cancer subtypes, allowing us as readers to gain an understanding not only of the superficial processes involved, but also of the underlying scientific principles. I hope this book will prove to be a valuable resource for researchers, healthcare professionals, policymakers, and all stakeholders engaged in cancer prevention and treatment.

Finally, I would like to extend my gratitude to everyone who has supported and contributed to this endeavor: our colleagues at the National Research and Innovation Agency (BRIN), our external collaborators, and all those who have offered genuine assistance in any form. Together, we remain committed to striving for a healthier future, guided by knowledge, hope, and innovation. Let us continue working side by side in the fight against cancer.

Jakarta, November 27th, 2025

Professor Dr. Masteria Yunovilsa Putra

Head of the Research Center for Vaccine and Drugs, National Research and Innovation Agency

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PREFACE

As the global landscape of public health continues to evolve, one of the most pressing concerns that has come to the forefront is the enigmatic and multifaceted phenomenon of cancer. This disease, which has been a constant companion to humanity for centuries, has been transformed by the interplay of factors such as demographic shifts, lifestyle changes, and environmental degradation into a global pandemic that affects millions of people worldwide.

Despite the plethora of advances in medical technology and treatment modalities, cancer remains a confounding and complex problem that has eluded a comprehensive solution. The etiology of this disease is shrouded in mystery, with a multitude of contributing factors that are often intertwined and interdependent. From the genetic predispositions that render certain individuals more susceptible to the environmental toxins that can trigger carcinogenic pathways, the causes of cancer are as varied and nuanced as they are elusive.

In this context, it is imperative to examine the national trends and responses to cancer in Indonesia, a country with a rapidly growing population and a burgeoning middle class that

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is increasingly susceptible to the risks associated with cancer. The Indonesian government's efforts to regulate and manage cancer, which are shaped by a complex interplay of factors including cultural norms, socioeconomic conditions, and public health infrastructure, present a fascinating case study in the challenges of addressing this global health problem.

This book, Cancer Conundrum: The Etiology, Global Trends, and National Response, seeks to provide a comprehensive analysis of the complex issues surrounding cancer. Through a nuanced examination of the global trends and national responses to this disease, we hope to shed light on the multifaceted nature of cancer and its impact on individuals, communities, and societies.

Ultimately, our goal is to provide a comprehensive understanding of cancer as a global health problem that requires a collaborative and multifaceted response. By exploring the complexities of cancer in both its global and national contexts, we hope to contribute to a deeper understanding of this disease and its impact on human health and society.

Editor

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CHAPTER I
CANCER EMERGENCE

The global landscape of cancer is a stark reminder of the unrelenting threat that this disease poses to human health and well-being. According to the World Health Organization (WHO), cancer is the second leading cause of mortality worldwide, accounting for over 10 million deaths in 2020 alone. The alarming rise in cancer incidence and mortality rates is a pressing concern that requires immediate attention and concerted action. As the world grapples with the complexities of this disease, it is essential to recognize the unique context and characteristics of cancer emergence in various regions, including Indonesia. As a country with a rapidly growing population and urbanization, Indonesia is particularly vulnerable to the increasing burden of cancer.

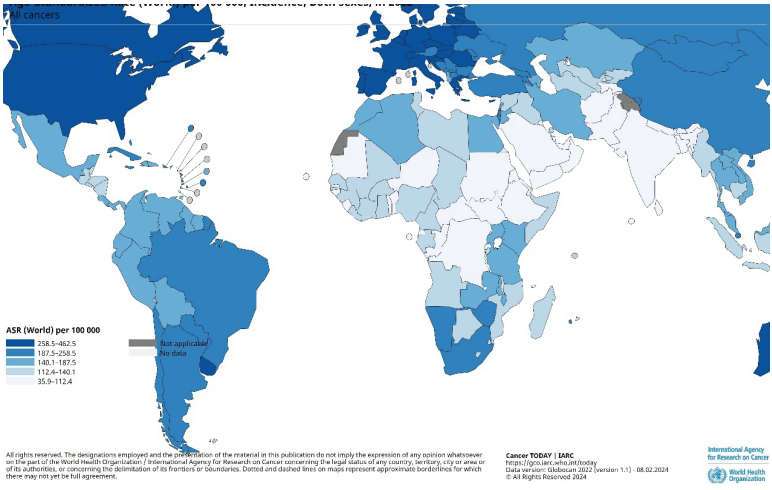
This Chapter will talk about the nuances of cancer emergence globally and in Indonesia, examining the patterns, trends, and risk factors that are shaping the disease landscape in this country. By shedding light on the epidemiological characteristics of cancer in Indonesia, we aim to contribute to a deeper understanding of this

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complex issue and inform evidence-based strategies for prevention, early detection, and treatment. Moreover, this study will highlight the importance of incorporating local perspectives and contextual factors into global cancer research, emphasizing the need for a more nuanced and culturally sensitive approach to addressing this pressing public health concern.

A. Global Cancer Emergence

The World Health Organization (WHO) estimated that in 2020 alone, incidence of cancers globally reached 60 million with 10 million deaths of both sexes(WHO, 2020). As seen in Fig. 1, in general North American, European countries, Australia and New Zealand have the highest age standardized rates with beyond 257.1 incidence per 100 000 population. In contrast Central African, Southeast Asian countries and West Asian countries reported less than 111.9 incidence per 100 000 population (International Agency for Research on Cancer (IARC), 2020).



Source: **Cancer TODAY (https://gco.iarc.who.int/today, 2024)**

Figure 1.1 Worldwide cancer incidence by age and sex: Estimated age-standardized rates in 2022

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New incidence of cancer in Indonesia, like other Southeast Asian countries, accounted for 140.4-188.8 per 100 000 in 2020 (International Agency for Research on Cancer (IARC), 2020). Mortality due to cancer in Indonesia was observed at 85.1 per 100 000 population, considerably lower than that seen for neighborhood countries such as Thailand, Vietnam, Malaysia, Brunei Darussalam and even Singapore as a country with the most advanced diagnostic and therapeutic technologies.

The recent factsheet released by the WHO has listed top ten most common cancers in Indonesia as follows (Table 1.1).

Table 1.1 Top Ten Most Common Cancers in Indonesia

Cancer	Total new emergence	% of total new cancer emergence (all cancer types)	Cumulative Risk
Breast	65858	16.6	4.83
Cervix Uteri	36633	9.2	2.69
Lung	34783	8.8	1.54
Liver	21392	5.4	0.92
Nasopharynx	19943	5.0	0.75
Colon	17368	4.4	0.74
Non-Hodgkin Lymphoma	16125	4.1	0.66
Rectum	16059	4.0	0.68
Leukaemia	14979	3.8	0.52
Ovary	14896	3.8	1.09

Source: Globocan (2020)

The ranking alters when viewed from the perspective of mortality rates. While breast cancer (BC) exhibits the highest incidence, lung cancer significantly surpasses all other types in terms of mortality, as illustrated in Table 1.2.

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Table 1.2 Top Ten Most Deadly Fatal Cancers in Indonesia

Cancer	Number of deaths	% of death in total respective cancer	Cumulative Risk
Lung	30843	13.2	1.39
Breast	22430	9.6	1.78
Cervix Uteri	21003	9.0	1.73
Liver	20920	8.9	0.91
Nasopharynx	13399	5.7	0.56
Leukaemia	11530	4.9	0.42
Ovary	9581	4.1	0.77
Colon	9444	4.0	0.38
Non-Hodgkin Lymphoma	9024	3.8	0.38
Rectum	8342	3.6	0.35

Both incidence- and death rates remain scary although we, on the other, must also appreciate that there are advancements made in the context of early detection as well as therapy platforms to favor overall clinical outlooks. This has been evident in some cases but to make it more successful it requires much more effort.

As of 2023, the global incidence of cancer has continued to be a significant public health concern. With advancements in medical research, early detection, and treatment options, the overall cancer burden has shown a slight decline in certain regions (K. D. Miller et al., 2022; Pulumati et al., 2023). However, the disease remains a major challenge worldwide, affecting millions of people each year (Sung et al., 2021).

According to the World Health Organization (WHO) and various cancer research organizations, the highlight of cancer-related phenomena in 2023 including:

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1. **Rising Incidence**

   The global cancer burden has been on the rise, primarily due to an aging population, increased life expectancy, and lifestyle factors such as unhealthy diets, physical inactivity, and tobacco use (Ngoma & Ngoma, 2021). In 2023, it is estimated that over 19.3 million new cancer cases will be diagnosed worldwide, which is an increase from previous years (Sung et al., 2021).

2. **Most Common Types**

   The most prevalent types of cancer in 2023 include lung, breast, colorectal, prostate, and skin cancers (Siegel, Miller, et al., 2023). These cancers account for a significant proportion of the global cancer burden. Lung cancer remains the leading cause of cancer-related deaths, with a large number of cases attributable to tobacco use (Thandra et al., 2021).

3. **Geographical Differences**

   Cancer incidence varies across different regions and countries. High-income countries generally have higher rates of certain types of cancer, such as breast and prostate cancers, while low- and middle-income countries often experience a higher prevalence of cancers such as liver, stomach, and cervical cancers. This disparity is attributed to several factors such as access to healthcare, socioeconomic status, and environmental exposures (Minas et al., 2021).

4. **Advancements in Early Detection and Treatment**

   Over the years, advancements in early detection, screening, and treatment have led to improved survival rates for many cancer types. In 2023, the global cancer mortality rate is expected to decline, thanks to better diagnostic tools, targeted therapies, and personalized treatment approaches (Siegel, Miller, et al., 2023). However, this hope does not imply the ending of the long story of fighting cancers at all means (Nature Editorial, 2022). Rather, it exhibits the growth of comprehension through

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which the diagnostics and therapeutics platforms are redefined (Pulumati et al., 2023).

5. **The Role of Prevention**

   Prevention remains a crucial aspect of addressing the global cancer burden. Public health initiatives focused on promoting healthy lifestyles, reducing tobacco use, and increasing vaccination rates for preventable cancers (such as human papillomavirus (HPV) and hepatitis B) have contributed to a decrease in the number of new cancer cases in certain regions(St. Jude Children's Research Hospital, 2021).

6. **The Impact of COVID-19**

   The COVID-19 pandemic has had a significant effect on cancer care, with many patients experiencing delays in diagnosis and treatment. As a result, there are concerns about the potential increase in cancer-related morbidity and mortality in the coming years (Patt et al., 2020).

It is anticipated that there would be over 35 million new cases of cancer in 2050, a 77% increase over the projected 20 million cases in 2022. The fast-expanding worldwide cancer burden reflects both population aging and growth as well as changes to people's exposure to risk factors, several of which are connected with socioeconomic development. Air pollution continues to be a major contributor to environmental risk factors, along with obesity, alcohol consumption, and tobacco use as major causes of the rising prevalence of cancer (WHO, 2024). High Human Development Index (HDI) nations are anticipated to bear the largest absolute rise in incidence, with an extra 4.8 million new cases expected in 2050 compared with estimates for 2022. However, the low HDI countries (142% rise) and medium HDI countries (99% increase) show the most notable proportional increase in incidence. Similarly, it is anticipated that in these nations, the cancer death rate will nearly quadruple by 2050 (WHO, 2024).

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Between 1990 and 2019, there was a 79.1% increase in the global incidence of early-onset cancer and a 27.7% increase in the number of early-onset cancer fatalities. The largest mortality and the disability-adjusted life years (DALYs) were seen in early-onset malignancies of the stomach, lungs, trachea, bronchi, breast, and colorectal in 2019. Early-onset liver cancer showed the steepest decline in incidence rates worldwide, while early-onset nasopharyngeal and prostate cancers exhibited the fastest rising trends. For both men and women, early-onset colorectal malignancies showed significant DALYs that were among the top five. The regions with high sociodemographic index (SDI) and intermediate SDI had the highest early-onset cancer burden. When the SDI rose from 0.7 to 1, the death rate significantly decreased, and the morbidity of early-onset cancer increased. According to the forecasts, there would be a 31% increase in early-onset cancer occurrences and a 21% increase in fatalities from the disease globally by 2030. The main risk factors for malignancies with an early onset are tobacco use, alcohol intake, and dietary risk factors (such as a diet high in red meat, low in fruits, high in sodium, low in milk, etc.) (J. Zhao et al., 2023).

An 11-year retrospective cross-sectional study was conducted to investigate the clinicopathological differences between Indonesian patients with malignancies diagnosed before and beyond the age of 50. The study included the analysis of data from 1584 eligible cases. It turned out that colorectal cancer (CRC) showed concerning patterns: a marked increase in colon cancer rates among young Indonesian patients. In addition, certain clinicopathological features in younger individuals exacerbated the severity of the disease. For CRC cases, there was a notable increase in APC among older patients (+2.38%). While rectal cancer trends were either constant or dropping, colon cancer rates among younger patients rose noticeably (+9.24%). While the trend for left-sided CRC remained steady, the right-sided CRC trend rose in both elderly patients (+6.57%) and the general population (+6.52%). In the ensuing ten years, these

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instances are anticipated to represent a substantial health burden. The patients' sex ratio was 1.21, their mean age was 53.17±13.94, and 38.1% of them were young. Tumor size ≥5 cm, exophytic development, adenocarcinoma, histologically low grade, pT3, pN0, poorly dissected lymph nodes (LNs), LN ratio <0.05, absence of distant metastases, early-stage cancer, absence of lymphovascular invasion, and absence of perineural invasion (PNI) were among the prominent characteristics of left-sided colorectal cancer. The number of dissected LNs, PNI, and histological subtype of the tumor showed differences between that seen in the elderly and younger patients (Rahadiani et al., 2022).

Likewise, the demographics of women with breast and cervical cancer have been gradually changing from old or late adulthood to middle and early adulthood. This was revealed by a study that involved six public health centers (PHCs) (9.68%) out of the 62 PHCs in Surabaya, Indonesia, which were chosen using a one-stage cluster random sampling were included in this cross-sectional study. In this study, 279 women, 140 with cervical cancer and 139 with breast cancer, respectively, were involved. The result of the study showed that the incidence of breast cancer is lower than that of cervical cancer. Women with cervical cancer were shown to be more long-term survivors. There was no significant difference in the present stage of cancer across patients, although there were differences in the first diagnosis and the type of therapy. The period of the initial diagnosis and the cancer's current stage were highly and significantly correlated. Proactive cancer prevention and promotion initiatives should be launched right away in the community through public health center (PHC) services in order to improve cancer care and ensure the greatest possible national benefit (N. P. W. P. Sari, 2019).

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B. THE MOST PREVALENT CANCERS IN INDONESIA

As the global cancer burden continues to rise, Indonesia is witnessing a corresponding surge in cancer cases with approximately 400 000 new cases diagnosed in 2020 alone (Prasetya, Layyinah, Maftuchan, et al., 2023a).

Among the various types of cancer that affect Indonesia, there are some that are considered rare cases based on their prevalence (National Cancer Institute, 2019). The incidence of certain types of cancer, such as pancreatic cancer, ovarian cancer, and thyroid cancer, is relatively low compared to more common types like breast cancer, lung cancer, and colorectal cancer. For example, pancreatic cancer ranked the 16th and accounts for only about 5734 new cases in Indonesia in 2022 alone, while ovarian cancer makes up 15130 new cases hence ranked the 8th in the same year (International Agency for Research on Cancer, 2022).

These rare types of cancer often have distinct demographic and clinical characteristics that set them apart from more common types (de Heus et al., 2021; Jose et al., 2023; Lövgren et al., 2008). For instance, pancreatic cancer tends to affect older adults and is often associated with a poorer prognosis due to its late diagnosis and limited treatment options (Vareedayah et al., 2018). Ovarian cancer, on the other hand, is often diagnosed at an advanced stage and has a high mortality rate (Braat 1997; Gaona-Luviano, Medina-Gaona, and Magaña-Pérez 2020; Momenimovahed et al. 2019).

The rarity of these cancers can also make it challenging for healthcare providers in Indonesia to develop effective treatment strategies and diagnostic protocols, as they may not have as much experience or resources to devote to these specific types of cancer (Tjindarbumi & Mangunkusumo, 2002). However, advances in medical technology and research have improved diagnostic capabilities

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and treatment options for these rare cancers, offering new hope for patients and their families (Pulumati et al., 2023; Supriyadi, 2012).

According to the WHO data for 2022, the top most common cancers in Indonesia are as follows.

1. Liver Cancer

Liver cancer is a formidable global health concern, claiming over 830,000 lives annually and diagnosed in approximately 900,000 people in 2020 alone making it the fourth most common cause of death worldwide (Rumgay et al., 2022). The majority of primary liver cancers, approximately 90%, are attributed to hepatocellular carcinoma, with intrahepatic cholangiocarcinoma and other primary liver malignancies being less prevalent. Interestingly, the underlying causes of the cancer are predominantly known, with chronic viral hepatitis, heavy alcohol use, and non-alcoholic fatty liver disease being the most common culprits. What is more, the distribution of these etiologies exhibits significant geographical disparities (Oh & Jun, 2023).

The global burden of liver cancer is characterized by significant geographical disparities, with East Asia bearing the highest disease-adjusted life years (DALYs) and mortality rates. However, a remarkable trend has emerged in East Asia, where DALYs and mortality rates have declined by approximately 60% over the past two decades. In stark contrast, age-standardized DALYs rates in North America and Australasia have increased by 107% and 94.8%, respectively, despite having lower incidence and mortality rates. A closer examination of liver cancer DALYs and mortality rates reveals a worrying trend in high-income Asia-Pacific regions, North America, and Australia, where these rates are increasing (Oh & Jun, 2023). Hepatitis B and C viruses remain the primary causes of liver cancer DALYs and mortality, although the rates appear to be declining due to the introduction of hepatitis B virus vaccines and antiviral therapies. In contrast, the burden of alcohol consumption

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and non-alcoholic fatty liver disease is increasing, particularly in North America, Eastern Europe, and other high-income countries (Kim et al., 2022). This trend is concerning, as the criteria for identifying high-risk groups of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NASH)-related liver cancer have not been established, leading to a lack of social consensus on how to screen, evaluate, and manage these individuals. Furthermore, the absence of pharmaceutical interest in developing relevant medications and screening strategies for high-risk groups highlights a significant unmet social need. Another important finding is that alcohol-related liver cancer remains a significant cause of liver cancer worldwide, with an increase in crude cases despite stable age-standardized incidence rates. This phenomenon warrants greater social attention and investment in research and development (Oh & Jun, 2023).

Liver cancer has emerged as the most prevalent type of cancer in Indonesia, posing a significant health challenge for the nation (Mitra et al., 2019). Like in mano other countries, hepatitis B and C infections are the leading causes of liver cancer in Indonesia (H Muljono, 2017). According to WHO, Indonesia has one of the highest rates of hepatitis B and C infections globally, making it more vulnerable to liver cancer cases (Jonathan et al., 2018). In addition to these infections, alcohol and tobacco consumption also contribute significantly to the rising liver cancer rates in the country. Alcohol, particularly when combined with certain chemicals in tobacco, can cause liver damage and increase the risk of liver cancer. In Indonesia, where tobacco consumption is widespread, and alcohol is easily accessible, the risk of developing liver cancer is further amplified (Petrick et al., 2018). Although there has been a slight decline in the prevalence of liver cancer, it remains a pressing public health concern in Indonesia. The data unequivocally suggests that liver cancer has become the second most common cause of cancer-related deaths in the country. It is imperative that urgent public health

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interventions be implemented to improve diagnosis, treatment, and early detection strategies for liver cancer in Indonesia. Only through concerted efforts can we hope to reduce the staggering mortality rates and alleviate the burden of this devastating disease on our society (Suardi & Suardi, 2021).

2. Lung Cancer

Lung cancer has emerged as the second most diagnosed tumor worldwide; with a staggering 2.2 million new cases reported across both genders. Moreover, it is the leading cause of cancer-related deaths, accounting for up to 1.8 million fatalities in 2020 alone. While the global distribution of lung cancer is relatively consistent, some regions exhibit significantly higher incidence rates when adjusted for age. A notable example of this phenomenon is observed in Hungary and Serbia, where lung cancer rates are significantly higher compared to other European countries. In a similar vein, French Polynesia in Oceania and certain regions in Africa, such as Western and Middle Africa, exhibit strikingly low lung cancer incidence rates. These disparities can be attributed to variations in the distribution of risk factors, including differences in reporting practices, which underscore the importance of considering local epidemiological factors when developing prevention and treatment strategies (Alberg et al., 2013).

Lung cancer, a formidable global health concern, is characterized by a multitude of risk factors that contribute to its development. While tobacco consumption is undeniably the most significant etiological factor, accounting for up to 80-90% of cases (Alberg et al., 2013), WHO has identified numerous other carcinogens that pose a significant threat to public health. These include indoor radon gas, environmental pollution, asbestos, occupational exposure, and radiation, all of which have been linked to an increased risk of lung cancer (American Cancer Society, 2024). Furthermore, recent research has shed light on the role of ethnicity and genetic predisposition in

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lung cancer risk and the molecular profile of the lung tumor (Belleau et al., 2023). In particular, studies have demonstrated that individuals with certain genetic variants, such as germline pathogenic variants in high- or moderate-penetrance cancer predisposition genes, are at a higher risk of developing lung cancer (Mukherjee et al., 2022). This underscores the importance of considering both environmental and genetic factors in understanding the complex etiology of lung cancer (Alberg et al., 2013).

In Indonesia, lung cancer has emerged as the second most common type of cancer, affecting a substantial number of people and posing a significant challenge to the nation's public health. The primary causes of lung cancer in the country include smoking, exposure to air pollution, and occupational hazards (Kusumawardani et al., 2023). Among all, smoking is the leading cause of lung cancer in Indonesia, with a high prevalence of tobacco use among the population. Cigarette smoke contains numerous toxic chemicals that can damage lung cells, eventually leading to the development of lung cancer. According to the Global Adult Tobacco Survey, Indonesia has one of the highest smoking rates globally, with a significant proportion of the population being exposed to this preventable risk factor (Holipah et al., 2020; Kusumawardani et al., 2023). It was indicated that in 2013, smoking-related cancers incurred an estimated economic burden of USD 1,309 million in Indonesia, with USD 1,280 million attributed to males and USD 29.5 million to females. Furthermore, the burden of cancers attributed to smoking in Indonesia is estimated at 638,682 Disability Adjusted Life Years (DALYs), with lung cancer being the highest priority for both men and women (Kristina et al., 2015, 2019). Additionally, secondhand smoke exposure contributes significantly to cancer burden, accounting for 283,360 DALYs across six cancer types (Permitasari, Satibi, and Kristina 2018).

Air pollution, particularly particulate matter (PM), is a major concern in Indonesia, contributing significantly to lung cancer and

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other health issues (Nurlaila & Purwandari, 2023). Studies have shown that $PM_{2.5}$ and PM_{10} concentrations in many Indonesian cities exceed both national and WHO standards (Istiqomah & Marleni, 2020). As the growth of energy consumption increases every year, it is projected that the production of $PM_{2.5}$ will reach 110.5 kiloton (kt) in 2030, which is an approximately 26% increase from 2015 where $PM_{2.5}$ was observed at 87.7 kt. Meanwhile, NOx pollution outnumbered this with the level was detected at 814 kt in 2015 and is projected to rise to 1225 kt after 15 years (Haryanto, 2018).

Other than these major air pollutants, occupational hazards, such as exposure to asbestos, radon, and certain chemicals, also contribute to the rising lung cancer rates in the country. Workers in industries like construction, mining, and manufacturing may be at higher risk due to their exposure to these hazardous substances (Shankar et al., 2019; Suraya et al., 2020, 2021) .

To combat the bulking up lung cancer-caused burden in Indonesia, it is crucial to implement preventive measures and raise awareness about the risks associated with smoking, air pollution, and occupational hazards (Kosen et al., 2017; Nurlaila & Purwandari, 2023; Rejeki & Kartikawati, 2020). Public health initiatives should focus on promoting tobacco control, improving air quality, and providing safe working conditions for employees (Bloomberg Philanthropies & Vital Strategies, 2019; National Development Planning Agency (BAPPENAS), 2018; Padmawati et al., 2018).

Early detection and screening programs can also help identify lung cancer at an early stage, increasing the chances of successful treatment and improving patient outcomes. Encouraging regular health check-ups and providing accessible healthcare services can significantly contribute to reducing the impact of lung cancer on the Indonesian (Andarini et al., 2023; Asmara et al., 2023).

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3. Stomach Cancer

In 2019 alone in developing nations, stomach cancer is a somewhat prevalent occurrence. Male incidence rates are 20 per 100,000 in high-middle Human Development Index (HDI) countries and 6.6 per 100,000 on average in low-middle HDI countries. Incidence rates of stomach cancer in East Asia are 13.2 per 100,000 for women and 32.1 per 100,000 for men. With over 60 new cases per 100,000 males yearly, the Republic of Korea has the highest national incidence; however, the incidence rates for females are comparatively lower, with roughly 25 cases per 100,000 in Korea (Warsinggih et al., 2022).

However, in Southeast Asia, stomach cancer ranks the fifth-highest death rate and the fourth-highest incidence rate. The South-East Asia Region (SEARO) reported 90,598 new cases in 2020, with 78,823 deaths and a 5-year prevalence of 122,780 cases across all ages. Whereas in Indonesia, stomach cancer has emerged as the third most common type with 3484 new cases and 2946 deaths reported in the same year. The primary cause of stomach cancer in the country is attributed to a diet high in preserved foods, smoked foods, and low intake of fruits and vegetables (Warsinggih et al., 2022).

A diet rich in preserved and smoked foods, such as salted fish, pickled vegetables, and processed meats, can increase the risk of developing stomach cancer. These foods often contain high levels of preservatives, salt, and nitrites, which can lead to the formation of cancer-causing substances called nitrosamines. Additionally, a diet low in fruits and vegetables, which are rich in essential nutrients and antioxidants, can further contribute to the development of stomach cancer (H.-Y. Huang, 2013).

In Indonesia, where a significant portion of the population relies on a diet consisting of preserved and smoked foods, the risk of stomach cancer is amplified. Improving dietary habits and promoting the consumption of fresh, unprocessed foods, along with a variety of fruits and vegetables, can significantly reduce the burden

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of stomach cancer in the country (Miftahussurur et al., 2019; Soeripto et al., 2003).

Other factors, such as *Helicobacter pylori (H. pylori)* infection, smoking, and excessive salt intake, can also contribute to the development of stomach cancer. *H. pylori*, a bacterium that infects the stomach lining, can cause chronic inflammation and increase the risk of stomach cancer (Malfertheiner et al., 2023; Wroblewski et al., 2010).

Indonesia has a low prevalence of *H. pylori* infection and gastric cancer compared to countries with high gastric cancer incidence. Studies in Surabaya and Bali reported *H. pylori* infection rates of 11.5% and 7-9%, respectively (Miftahussurur et al., 2019, 2020; Tanaka et al., 2016). The low infection rate varies among ethnic groups, with higher rates in Bataknese, Papuans, and Buginese compared to Javanese (Miftahussurur et al., 2020). Genetic characteristics of *H. pylori* strains in Indonesia differ from those in high-incidence countries, with a predominance of East-Asian-type cagA, EPIYT motifs, and less virulent genotypes (Miftahussurur et al., 2015, 2020). These factors, along with the low prevalence of precancerous lesions, may contribute to the low gastric cancer incidence in the country (Miftahussurur et al., 2015, 2020). However, antibiotic resistance is a concern, with high resistance rates to second-line treatments like levofloxacin and metronidazole (Miftahussurur et al., 2020).

4. Cervical Cancer

Cervical cancer has emerged as the fourth most common type of cancer in Indonesia, contributing to 20 708 deaths and 36 964 new cases in 2022 alone, making it the third highest new emergence and the fourth deadliest cancer in both sexes(International Agency for Research on Cancer, 2022). Primarily, it is attributed to the human papillomavirus (HPV) infection. But the good news is that this disease can be prevented through vaccination and regular screening (Charde & Warbhe, 2022).

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HPV is a group of more than 200 related viruses, some of which are known to cause cervical cancer. In Indonesia, the most common high-risk HPV types associated with cervical cancer are HPV 16 and HPV 18. Infections with these high-risk HPV types can lead to the development of cervical cancer over time, making prevention and early detection crucial for reducing the disease's impact(de Boer et al., 2006; Wulandari et al., 2023).

Prevention of HPV infection and cervical cancer can be achieved through vaccination and regular screening. The HPV vaccine is highly effective in protecting against the most common high-risk HPV types, significantly reducing the risk of cervical cancer. The Indonesian government has introduced a national HPV vaccination program, which aims to provide vaccines to girls aged 9 to 13 years old, protecting them from HPV-related diseases (Setiawan et al., 2020; Suryoadji et al., 2022).

In addition to vaccination, regular cervical cancer screening plays a vital role in early detection and prevention. Pap smear tests and HPV DNA tests are essential tools for detecting precancerous changes in the cervix, allowing for timely intervention and treatment. Encouraging women to undergo regular screening and adhere to recommended screening guidelines can significantly reduce the incidence and mortality rate of cervical cancer in Indonesia (Ekawati et al., 2024; Nuranna, 2022).

5. Breast Cancer

The prevalence of breast cancer (BC) in Indonesia is a pressing concern, with 19.2% of all cancer cases being attributed to this disease. Despite advancements in early detection and treatment methods, a significant proportion of patients are still present at medical centers in late stages, with a staggering 68-73% of cases being diagnosed at stage III or IV. This phenomenon is perplexing, as one would expect improved diagnostic and therapeutic measures to result in better patient outcomes (Gautama, 2022).

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A closer examination of the data reveals that Yogyakarta province stands out as the epicenter of the issue, with a staggering 2.4% prevalence, equivalent to approximately 4,325 cases. This is followed by East Kalimantan and West Sumatra, with respective rates of 1.0% and 0.9%, resulting in 1,879 and 2,285 cases, respectively. What is particularly noteworthy is that more than half of BC patients in Indonesia seek treatment only after being diagnosed at an advanced stage, indicating a significant delay in detection. This phenomenon is strikingly different from that observed in Western countries, where nearly 80% of BC patients are diagnosed at an early stage, often allowing for more effective treatment and improved outcomes. The disparity in BC detection rates between Indonesia and Western countries highlights the urgent need for increased awareness and early detection efforts among BC survivors in Indonesia, thereby reducing the likelihood of delayed treatment and improving overall health outcomes (Nindrea et al., 2023).

The distribution of BC subtypes in Indonesia is consistent with previous research in Asia and Europe, with Luminal A being the most common subtype, followed by Triple Negative Breast Cancer (TNBC), Luminal B, and HER2-positive subtypes. In contrast, studies in African American women have reported a higher incidence of TNBC. These disparities may be attributed to differences in population characteristics, age, genetic profiles, lifestyle factors, and access to mammography screening (Widodo et al., 2017). While Luminal A is characterized by favorable prognostic factors, such as older age at diagnosis, smaller tumor size, negative lymph node infiltration, early stage, and low grade, non-luminal subtypes are associated with poor outcomes, including higher relative mortality risk. This is likely due to the presence of genetic abnormalities, such as p-53 mutations, HER2 amplification, BRCA-1 dysfunction, genomic instability, and high cell proliferation (Allison, 2012; Yanagawa et al., 2012).

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The majority of luminal BC (84.2%) were diagnosed at an early stage, with a corresponding mortality rate of 17.3% (14 patients) and 5-year survival rate for early-stage breast cancer is approximately 88%. The good response to anti-hormonal therapy in patients with luminal breast cancer may contribute to their improved survival outcomes. In contrast, patients with non-luminal had a poorer prognosis, with lymph node status and stage emerging as independent predictors of survival. Similarly, stage was found to be an independent prognostic factor for survival in HER2-positive breast cancer patients, while lymph node metastasis was an independent predictor of survival in patients with TNBC (Widodo et al., 2017).

Despite the limited availability of genetic data on BC in Indonesia, some existing reports offer a valuable foundation for future research and inform the development of effective strategies for early detection, prevention, and treatment of this disease, highlighting the importance of building upon these findings to improve breast cancer outcomes in the Indonesian population. One of which is from Dewajani and colleagues who investigated polymorphisms as risk factor in Indonesian patient cohorts with BC. Their results showed the relationship between the P21 Se31Arg polymorphism and the risk of breast cancer in Indonesia which suggested that the AA genotype and A allele of P21 are significantly associated with an increased risk of early-onset breast cancer. In addition, the study also revealed that FGFR polymorphism (FGFR2 rs2981582) was deemed to be related to the higher risk of BC. Specifically, the TT genotype has been linked to an elevated risk of BC, but the underlying mechanisms of this association have not been fully elucidated. Our study examined the frequency of the C/C and T/T genotypes in patients with early-onset and late-onset BC. While the results did not reach statistical significance, we observed that the frequency of the C/C genotype was higher in patients with late-onset BC, whereas the T/T genotype was more common in younger patients with BC. Nota-

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bly, their analysis revealed a statistically significant difference in the proportion of allele T between early-onset and late-onset BC cases. These findings strongly support the association between the FGFR2 gene polymorphism rs2981582 TT genotype and an increased risk of early onset BC in Yogyakarta, Indonesia. Notably, there was no other studies that have investigated the relationship between FGFR2 polymorphism and early onset BC in other populations (Widodo et al., 2017). However, it was found that there was a strong association between TT mutant genotypes and T alleles of the same FGFR2 polymorphism as risk factors for BC in premenopausal women in Chinese women (Liang et al., 2008).

In addition to FGFR2 gene polymorphisms, other study had also identified pathogenic germline mutations in some genes as contributors to early onset breast cancer in Indonesia. Analysis of 116 breast cancer patients revealed that 9 patients (7.8%) carried pathogenic mutations, particularly in early onset patients. Three of these mutations were found in BRCA1 (2.6%) and 6 were found in BRCA2 (5.2%), which is consistent with previous studies. It was found that BRCA1 and BRCA2 mutations were more common in early onset breast cancer patients, with a higher frequency of BRCA2 mutations compared to BRCA1 mutations. This is comparable to other Asian regions, but differs from non-Asian ethnic groups where the reverse trend was observed (Liede & Narod, 2002; Takeda et al., 2004). The seven pathogenic mutations identified included three in BRCA1 and four in BRCA2. All these mutations were predicted to result in protein truncation and were classified as pathogenic. Notably, two of the novel nonsense mutations identified in BRCA2 had not been previously reported in the Breast Cancer Information Core (BIC, Bethesda, MD) database. One of the pathogenic mutations found in BRCA1 had a significant clinical impact on the patient, who suffered from bilateral breast cancer at a relatively early age (25 years). The mutation led to frameshift and created a premature stop codon in exon 11, which affects the interaction between BRCA1 and RAD51

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proteins, which is essential for homologous recombination repair of double-strand breaks. The patient presented with advanced stage disease and had a poor prognosis (Purnomosari et al., 2007).

In addition to adverse genetic mutations, hormonal imbalance, particularly with regards to estrogen and progesterone, is a significant risk factor for the development of breast cancer. Estrogen, a hormone primarily produced by the ovaries, plays a crucial role in the growth and development of breast tissue, promoting cell proliferation and regulating gene expression. Progesterone, also produced by the ovaries, prepares breast tissue for potential pregnancy, and supports the growth and differentiation of mammary gland cells. An imbalance in these hormones can lead to an abnormal activation of estrogen and progesterone receptors in breast cells, resulting in uncontrolled cell growth and tumor formation. Furthermore, hormonal imbalances can also influence the microenvironment of the breast tissue, promoting tumor angiogenesis, metastasis, and immune evasion. The presence or absence of hormone receptors such as estrogen and progesterone receptors in breast cancer cells is critical in determining treatment options and patient outcomes, with hormone receptor-positive tumors often responding well to hormonal therapies and hormone receptor-negative tumors being more aggressive and less responsive to these treatments (Satpathi et al., 2023).

Next risk factor is Body Mass Index (BMI). BMI is often overlooked as a potential risk factor for breast cancer, but it plays a significant role in determining an individual's likelihood of developing the disease. In premenopausal women, a higher BMI is associated with a lower risk of breast cancer, but this effect is relatively small and has little impact on an individual's absolute risk. However, in postmenopausal women, the relationship between BMI and breast cancer risk is reversed, with a higher BMI being linked to a greater risk of the disease. Moreover, the difference in absolute risk between women with high and low BMI increases with age and underlying

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familial risk. This means that women who are at higher risk of breast cancer due to family history or other factors may be more likely to benefit from maintaining a healthy weight throughout their adult life. In fact, research suggests that maintaining a healthy weight throughout adulthood, rather than just in early adulthood, is crucial for all women, and particularly those with a family history of breast cancer. By acknowledging the importance of BMI in breast cancer risk, healthcare providers can better advise their patients on strategies to reduce their risk of developing the disease (Hopper et al., 2018).

A key factor influencing patients' accessibility to medical attention is the availability of trained oncologists. Indonesia, with a population of over 273 million people, has an inadequate number of surgical oncologists, with only 233 practicing as of 2002 (Gautama, 2022). This falls short of the recommended ratio proposed by the Indonesian Society of Surgical Oncologists, which is 0.2 per 100,000 population (Gautama, 2022). The shortage extends to radiation oncologists as well, with only 70 certified oncologists available in 2017, far below the estimated need of 740 (Hiswara 2017). This scarcity of specialists contributes to inequities in access, utilization, and clinical outcomes for cancer patients across different socioeconomic groups (Ramadani et al., 2018).

Another challenge that demands solutions is referral system and supportive regulations that inevitably crucial for ensuring patients' accessibility to medical attention in Indonesia. Studies have shown that regulation significantly influences patients' acceptance of health referrals (P. W. Handayani et al., 2018). However, challenges persist in implementing an effective referral system, including inadequate infrastructure and healthcare personnel shortages (Rahayu & Hosizah, 2021). The lack of a concise referral system and supportive regulations contribute to diagnostic and treatment delays, particularly for breast cancer patients (Gautama, 2022). To address these issues,

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Indonesia has transitioned from a manual to an online-based referral system for National Health Insurance participants. This online system has shown promise in improving patient satisfaction regarding time certainty, referral certainty, and service quality (Andani et al., 2023). Nevertheless, further supportive measures and regulatory reforms are necessary to enhance the efficiency and effectiveness of the referral system in Indonesia (Pinem et al., 2020).

Lifestyle choices, such as alcohol consumption and obesity, also contribute to the prevalence of BC in Indonesia. Excessive alcohol consumption can increase estrogen levels, leading to a higher risk of breast cancer. Similarly, obesity is associated with an increased risk of breast cancer, particularly after menopause. Promoting a healthy lifestyle, including moderate alcohol consumption and maintaining a healthy weight, can help reduce the incidence of breast cancer.

Preventive measures and early detection are vital in reducing the impact of BC in Indonesia. Public health initiatives should focus on raising awareness about the risk factors associated with BC, promoting healthy lifestyle choices, and encouraging regular screening. Mammography and breast self-examination are essential tools for early detection, allowing for timely intervention and treatment.

C. RARE CANCERS IN INDONESIA

The notion of "rare cancer" is often defined as a malignant disorder with an incidence of less than 6 per 100,000 per year, as stipulated by the Surveillance of Rare Cancers in Europe (RARECARE). Notably, the incidence of rare cancers varies widely across different subtypes, underscoring the complexity of this disease category. Rare cancers account for approximately 20-25% of all new cancer diagnoses, highlighting the significance of these diseases in the global oncological landscape. The advent of molecular biology and extensive genomic analyses has enabled the identification of novel, molecularly defined subgroups of cancer, thereby expanding the scope of rare cancer

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classification. In Europe, the 5-year overall survival rate for patients with rare cancers is remarkably lower, at 47%, compared to 67% for patients with common cancers. Even when excluding common cancers with favorable prognosis, such as prostate, breast, or skin cancers, the survival disparity between rare and common tumors remains statistically significant (Blay et al., 2021).

The enigmatic nature of rare cancers is a significant challenge in the field of oncology. Many rare cancers remain shrouded in mystery, with a dearth of information available in medical literature. In fact, it is not uncommon for rare cancers to be characterized by a scarcity of research, with a lack of established diagnostic protocols, treatment options, and understanding of their underlying biology. This knowledge gap is further compounded by the absence of standardized definitions and classification systems, making it difficult to accurately identify and track these rare entities. The research landscape surrounding rare diseases is still in its infancy. Despite the increasing recognition of the importance of rare cancer research, there remains a significant shortage of dedicated funding, expertise, and resources. As a result, many researchers are forced to confront the challenges posed by rare cancers with limited access to high-quality data, inadequate patient populations for study, and a lack of well-established collaborations and infrastructure. The dearth of research on rare cancers not only hinders our understanding of these diseases but also perpetuates disparities in diagnosis, treatment, and outcomes for patients affected by these devastating conditions (Eslick, 2012).

A deeper understanding of the biological mechanisms underlying rare cancers, enhanced access to optimal diagnosis and treatment, and evidence-based therapeutic guidelines are all essential for improving patient outcomes in this population. However, disparities persist across Europe, characterized by heterogeneous patient pathways, variable access to initial healthcare management, and health migration issues that exacerbate inequities in care. Addressing these

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disparities is crucial to ensuring equitable healthcare outcomes for patients with rare cancers in Europe (Blay et al., 2021).

In the absence of a standardized definition for rare cancers in Indonesia, we will adopt the definition established by RARECARE as a guiding framework This definition is widely accepted in the international medical community and has been utilized in various research studies and cancer registries. By adopting this definition, we can ensure consistency and comparability with global research standards, thereby facilitating the exchange of knowledge and best practices in the field of oncology. This approach will also enable us to better understand and address the unique challenges and needs associated with rare cancers in Indonesia, ultimately improving patient outcomes and healthcare services in the country.

1. Penile squamous cell carcinoma (PSCC)

Penile squamous cell carcinoma (PSCC) is a rare cancer that is classified as an orphan disease. It affects 0.1–1 male per 100,000 in high-income countries, but in some African, Asian, and South American locations, it can account for as much as 10% of all male cancers. The absence of childhood circumcision, phimosis, chronic inflammation, poor penile cleanliness, smoking, immunosuppression, and human papillomavirus (HPV) infection are risk factors for PSCC (A. Thomas et al., 2021). In Indonesia, although the new cases were 1098—which was considerably low—the death number reported was 419, hence the death rate was around 38.2% (International Agency for Research on Cancer, 2022). In the country, PSCC is an uncommon phenomenon, with a notable exception being the Bali Province, where it is a relatively frequent occurrence. In fact, it is the most common type of cancer affecting men in Bali, with prostate cancer being a distant second. The underlying causes and risk factors for penile cancer remain unclear, although a multitude of factors have been identified as contributing to its development. These include a history of uncircumcised status, chronic inflam-

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mation conditions such as balanoposthitis, phimosis, and balanitis xerotica obliterans, poor hygiene practices, low socioeconomic status, multiple sexual partners, ultraviolet phototherapy, HIV and HPV infections, obesity, smoking, and even unconventional sexual practices such as zoophilia. Research conducted in Brazil has also revealed that men working in agricultural professions have a heightened risk of developing PSCC. Typically, patients present with symptoms such as pruritus, as well as more severe manifestations including ulcers, nodules, or tumors with secretions. A study conducted at the Sanglah General Hospital in Denpasar, Bali, has further highlighted the association between PSCC and risk factors such as non-circumcision (100%), history of phimosis (87%), and urinary tract infections (72%) (D. P. O. Lestari et al., 2021).

Globally, regions with high incidence rates are characterized by a prevalence of human papillomavirus infection and phimosis, alongside low socioeconomic status, which are potent risk factors for developing PSCC. The disease typically peaks in the sixth decade of life, although it can also affect younger men. In such cases, organ-sparing penile cancer treatment is generally preferred, involving non-invasive and localized methods such as topical chemotherapy, laser ablation, or resurfacing of the gland (Harju et al., 2021).

Radiotherapy modalities may be considered in specific cases of invasive penile cancer; however, surgery remains the most reliable option for achieving long-term healing (Kieffer et al., 2014). Notably, most studies report compromised quality of life among patients with penile cancer, with a correlation between surgery rates and symptoms. Furthermore, as many as 50% of patients may experience symptoms resembling traumatic stress disorder, highlighting the disease's profound impact on their psychological well-being (Suarez-Ibarrola et al., 2018).

An observational study which employed a cross-sectional design described the situation of penile cancer patients receiving

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treatment at Haji Adam Malik Hospital from September 2020 to September 2021. The population comprised all patients with a PSCC diagnosis who underwent therapy during this period. Quality of life was assessed using the EORTC QLQ-C30. All patients reported poor quality of life, with significant correlations between erectile function, changes in sexual function, and overall sexual function, and health-related quality of life (HRQoL) post-treatment which suggest the lack of sexual activity is the primary factor contributing to decreased HRQoL in penile cancer patients. A staggering 70% of patients reported a negative impact on sexuality post-treatment (Firmansyah et al., 2023).

2. Gallbladder Cancer (GBC)

GBC is the most typical bile tract cancer and the deadliest form of the disease. It typically has a bad prognosis when it is diagnosed late. Approximately 95% of GBCs are epithelial in origin with cholangiocyte differentiate from the lining of the gallbladder mucosa (Roa et al., 2022). GBC is uncommon in the United States, but in certain geographically diverse parts of the world, such as Chile, North India, Korea, Japan, and the US state of New Mexico, it is more common. In New Mexico, the incidence of gallbladder cancer is significantly greater in people of Native American descent than in Hispanic and non-Hispanic white populations. One of the few bi-gendered tumors, gallbladder cancer is more common in women than in men. The genesis of gallbladder cancer is probably multifactorial, comprising a mix of genetic, immunological, and environmental components, much like other gastrointestinal malignancies (Nemunaitis et al., 2018).

Studies have reported varying rates of gallbladder cancer incidence in patients with gallstones, ranging from 0.5% to 24%. A Swedish study found that the incidence of gallbladder cancer in patients with gallstones was 0.5% (Muszynska et al., 2017). Additionally, the risk of developing gallbladder cancer increases with the size

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of the gallstones, with a relative risk of 2.4 for stones measuring 2.0-2.9 cm and 10.1 for stones measuring 3 cm or larger. Interestingly, cholesterol stones appear to be more common in individuals with gallbladder cancer (Diehl, 1983; Hundal & Shaffer, 2014).

The incidence of gallbladder cancer is disproportionately high in certain ethnic groups, including American Indians, Chilean Mapuche Indian females, East Indian females, and New Zealand Maori. These populations often have a high prevalence of cholesterol gallstones, which may contribute to their increased risk of developing gallbladder cancer. Overall, the evidence suggests that a history of gallstones is a significant risk factor for gallbladder cancer, and that further research is needed to understand the underlying mechanisms and identify effective prevention strategies (Rawla et al., 2019).

In Indonesia, its death rate reaches 69% with 5-year prevalence per 100 000 population was 0.07 in 2022. And like other types of cancers, it is projected to rise annually (International Agency for Research on Cancer, 2022). Like in many other countries, GBC in Indonesia is characterized by its high mortality rate, largely due to the lack of specific symptoms, advanced stage at diagnosis, and the proximity of vital organs to the gallbladder. The primary treatment for gallbladder cancer is surgery, which involves radical cholecystectomy, the removal of segments IVb and V of the liver parenchyma, and local lymphadenectomy. This comprehensive approach is crucial in improving staging and reducing the risk of recurrence. It was shown in a Case Report article by Sampetoding and colleagues in 2022 that they employed a radical surgical approach, including extended cholecystectomy with a margin of normal liver tissue and regional lymphadenectomy. This procedure allowed for accurate staging and minimized the risk of recurrence. Moreover, the removal of involved organs and lymph nodes is essential in achieving clear margins, particularly in cases of advanced tumors that involve the proximal transverse colon and liver. In their patient, surgery was

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performed despite the tumor being unresectable, as this treatment option was deemed to offer a good prognosis due to her young age, good performance status, and clear tumor boundaries (Sampetoding et al., 2022).

The significance of regional lymphadenectomy in gallbladder cancer treatment cannot be overstated. Studies have consistently shown that this procedure improves survival rates in patients with T1b to T3 gallbladder cancer. In fact, lymph node dissection is widely recommended by leading organizations, including the American Joint Committee on Cancer and the National Comprehensive Cancer Network. The presence of positive lymph nodes is a significant predictor of poor long-term survival and is often an indication for adjuvant systemic therapy. In their case, histological examination revealed free margins without damaged lymph nodes among the 10 resected lymph nodes, confirming the success of their surgical approach (Sampetoding et al., 2022).

3. Vaginal Cancer (VC)

This is rigorously defined as a vaginal cancer that is discovered without any clinical, histologic, or previous history of cervical or vulvar cancer during the previous five years. This is corroborated by the fact that the majority of suspicious vaginal malignancy lesions correlate with metastatic lesions of vulvar or cervical cancer, or other lesions that spread to the vagina (e.g., breast, endometrial, trophoblast, ovary, lymphoma). Only 1%–2% of all female genital tract malignancies or 10% of all vaginal malignant neoplasms are primary vaginal cancers, indicating their rarity. Historically, older and postmenopausal women have been more likely to get these tumors. In younger women, vaginal malignancy is typically associated with a persistent high-risk HPV infection, which is the etiological link to cervical cancer. Even though they are uncommon, vaginal malignancies are becoming more common in younger women because of the rise in high-risk, ongoing HPV infections, particularly

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in areas where the HIV virus is highly prevalent (Adams et al., 2021). The death ratio of vaginal cancer per 2022 was 41% and the 5-year prevalence per 100 000 population was 0.1.

4. Hypopharyngeal Cancer (HC)

Head and neck cancers (HNC) are a significant concern globally, with over 744,000 new cases and 364,000 cancer-related deaths reported in 2020 alone. These cancers include lip and oral, oropharyngeal, hypopharyngeal, and laryngeal cancers which altogether—according to GLOBOCAN 2020—accounted for approximately 9.6% of all new cancer cases and 4.72% of all new cancer deaths worldwide. The statistics are even more striking when broken down by gender, with head and neck cancers accounting for 14.6% of new cancer cases in men and 4.39% of new cases in women in 2020 (Tsai et al., 2023).

Hypopharynx cancers (HC) are a rare but aggressive type of HNC, with approximately 2,000 to 3,000 cases reported each year in the United States. Despite their rarity, HCs are often managed similarly to laryngeal cancers. The hypopharynx is a narrow region that extends from the hyoid bone to the bottom of the cricoid cartilage and includes the pyriform sinus, posterior pharyngeal wall, and postcricoid area. Most hypopharynx cancers arise from the pyriform sinus, and they drain to similar lymph node beds as laryngeal cancers. However, they can also drain to the lateral retropharyngeal lymph nodes. Symptoms are often asymptomatic, but may include a neck mass, sore throat, and odynophagia. A thorough workup typically includes a history and physical examination, fiberoptic examination, axial imaging (CT scan or MRI), and consideration of PET/CT for locally advanced disease (Zidar & Gale, 2022).

HC accounts for approximately 3% of head and neck cancer (HNC) cases and is the worst prognosis. The overall 5-year survival rate of this cancer is about 30-35%. Pathologically, HC is characterized by the presence of squamous cell carcinoma with low differentiation level (Garneau et al., 2018). Only slightly better than

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that shown in mesothelioma, new cases of HC in 2022 in Indonesia reached 292 people with 55% of death ratio (death number: new emergence). The 5-year prevalence of HC was observed at 0.06 per 100 000 population (International Agency for Research on Cancer, 2022).

The most common histological type of hypopharyngeal cancer is squamous cell carcinoma, accounting for approximately 95% of cases, while adenocarcinoma, sarcoma, and non-epidermoid carcinoma comprise the remaining cases. Tumours of the hypopharynx are characterized by local invasion and lymphatic spread, with a significant proportion of patients presenting with lymph node involvement at diagnosis (Sanders & Pathak, 2024).

The symptomatic burden of hypopharyngeal cancer is primarily determined by the size and location of the primary tumour. Patients often present with symptoms such as pain, bleeding, and dysphagia, with concomitant malnutrition being a poor prognostic factor. In advanced cases, tumours may invade the larynx, leading to features of airway compromise and aspiration. Surgical management typically involves a combination of partial or total pharyngectomy and laryngectomy, which can result in significant functional morbidity. The prognosis is often poorer due to the advanced stage commonly seen at presentation, which is less common than laryngeal cancer. Notably, the rate of nodal involvement and metastasis is high at diagnosis, with 50% to 70% of patients presenting with N1 disease or worse. The prognosis for hypopharyngeal cancer is largely determined by stage, with early disease (T1-T2) having a 5-year survival rate of around 60%, compared to less than 25% in larger tumours (T3-T4) or those with multiple nodal spread (Sanders & Pathak, 2024).

HC treatment often involves surgical resection, which can be performed as a standalone procedure or in combination with post-operative radiotherapy. The type of surgery required depends

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on the extent of the tumour and the affected areas and may necessitate reconstruction to restore the affected regions. The reconstructive approach used will depend on whether the larynx has been preserved in its entirety or partially resected, as this can significantly impact the rehabilitation process.

Surgical management of HC is a complex and multifaceted process that requires a comprehensive understanding of the lesion's extension, and the subsites involved. In many cases, reconstructive strategies are necessary to address defects in the upper aerodigestive tract, and the choice of reconstruction method depends on whether the larynx has been preserved or totally resected. If the larynx is entirely removed, the creation of a separate conduit for breathing and swallowing is crucial, and restoration of the region's primary functions is significantly altered (Mura et al., 2013).

In 2003, Disa et al. proposed a new classification system that categorizes defects of the pharyngo-oesophageal segment after total laryngectomy into four types: Type 0, Type I, Type II, and Type III/IV. Type 0 lesions are minimal and can be closed primarily, while Type I and II lesions require the use of a pharyngeal strip of native mucosa to prevent circumferential scarring. Type III lesions involve extended longitudinal defects, and Type IV lesions involve defects that extend to the cervical oesophagus (Disa et al., 2003).

Despite the growing burden of HC in Indonesia, there is a dearth of information on the demographic characteristics, risk factors, and clinical presentation of hypopharyngeal cancer in Indonesia, as well as the effectiveness of different treatment strategies for this disease. Recent studies highlight the prevalence and challenges of head and neck cancers in Indonesia. Nasopharyngeal carcinoma (NPC) is the most common, with an estimated incidence of 6.2/100,000 or 12,000 new cases annually (S. A. Gondhowiardjo et al., 2020). NPC patients are predominantly male, with a median age of 47 years, and most present with advanced-stage disease (S. A. Gondhowiardjo

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et al., 2020; Jayalie et al., 2016). Laryngeal cancer is also prevalent, particularly in developing regions like West Nusa Tenggara, where patients often present with late-stage disease (Kadriyan et al., 2021). Risk factors for these cancers include smoking, salted fish consumption, and air pollution (Jayalie et al., 2016; Kadriyan et al., 2021). Treatment typically involves a combination of surgery, chemotherapy, and radiotherapy, with concurrent chemoradiotherapy being the standard for locally advanced NPC (Faisal et al., 2020; S. A. Gondhowiardjo et al., 2020). Despite the high disease burden, there is limited clinical evidence on head and neck cancers in Indonesia, highlighting the need for further research and improved cancer registration (Faisal et al., 2020).The management of laryngeal cancer in Indonesia is predominantly focused on surgical resection and radiotherapy. Notably, patients with early-stage disease tend to receive radiotherapy as their primary treatment modality, whereas those with advanced-stage cancer undergo either radiotherapy or multimodal therapy. In cases of bulky or deeply invasive T2 tumours, total laryngectomy may be the only viable option. Conversely, patients with preserved laryngeal function may be more likely to receive radiotherapy due to concerns about post-operative functional outcomes. In cases of locally advanced disease, organ-preservation surgery, chemoradiation, or radiation therapy alone may be viable options to maintain laryngeal function (Pinakaratna et al., 2023).

Notably, patients with low laryngeal function or extensive advanced-stage disease may benefit from total laryngectomy, which can provide improved survival rates and better quality of life. This study highlights that some patients with advanced-stage disease are not eligible for surgery due to the spread of cancer to the upper gastrointestinal tract or fixation of the mass, leading to a poor surgical prognosis (Pinakaratna et al., 2023).

Among patients who underwent surgery, total laryngectomy (TL) was the most common procedure performed. TL is widely

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considered the standard treatment for advanced laryngeal cancer and is not recommended for organ preservation due to the risk of cancer spreading to the thyroid cartilage and poor laryngeal function. Previous studies have demonstrated that TL has an advantage in terms of survival and locoregional control in stage IV laryngeal cancer; however, further evidence is needed to confirm its superiority over other non-surgical treatments (Pinakaratna et al., 2023).

5. Mesothelioma

The malignant pleural mesothelioma is a highly aggressive and insidious tumor that originates from mesothelial cells, with a profound association with asbestos exposure. This heterogeneous cancer exhibits a complex pattern of molecular aberrations, encompassing genetic, chromosomal, and epigenetic abnormalities (Schumann et al., 2021).

The clinical presentation of mesothelioma is often characterized by a combination of chest pain, dyspnea, and pleuritic symptoms. Typically, the pain is dull and diffuse, occasionally pleuritic, and worsens as the disease progresses. Patients may experience heaviness or aching sensations in the shoulder, arm, chest wall, and upper abdomen, which can be exacerbated by entrapment of nerves such as intercostal thoracic, autonomic, or brachial plexus nerves. In some cases, patients may present with persistent chest wall pain, accompanied by clear chest radiographs, which later develop into pleural masses or effusions (British Thoracic Society Standards of Care Committee, 2007).

Dyspnea is a common symptom in the early stages of the disease, typically caused by a pleural effusion. However, as the disease progresses, it may be due to the restrictive effects of pleural thickening. Other less common presentations include coughing, particularly in patients with pleural effusions, as well as chest wall masses, weight loss, abdominal pain, and ascites due to peritoneal

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involvement. Profuse sweating may also occur (Bianco et al., 2017; Bintcliffe et al., 2016).

The disease tends to progress through local extension rather than hematogenous spread. Direct involvement of mediastinal structures is common, although hoarseness and superior vena cava obstruction are relatively rare causes of major symptoms. Dysphagia tends to occur pre-terminally. In some cases, patients may present with acute pleuritic chest pain and a small effusion, but initial investigations may fail to provide a diagnosis. The patient may then remain symptom-free for several months until recurrence of fluid or development of chest pain leads to further investigation and ultimate diagnosis of mesothelioma (British Thoracic Society Standards of Care Committee, 2007).

The disease is characterized by silent and gradual clinical progression, with an average latency period of 20-40 years from initial asbestos exposure to the onset of symptoms. Unfortunately, the therapeutic options remain limited, particularly when the tumor is diagnosed late. This comprehensive review aims to provide an exhaustive overview of the current evidence in the literature regarding epidemiology, diagnostic pathways, and treatment strategies for malignant pleural mesothelioma. Over the past two decades, treatment modalities have evolved significantly, with advancements in surgical techniques, radiotherapy, chemotherapy, and immunotherapy. Various surgical approaches are available, including extra pleural pneumonectomy and cytoreductive surgery, although a multidisciplinary approach is now considered essential, as a single modality has yet to demonstrate consistent efficacy. Notably, promising non-surgical treatment options are emerging; however, these must be interpreted with caution pending the availability of high-quality evidence from rigorous studies (Schumann et al., 2021).

This cancer is the least common in Indonesia. Its 5-year prevalence in 2022 only accounted for 0.02 cases per 100,000 people.

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Nevertheless, 227 deaths out of 243 new cases indicated that this subtype had the largest mortality toll, indicating a dismal survival of fewer than 7% (International Agency for Research on Cancer, 2022).

Asbestos, a substance of significant global concern, poses a substantial threat to human health. According to the World Health Organization, approximately 125 million people worldwide are exposed to asbestos at work, leading to a staggering 107,000 annual fatalities resulting from asbestos-related lung cancer, mesothelioma, and asbestosis (Hernández-Blanquisett et al., 2021; Wagner & Lemen, 2017). Indonesia, in particular, has a long history of importing asbestos legally since the 1950s, and is currently among the top five countries in the world still utilizing this hazardous material (A. D. Lestari & Hairunisa, 2023).

Despite the alarming statistics, cases of asbestos-related diseases (ARD) are grossly underreported and undiagnosed in Indonesia. Studies have estimated that the country should be experiencing hundreds to thousands of cases per year. However, the government has only approved six cases of non-malignant ARD as occupational diseases, resulting in limited compensation for affected workers. It is noteworthy that while Indonesia has prohibited the use of crocidolite asbestos since 1985, there is no corresponding regulation restricting the use of chrysotile asbestos. Furthermore, the threshold limit value for asbestos in Indonesia is set at an alarmingly low 0.1 fiber per cubic centimeter, which does not necessarily translate to a low incidence of diseases (A. D. Lestari & Hairunisa, 2023).

The most effective means of eliminating asbestos-related diseases is to ban the use of all types of asbestos altogether. Fortunately, safe and affordable substitutes for asbestos-containing materials are already being utilized in countries that have successfully banned asbestos. To achieve this goal, it is essential to raise awareness and foster cooperation among all stakeholders, including government agencies, employers, workers, unions, researchers, scientists, doctors,

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and society. The urgency of this issue cannot be overstated (A. D. Lestari & Hairunisa, 2023).

Indonesia's persistence in utilizing asbestos, despite being among the top five countries worldwide still employing this hazardous material, stands in stark contrast to the rarity of asbestos-related diseases (ARD) being diagnosed and reported in the country. In stark juxtaposition, developed nations like Great Britain, which have long since prohibited the use of asbestos, experienced a staggering 4,500 occupational mortalities per annum due to ARD. The World Health Organization's unequivocal recommendation to ban the use of asbestos in all its forms is rooted in the devastating impact of this substance on human health. Indonesia remains one of the 35% of countries worldwide that have yet to outlaw the use of all types of asbestos, a stark reminder of the urgent need for regulatory reform (A. D. Lestari et al., 2023).

The alarming rise of cancer cases worldwide and in Indonesia, in particular, serves as a poignant reminder of the imperative to prioritize collective health and well-being. As we grapple with the multifaceted nature of this disease, we are confronted with the stark reality that our individual actions, choices, and lifestyles have far-reaching consequences that transcend geographical boundaries. The emerging trend of cancer in Indonesia, with its unique epidemiological profile, underscores the need for a holistic approach to healthcare, one that integrates scientific research, public awareness, and community engagement. Ultimately, the battle against cancer is not just a medical issue, but a social and cultural imperative that demands our collective responsibility, cooperation, and commitment to creating a healthier future for all.

D. IMPORTANT ASPECT OF THE BOOK

The opening of this book explores the emergence of cancer globally and in Indonesia, highlighting the key patterns, trends, and risk

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factors shaping the nation's disease landscape. This first chapter discusses the rising cancer burden in Indonesia and reviews the strategies implemented to address its rapid escalation. Ultimately, this book, *Cancer Conundrum: The Etiology, Global Trends, and National Response*, will provide an in-depth overview of cancer hallmarks, anticancer treatment platforms, disparities in patient responsiveness to anticancer treatments, the biology of less survivable cancers, and emerging therapeutic innovations. It also outlines intervention strategies tailored to cancer treatments done in Indonesia. In summary, this book presents a broad, up-to-date perspective on cancer and its treatments worldwide, with a focused discussion of the Indonesian context.

In chapter 2, we engage in a comprehensive discussion regarding the Warburg effect—a phenomenon defined by the inhibition of oxidative phosphorylation and the subsequent adaptation to hypoxic conditions. It has been recognized as a critical metabolic enigma; wherein certain reactions may be harnessed to establish novel platforms for cancer therapeutics. This chapter serves as a foundational basis for our subsequent discourse on the chemical reactions that dictate the trajectory of tumor progression. Additionally, we introduce the terminology of tumor microenvironment. This encompasses the varied profiles of immune cells that infiltrate the tumor core and examines the mechanisms by which they are reprogrammed, or conversely, how they influence tumor cells in the context of the Warburg effect. From this chapter, we will derive comprehensive insights into the metabolic manifestations of the hallmarks of cancer.

The General Hallmarks of Cancer in chapter 3 represent a comprehensive paradigm that incorporates molecular characteristics distinguishing neoplastic processes from normative physiological states. This framework was first articulated by Hannahan and Weinberg in the year 2000, subsequently evolving into a pivotal foundational theory within the realm of molecular oncology, with their

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publication remaining the most frequently cited and irreplaceable to date. The concept has progressed in alignment with contemporary discoveries, yet continues to be rooted in its original definition. In Chapter III, we present an organized compendium of knowledge regarding each hallmark and its clinical manifestations. A thorough comprehension of these hallmarks will enhance our understanding of the complexities surrounding cancer—despite its origin as a component of the host's own anatomy, it poses considerable challenges in terms of treatment and management. Nonetheless, the optimistic development lies in the fact that, although formidable, advancements in technology are rendering these hallmarks increasingly amenable to intervention.

Next in the chapter 4, we present a comprehensive overview of all anticancer treatment modalities, encompassing those commonly referred to as conventional therapies, which include chemotherapy, radiotherapy, and surgical interventions. Additionally, we elucidate the underlying principles that account for the efficacy of these modalities in successfully inducing apoptosis in cancer cells. Conversely, we also provide a thorough examination of the limitations of these same modalities, highlighting the reasons they cannot be universally applied and the emergence of therapeutic resistance. It is this phenomenon of resistance that necessitates the exploration of cancer immunotherapy in conjunction with gene-targeted therapies. As our understanding of cancer—originating from a singular cell—reveals its heterogeneity across different histological types and individual patients, there is an impetus for the development of more precise and personalized treatment modalities. Furthermore, we reference facilities in Indonesia that offer innovative treatment strategies currently under discussion. This serves to illustrate to the readers that the landscape of anticancer therapies continues to evolve, driven by long-term outcome assessments and new discoveries that aim to steer the field toward more effective and accessible treatment options.

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Following the discussion of existing anticancer regiment, in chapter 5 we discuss about responsiveness disparity on anticancer treatments. It is evident that in this long battle against cancer, not only must individuals possess an optimal immune profile akin to a protective armor, but they also require an external support system that facilitates the effective administration and management of therapeutic interventions, as well as the long-term follow-up of patients who have triumphed over the disease. From the perspective of intrinsic protective mechanisms, the genetic and immunological profiles of individuals play a crucial role. Certain individuals exhibiting particular genetic and immune characteristics are considered to be at greater risk relative to others. This chapter dig in-depth into this topic to foster foundational knowledge regarding immune and genetic identities, which are unequivocally influenced by factors such as race or ethnicity.

Chapter 6 about the biology of less survived cancers. This Chapter elaborates cancers with lower survival rates, with a specific focus on the Indonesian context. It is acknowledged that cancer arises from a complex interplay of internal and external factors that influence an individual's susceptibility to the disease. Certain types of cancer are associated with higher mortality rates, and the quality of the environment—including air pollution and overall sanitation—fails to meet safety standards, rendering these conditions somewhat inescapable. We aim to enhance individual awareness regarding potential exposure to daily carcinogenic variables and elucidate how such exposures may contribute to the development of cancer.

As we delve further into the realm of personalized therapeutic interventions, chapter 7 delineates the mechanistic evolution of the most recent therapeutic platforms, which represent a significant progression from the antecedent generation of personalized medicine. Furthermore, we elucidate the scientific rationale underlying each advancement concerning molecular and pathway targets. Each target

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yields distinct ultimate outcomes, which may be particularly advantageous for patients with specific conditions that warrant attention.

Chapter 8 elucidates a variable that is frequently overlooked: aging. It is widely acknowledged that as individuals advance in age, the likelihood of developing cancer increases, even in the absence of a familial predisposition. This demographic necessitates specialized management strategies that cannot be generalized to younger patient cohorts. Specifically in Indonesia, cancer treatment for the elderly is comparatively uncommon. This phenomenon can be attributed to the fact that a significant proportion of Indonesia's population is under the age of 35, thereby creating a demographic advantage for the youth. As a result, the primary focus tends to be on the predominant younger population. In this context, we aim to present to our audience the biological relationship between aging and cancer, along with the strategies implemented in various developed nations that serve as role models. Furthermore, we will reference the measures that Indonesia has undertaken thus far and how these initiatives are expected to evolve through the adoption of more comprehensive strategies at the level of national stakeholders.

Finally, in chapter 9 we discuss about intervention strategies for cancer treatment in Indonesia. With its unique dynamics, the application of established strategies from developed countries presents considerable challenges and is not universally applicable within the Indonesian context. The country adopts a distinct strategy that takes into account the availability of all relevant factors, primarily the feasibility of implementation. A particularly notable instance is breast cancer, which is addressed through a preventive measure known as SADARI, emphasizing independent and individualized assessment. Furthermore, at the community level, the government has initiated anticancer vaccination programs aimed at mitigating the risk of ovarian cancer. Additionally, the nation has capitalized on its rich mega biodiversity, which harbors a plethora of medicinal herbs that can enhance individual immunity. Such mega biodiversity is unique to Indonesia and is not found in other nations.

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CHAPTER II
WARBURG EFFECT DECIPHERS THE CANCER CONUNDRUMS

The enigmatic nature of cancer has long fascinated scientists, and one critical component that has been shrouded in mystery is the metabolic mechanism. Not until Otto Warburg's groundbreaking discovery in the 1920s did the concept of aerobic glycolysis come to light. Warburg's pioneering work revealed that cancerous cells exhibit an extraordinary predilection for glucose consumption, consuming more of this essential nutrient than their healthy counterparts (X. Li et al., 2022). The significance of the Warburg effect was initially overlooked by the broader scientific community. However, it was Warburg himself who continued to articulate his hypothesis throughout his career. In his 1966 lecture at the meeting of Nobel-Laureates at Lindau, Germany, Warburg presented additional evidence supporting his theory that elevated anaerobiosis in cancer cells was a consequence of damaged or insufficient respiration. He succinctly stated that "the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar (A. Le et al., 2021; The Nobel Foundation, 2024)

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Otto Warburg's groundbreaking study in the early 20th century forever altered the landscape of cancer biology. By examining oxygen consumption in rat tumor sections, Warburg discovered a stark contrast between tumors and healthy tissues. Tumors exhibited significantly lower oxygen consumption, leading Warburg to hypothesize that they lacked the necessary fuel for cellular respiration. To test this theory, he added glucose to the solution, only to observe that oxygen consumption ceased entirely and lactate production skyrocketed. This marked a turning point in his research, as he realized that mitochondria in tumor tissues were malfunctioning, consuming little to no oxygen. The shift from oxidative phosphorylation to anaerobic glycolysis enables tumors to sustain their rapid growth and proliferation. Had Warburg had access to a broader range of tumor types during this initial investigation, he may not have been compelled to pursue the observation of increased lactate production in tumors under aerobic conditions, which ultimately secured his place in scientific history.

The Warburg effect, a phenomenon characterized by the suppression of oxidative phosphorylation and the adaptation to hypoxia, has emerged as a crucial aspect of this metabolic puzzle. This distinct energy-generating pathway, marked by the preferential use of anaerobic glycolysis, enables cancer cells to acquire the necessary energy to sustain their growth and invasion (T. Epstein et al., 2017; Jaworska et al., 2023).

The phenomenon of the "Warburg effect" is characterized by a metabolic shift in cancer cells, whereby they adopt a reliance on aerobic glycolysis to meet the elevated energy demands and metabolite requirements that are hallmark features of cancerous growth. This metabolic reorientation is achieved by a suppression of oxidative phosphorylation, resulting in the redirection of cellular resources towards glycolysis. Furthermore, the tricarboxylic acid (TCA) cycle is effectively silenced in cancer cells as a direct consequence of this

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metabolic adaptation. The interplay of various factors, including the activation of oncogenes, the failure of tumor suppressor genes, and the deregulation of gene expression, also contributes significantly to the alterations in cellular metabolism that are characteristic of cancer (A. Kumar et al., 2021; Niu et al., 2022).

Enya and colleagues in 2018 pioneered and published the creation of their novel intestinal tumor model, which enabled us to meticulously elucidate four distinctive phenotypes that are also characteristic of human cancer patients. Their comprehensive analysis of whole-organism transcriptomes revealed aberrant gene expression and metabolic patterns in both the intestinal tumor and the distant liver. Building upon these discoveries, they uncovered a tumor-liver crosstalk mechanism that can be defined by the hepatic expression of cyp7a1 and altered cholesterol-bile acid flux, leading to the infiltration of neutrophils into the liver (liver inflammation) in tumor-bearing larvae. This novel insight has significant implications for recent understanding of the complex interplay between tumor cells and their microenvironment (Enya et al., 2018).

Lactic acid is both a byproduct of glycolysis, a process that occurs in the absence of oxygen, and a substrate for oxidative metabolism, which requires oxygen. Research has shown that cancer cells exhibit both glycolytic and oxidative metabolic profiles, with lactic acid serving as a key link between these two processes (X. Li et al., 2022). Glycolytic tumor cells convert glucose to pyruvate through aerobic glycolysis, and then pyruvate is converted to lactic acid by lactate dehydrogenase A (LDHA). This lactic acid is then excreted via monocarboxylate transporter 4 (MCT4) (Z. Li & Cui, 2023; Sharma et al., 2022). Aerobic glycolysis in cancer cells is efficient due to the unique ability of LDHA to regenerate nicotinamide adenine dinucleotide (NAD+) from NAD+ hydrogen (NADH) within the cytoplasm, thereby bypassing the mitochondrial electron transport chain. This distinctive process ensures a constant supply of NAD+, which is es-

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sential for maintaining the optimal rate of glycolysis. In the absence of this mechanism, the depletion of NAD+ would severely restrict glycolysis, particularly at the glyceraldehyde-3-phosphate dehydrogenase (GAPDH)-mediated step. Furthermore, the perpetual activation of key signaling molecules, including hypoxia-inducible factor-1α (HIF-1α), cellular myelocytomatosis oncogene (c-Myc), and the mammalian target of rapamycin (mTOR) pathway, drives the aberrant expression of multiple glycolytic enzymes, thereby fostering aerobic glycolysis in cancer cells (Z.-H. Wang et al., 2021).

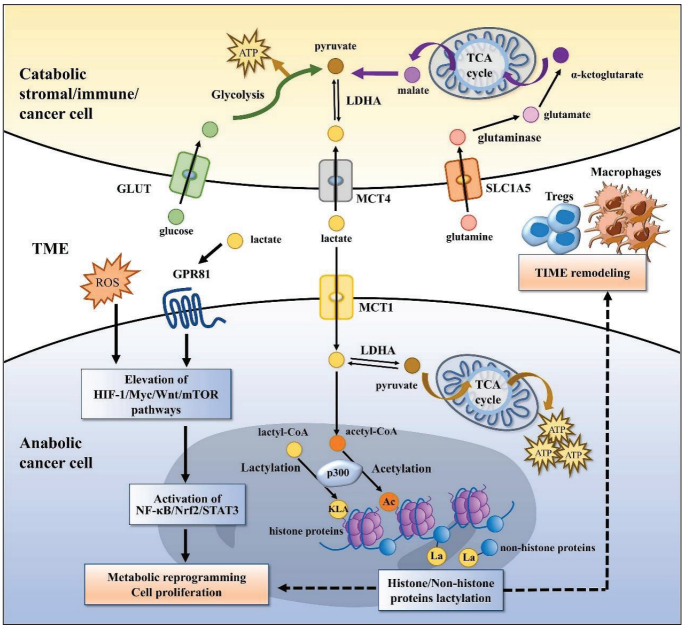
The activation of the mTOR pathway which in turn enhances the expression of key glycolytic enzymes, including hexokinase 2 and pyruvate kinase muscle isoform 2 (PKM2). The latter enzyme plays a crucial role in facilitating lactate production. Moreover, the upregulated PKM2 feeds back into the system, stimulating the mTOR complex 1 (mTORC1) in cancer cells. This positive feedback loop reinforces the glycolytic response, thereby amplifying the lactate production in cancer cells (Q. Sun et al., 2011).

In addition to aerobic glycolysis, cancer cells have the ability to convert glutamine into lactate through a process called glutaminolysis. This process is characterized by the increased uptake of glutamine and its subsequent conversion into glutamate via glutaminase, which is regulated by c-Myc. The glutamate then enters the mitochondria, where it is converted into α-ketoglutarate and subsequently malate, which is transported into the cytoplasm to generate pyruvate for lactate production (Wise et al., 2008). This metabolic pathway not only provides sufficient ATP for tumour growth but also generates important intermediates that are essential for anabolic pathways and antioxidant stress in cancer cells. These intermediates include NADPH production, nucleotide synthesis, and purine-pyrimidine synthesis, as well as amino-acid, fatty-acid, and sterol synthesis (Z.-H. Wang et al., 2021).

It has been discovered that lactic acid plays a crucial role in facilitating communication between different cell populations within

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the tumor microenvironment (TME) (Niu et al., 2022). In TME, cancer cells undergo dramatic metabolic reprogramming. Cancer cells have a propensity to divert pyruvate towards anaerobic oxidation, thereby meeting the increased energy demands and facilitating growth. As a consequence, lactic acid accumulates in the TME, playing a crucial role in the malignant process. Cancer cells exhibit elevated glutamine uptake, which leads to the production of α-ketoglutarate, subsequently entering the tricarboxylic acid (TCA) cycle. Following conversion to malate, this intermediate is transported into the cytoplasm, ultimately providing pyruvate for lactate synthesis. Notably, the abnormal mobilization of glutamine from skeletal muscle, which is a primary source of this amino acid, contributes to the development of cachexia in patients with cancer (S. Chen et al., 2024; Y. Gao et al., 2022). This interplay is shown in Figure 2.1.



Source: Adapted from S. Chen et al. (2024)

Figure 2.1 Metabolic Reprogramming in the Tumor Microenvironment

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Despite the challenging conditions of hypoxia, cancer cells have adapted to maintain their proliferation rate by leveraging lactate as a key facilitator. As researchers continue to unravel the intricate mechanisms underlying lactate's role, new complexities emerge, posing conundrums that necessitate further investigation (S. Chen et al., 2024).

A. LACTIC ACID AND CANCER CELL MULTIPLICATION

The significance of lactate in metabolic processes is well-established, encompassing its role as a vital energy source for various tissues and cancers. The classic Cori cycle illustrates the process by which muscles produce lactate, which is subsequently taken up by the liver for gluconeogenesis. Prior research has underscored the potential of lactate to facilitate carbon transfer between and within tissues, thereby enabling the exchange of metabolites. It was indicated that this shuttling mechanism is responsible for the majority of lactate turnover in the circulation, with glucose primarily fueling the TCA cycle through circulating lactate. This phenomenon relies on the presence of high lactate dehydrogenase (LDH) activity and rapid lactate transport across the plasma membrane. In mammals, two ubiquitous LDH isozymes (LDHA and LDHB) and four monocarboxylate transporters (MCT1-MCT4) are encoded to facilitate this process (S. Hui et al., 2017). The adequate amounts of NADH produced through lactate oxidation can efficiently traverse the mitochondrial membrane via the malate-aspartate pathway, thereby supplying the electron transport chain with the necessary energy to function effectively (Van Hée et al., 2015).

Beyond its role in signaling mediators, lactic acid can also function as an extracellular ligand. The GPR81 receptor, typically found in adipocytes and meningeal fibroblasts, plays a crucial role in regulating lipolysis and promoting brain vascularization (P. Wu et al.,

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2023). In contrast, GPR81 is a vital receptor for lactate uptake in cancer cells, where it fosters the proliferation of cancer cells by regulating the expression of key proteins. Specifically, GPR81 modulates the expression of PGC1α, CD147, and MCTs, thereby sustaining the high activity of mitochondria and ultimately benefiting cancer cell multiplication (Roland et al., 2014).

Lactic acid has a profound impact on the immune system, extending beyond its role in energy metabolism. When lactate levels are elevated, they can have a detrimental effect on immune cells such as CD4+ T cells, CD8+ T cells, NK cells, and NKT cells, hindering their ability to combat inflammation and tumour growth. Conversely, elevated lactate levels can also promote the activity of immunosuppressive cells, including Treg cells, thereby contributing to an imbalance in the immune response. In a healthy physiological context, the regulatory effects of lactic acid help maintain the equilibrium between effector T cells and other immune cell subsets, thereby preserving immune balance. However, in pathological conditions, the surge in lactic acid levels can disrupt the energy metabolism cycle, particularly glycolysis, leading to a rapid breakdown of immune balance and potentially even facilitating immune escape and immunosuppression (Y. Lin et al., 2023).

B. LACTIC ACID AND CANCER CELL METASTASIS

Lactic acid plays a crucial role in the development of local tumor invasiveness and metastatic disease. One notable aspect of this process is the unique metabolic profile of cancer cells. Warburg-type cells, which are enriched in hypoxic regions, exhibit a high level of lactate production and export, facilitated by the upregulation of proteins such as LDHA/LDH5 and MCT4. Conversely, reverse Warburg cells, found in normoxic tumor regions, exhibit a distinct metabolic profile, upregulating enzymes and transporters like MCT1 to utilize

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lactate as a primary energy source. This dichotomy creates a lactate shuttle within the tumor, influenced by the tumor's oxygen gradient.

The increased production and export of lactate lead to a significant ion gradient and a corresponding drop in extracellular pH. This acidification has a profound impact on immune surveillance, impairing the recognition of aberrant cells by T-cells and NK cells, impeding NK cell generation, and reducing monocyte motility. Moreover, the acidification disrupts the binding of integrins to the surrounding extracellular matrix (ECM), allowing tumor cells to detach from the central mass and undergo local invasion (Pennington et al., 2019).

The upregulation of matrix metalloproteinases (MMPs) facilitates the digestion of the local ECM, enabling tumor cells to migrate and invade nearby tissues (Mustafa et al., 2022). Additionally, the overexpression of CD44 allows tumor cells to bind and migrate along hyaluronan-based proteoglycans. Furthermore, lactate indirectly promotes the upregulation of vascular endothelial growth factor (VEGF), which drives angiogenesis and vascularization of the tumor mass (Pennington et al., 2019; P. Wu et al., 2023).

A secondary function of VEGF is to promote the detachment of pericytes from local blood vessels, creating fenestrations in the vessel wall that facilitate tumor cell diapedesis and subsequent dissemination to distant sites, including the bones of the vertebral column through the veins of Batson's plexus. This complex interplay between lactate metabolism, immune surveillance, and angiogenesis plays a crucial role in the development of metastatic disease (Pennington et al., 2019).

C. LACTIC ACID AND ANTICANCER IMMUNITY

Cancer cells exhibit a peculiar metabolic adaptation, characterized by a persistent reliance on glycolysis even in the presence of oxygen

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(T. Epstein et al., 2014). This phenomenon is thought to be driven by the rapid fluctuations in energy demands required for cell membrane activities, such as cell division, growth, and migration. As a result, cancer cells are better equipped to rapidly adapt to changing environmental conditions, thereby outcompeting non-glycolytic cells (Kareva & Hahnfeldt, 2013).

The microenvironmental conditions within tumours can exert a profound impact on the function of T-lymphocytes. Notably, CD4+ regulatory T cells appear to be resilient to acidic conditions, which may be attributed to their reliance on fatty acid oxidation as a primary metabolic pathway. In contrast, tumour-specific CD8+ T cells are highly susceptible to the acidic environment, which induces an anergic state characterized by diminished cytolytic activity, reduced cytokine secretion, and decreased expression of key surface receptors. This anergic state is mediated by the disruption of signal transduction pathways, including the suppression of STAT5/ERK signaling, as well as the altered dynamics of plasma membrane and microtubule mobility. Specifically, the reduced association of T-cell receptor components with co-receptors such as CD8 may contribute to the development of T-cell anergy. Furthermore, in vitro studies have demonstrated that restoration of normal pH levels can reverse T-cell anergy, while prolonged exposure to acidic conditions can lead to irreversible damage or apoptosis. Interestingly, the short-term persistence of T cells in acidic environments may be attributed to their anergic state, which allows them to evade immune surveillance (Damgaci et al., 2018).

Research has highlighted the multifaceted role of lactate and tumor microenvironment factors in shaping immune responses. Elevated T cell frequencies have been observed in subjects depleted of lactate dehydrogenase-A (LDH-A) on a ketogenic diet (KD), suggesting that enhanced T cell viability may be linked to reduced lactate levels (Husain et al., 2013). Notably, a pronounced decrease

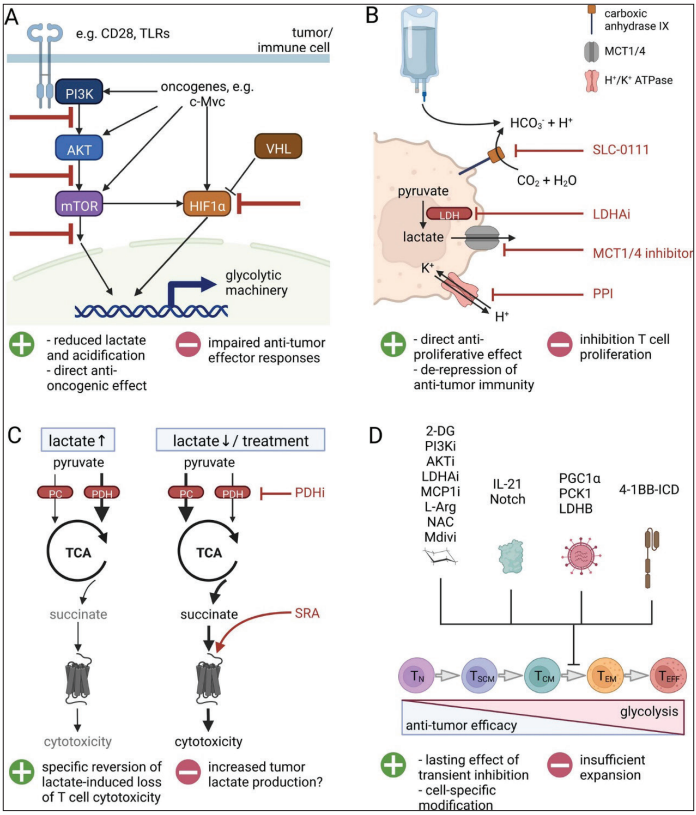
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in regulatory T cells (Tregs) across both KD and LDH-A–depleted tumor-bearing models was also reported, potentially attributable to secondary effects such as improved natural killer (NK) cell activity and/or diminished myeloid-derived suppressor cell (MDSC) populations—both known to facilitate Treg expansion. These findings underscore the pivotal role of tumor-derived lactate in orchestrating the immune microenvironment, particularly through its influence on MDSCs, NK cells, and Tregs. Additionally, research has focused on how low pH conditions within tumors regulate macrophages, especially through the activation of the inducible isoform of nitric oxide synthase (iNOS) via a nuclear factor-κB-dependent pathway; however, human macrophages appear unaffected in their angiogenic activity by low pH levels, with tumor necrosis factor-α (TNF-α) being a key trigger for angiogenesis (Bellocq et al., 1998). Lactate, as a byproduct of tumor cell metabolism, also modulates the polarization of tumor-associated macrophages (TAMs) towards an M2-like phenotype, inducing the expression of arginase 1, which inhibits T-cell proliferation and activation (Colegio et al., 2014). Our study further demonstrates that macrophage adaptation to low pH conditions prompts a phenotypic switch from M1 to M2, characterized by the loss of iNOS expression and the induction of arginase and the mannose receptor CD206 (El-Kenawi et al., 2015). Moreover, lactate, either alone or combined with tumor-produced cytokines, significantly influences the antigen-presenting capabilities and functional performance of dendritic cells, suggesting that lactate exerts a metabolic impact on these immune cells independent of pH effects (Damgaci et al., 2018).

Lactic acid, either on its own or in conjunction with cytokines produced by tumors, significantly modulated the antigen-presenting capabilities and functional performance of dendritic cells. This finding suggests that lactate may exert a metabolic influence on dendritic cells, independent of its pH-related effects (Damgaci et al., 2018).

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The metabolic byproduct of lactic acid has been implicated in the intricate dynamics of tumor development and progression, as well as the adaptive response to treatment. As such, the manipulation of lactic acid metabolism has emerged as a promising therapeutic paradigm for the prevention and treatment of cancer (Z. Li & Cui, 2023; Ser et al., 2016). Current research endeavors are focused on manipulating the lactic acid pathway to improve cancer immunotherapies as elucidated in Fig.2.2.



Source: Adapted from Heuser et al. (2023)

Figure 2.2 Targeting Aerobic Glycolysis in Tumor and Immune Cells to Boost Cancer Immunotherapies

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1. Inhibition of the glycolysis-inducing pathways

The Warburg effect, a hallmark of tumor metabolism, is orchestrated by the intersection of mTOR and HIF-1α signaling pathways, which are downstream of oncogenic stimuli. Disrupting these signaling cascades can be employed as a strategy to suppress aerobic glycolysis in cancer cells, thereby impeding tumor growth. Furthermore, Warburg metabolism is also induced in immune cells in response to pro-inflammatory and costimulatory signals, such as those mediated by TLRs and CD28, which activate the PI3K/AKT/mTOR axis (S. Ma et al., 2024; Mafi et al., 2021; S. Zhang et al., 2024). Consequently, unselective targeting of these pathways may compromise the efficacy of immune anti-tumor effector responses.

2. Targeting Lactate Production and Acidification of The TME To Counter Immunosuppression

The development of novel inhibitors, specifically targeting LDHA, is aimed at disrupting the pyruvate-lactic acid axis, thereby preventing the excessive accumulation of lactic acid (Z. Li & Cui, 2023). Furthermore, the inhibition MCT1, MCT4, or dual MCT1/4 can effectively block the efflux of lactate from cancer cells. Additionally, proton pump inhibitors (H+/K+ ATPase) can reduce the extracellular release of protons, while bicarbonate infusions can neutralize these protons (Benjamin et al., 2018; Koltai & Fliegel, 2024). The enzyme carboxy anhydrase IX, located on the extracellular surface of cancer cells, produces protons and bicarbonate, which play a crucial role in maintaining intracellular pH homeostasis (Benej et al., 2020). By targeting these pathways, we can not only modulate the tumor microenvironment and stimulate anti-tumor immune responses but also exhibit direct anti-proliferative effects on both tumor cells and T cells (F. Khan et al., 2024; Y. Tang et al., 2022).

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3. Reversing Lactate-Induced Re-Routing of Pyruvate into the TCA

The accumulation of lactate in the cell has been shown to suppress the anaplerotic pathway, specifically targeting pyruvate carboxylase (PC) and succinate-mediated autocrine signaling (Mortazavi Farsani & Verma, 2023). In contrast, inhibiting pyruvate dehydrogenase (PDH) activity can restore PC function, enhance succinate secretion, and augment the cytotoxic potency of CD8+ T cells (J. Cao et al., 2023; Elia et al., 2022). The use of PDH inhibitors, such as PDHi, has been demonstrated to have a synergistic effect with succinate receptor agonists (SRA) in promoting this metabolic shift (Cevatemre et al., 2022; K. Wang et al., 2023).

4. Targeting Aerobic Glycolysis to Enhance T Cell Fitness for Adoptive Cell Therapies.

The manipulation of aerobic glycolysis through various means can be leveraged to induce the generation of stem-like T cells with enhanced anti-tumor efficacy (H. Wu et al., 2023). This can be achieved by exploiting the inhibitory effects of small molecules, cytokines, transmembrane ligands, or the overexpression of metabolic regulators on glycolysis. Additionally, the design of chimeric antigen receptor constructs that selectively engage oxidative phosphorylation pathways can also be utilized to promote the development of stem-like T cells. By modulating these metabolic pathways, it is possible to create a more favorable environment for the proliferation and differentiation of T cells with improved anti-tumor activity (W. Li et al., 2023; Nanjireddy et al., 2023).

To achieve this, researchers have employed various strategies, including the use of 2-Deoxy-D-glucose, a glucose analog that inhibits glycolysis, and mitochondrial-targeted compounds such as mitochondrial pyruvate carrier inhibitors and mitochondrial division inhibitors (Pantic et al., 2021; Singh et al., 2023). The supple-

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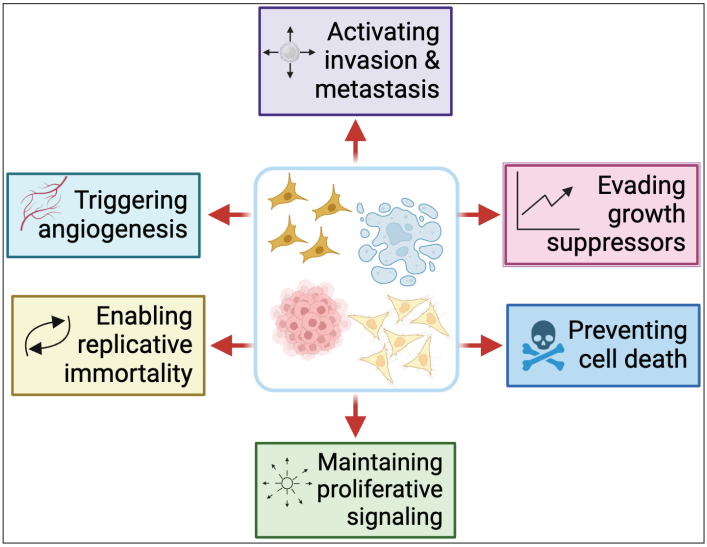
mentation of L-arginine and N-acetyl cysteine has also been shown to promote the development of stem-like T cells (Kalyanaraman, 2022; Karlsson et al., 2009; Scheffel et al., 2018). Furthermore, the manipulation of transmembrane ligands, such as δ-like ligand, and the overexpression of metabolic regulators, including peroxisome proliferator-activated receptor-γ coactivator-1α and phosphoenolpyruvate carboxykinase-1, have been demonstrated to influence glycolytic activity and enhance anti-tumor function (Grabacka et al., 2013; G. Wang et al., 2022). The intracellular domain of certain receptors has also been shown to play a crucial role in regulating glycolytic activity and promoting the development and differentiation of T cells (Chou et al., 2022; S. Ma et al., 2024).

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CHAPTER III
GENERAL HALLMARKS OF CANCERS

One might be wondering what cancers are and why they are hard to handle. Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of transformed cells. These cells exhibit a range of phenotypic properties that enable them to evade normal cellular processes and proliferate, ultimately forming tumors and potentially metastasizing to other parts of the body (J. S. Brown et al., 2023). Hanahan and Weinberg have proposed six capabilities that all cancers share in common—as shown in Figure 3.1.—which shed light on why cancer is challenging to handle(Hanahan, 2022; Hanahan et al., 2000; Hanahan & Weinberg, 2011a):

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Source: Modified from Hanahan (2022)

Figure 3.1 Six of the Most Currently Recognized Hallmarks of Cancer

A. SELF SUFFICIENCY IN GROWTH SIGNALS

Normal cells need mitogenic growth signals (GS) prior to moving from a quiescent state into an active proliferative state. Hitherto, no normal cell can proliferate without such stimulatory signals. Many of the oncogenes in the cancer catalog mimics normal growth signaling in one way or another (Hanahan et al., 2000). In some cases, however, cancer cells produce growth factors which stimulate their own proliferation. Such abnormal production of the growth factor by responsive cells facilitates auto stimulation of cell division (autocrine growth stimulation). In other cases, the less-growth factor-dependent cancer cells result from aberrant intracellular signaling, such as upregulation of growth factor receptors or Ras proteins as well as kinases lead to cell proliferation(Geoffrey M. Cooper, 2000).

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B. EVASION OF APOPTOSIS

As an organism develops or experiences cellular stress, apoptosis—a programmed cell death—enables it to eliminate unneeded cells from the body. The event is mostly dependent on a sequence of cellular processes that trigger the activation of the caspase's family of cysteine proteases. The presence of apoptotic stimuli activates initiator caspases, which are caspase-2, -8, -9, or -10. Proteolytic cleavage of particular cellular substrates and eventual cell death are the outcomes of these caspases' subsequent cleavage and activation of zymogenic "executioner" caspases, namely caspase-3 and caspase-7(Fernald & Kurokawa, 2013).

The executioner caspases share a 20-30 amino acid long prodomain residue which lack any defined motif or protein interaction site in common. They are known as "executioners" because they initiate the apoptotic execution phase by cleaving regulatory and structural proteins, which shut down the cell's ability to function and contribute to the apoptotic morphological characteristics. When an extra protease or an upstream initiator caspase is cleaved, the executioner caspases become active. Unlike executioner caspases that do not have protein interaction site, initiator caspases have a long prodomain which codes for a protein: protein interaction motif to allow dimerization of the catalytic domains. These motifs consist of the caspase recruitment domain (CARD) in caspase-2 and caspase-9, and the death effector domain (DED) in caspase-8 and caspase-10 (Boice & Bouchier-Hayes, 2020).

Cancer cells, on the other hand, develop a set of means to restrict cell death. A classic example is the widespread loss of p53 tumor suppressor function seen across the tumor spectrum. p53 carries multiple effector functions. One of which is to induce apoptosis via the upregulation of Bcl-2 homology domain (BH3-) only proteins particularly p53 upregulated modulator of apoptosis (PUMA). The loss of p53 prevents DNA-damage-induced apoptosis. Fortunately,

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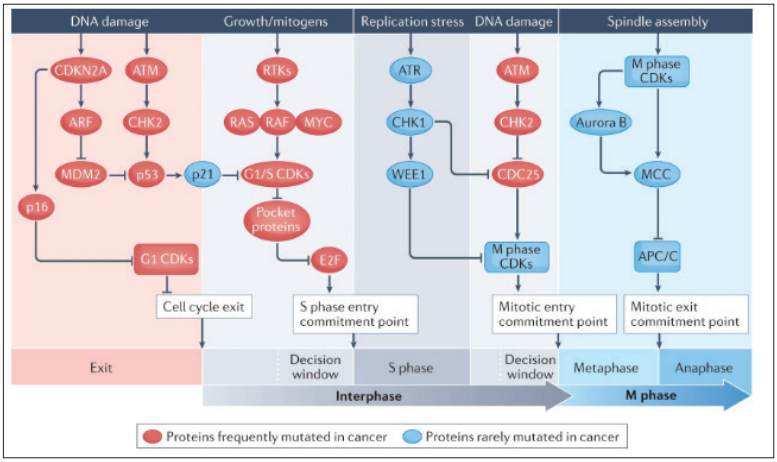
chemo- or radiotherapy-induced DNA damage can elicit p53-independent apoptosis. In addition to the loss of p53, loss of pivotal apoptotic effectors BAX or BAK has also been detected in diverse cancer types. A recent study demonstrated that the loss of either BH3-only or anti apoptotic BCL-2 protein leads to an apoptotic dependence for either BAX or BAK (Pfeffer & Singh, 2018). While cell death is usually induced when the damage—which can be from cell starvation, hypoxia, irradiation, ER stress, reactive oxygen species (ROS) and DNA damaging drugs, to name a few—is too severe, a broad range of stress signals which evoke a cell survival program in case of sublethal damage has been characterized (Fulda, 2010).

C. UNLIMITED CELL REPLICATION

The cell cycle is a mechanism by which a cell divides through orderly and tightly regulated steps involving four phases (G1, S, G2 and M). The gap phases (G1 and G2) separate the DNA synthesis (S phase) and mitosis (M phase). These phases are tightly controlled by a number of cyclin dependent kinases (CDKs) which are heterodimeric complexes composed of a catalytic kinase subunit and a regulatory cyclin subunit. Cyclin D-associated kinases CDK4 and CDK6, as well as cyclin E-CDK2 complexes are known to phosphorylate the retinoblastoma protein (Rb) thus the E2F1 is released (Deep & Agarwal, 2008). E2F1 transcription factor can play a role as either a tumor suppressor or an oncogene depending on its transcriptional targets. Elevated expression of E2F1 causes transformation and tumor development. This is deregulated by the overexpression of retinoblastoma (Rb) that subsequently cause DNA damage and cancer (Pradhan et al., 2017).

Because E2F1 is a pivotal transcription factor, it may also modulate cell cycle progression via its regulation of the transcription of other genes. Stathmin1 and transforming acidic coiled-coil-containing protein 3 (TACC3) are two microtubule binding factors that are

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Source: Adapted from Matthews et al. (2022)

Figure 3.2 Important Signaling Pathways Linked to Cancer and Cell Cycle Regulation

overexpressed in cancer cells to stabilize the microtubules. Stathmin1 plays a role in depolymerizing tubulin filament. Phosphorylation of Stahmin1 at Ser16 increases during G2/M and stabilizes microtubules during the regulation of mitotic spindles. TACC3, on the other hand, is a clathrin binding protein. Phosphorylation of this protein at Ser558 allow interaction of clathrin and tubulin to take place thus the stability of spindle fiber arrays is maintained (Fang et al., 2022).

Cancer cells' ongoing cell cycle progression is mostly caused by protein mutations, or dysregulation, in signaling pathways that control the cell cycle. These mutations, however, are more frequently linked to particular cell cycle regulatory pathways than to others. Red-colored mutations are frequently detected in cancer cells and primarily impact how the cell cycle responds to signals of growth in the pre-S phase and damage to DNA. These mutations initiate the S-phase and stop the cell cycle from ending. Proteins involved in the response to inadequate spindle assembly or replication stress

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have very few mutations associated with cancer; these rare mutations are indicated in blue. These pathways indicate potential therapeutic avenues in the context of cancer treatment. Retinoblastoma protein (RB), p107, and p130 are examples of pocket proteins (Matthews et al., 2022).

Despite a number of compelling evidence of effectors of E2F1-induced apoptosis can kill cancer cells, their potential as a target for anticancer therapy is only emerging. Hitherto, in clinical realm, antiapoptotic E2F1 regulated genes were employed to hinder tumor growth for instance Bcl-2 that has been targeted massively by antisense oligonucleotide which downregulate Bcl-2 expression thus apoptosis increases (Pützer, 2007).

D. SUSTAINED ANGIOGENESIS

Angiogenesis refers to the growth of blood vessels that occurs throughout life. No metabolically active tissue in the body has the distance of hundreds of micrometers from a blood capillary. These capillaries are formed via angiogenesis--that is formed via angiogenesis. They are necessitated by all tissues in the body for nutrients and metabolites exchange (Adair & Montani, 2010).

Normal angiogenesis occurs in the embryo where the primary vascular tree as well as a sufficient vasculature for growing and developing organs are established. But in adults, angiogenesis takes place during the ovarian cycle and in wound healing. Very little does turnover of endothelial cells occur in the adult vasculature (Papetti & Herman, 2002). Under normal circumstances, angiogenesis is tightly regulated because it needs quiescent endothelial cells in a monolayer to multiply then spread to the extent of the demands of growing tissues (Papetti & Herman, 2002).

Angiogenesis in tumor is highly associated with its microenvironment (TME) which is composed of extra-cellular matrix (ECM), blood vessels, glandular cells, immune cells, fibroblast as well as

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adipocytes. But among them, the hypoxic tumor microenvironment is the key feature of many solid tumor tissues. Tumor cells and tumor microenvironment form a mutually beneficial and coexisting relationship, promoting angiogenesis, and favoring its growth. Current mainstream research results still indicate that angiogenesis is necessary for tumor growth and metastases (S. Tan et al., 2021).

Tumors can be vascularized either from the pre-existing vasculature or by inducing new blood vessel formation through a set of molecular and cellular mechanisms which is coined as angiogenic switch. In homeostatic balance, the vasculature is quiescent and the endothelial cells are non-proliferative (S. Tan et al., 2021). Tumor angiogenesis is induced by angiogenic growth factors, for instances vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), secreted by tumor cells which post release bind with tyrosine kinase receptor expressed on the endothelial cells (ECs). This binding leads to dimerization of the receptors and activation of autophosphorylation of tyrosine to initiate a few of signaling proteins including PI3-kinase, Src,Grab/mSOS-1 (a nucleotide exchange factor for Ras) and signal transducers and activator of transcription (STATs) with each of which contains Src-homology-2 (SH2) domains. Binding of the SH-2 regions of these proteins to the phosphotyrosines on the receptor tyrosine kinases (RTKs) activates paramount pathways to modulate cell cycle machinery (M. K. Gupta & Qin, 2003). In the case that preponderance of angiogenic factors in the local milieu present, neovasculature may persist either as capillaries or differentiate into mature venules or arterioles. In contrast, when angiostatic factors are preponderant, they mediate regression of the neovessels via apoptosis or cell cycle arrest of ECs. Thereby, the switch to the angiogenic phenotype is regulated by the dynamic of positive and negative regulators of the growth of microvessels in the local equilibrium (M. K. Gupta & Qin, 2003). As loss of tumor suppressor genes transforms normal cells into malignant cells, an inhibitory is switched into angiogenic phenotype.

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This is well observed in one tumor suppressor gene, p53, whose loss will cause fibroblast turns to be angiogenic. The p53 protein is mutated in human tumors more frequently than any other known oncogene or suppressor gene. In normal cells it is hypothesized to act as a transcriptional regulator, enhancing the expression of genes that contain specific p53-binding sites and interacting with a variety of transcription factors to inhibit the expression of other genes. Wild type p53 protein can mediate a number of cellular activities, including apoptosis, the maintenance of genetic stability, GI growth arrest, cell differentiation, and the suppression of tumorigenicity. The up-regulation by p53 of the gene encoding p2l, an inhibitor of GI cyclin-dependent kinases, appears to be responsible for p53-mediated growth arrest (Dameron et al., 1994).

E. ACTIVATION OF INVASION AND METASTASES

Cancer metastases define a dissemination process of tumor cells from a primary site to a different site via blood and lymphatic vessels. It involves a complex cell-biological event coined as the invasion-metastasis cascade which includes angiogenesis (the development of new blood vessels),detachment and migration, the invasion through the base membrane (BM) and extracellular matrix (ECM) around the tumor, intravasation of the metastatic cells into the blood or lymphatic vessels, adhesion of the circulating metastatic cells to the endothelium of capillaries of the new organ site and ultimately the settling and growth of the secondary tumors at the new organ site (Guan, 2015). These processes are mediated by cell adhesion molecules (CAMs), a group of membrane glycoprotein and carbohydrate molecules that adhere cells to cells or cells to the ECM thus not only maintain tissue integrity but also facilitate intercellular communication. Structurally, the cytoplasmic domain anchors to the cytoskeletal filaments and on the other side the extracellular domains attach to either the same (homophilic binding) or different

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(heterophilic binding) types of CAMs. Based on the sequence and structural homology, CAMs are sub grouped into four major families being Cadherin, Selectins, Integrins and Immunoglobulin-like CAMs (Ig-CAMs) (N. Wang, 2014).

Among these, E-Cadherin is hitherto the most investigated molecule. This is a key adhesion molecule which is severely downregulated in carcinoma. E-cadherin assists assembling among adjacent epithelial cells and ensuring that these cells remain in a quiescence state (Hanahan & Weinberg, 2011b). E- cadherin is expressed in almost all types of epithelial tissues where it is constantly renewed with a 5-to-10-hour half-life on the cell surface. The protein is encoded by the *Cadherin 1* gene (CDH1) which governs the production of calcium dependent membrane glycoprotein. Located at 16q22.1, the gene plays a crucial role in maintaining polarity. It is built up by 5 cadherin repeats in the extracellular domain, a transmembrane domain and an intracellular domain which attach to p120-catenin (p120.ctn) and β-catenin. The intracellular domain encompasses a highly phosphorylated β-catenin binding site that is critical for the E-Cadherin function (Burandt et al., 2021).

In majority of cancer cases, the loss of E-Cadherin is attributable to the activation of many transcription factors being SNAIL, SLUG and ZEB1 and ZEB2—the zinc-finger transcription factors with the two last mentioned are the E homeobox-binding transcription factors, as well as TWIST1—a basic helix-loop-helix transcription factor. While overexpression of Snail1 and Snail2 is typically seen in breast-, ovarian and diffuse type gastric carcinomas, the TWIST is seen to be upregulated in breast-, gastric-, liver-, prostate-, and bladder carcinomas. In contrast, ZEB1 and ZEB2 are downregulated in non-small cell lung cancer (NSCLC), oral squamous cell carcinomas and gastric cancers (Rubtsova et al., 2022).

Although E-cadherin loss is one paramount molecular signature in carcinogenesis, the loss alone is not adequate to trigger subsequent

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cascade mechanisms because the β-catenin is highly degraded in a Wnt-signaling-dependent pathway. In the degradation process, β-catenin is phosphorylated by glycogen synthase kinase (GSK) which leads to its ubiquitination and degradation in the 26S proteasome that causes β-catenin to remain low in the cytoplasm and nucleus. The signaling pathway is initiated when Wnt binds to Frizzled. As the disheveled protein binds, the degradation of the complex is abrogated which result in the blocking of GSK on β-catenin hence β-catenin accumulates in the cytoplasm prior to translocation to the nucleus where it inhibits a suppressor of T cell factor/lymphoid enhancer factor (TCF/LEF) (MacDonald et al., 2009).

As aforementioned, the loss of E-cadherin is frequently found in tumor metastasis, but in some cases, it remains highly expressed even on distant metastasis. For this matter, Petrova, and colleagues in 2016 hypothesized that the ability of E-Cadherin-expressing tumor cells to metastasize is attributed to the downregulation of the adhesive activity state of E-Cadherin at the surface instead of its quantity. To check the hypothesis, the team employed a 4T1 mouse mammary cell line which metastasizes from mammary gland to lung. The cell line carries high levels of E-Cadherin and is epithelial-like and seems to metastasize without undergoing an epithelial-mesenchymal transition (EMT). However, since the E-Cadherin-activating mAbs were raised in mice, they did not recognize mouse E-Cadherin. Therefore, the team generated a 4T1 cell line expressing human E-Cadherin (4T1-hE), which was like endogenous mouse E-Cadherin, renders them responsive to the E-Cadherin-activating mAb. They inoculated 4T1-hE orthotopically into the mammary fat pad of BALB/c mice and treated the mice with either 19A11-activating mAb 9 (this is an IgG2a monoclonal antibody for mouse or primate complement receptor 1 (CR1) or anti-Cadherin-1) or a neutral mAb which binds well to human E-Cadherin but does not activate adhesion nor block it. The results showed that there was a marked decrease in the num-

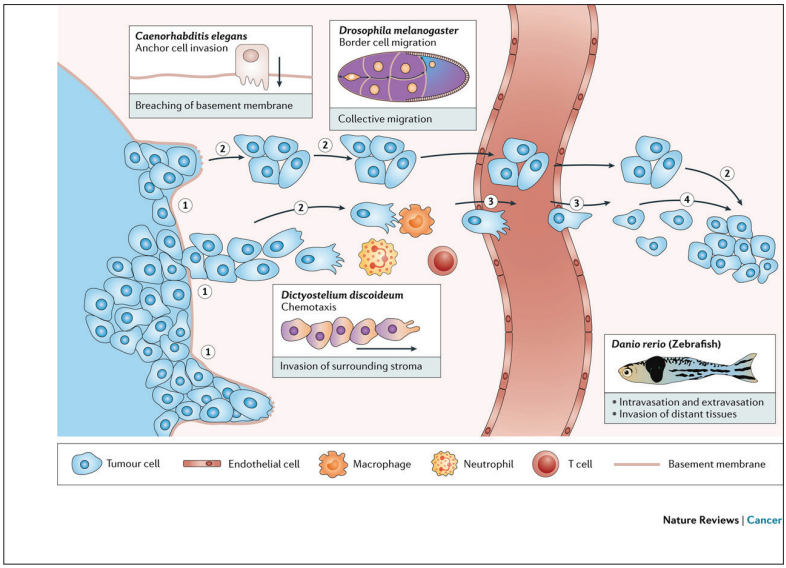
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ber of 4T1-hE cells metastasized to the lung in mice treated with 19A11 activating mAb compared to that seen for the neutral mAb which suggested that the treatment, which activated E-Cadherin adhesive activity, reduced metastasis. It was, hence, concluded that physiological down-regulation of adhesion activity contribute to the metastatic process(Petrova et al., 2016).

The metastatic process is a complex phenomenon that underscores the remarkable ability of cancer cells to evade and subvert the normal mechanisms of tissue organization (Gerstberger et al., 2023). In epithelial-derived carcinomas, this process is characterized by a profound disruption of the normal epithelial architecture, as tumour cells abandon their characteristic polarity and begin to adopt a more invasive phenotype (J. Yang et al., 2020). The loss of polarity is accompanied by a breakdown of the intricate tissue structure, as tumour cells breach the basement membrane, a critical barrier that separates the epithelial layer from the underlying stroma. The subsequent intravasation of tumour cells into blood and/or lymphatic vessels marks a critical step in the metastatic process, as these cells exploit the vascular system to gain access to distant sites (Chiang et al., 2016).

Upon entering the bloodstream or lymphatic circulation, tumour cells must evade the host's immune response and avoid recognition by immune cells, allowing them to escape from the vessels and establish themselves in a new tissue. This process, known as extravasation, is a critical step in the metastatic cascade, as it enables tumour cells to colonize distant sites and establish a foothold for further growth and expansion (X. Cheng & Cheng, 2021). Once established in the new tissue, these tumour cells can undergo a series of complex transformations, including migration, proliferation, and differentiation, ultimately giving rise to a new metastatic colony (Lambert et al., 2017).

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Source: Adapted from Stuelten et al. (2018)

Figure 3.3 Simple model organisms can be used to investigate aspects of tumour invasion and metastasis.

Cancer is a complex and multifaceted phenomenon that has far-reaching implications for our understanding of human biology and disease. Its vast scope encompasses a broad range of disciplines, including genetics, cell and tissue biology, pathology, and response to therapy. The sheer scale and diversity of cancer's manifestations are staggering, with each subtype presenting a unique set of characteristics and challenges (Swanton et al., 2024). However, the rapid advancement of experimental and computational technologies is now providing an unprecedented volume of data about the various forms of cancer, from genetic mutations to molecular signaling pathways. This "big data" avalanche is revolutionizing the field, allowing researchers to identify patterns and correlations that were previously hidden (Hanahan, 2022).

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The integrative concept of the hallmarks of cancer, which distills the complex biology of cancer into a set of key principles, has been instrumental in guiding this research. By identifying the commonalities and differences between various types of cancer, researchers are beginning to develop a more nuanced understanding of the mechanisms underlying cancer development and progression. This knowledge has the potential to inform the development of more effective therapeutic strategies, as well as improve our ability to diagnose and treat cancer patients (Hanahan, 2022).

The provisional new dimensions presented in this perspective offer a fresh perspective on the complex interplay between genetic and environmental factors that contribute to cancer development. By exploring the ways in which these factors interact and influence one another, researchers may uncover new insights that can be used to develop more effective prevention and treatment strategies. Furthermore, this perspective highlights the importance of integrating cutting-edge research in genetics, epigenetics, and precision medicine to develop more personalized approaches to cancer care (De Palma & Hanahan, 2012). As we continue to grapple with the complexities of cancer, it is essential that we continue to push the boundaries of our understanding, leveraging advances in technology and data analysis to drive progress towards a better future for cancer patients (Heudel et al., 2023).

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CHAPTER IV
ANTICANCER REGIMENT PLATFORMS

The quest to vanquish cancer has long been a cornerstone of medical research, with scientists and clinicians striving to develop more effective and efficient treatment regimens that can combat this complex and multifaceted disease at every stage. The advent of precision medicine has already ushered in a new era of targeted therapies, where tumors are tailored to individual patients based on their unique genetic profiles. However, despite these advances, the treatment of cancer remains a formidable challenge, with many patients still succumbing to the disease due to the lack of effective therapies or the emergence of treatment-resistant mutations. As we move forward, it is imperative that we continue to push the boundaries of our understanding of cancer biology, leveraging cutting-edge technologies and innovative approaches to develop more sophisticated and personalized treatment regimens.

In the near future, we can expect significant breakthroughs in cancer therapy, driven by advances in areas such as immunotherapy, gene editing, and biomarker discovery. For instance, the develop-

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ment of CAR-T cell therapy has already shown remarkable promise in treating certain types of blood cancer, while the discovery of novel biomarkers is enabling clinicians to identify high-risk patients earlier and more accurately. Furthermore, the increasing use of artificial intelligence and machine learning algorithms is revolutionizing the way we analyze and interpret large datasets, allowing researchers to identify patterns and correlations that were previously unknown or uncharacterized.

It is essential to examine the dominant conventional cancer therapies that have been extensively employed in the treatment of this disease. These treatments have been the cornerstone of cancer care for many decades, and their widespread adoption has been predicated on their demonstrated efficacy in improving patient outcomes. By scrutinizing these conventional therapies, we can gain a deeper understanding of their strengths and limitations, ultimately informing the development of more effective and personalized treatment strategies.

A. SURGERY

Surgical removal of the tumor is often the first line of treatment for many cancers. The goal of surgery is to completely remove the cancerous tissue while preserving as much healthy tissue as possible. In some cases, nearby lymph nodes may also be removed to prevent the spread of cancer (Mayo Clinic Staff, n.d.).

There are several types of anticancer surgical procedures (Standford Medicine, 2021):

1. Curative surgery

Curative surgery is a primary modality that involves the removal of cancerous tumors or growths from the body, often employed when the disease is localized to a specific area (National Cancer Institute, 2024). This treatment is frequently supplemented by

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adjunctive therapies such as radiation, which can be administered before or after the surgical procedure. In contrast, preventive surgery is a prophylactic approach that targets tissue that may be at risk of developing into a malignant tumor, thereby precluding the onset of cancer (Vogelsang, 2019).

Recent studies have explored the impact of curative treatments on cancer outcomes and quality of life. In breast cancer patients with oligometastatic disease, surgical removal of the primary tumor combined with systemic therapy improved survival rates compared to systemic therapy alone (Abdelhamid et al., 2020). For non-small cell lung cancer, the quality of surgical resection, particularly lymph node evaluation, significantly influences patient outcomes (Osarogiagbon, 2022). While the potential benefit of regional anesthesia in cancer surgery remains speculative, it continues to be used for its primary indications such as stress reduction and postoperative pain management (Buggy et al., 2021). In esophageal and gastric cancers, curative treatments showed varying short-term effects on health-related quality of life, with neoadjuvant chemo(radio)therapy and surgery demonstrating better outcomes than definitive chemoradiotherapy in esophageal cancer. However, no long-term differences were observed between treatments (van den Boorn et al., 2020).

2. Diagnostic surgery

Recent advancements in cancer diagnostics have improved the accuracy and efficiency of detecting and staging tumors. Intraoperative techniques like frozen section and cytology show high diagnostic accuracy for margin assessment in breast cancer surgery, though they are resource-intensive (John et al., 2017). Novel molecular imaging techniques, including enzymatically activatable MRI probes and dual-labeled fluorescent probes, offer potential for earlier diagnosis, accurate staging, and improved surgical guidance (Hussain & Nguyen, 2014). Diagnostic laparoscopy as an add-on to

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CT scanning can reduce unnecessary laparotomies in pancreatic and periampullary cancer patients by detecting metastases not visible on CT, with a summary sensitivity of 64.4% (Allen et al., 2016).

In low- and middle-income countries, efforts are being made to identify and implement cost-effective surgical procedures that can significantly reduce mortality rates (Debas et al., 2015). The integration of digital pathology into diagnostic settings is also gaining traction, with academic medical centers developing systematic approaches to implementation, including workflow optimization and comprehensive staff training (C. L. Cheng et al., 2016). These developments highlight the global trend towards improving surgical diagnostic capabilities, although challenges remain in terms of resource allocation, infrastructure development, and adapting to new technologies across different healthcare systems worldwide.

3. Staging laparoscopy

Staging laparoscopy is a valuable tool in the management of upper gastrointestinal and peritoneal surface malignancies, offering accurate disease assessment and guiding appropriate treatment (Conlon & Minnard, 1997; Seshadri & E, 2016). It can prevent unnecessary laparotomies and has high sensitivity in identifying suitable candidates for cytoreductive surgery (Seshadri & E, 2016). Laparoscopic staging laparotomy with intra-abdominal manipulation has been described as a minimally invasive approach comparable to standard staging laparotomy, with reduced morbidity and hospitalization time (Kusminsky et al., 1994). However, the use of laparoscopy in early-stage ovarian cancer staging remains controversial. While a meta-analysis suggested compatibility with laparotomy outcomes concerns about oncologic safety persist (Heitz, Harter, and du Bois 2013). The quality of surgical staging has been associated with patient outcomes in early ovarian cancer, and laparotomy is still considered the standard procedure for staging in this context (Heitz et al., 2013).

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4. Debulking surgery

Debulking surgery, also known as cytoreductive surgery, involves removing as much tumor mass as possible in cases of advanced cancer (Hishida et al., 2021). It has been studied extensively in ovarian cancer treatment, where it can be performed as primary debulking surgery (PDS) or interval debulking surgery (IDS) following neoadjuvant chemotherapy (Chiofalo et al., 2019). While PDS followed by chemotherapy has been the standard approach, IDS has shown promise in increasing complete cytoreduction rates and reducing surgical complications (Khatchapuridze et al., 2019). Laparoscopic debulking has emerged as a feasible option for some patients, potentially decreasing surgical impact on high-risk individuals (Corrado et al., 2015). However, recent meta-analyses have not demonstrated clear superiority of either PDS or IDS in terms of overall survival and progression-free survival, though IDS is associated with reduced surgical complexity and postoperative complications (Chiofalo et al., 2019).

5. Palliative surgery

Palliative surgery plays a crucial role in managing advanced cancer, particularly in low-middle income countries with a high burden of advanced cases (Deo et al., 2021). It is designed to enhance quality of life, control symptoms, and prevent complications in patients with incurable cancer (V. Sun & Krouse, 2014). Gastrointestinal cancers constitute a major proportion of palliative surgeries, with symptom relief achieved in 80-90% of patients (Deo et al., 2021). However, patient selection for palliative surgery requires careful consideration of various factors, including symptom control, prognosis, performance status, and quality of life (Foster et al., 2016). The decision-making process should involve assessing optimal timing and selecting suitable procedures with minimal perioperative morbidity and mortality (A. Goel & Garg, 2018). While palliative surgery can provide significant benefits, it is essential to balance the potential

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risks and ensure that the intervention does not become unfavorable for the patient (A. Goel & Garg, 2018).

6. Supportive surgery

Viewed as a complementary approach, supportive surgery facilitates the effectiveness of other cancer treatments. For instance, the insertion of a catheter can aid in the administration of chemotherapy. Restorative surgery, on the other hand, serves as a follow-up to curative or other surgeries, aimed at restoring physical appearance or functional ability. Examples include breast reconstruction following breast cancer treatment and oral reconstruction after oral cancer surgery.

In addition to other forms of cancer treatment, there are various specialized surgical procedures that can be used to help treat cancer. The following is a list of some of these surgical options (Standford Medicine, 2021).

7. Cryosurgery

Cryosurgery is a minimally invasive technique that uses ultra-low temperatures to destroy cancer cells, particularly in breast cancer treatment (Mokbel et al., 2023). It offers advantages such as simplicity, cost-effectiveness, and improved aesthetic outcomes (Mokbel et al., 2023; Tarkowski & Rząca, 2014). Cryosurgery has shown promise in managing early-stage breast cancer, metastatic disease, and potentially ductal carcinoma in situ (Mokbel et al., 2023). The technique is painless, safe, and applicable across multiple medical specialties (Villarreal et al., 2022). To enhance its effectiveness, cryosurgery can be combined with other physical medicine techniques, including hemodilution, radiofrequency ablation, laser therapy, and electroporation (Chyzh et al., 2021). Additionally, cryosurgery may elicit an antitumor immune response, setting it apart from other ablative techniques (Mokbel et al., 2023). While research is ongoing to optimize the method, cryosurgery

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shows potential as an alternative to traditional surgical excision for breast cancer treatment (Tarkowski & Rząca, 2014).

8. Electrosurgery

Electrosurgery is widely used in gynecologic procedures, including the treatment of cervical intraepithelial neoplasia (CIN) and microinvasive carcinomas (Aminimoghaddam et al., 2018; Xiang et al., 2015). Conization using an electrosurgical knife has shown promising results for CIN and microinvasive carcinomas, with relatively low recurrence rates and acceptable complication rates (Xiang et al., 2015). In head and neck cancers, electroporation has emerged as a safe and effective approach, particularly when combined with chemotherapy (electrochemotherapy) for treating cutaneous metastases and primary skin and mucosal cancers (Pisani et al., 2022). This technique enhances the uptake of antineoplastic agents by cancer cells and stimulates the immune system. While there have been concerns about using electromedical devices in cancer patients, a review suggests that moderate, periodic use of cosmetic medical devices is generally safe for patients with tumors (Palmieri et al., 2021).

9. Microscopically controlled surgery

This is a delicate procedure that involves removing layers of skin and examining them under a microscope until all cancerous cells are removed. This technique is particularly useful for treating cancers that affect sensitive areas of the body, such as the eye.

In the previous two decades, the surgical method has progressed markedly. The Indonesian government has established several cancer centers, up to the 2nd tier, which is in the municipal level, which serve comprehensive care including surgery, chemotherapy, and radiotherapy. These centers are equipped with the state-of-the-art facilities and highly trained medical staff through which patients who need this service do not have to be referred to the national level cancer referral hospital but rather to be treated in their adjacent

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municipal hospital unless they have a particular condition that need specific treatment that only the facility in the national level hospital can handle (Mahendradhata et al., 2017). It is also a breakthrough that surgeons are now employing advanced surgical techniques which also involve robotic surgery for prostate cancer, minimally invasive surgery for breast cancer, and laparoscopic for colorectal cancer. These techniques are shown to reduce the pain, hospital stay, infection and on the other hand speed up the recovery rate, compared to traditional surgery (Grosek et al., 2021; Uk Bae, 2022).

The shifting of surgical paradigms is best seen in breast cancer surgery procedures where total and radical removal has been substituted by partial or conserving surgery. This was underpinned by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, a device used to transition radical surgery to conserving counterparts. The NSABP B-04 trial included smaller than 4-cm-tumor-carrying patients who underwent mastectomy, lumpectomy, or lumpectomy in combination with radiotherapy, respectively, and compared the relapse-free survival, disease-free survival, distant-disease-free survival or total survival among the groups. No statistical differences in all survival forms. But intriguingly, those who were treated with radiotherapy-assisted lumpectomy showed much lower frequency of local recurrence. Taken together, these features supported the outperformance of conserving surgery over the radical or total removal which made the conserving platform more common these recent years (Maughan et al., 2010; Waks & Winer, 2019).

As is seen for surgical procedures in breast cancer, surgical procedures in colorectal cancer have also been experiencing a huge shift. Laparoscopy is, thus far, accepted to outperform the open method surgery in the context of disease-free survival. This was shown in United Kingdom's colorectal cohorts. However, its superiority was somewhat weakened as more recent findings showed

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that no significance was derived from the 5-year-overall survival (OS) of those treated laparoscopically and open surgically but in Japanese cohort. These suggested that laparoscopic D3 surgery was acceptable to treat patients with colorectal cancers in stage II or III. The D3 alone describes a complete resection of regional lymph nodes, including periodic nodes (N1 region), intermediate nodes (N2 region) and main nodes along superior mesenteric vessels (N3 region) as defined by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (Matsuda et al., 2018), which means that the area of D3 lymphadenectomy comprises anatomical borders being: 1) cranial site-5 mm adjacent to the horizontal line through the Henle trunk and middle colic artery origins, 2) caudal site-5 mm distal to the horizontal line through the origin of the ileocolic artery, 3) medial region-the left edge of the superior mesenteric artery (SMA), and 4) lateral region-10 mm from the right edge of the superior mesenteric vein (SMV) (Włodarczyk et al., 2019).

It is clear from the elaboration above that—led by the concerns on the procedures which underpinned the subsequent modification—the surgery procedures lately tend to remove less or to conserve the unaffected site/zone in the organ to maintain the aesthetical value. On the other hand, this is set to still and as thorough as it possibly can that the detrimental cancer sites are completely removed from the body (Fajdic et al., 2013; Gardfjell et al., 2019; M. P. Tan, 2017). In surgical procedure for cervical cancer, however, the concerns are not only about conserving unaffected sites of the cervix but also preserving fertility (Silvestris et al., 2022).

It was in 2013, Cao and colleagues conducted a case-control study to compare the outcome of surgical approaches in 126 patients (Chinese cohorts) with early stage of cervical cancer who underwent radical trachelectomy. It was shown that there was no marked difference between radical vaginal trachelectomy (VRT) and abdominal radical trachelectomy (ART) in terms of mean of

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operation time, complications at either peri- or postoperative phase. However, VRT was seen to outperform ART in regards with both pregnancy (35.5% vs 8.8%) and live birth (23.3% vs 8.8%) rates. Unfortunately this was also followed with some adverse effect as recurrence and death from the disease by VRT were also higher than that of ART with values of 9.8% and 2.8%, respectively, vs 0% for both categories in ART (D. Y. Cao et al., 2013).

The treatment of localized cancer often relies on a combination of surgical interventions, aimed at removing cancerous tissue while preserving as much healthy tissue as possible. This approach is particularly crucial in cases where organ functionality is at stake, such as in lung cancer, or where aesthetic considerations are paramount, such as in BC (J. Zhang et al., 2017). Other types of cancer, including thyroid, ovarian, colon, and prostate cancer, also frequently require surgical intervention. However, imperfect surgical techniques and difficulties in distinguishing between cancerous and healthy tissue during surgery can result in positive surgical margins (PSM), which increases the risk of biochemical recurrence (BCR) due to the presence of cancerous cells at the tumor site. To mitigate this risk, secondary therapies such as surgery, radiation, chemotherapy, or a combination of these may be employed (O. M. Hall et al., 2018).

For instance, studies have shown that patients who undergo mastectomy without post-operative radiation are at a higher risk of recurrence, with a 20-year follow-up rate of 39.2% (Fisher et al., 2002). Similarly, prostate cancer patients who undergo prostatectomy without post-operative therapy experience a biochemical recurrence rate of 20.7% (Suh et al., 2014). By eliminating positive surgical margins, healthcare providers can significantly reduce patients' future morbidity and mortality rates, thereby enhancing patient care (O. M. Hall et al., 2018).

To achieve a higher rate of negative surgical margins, it is essential to develop intraoperative tests that can rapidly distinguish between healthy and tumor tissue. Currently, *ex vivo* techniques

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such as immunohistochemistry and gene sequencing are used to identify and characterize cancer cells (J. Zhang et al., 2017). While these methods are effective in analyzing biopsies post-operatively, they are too time-consuming to be useful during tumor excision. Traditional methods of fixing biopsies with paraffin and storing them until subsequent microscopic analysis by a trained pathologist are also time-consuming and labor-intensive and are subject to human interpretation. As such, there is a pressing need for more efficient and reliable methods to enable healthcare providers to make critical decisions for patients in a timely manner (J. Zhang et al., 2017).

B. RADIATION THERAPY

In recent years, significant strides have been made in deciphering the underlying mechanisms of cancer development and treatment. Despite this progress, clinical management of cancer remains a daunting task for the 21st century. A diverse range of treatment modalities, including radiation therapy, surgery, chemotherapy, immunotherapy, and hormonal therapy, are currently employed to combat this complex disease. Radiation therapy has emerged as a crucial component of cancer treatment, with approximately half of all cancer patients receiving this form of therapy during their course of illness. This modality plays a vital role in curative treatment, accounting for nearly 40% of successful treatments (Baskar et al., 2012).

The primary objective of radiation therapy is to disable cancer cells' ability to multiply and divide. As we mark a century of advances since Marie Curie's groundbreaking research into radium, 2011 has been designated as the Year of Radiation Therapy in the UK. Over the past 100 years, continued advancements in radiation treatment techniques and our understanding of cancer cell responses to radiation have been instrumental in improving patient outcomes and reducing treatment-related side effects (Baskar et al., 2012).

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Radiotherapy is an indispensable component of cancer treatment regimens in Western countries, with over two-thirds of patients receiving this form of therapy as part of their treatment plan. In fact, radiotherapy has emerged as a crucial curative treatment modality for uncomplicated locoregional tumors, offering a high degree of efficacy and precision (Baumann et al., 2016).

Recent technological advancements have revolutionized the field of radiotherapy, enabling the development of cutting-edge treatment modalities such as stereotactic body radiotherapy (SBRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT). These innovations have facilitated the delivery of precise radiation doses to tumors, while minimizing the exposure of surrounding normal tissue to potentially harmful radiation. Furthermore, a deeper understanding of tumor biology at the molecular, cellular, and physiological levels has significantly improved the treatment efficacy of radiotherapy (Baumann et al., 2016).

For instance, studies have shown that overall survival rates for cancer patients undergoing radiation therapy have increased dramatically over the past two decades. In head and neck cancers, for example, survival rates have improved from around 30% to over 80% (Baumann et al., 2016; Q.-T. Le et al., 2015).

Traditionally, cancer radiotherapy has been limited by the maximum tolerated dose to adjacent normal tissues. As such, effective radiotherapy is often measured by its ability to maximize cancer cell killing capacity while minimizing radiation-induced damage to healthy tissues. Given the complex and multifaceted nature of cancer, significant efforts have been devoted to identifying biomarkers associated with intrinsic and acquired radioresistance. In recent years, numerous radiation sensitizers and protectors have been identified, allowing radiotherapy to evolve from a one-size-fits-all approach to a more dynamic and patient-tailored treatment modality (H. H. W. Chen & Kuo, 2017).

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When cancer cells are exposed to radiation, DNA double-strands break, leading to DNA fragmentation and apoptosis. Simultaneously, water molecules are damaged, triggering the formation of reactive oxygen species (ROS). These ROS molecules generate cytosolic DNA, which is detected by cGAS, a key sensor molecule. This activation subsequently leads to the upregulation of type-1 interferon, inflammatory genes, and senescence-associated secretory phenotype genes. The immune system's response is further amplified by the secretion of interferon-γ by surveilling immune cells, such as T-cells, natural killer cells, and Th1 cells. These immune cells enhance the expression of major histocompatibility complex (MHC-)I molecules on the surface of antigen-presenting cells (APCs), facilitating the processing of tumor antigens (Vanpouille-Box et al., 2017). On the other hand, radiation therapy increases the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on cancer cells, allowing T-cells to bind and reject the tumor (Riegler et al., 2019).

Radiation therapy is often administered post-surgery to reduce the risk of locoregional recurrence and improve overall survival. However, this treatment comes with adverse effects, including significant declines in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function tests. Additionally, breast radiation therapy may pose a risk to the heart due to anatomical proximity. The German Society for Radiation Oncology (DEGRO) has emphasized the importance of considering individual patient risk factors for breast cancer-specific mortality and cardiac risk when evaluating radiation-induced cardiotoxicity (Piroth et al., 2019).

The effectiveness of radiation therapy is often hindered by the inherent resistance of cancer cells to radiation, which increases the likelihood of local tumour recurrence. Consequently, there is a pressing need to overcome radioresistance and enhance radiosensitivity. This is driving intense research efforts to identify novel molecules that can synergize with radiation therapy (Garibaldi et al., 2017).

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One approach to boost the efficacy of radiation therapy is to administer chemotherapy or targeted agents concurrently, thereby modifying the radiosensitivity of tumour cells at the molecular level (Torres-Roca, 2012). This burgeoning field of radiation and cancer biology is rapidly yielding exciting breakthroughs, including T-cell checkpoint inhibitors, hypoxic radiosensitizers, and cytotoxins, as well as antiangiogenic agents, DNA repair inhibitors, signal transduction blockers, chemokine inhibitors, and oxygen metabolism modifiers. However, there is a significant gap between the numerous promising ideas emerging from pre-clinical studies in modern radiation and tumour biology and the lack of clinical trials testing these new concepts (J. M. Brown & Adler, 2015).

Approximately a decade ago, a comprehensive monograph entitled *"Precision Radiation Oncology"* in Chinese, which identified the concept as: "the precise simulation, planning, and delivery of conformal and high-dose radiation to the target volume, with the aim of enhancing local control and therapeutic efficacy" was published. At that time, the concept primarily focused on advancements in physics. However, the rapid progression of biotechnological innovations has led to a surge in molecular data relevant to disease, offering significant potential for improving patient care. While this progress presents new opportunities, it also brings new challenges. The success of precision radiation oncology will ultimately hinge on the accelerated development of biological knowledge (J. Yu & Xing, 2017).

The pursuit of precision radiation oncology has given rise to two distinct approaches: physical precision, which leverages imaging and geometric modifications to tailor treatment plans to individual patient needs; and biological-driven precision, which harnesses the power of genomics and other omics to optimize treatment outcomes. The integration of imaging technologies has enabled the accurate visualization of targets and organs at risk during treatment, allowing

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for rapid adjustments to treatment plans and the development of adaptive radiation therapy. This innovative approach can account for variations in anatomy and treatment responses, ensuring that radiation is delivered with precision and efficacy (W. A. Hall et al., 2018).

Building on the use of functional imaging for planning, researchers have also explored its application in modifying radiation target volumes and boost doses during treatment. This approach can enable dose escalation to high-risk areas and minimize radiation exposure to normal tissue, ultimately enhancing the therapeutic ratio. The ultimate goal of precision radiation oncology is to optimize treatment outcomes for individual patients by measuring their unique genomic profiles and adjusting radiation therapy accordingly. This may involve tailoring radiation dose, incorporate concurrent chemotherapy or targeted therapies, or use adjuvant therapy to overcome radioresistance. Additionally, by predicting patients at high risk for radiation-related side effects, clinicians can optimize treatment conformality, adjust fractionation schemes, or offer alternative treatments to minimize complications and enhance efficacy (W. A. Hall et al., 2018).

C. CHEMOTHERAPY

Chemotherapy, a widely recognized cancer treatment, holds significant importance in Indonesia and across the globe. Its fundamental objective of chemotherapy is to target and destroy rapidly multiplying cancer cells within the body (Anand et al., 2023). It is often used in conjunction with other cancer treatments such as surgery, radiation therapy, or immunotherapy. Chemotherapy can be administered in various forms, including oral medications, injections, or intravenous infusions. It can be tailored to target specific types of cancer, such as breast, lung, or colon cancer. This customization allows for more effective treatment plans based on the patient's unique needs. In some cases, chemotherapy can help shrink tumors before

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surgery, making it easier to remove the cancerous tissue. This is known as neoadjuvant therapy. Moreover, chemotherapy is also often used to alleviate symptoms and improve the patient's quality of life, even if it cannot cure the cancer. This is referred to as *palliative care*.

Chemotherapy agents used in Indonesia are similar to those employed worldwide, as they are often sourced from international pharmaceutical companies or manufactured under license. These agents can be classified into several categories based on their chemical structure and mode of action. Here, we will discuss some common chemotherapy agents used in Indonesia, divided into alkylating agents, antimetabolites, topoisomerase inhibitors, and targeted therapies.

1. Alkylating agents

Alkylating agents are a class of chemotherapy drugs that have proven to be highly effective in treating various types of cancer. These compounds work by forming covalent bonds with the DNA molecule, leading to DNA damage and inhibiting cancer cell growth(Lajous et al., 2019). To understand their mechanism of action, it is crucial to delve into the structure and function of DNA and the significance of covalent bonds.

DNA, or deoxyribonucleic acid, is the genetic material that carries the blueprint for life in all living organisms. It is composed of four nucleotide bases - adenine (A), guanine (G), cytosine (C), and thymine (T) - which pair up in a specific manner, known as base pairing. A always pairs with T, and G pairs with C. This double helix structure ensures the accurate transmission of genetic information from one generation of cells to the next (Minchin & Lodge, 2019).

Covalent bonds are strong chemical bonds that involve the sharing of electrons between atoms. In the context of alkylating agents, these drugs form covalent bonds with specific sites within the DNA molecule, such as the nitrogen atoms in the nitrogenous bases or

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the phosphate backbone. This interaction disrupts the integrity of the DNA structure, leading to several consequences that ultimately inhibit cancer cell growth (Thirumaran et al., 2007).

Firstly, the formation of covalent bonds with DNA results in the alteration of the DNA structure. This change can lead to mutations, which may be in the form of base substitutions, insertions, or deletions. As a consequence, the genetic information carried by the affected DNA strand is altered, and the cancer cells may lose their ability to function properly or even die(M. S. Rocha, 2023).

Secondly, the covalent bonds formed by alkylating agents can cause DNA cross-linking. This process involves the linking of two separate DNA strands or the attachment of a DNA strand to a protein. Cross-linking can hinder the essential processes of DNA replication and transcription, as the DNA molecule becomes physically entangled. This further impairs cancer cell growth and division, as the cell's ability to reproduce its genetic material is compromised(Weber, 2014).

Lastly, alkylating agents can also cause DNA strand breaks. The covalent bonds formed by these drugs can weaken the DNA backbone, leading to the separation of the two DNA strands. This damage can trigger cellular repair mechanisms, which may either successfully fix the damage or lead to further mutations and cell death (C. R. R. Rocha et al., 2018).

Some commonly used alkylating agents for cancer treatment include:

1. Cyclophosphamide: Used for various types of cancer, such as breast cancer, leukemia, lymphoma, and multiple myeloma (Mittal et al., 2015).
2. Chlorambucil: Primarily used for chronic lymphocytic leukemia, lymphoma, and multiple myeloma(Catovsky et al., 2011).
3. Melphalan: Often used for multiple myeloma, ovarian cancer,

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and as a high-dose treatment for stem cell transplantation (Aronson, 2016).

4. Busulfan: Used for chronic myeloid leukemia, myelodysplastic syndrome, and as part of the conditioning regimen before stem cell transplantation (Pasquini et al., 2016).
5. Temozolomide: Commonly used for brain tumors, particularly glioblastoma multiforme (S. Y. Lee, 2016).

2. Antimetabolites

Antimetabolites are a class of chemotherapy agents that mimic essential cellular components, such as nucleotides, and disrupt DNA synthesis and repair processes. While 5-Fluorouracil (5-FU) is a well-known antimetabolite (Ser et al., 2016; H. Wu et al., 2022), there are other antimetabolites used in chemotherapy platforms such as:

a. Methotrexate:

Methotrexate is a chemotherapy agent that belongs to a class of drugs called antimetabolites. It is primarily used to treat certain types of cancer, including breast cancer, lung cancer, head and neck cancer, and leukemia(Hanoodi & Mittal, 2023). However, it also finds application in the management of autoimmune diseases like rheumatoid arthritis and psoriasis.

Methotrexate works by interfering with the process of cell division in rapidly growing cells, such as cancer cells. It does this by inhibiting an enzyme called dihydrofolate reductase (DHFR), which is essential for the synthesis of DNA and RNA. By blocking DHFR, methotrexate disrupts the production of these nucleic acids, ultimately stopping the cancer cells from multiplying and growing(J. A. Hess & Khasawneh, 2015).

In addition to its anticancer properties, methotrexate is also used to treat autoimmune diseases. In these cases, the drug works by reducing the activity of the immune system, thereby

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alleviating inflammation and pain associated with conditions like rheumatoid arthritis and psoriasis(Pålsson-McDermott & O'Neill, 2020).

Methotrexate is usually administered through injections, either intravenously or intramuscularly. It can also be taken orally or as a liquid for certain conditions. The dosage and frequency of administration depend on the specific condition being treated, the patient's age, and their overall health (Chiaravalloti & Strober, 2014).

Like other chemotherapy agents, methotrexate can cause side effects. Common side effects include nausea, vomiting, fatigue, and hair loss. However, more severe side effects can occur, such as damage to the liver and kidneys, bone marrow suppression, and an increased risk of infections (Hamed et al., 2022).

To minimize the risk of side effects and maximize the effectiveness of methotrexate, patients are often given additional medications, such as vitamin B12 and folic acid supplements, to help counteract the drug's toxicity(Shea et al., 2013). It is crucial for patients receiving methotrexate to closely follow their healthcare provider's instructions and report any side effects or changes in their condition promptly.

b. Mercaptopurine (6-MP) and Azathioprine (Imuran):

Both 6-MP and Azathioprine are purine antimetabolites that inhibit the enzyme inosine monophosphatase, which is crucial for the synthesis of DNA and RNA. Mercaptopurine is commonly used in the treatment of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)(L. Chen et al., 2020). Azathioprine can also be employed in combination with other chemotherapy agents for specific cancer types(IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals, 2012).

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c. Cytarabine (Ara-C):

Cytarabine, also known as Ara-C, is a potent chemotherapy agent widely used for the treatment of various cancers, particularly those affecting the blood and bone marrow. It belongs to a class of drugs called pyrimidine analogs, which interfere with the cancer cells' ability to divide and grow(Vardanyan & Hruby, 2006).

Cytarabine was first synthesized in the 1950s and has since become a cornerstone of cancer treatment. It is often used in combination with other chemotherapy drugs to increase its effectiveness against cancer cells. The primary cancers treated with Ara-C include acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and non-Hodgkin's lymphoma(Di Francia et al., 2021).

The mechanism of action of cytarabine involves its conversion into its active triphosphate form within the cancer cells. This active form mimics the natural building block of DNA, deoxycytidine triphosphate (dCTP). When incorporated into the growing DNA strand during replication, cytarabine triphosphate causes premature termination of DNA synthesis, leading to cell death (Gustafson & Page, 2013).

Cytarabine can be administered through various routes, including intravenous (IV), intrathecal (into the spinal canal), and oral. The choice of administration depends on the type and location of the cancer being treated. For example, intravenous administration is commonly used for blood cancers, while intrathecal administration is preferred when the cancer has spread to the central nervous system (Baker et al., 1991).

As with most chemotherapy agents, cytarabine has potential side effects. Common side effects include myelosuppression, pancytopenia, hepatotoxicity, and gastrointestinal issues (R. Sato & Park, 2017).

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The effectiveness of cytarabine in treating cancer depends on various factors, including the type and stage of the disease, the patient's overall health, and the specific combination of chemotherapy drugs used. In many cases, cytarabine has shown significant success in inducing remission and improving survival rates for patients with blood cancers (Stock et al., 2013).

d. Gemcitabine:

Gemcitabine (2',2'-difluoro-2'-deoxycytidine, dFdC) is a potent antimetabolite chemotherapy agent used to treat various solid tumors and blood cancers (Alvarellos et al., 2014). It interferes with DNA synthesis by incorporating into elongating DNA and inhibiting the nucleoside salvage pathway (Alvarellos et al., 2014). Gemcitabine's cellular pharmacology involves complex intracellular conversion to active nucleotides, which compete with deoxycytidine triphosphate and inhibit ribonucleoside reductases (Mini et al., 2006). Despite its efficacy, gemcitabine faces challenges such as short plasma half-life and potential drug resistance (Dubey et al., 2016). To address these limitations, researchers are exploring macromolecular prodrugs and nanocarrier-based formulations to improve bioavailability, therapeutic efficacy, and reduce adverse effects (Dubey et al., 2016). Gemcitabine has demonstrated superior antitumor activity compared to other cytidine analogs in various murine tumor models, making it a promising candidate for clinical trials (Hertel et al., 1990).

Gemcitabine works by mimicking a natural component of the DNA called deoxycytidine, which is essential for the replication and growth of cancer cells (Bergman et al., 2002). As a nucleoside analog, gemcitabine gets incorporated into the growing DNA strand during replication. However, once incorporated, it halts the replication process by causing premature termination of the DNA chain. Additionally, gemcitabine also inhibits the

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synthesis of RNA, further disrupting the cancer cell's ability to multiply and grow. This dual mechanism of action makes gemcitabine an effective chemotherapy agent (Alvarellos et al., 2014; Bergman et al., 2002).

Gemcitabine, a nucleoside analog effective against solid tumors, is traditionally administered intravenously (Y. F. Hui & Reitz, 1997). However, research has explored alternative administration routes to improve efficacy and patient compliance. Oral administration has shown promise, with some regimens achieving higher AUC compared to IV infusion (Ferreira et al., 2021). Prolonged infusion at a fixed dose rate of 10 mg/m2 per minute has demonstrated higher intracellular accumulation of the active metabolite dFdCTP and improved response rates in pancreatic cancer patients (Veltkamp et al., 2008). Pulmonary delivery has also been investigated, showing rapid absorption and high bioavailability without causing acute lung injury in animal studies (Min et al., 2008). These alternative routes aim to address limitations of IV administration, such as metabolic inactivation and rapid systemic clearance, while potentially enhancing gemcitabine's therapeutic efficacy (Ferreira et al., 2021; Veltkamp et al., 2008). One of the main advantages of gemcitabine is its relatively mild side effects compared to other chemotherapy drugs. Multiple studies consistently report low incidences of severe hematological toxicities, with grade 3-4 neutropenia occurring in 18.7-28.3% of patients (Cortés-Funes et al., 1997; Tonato et al., 1995). Gemcitabine exhibits minimal gastrointestinal side effects, with nausea and vomiting being mild and well-controlled using standard antiemetics (Cortés-Funes et al., 1997; Tonato et al., 1995). Notably, alopecia is rare, with no grade 4 cases reported (Aapro et al., 1998; Tonato et al., 1995). Transaminase elevations are common but usually mild and rarely dose-limiting (Martín & Pollera, 1996). The

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drug's favorable toxicity profile is maintained across different starting doses, suggesting a broad therapeutic index (Martín & Pollera, 1996). Gemcitabine's mild side effect profile makes it a promising candidate for combination chemotherapy regimens (Cortés-Funes et al., 1997; Tonato et al., 1995).

e. Fudarabine

Fudarabine, also known as 9-β-D-arabinofuranosyladenine or 9-β-D-arabinofuranosyladenine (Ara-A), is a chemotherapy agent that belongs to the class of antimetabolites. It is widely used in cancer treatment, particularly for chronic lymphocytic leukemia (Schleser et al., 2023). Recent studies have explored ways to enhance its efficacy and reduce side effects. (Mehrmohamadi, Jeong, and Locasale 2017) developed a computational method to identify gene expression signatures predicting response to antimetabolite therapies, challenging the notion of non-specific cytotoxicity. Furthermore, (Gorzkiewicz et al. 2019) demonstrated that maltose-modified poly(propyleneimine) dendrimers could improve fludarabine delivery, potentially overcoming drug resistance mechanisms. (Schleser et al. 2023) synthesized platinum and palladium complexes of fludarabine, showing enhanced selectivity for tumor cells over non-malignant cells, with platinum complexes exhibiting higher cytotoxicity and cellular uptake. These advancements in fludarabine research align with the broader trend in developing novel nucleoside analogs with improved therapeutic windows, as discussed by (Burke, Borland, and Litosh 2016) in their review of base-modified nucleosides as chemotherapeutic agents.

Fludarabine exhibits multiple mechanisms of action against lymphoid cancers. It induces DNA strand breaks, accumulates p53, and triggers apoptosis (Christopherson et al., 2014). Fludarabine's effectiveness stems from its ability to inhibit human primase, a crucial enzyme in DNA replication initiation (Holzer

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et al., 2019). Unlike 5-fluorouracil, which is rapidly cleaved from DNA, fludarabine's incorporation into DNA leads to sustained damage (Lenz et al., 2015). Additionally, fludarabine nucleotides act as reversible inhibitors of ribonucleotide reductase (RNR), a major anticancer drug target. This inhibition is coupled with the formation of RNR-α hexamers, a mechanism shared with cladribine nucleotides (Wisitpitthaya et al., 2016). Fludarabine's di- and triphosphates interact with RNR-α's catalytic and allosteric activity sites, respectively. This multifaceted approach, targeting DNA synthesis, primase inhibition, and RNR regulation, contributes to fludarabine's efficacy against various lymphoid malignancies (Wisitpitthaya et al., 2016).Fludarabine can cause significant side effects, primarily dose-dependent bone marrow suppression and secondary infections (Hong, 2014). A case study reported pancytopenia as a clinical manifestation of myelosuppression from long-term fludarabine use (Tandya, 2023). To mitigate these adverse effects and improve efficacy, researchers are exploring advanced drug delivery systems such as polymeric nanoparticles, liposomes, and stimuli-responsive systems (Pourmadadi et al., 2024). These novel approaches aim to enhance targeted delivery, reduce toxicity, and allow for co-delivery of drug combinations for synergistic effects (Pourmadadi et al., 2024). Similar efforts are being made with other chemotherapy drugs like cytarabine, where pharmacogenomic biomarkers are being investigated to predict treatment response and optimize dosing (Di Francia et al., 2021).The conventional approaches to cancer treatment have been plagued by significant adverse effects, which can have a profound impact on patients' quality of life. Despite the efficacy of these treatments, the toxicity associated with chemotherapy, radiation, and surgery can lead to debilitating side effects, including nausea, fatigue, and hair loss (Muhamed et al., 2023). Moreover, the long-term consequences of these treatments can be just as severe, increasing

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the risk of secondary cancers, cardiac complications, and other health problems.

In light of these challenges, there is a growing need for innovative and more targeted approaches to cancer treatments, as conventional therapies are increasingly recognized as being woefully inadequate for addressing the complex nature of this disease (Sapio & Naviglio, 2022). Furthermore, the lack of precision in current treatment strategies has resulted in significant morbidity and mortality rates (Lustberg et al., 2023), highlighting the urgent need for more targeted and personalized approaches that can effectively mitigate the toxic effects of therapy (Kahn et al., 2022) . The development of innovative treatments that can address the unique genetic and molecular characteristics of each patient's cancer is critical, as it is only through such a personalized approach that we can hope to achieve meaningful improvements in patient outcomes (Al Meslamani, 2023; Tsimberidou et al., 2020). Some of the recently proposed platforms which are deemed to lower the adverse effects from the conventional therapies are elucidated in the following subchapters.

D. IMMUNOTHERAPY

This innovative treatment strategy aims to harness the power of the body's immune system to fight cancer. Immunotherapy can involve the use of immune system stimulants, immune system suppressors, or engineered immune cells to target cancer cells. Some examples of immunotherapy include immune checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines (S. L. Gupta et al., 2022).

One of the anticancer immunotherapy platforms is adoptive T cell therapy which is being investigated to treat various cancers including lymphoma, leukemia and a few solid cancers (Du et al., 2023). In Indonesia, unfortunately, it is in its early stages of development with so limited access and availability (Hwang et al., 2024).

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Only a few hospitals, if not saying even only one sole hospital, and a research center in the nation that has facilities and expertise to conduct this therapy. In the context of price, adoptive T cell therapy is an expensive treatment since it requires a complex and rigor laboratorial setting for T cell isolation, expansion and modification (epitope engineering) that cannot be automatically generalized but rather individualized thus demand well-trained practitioners as well as the well-optimized and high standardized procedures (Perica et al., 2015). These render it almost inaccessible for common people especially those who live in rural areas or at distant to the top-notch cancer referral hospitals.

In terms of regulatory and ethical issues, adoptive T cell therapy is still subject to both issues because The Ministry of Health has yet to release guidelines or standard of the use of this therapy which has led to flurry realization or on bed implementation. Moreover, there are concerns regarding safety as well as potential adverse effects which may potentiate unprecedented deleterious effects on pertinent patients. In the other words, adoptive T cell therapy has yet to commence approved and general implementation in Indonesia although should the patients opt to proceed with this platform, they should be responsible for the cost the therapy might charge them. The National Health Insurance hitherto does not consider this kind of therapy in its (Acc One, 2023; My Oona, 2024).

Regardless the fact that the adoptive T cell therapy has yet to be covered by The National Health Insurance, Indonesia has established its first clinical research institute that implements adoptive cell therapy. The Indonesian Army CellCure Center (IA2C) is a cutting-edge facility that has been established in collaboration with Professor Fandrich, Clinical Director of Applied Cellular Medicine in Germany. Located at RSPAD Gatot Soebroto, the center is dedicated to the development of personalized medicine, with the goal of curing and preventing diseases. As a Center of Excellence,

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IA2C combines state-of-the-art clinical and laboratory facilities to coordinate research and academic collaborations with national and international partners. This pioneering initiative is unique in Indonesia, with only a few other centers worldwide offering similar capabilities. The center's advanced examination techniques include dendritic cells, tolerogenic macrophages, and regenerative macrophages (Cell Cure Center, 2021).

The cell product, derived from somatic blood cells, exhibits remarkable regenerative and regulatory properties similar to those of stem cells. In contrast to stem cells, these programmed cells offer several advantages, making them an attractive alternative for therapeutic (Cell Cure Center, 2021; Kementrian Pertahanan Republik Indonesia, 2017).

Cellcure Cellular offers a range of innovative products, including Dendritic Cells (DCs) for the treatment of cancer, Repair Macrophages Cells (REMs) for the repair and regeneration of damaged heart and brain blood vessels, and Regulatory Macrophages (TOMs) for the treatment of immune system-related disorders. These products leverage the unique characteristics of macrophages to promote tissue repair, regeneration, and immune modulation, providing a promising new approach to treating various diseases (Kementrian Pertahanan Republik Indonesia, 2017).

Other than adoptive T cell therapy, immune checkpoint inhibitor (ICIs) has found their particular market in Indonesia (Haryati & Mayasari, 2020). Like adoptive T cell therapy, ICIs are considerably pricey. However, as this does not demand real time as rigorous laboratorial setting as the Adoptive T cell therapy does, ICIs are clinically more famous.

The immune checkpoint inhibitor approach has gained significant attention in recent years, particularly after the FDA approval of ipilimumab for treating melanoma. Researchers have been investigating various immune checkpoints, including CTLA-4, PD-1,

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LAG-3, and TIGIT, to treat different types of cancers. These checkpoints are named for their role as "gatekeepers" of immune responses in healthy conditions. They work by sending inhibitory signals to prevent excessive immune responses. By blocking these signals with antibodies, scientists can prevent the ligation of ligand-receptor and develop immune checkpoint blockade therapies. The success of anti-PD-1/PD-L1 treatments has encouraged further exploration of other identified checkpoints, which have shown promise in animal models (Nurlaila, 2022).

There are four globally identified and FDA-approved ICIs:

1. PD1/PD-L1

Several anti-PD-1 and anti-PD-L1 antibodies have been developed to date. Two notable examples are Nivolumab (Opdivo) and Pembrolizumab (Keytruda), which are both antibodies that block the binding of PD-1 to its ligands. Nivolumab received its first approval in 2014 for treating unresectable metastatic melanoma, and later approvals for NSCLC and Hodgkin's lymphoma. Pembrolizumab was initially approved for metastatic melanoma, and later for locally advanced or metastatic urothelial carcinoma, non-Hodgkin's lymphoma, and neck squamous cell carcinoma (K. Sato et al., 2018). Another FDA-approved anti-PD-1 antibody is Cemiplimab (Libtayo), which is specifically designed for advanced cutaneous squamous cell carcinoma. It has been shown to have durable effects, with no recurrence observed even after 16 months (Migden et al., 2020).

As for anti-PD-L1 antibodies, Atezolimumab (Tecentriq), Avelumab (Bavencio), and Duravulumab (Imfinzi) have also been approved for various cancer types. Atezolimumab is widely used for urothelial carcinoma, while Avelumab and Duravulumab are used to treat patients with metastatic Merkel cell carcinoma and NSCLC, respectively. Duravulumab has also shown promise in treating head and neck squamous cell carcinoma, with an objective response rate of 9.2%. Additionally, it has been shown to have a 6-month progres-

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sion-free survival rate of 20% in all patients, and 25% in patients who are PD-L1 positive (Zandberg et al., 2019).

2. Cytotoxic T Lymphocyte Antigen 4 (CTLA-4)

CTLA-4 is a crucial braking mechanism that regulates the immune response. The genetic deletion of CTLA-4, which leads to fatal lymphoproliferative disorders, makes it distinct from other checkpoints. As a member of the CD28 family of receptors, CTLA-4 competes with CD28 for binding to ligands B7.1 and B7.2, thereby preventing co-stimulatory signals and inhibiting the immune system (Savoia et al., 2016).

In the context of tumor antigen recognition, CTLA-4 is highly expressed in regulatory T cells (Tregs) that express FOXP3. This means that instead of promoting T cell activation and cancer cell destruction, Tregs are actually brakes on the immune response, preventing it from effectively targeting cancer cells (Savoia et al., 2016).

Ipilimumab, the first FDA-approved anti-CTLA-4 antibody, exhibits a distinct response profile compared to traditional chemotherapy. While patients receiving conventional chemotherapy typically experience a rapid decline in tumor size, accompanied by no new lesions, patients receiving ipilimumab may initially observe an increase in their tumor burden before subsequently experiencing a reduction or complete eradication of all lesions. This unusual pattern is attributed to the delayed activation of the immune system, which requires infiltrating T cells to take time to eliminate the tumor. As the benefits of ipilimumab often become apparent after previously defined "progression" by WHO or RECIST criteria, new immune response criteria have been proposed. The therapeutic response to ipilimumab typically manifests between 12-24 weeks, with the response persisting even beyond 12 months. Notably, adverse effects are observed in approximately 10-15% of patients, primarily manifesting as immune-related issues such as colitis, hypophysitis,

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thyroiditis, rash, and hepatitis. With these being said, ipilimumab is deemed safe for administration (Wolchok et al., 2009).

3. Lymphocyte Activation Gene 3 (LAG-3)

The expression of LAG-3 is triggered by the activation of T cells via the T-cell receptor (TCR) or by the influence of cytokines such as interleukin-12 (IL-12). The transcription of LAG-3 is, however, intricately regulated by a delicate balance between inducing and repressing elements, including transcription factor binding sites. Several transcription factors have been identified to induce LAG-3 expression, including TOX, NFAT, and NR4A. In contrast, T-bet, a transcription factor crucial for cytotoxic T cell differentiation, exhibits an inverse correlation with LAG-3. While T-bet promotes immune exhaustion, its relationship with LAG-3 is bidirectional, with deletion of either T-bet or LAG-3 leading to increased expression of the other. This suggests that LAG-3 may either contribute to T cell exhaustion or be influenced by it in a reciprocal manner (Lecocq et al., 2020).

Bristol Myers Squibb has developed Opdualag, a second-generation checkpoint inhibitor combination, which combines anti-LAG-3 antibody Relatlimab with Opdivo (nivolumab) for the first-line treatment of metastatic or unresectable melanoma. Previous studies have shown that the combination therapy of Relatlimab and Nivolumab significantly improves progression-free survival (PFS) to 10.1 months, compared to Nivolumab alone, which only supported PFS to 4.6 months. Moreover, the percentage of patients achieving PFS of 12 months was significantly higher in the Relatlimab-Nivolumab combination group (47.7%) compared to the Nivolumab-only group (36%) (Einstein, 2022). Additionally, Novartis has developed a combination therapy targeting PD-1 and LAG-3, known as Spartalizumab plus LAG-525, which is currently in Phase II clinical trials for the treatment of unresectable or metastatic disease (Parra & Webster, 2022).

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Several other companies are also working on LAG-3-targeting therapies. Macrogenic's Tebolimab is a first-in-class bispecific antibody composed of antigen-binding fragments (Fab) targeting LAG-3 and PD-1, which is currently in Phase I clinical trials. Pieris has developed PRS-332, which consists of two Fab regions targeting PD-1 and engineered lipocalins designed to target LAG-3. F-star Therapeutics has also produced antibody FS118, which has a Fab targeting LAG-3 in its constant region and leaves the Fabs targeting PD-L1 domains intact (Lecocq et al., 2020).

4. Cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT)

TIGIT is a relatively recently discovered immune checkpoint molecule that has shown great promise in cancer immunotherapy. Through extensive research, it has been found that TIGIT plays a crucial role in preventing tumor antigens from being released by CD8+ T cells, impeding T cell priming by dendritic cells, and blocking cancer cell killing by CD8+ T cells. These findings have solidified its position as a top candidate for clinical development, making it a promising target for immune-checkpoint-based cancer therapies (L. Liu et al., 2022).

According to recent reports, six human-anti-TIGIT monoclonal antibodies (mAbs) of the IgG1 isotype are currently in clinical trials. One of these is Etigilimab, developed by OncoMed Pharmaceuticals, which has been shown to suppress colon and kidney tumors in mice and induce a TH1-type response. Etigilimab is now being evaluated in a Phase I trial for its pharmacokinetics. Additionally, Arcus Bioscience's AB154 and Merck's MK-7684 are being tested in Phase I trials as monotherapies for advanced solid cancers and solid cancers, respectively. Merck's MK-7684 is also being evaluated in combination with pembrolizumab, an anti-PD-1 mAb. Tiragolumab, developed by Genentech/Roche, is in Phase II trials as a combination therapy with atezolumab for advanced or metastatic non-small

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cell lung cancer. Bristol-Myers Squibb is also testing BMS-986207, an IgG1 mAb with a mutated Fc portion that prevents interaction with Fcγ receptors, which can inhibit anti-tumor activity. Astellas Pharma's ASP 8374, also an IgG1 mAb with a FcγR-null mutation, is being developed for the same purpose (Harjunpää & Guillerey, 2020).

5. T cell immunoglobulin and mucin-domain containing-3 (Tim-3)

Tim-3 plays a crucial role in regulating both innate and adaptive immune responses. When Tim-3 binds to its ligand galectin-9 (GAL-9), it triggers the death of T cells that express Tim-3, thereby inhibiting the immune response. As a result, T cells that overexpress Tim-3 respond less to antigen stimulation. Tim-3 plays a key role in T-cell exhaustion, which occurs during chronic immune stimulation, such as in cancer. This phenomenon is characterized by the loss of T-cell function, the expression of multiple inhibitory receptors, and altered gene expression. In tumor-infiltrating lymphocytes (TILs), Tim-3 is overexpressed in CD4+ and CD8+ T cells, whereas peripheral T cells have minimal expression. Blocking the Tim-3 pathway can enhance the proliferation of T cells specific to tumor antigens and their ability to produce pro-inflammatory cytokines. Additionally, blocking Tim-3 inhibits the function of regulatory T cells and myeloid-derived suppressor cells, leading to an improved immune response (Friedlaender et al., 2019).

In addition to its well-characterized binding partner, galectin-9, Tim-3 has been shown to interact with a diverse array of ligands, each triggering distinct effector mechanisms. One such ligand is phosphatidylserine (PtdSer), a phospholipid that is exposed on the surface of apoptotic cells, facilitating the engulfment of dying cells by macrophages and other immune cells. The binding of TIM-3 to phosphatidylserine (PtdSer) molecules on the surface of apoptotic cells has been linked to the phagocytic process, which is a critical

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mechanism for the clearance of cellular debris. As TIM-3 plays a pivotal role in this process, its expression is typically low in cancer-eliminating M1 macrophages, which are characterized by their high levels of pro-inflammatory cytokines. In contrast, M2 macrophages, which are involved in immune tolerance, exhibit elevated TIM-3 expression and fail to release cytokines. This suggests that TIM-3 acts as a negative regulator of macrophage activation, promoting an immunosuppressive microenvironment. Furthermore, the use of anti-TIM-3 antibodies may offer a promising therapeutic approach to activate macrophages and enhance their capacity to eliminate leukemic stem cells through antibody-dependent cellular phagocytosis (Zeidan et al., 2021a).

Another ligand that binds to Tim-3 is high mobility group protein 1 (HMGB1), a nonhistone nuclear protein that is released by damaged cells and can act as a danger signal to trigger immune responses. The binding of HMGB1 to Tim-3 has been shown to inhibit the activation of the innate immune response by preventing the recognition of nucleic acids by Toll-like receptors. Furthermore, Tim-3 has also been found to bind to carcinoembryonic antigen cell adhesion molecule 1 (CEACAM-1), a protein that is involved in cell adhesion and signaling processes. The binding of CEACAM-1 to Tim-3 disrupts the binding of nucleic acids to dendritic cells' endosomes, which impairs the activation of the innate immune response. Additionally, the binding of HMGB1 to Tim-3 blocks the activation of the immune response. In this process, Tim-3 competes with tumor-derived nucleic acids for HMGB1 binding, preventing HMGB1 from participating in the uptake of nucleic acids into the cell. This ultimately inhibits the activation of TLR signaling pathways in dendritic cells, which are crucial for immune response activation (Chiba et al., 2012).

Despite the growing importance of immunotherapy in cancer treatment, there is a dearth of clinical trials in nasopharyngeal car-

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cinoma (NPC) patients in endemic areas in Indonesia. The PD-1/PD-L1 pathway has emerged as a promising therapeutic target. However, the PD-L1 profile of NPC patients in Indonesia has poorly investigated. A particular study showed that the average PD-L1 concentration in NPC specimens was significantly higher than in non-NPC specimens, suggested that the PD-L1 protein is elevated in NPC specimens, both in tumor cells and immune cells. This preliminary result has significant implications for the development of immunotherapy strategies for NPC patients who have failed standard treatment. Furthermore, our future research will explore the relationship between PD-L1, Epstein-Barr virus (EBV), and tumor microenvironment in NPC specimens. This comprehensive understanding of the immunological landscape of NPC will be crucial for the development of effective immunotherapies tailored to the Indonesian population (Handoko et al., 2019).

More recently, in an expert consensus formulated by Hasan and colleagues (2022), sorafenib, lenvatinib, and atezolizumab plus bevacizumab were recommended as first-line treatments for hepatocellular carcinoma (HCC) patients, given that not all patients are eligible for atezolizumab plus bevacizumab. However, we acknowledge the importance of considering the unique challenges posed by remote areas in Indonesia. The country's vast geographical spread and limited healthcare infrastructure make it crucial to prioritize treatment options that are accessible and feasible for patients living in remote regions. Oral agents such as sorafenib and lenvatinib are more suitable for these patients, as they require less frequent hospital visits and can be administered more easily in remote areas. Moreover, these oral agents are more affordable than the combination of atezolizumab and bevacizumab, making them a more practical option for patients in these regions. In light of these considerations, sorafenib and lenvatinib as first-line options was embedded in their clinical guidelines (Hasan et al., 2023).

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E. HORMONE THERAPY

Hormone therapy for cancer has gained significant importance in Indonesia, as it is an effective treatment option for specific types of cancer, particularly those that are hormone sensitive. These include breast cancer, prostate cancer, and some types of gynecological cancers (Deliana et al., 2019). Hormone therapy aims to either reduce the production of hormones or block their effects on cancer cells, thereby slowing or stopping cancer growth (Deliana et al., 2019).

In Indonesia, hormone therapy for cancer is typically provided in hospitals, specialized cancer centers, and oncology clinics (Purwanto et al., 2020a; Rohman et al., 2024; Widiana & Irawan, 2020). The treatment is usually administered under the guidance of a team of oncologists, who specialize in cancer care, and other healthcare professionals, such as nurses, pharmacists, and psychologists (Eraso, 2019; Eraso et al., 2022; Lively et al., 2020).

There are several types of hormone therapies used in Indonesia, depending on the specific cancer type and the patient's condition. Some common hormone therapies include:

1. Selective Estrogen Receptor Modulators (SERMs)

Selective Estrogen Receptor Modulators (SERMs) are a class of drugs that play a crucial role in cancer treatment, particularly for hormone receptor-positive cancers. Hormone receptor-positive cancers are those cancers whose growth is stimulated or fueled by the presence of specific hormones, such as estrogen in breast cancer. SERMs work by selectively targeting estrogen receptors, either blocking or modulating the effects of estrogen on cancer cells, thereby slowing or stopping their growth (Jordan & O'Malley, 2007).

SERMs are primarily used in the treatment of breast cancer, as it is one of the most common types of cancer affecting both men and women worldwide. Approximately 70% of breast cancer cases are

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hormone receptor-positive, making SERMs an essential treatment option for many patients(Jordan & O'Malley, 2007).

Tamoxifen is the most well-known SERM, having been used for over 40 years in the treatment of breast cancer. It functions as an estrogen agonist in certain tissues, such as bones and the cardiovascular system, where estrogen has protective effects. However, in breast cancer cells, Tamoxifen acts as an estrogen antagonist, blocking the hormone's stimulating effects on cancer growth. This dual action helps reduce the risk of cancer recurrence and improve survival rates in patients with hormone receptor-positive breast cancer (Jordan, 2007).

Other SERMs, such as Raloxifene and Toremifene, have also been developed for breast cancer treatment. Raloxifene is primarily used for the prevention and treatment of postmenopausal osteoporosis but has also shown some efficacy in reducing breast cancer risk. Toremifene is used to treat advanced breast cancer in postmenopausal women, specifically estrogen receptor-positive metastatic disease(Mustonen et al., 2014; R. Patel et al., 2023).

In addition to their use in breast cancer treatment, SERMs are being investigated for their potential in preventing and treating other hormone receptor-positive cancers, such as prostate and ovarian cancers. For example, Fulvestrant, a SERM with a unique mechanism of action, has been approved for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer in postmenopausal women (Osborne et al., 2004).

2. Aromatase Inhibitors

Aromatase inhibitors (AIs) are a class of medications that play a vital role in the treatment of specific types of cancers, particularly hormone receptor-positive breast cancers and, in some cases, advanced prostate cancers. These drugs work by inhibiting the aromatase enzyme, which is responsible for the production of estrogen in postmenopausal women and, to a lesser extent, testosterone in

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men. By reducing the levels of these hormones, AIs help slow down or halt the growth of cancer cells that rely on estrogen to thrive (E. E. Sweeney et al., 2012).

In postmenopausal women, the primary source of estrogen is through the conversion of androgens (male hormones) into estrogen by the aromatase enzyme, which is found in fatty tissues, including breast tissue(Bhardwaj et al., 2019). In men, a small amount of estrogen is produced through the same process(R. A. Hess, 2003). Hormone receptor-positive breast cancers and some prostate cancers have receptors that bind to estrogen, promoting cancer cell growth (Ulm et al., 2019).

Aromatase inhibitors block the aromatase enzyme, thereby reducing the production of estrogen and, in turn, limiting the fuel source for cancer cells (Chumsri et al., 2011). This helps slow down or stop the growth of cancer cells, making them more susceptible to other cancer treatments like chemotherapy and radiation (Chumsri et al., 2011).

There are three main types of aromatase inhibitors:

1. Nonsteroidal selective aromatase inhibitors (NSAIs): These are the most commonly prescribed AIs and include drugs like letrozole (Femara) and anastrozole (Arimidex). They are usually prescribed after surgery and radiation therapy for early-stage breast cancer or for advanced breast cancer cases (Hamilton & Piccart, 1999).
2. Steroidal aromatase inhibitors (SAIs): These include exemestane (Aromasin), which is typically used after other hormonal therapies, like tamoxifen, have been tried. Exemestane is often prescribed for both early and advanced breast cancer cases(Walker et al., 2013).
3. Aminoglutethimide: This is an older, less specific aromatase inhibitor that is rarely used today due to its side effects and the availability of more targeted Ais (Cocconi, 1994).

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3. Luteinizing Hormone-Releasing Hormone (LHRH) Agonists and Antagonists

Luteinizing Hormone-Releasing Hormone (LHRH) agonists and antagonists are a class of medications primarily used in the treatment of certain types of cancer, particularly those that are hormone-dependent. These medications interfere with the hormonal pathways that contribute to cancer growth, making them an essential tool in managing and controlling specific types of cancer (Tolkach et al., 2013).

LHRH is a naturally occurring hormone in the human body that plays a crucial role in regulating the production and release of other hormones, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones, in turn, influence the function of the reproductive system and the production of sex hormones like estrogen and testosterone (Walters et al., 2008).

LHRH agonists and antagonists work by targeting the LHRH receptors in the pituitary gland, which is responsible for producing LH and FSH. By binding to these receptors, these medications can either stimulate or inhibit the production of LH and FSH, depending on the type of medication used (Tolkach et al., 2013).

a. LHRH Agonists:

LHRH agonists, such as goserelin, leuprolide, and triptorelin, are synthetic versions of LHRH that mimic the natural hormone(Y.-S. Lu et al., 2021). When administered, they initially stimulate the pituitary gland to produce more LH and FSH. However, after a few days, the continuous presence of the agonist leads to a downregulation of LHRH receptors, resulting in decreased production of LH and FSH. This reduction in sex hormones can help slow the growth of hormone-dependent cancers, such as prostate cancer and breast cancer(Rick et al., 2013).

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LHRH Agonists are often used in combination with other cancer treatments, such as chemotherapy or radiation therapy, to enhance their effectiveness. They may also be used to alleviate symptoms related to advanced-stage cancers, such as bone pain or excessive hormone production(Crawford, 2004; S. Goel et al., 2009).

b. LHRH Antagonists:

Unlike agonists, LHRH antagonists, such as degarelix and relugolix, directly block the binding of LHRH to its receptors without an initial stimulatory phase. This immediate inhibition of LH and FSH production leads to a rapid decrease in sex hormone levels. LHRH antagonists are particularly useful in treating cancers that are highly sensitive to changes in hormone levels, such as advanced prostate cancer(Crawford et al., 2019).

LHRH agonists and antagonists can cause a range of side effects due to the rapid decrease in sex hormone levels, which can impact various body systems (X. Zhang et al., 2023). Some of the most common side effects associated with the use of these medications include:

1. Hot flashes: A sudden sensation of warmth, often accompanied by blushing and sweating, hot flashes can be an uncomfortable side effect for many patients. They occur due to the rapid drop in estrogen levels in women or testosterone levels in men (Mohile et al., 2009).
2. Fatigue: Both LHRH agonists and antagonists can cause fatigue, which may be a result of hormonal changes or the cancer itself. It is essential for patients to maintain a balanced diet, stay hydrated, and engage in light physical activity to help combat fatigue (Perlmutter & Lepor, 2007).
3. Decreased libido: Hormonal changes caused by LHRH agonists and antagonists can lead to a reduced interest in

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sexual activity. This side effect can be distressing for patients but may improve over time as the body adjusts to the medication(Mazzola & Mulhall, 2012).

4. Bone pain: Some patients may experience bone pain, particularly those with advanced cancers that have metastasized to the bones. This pain can be managed through medications, physical therapy, and other supportive care measures(Brawer, 2004).
5. Emotional changes: Mood swings, anxiety, and depression are possible side effects of LHRH agonists and antagonists. Patients should discuss any emotional changes with their healthcare team, who may recommend counseling or additional support to help manage these symptoms(R. J. Kumar et al., 2005).
6. Muscle and joint pain: Some patients may experience muscle or joint pain as a result of hormonal changes caused by these medications. This discomfort can often be managed with over-the-counter pain relievers or physical therapy-(Seber et al., 2016).

4. Anti-Androgens

Anti-androgens function by blocking or inhibiting the effects of androgens in the body. They work by binding to androgen receptors, preventing the hormones from stimulating cancer cell growth. This, in turn, slows down or stops the cancer from spreading and may even induce cancer cell death (Piotrowski & Greenberg, 2016).

Prostate cancer is one of the most common cancers where anti-androgens are employed. Since prostate cancer cells often rely on androgens for their growth and survival, using anti-androgens as a chemotherapy agent can be highly beneficial in managing the disease. Some commonly used anti-androgens for prostate cancer include bicalutamide, enzalutamide, and nilutamide (Piotrowski &

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Greenberg, 2016). In addition to prostate cancer, anti-androgens can also be used to treat breast cancer in men (known as male breast cancer) and certain types of female breast cancer. In these cases, the cancer cells have androgen receptors that promote tumor growth, making anti-androgens a suitable treatment option (Dimitrakakis & Bondy, 2009; Kolyvas et al., 2022).

However, it is crucial to note that anti-androgens may cause side effects, as with most chemotherapy agents. These can include a decrease in sex drive, erectile dysfunction, hot flashes, fatigue, and mood changes. It is essential for patients to discuss these potential side effects with their healthcare team to understand how they can be managed effectively.

Indonesia, like many other nations, is actively endeavoring to develop and refine its anticancer treatment protocols. The push for innovative cancer care is also fueled by the recognition of the importance of precision medicine, which holds great promise for tailoring treatment to individual patients' unique needs (Adenijia et al., 2021; Krzyszczyk et al., 2018; Shams et al., 2023). By harnessing the latest advances in genomics, epigenomics, and other areas of cutting-edge research, Indonesia is poised to make significant strides in this field (East Ventures & Redseer Strategy, 2023; Natri et al., 2022). This forward-thinking approach will not only enhance the effectiveness of cancer treatments but also improve patient outcomes, ultimately leading to better survival rates and improved quality of life.

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CHAPTER V
RESPONSIVENESS DISPARITY ON ANTICANCER TREATMENTS

In the ever-evolving landscape of cancer research and treatment, one of the most intriguing and challenging aspects is the significant disparity in responsiveness observed among patients undergoing anticancer thesrapies. Despite advancements in targeted therapies and immunotherapies, the heterogeneity in treatment outcomes continues to pose a formidable obstacle in the quest for effective, personalized cancer care (Bhat et al., 2024). This chapter aims to provide an overview of the responsiveness disparity in anticancer treatments, highlighting the factors contributing to this variability and the potential avenues for improving treatment efficacy.

Responsiveness to anticancer treatments encompasses a wide range of factors, including the patient's overall health, tumor characteristics, and the specific therapeutic interventions employed. While some patients may experience remarkable clinical benefits and extended survival, others may exhibit minimal or no response to the same treatment regimen (Villaruz & Socinski, 2013). This variability in treatment outcomes has significant implications for

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patient prognosis, healthcare resource allocation, and the overall understanding of cancer biology.

Several factors have been identified as contributing to the responsiveness disparity in anticancer treatments. These include the genetic and molecular profile of both the tumor and the patient, the microenvironment surrounding the tumor, and the efficacy of the immune system in recognizing and targeting cancer cells(X. Wang et al., 2019). Additionally, the choice of treatment modality, dosage, and scheduling can greatly influence a patient's response to therapy(Gelhorn et al., 2011).

To address the challenges posed by responsiveness disparity in anticancer treatments, researchers and clinicians are exploring innovative strategies to personalize cancer care. These include the development of predictive biomarkers to identify patients likely to benefit from specific therapies, as well as the integration of multi-modal treatment approaches that target multiple aspects of cancer biology simultaneously. Furthermore, a deeper understanding of the complex interplay between cancer cells, the immune system, and the tumor microenvironment is crucial for unraveling the mysteries behind treatment responsiveness and paving the way for more effective, targeted therapies.

A. GEOGRAPHIC DISPARITIES

Cancer is a formidable foe that affects millions of people worldwide, including those in Indonesia. However, the challenges faced by cancer patients in the country are not limited to the disease itself; they also grapple with disparities in access to and quality of cancer care based on their geographic location. This issue has significant implications for the well-being and survival of Indonesian cancer patients (Feliciano et al., 2023; K. Handayani et al., 2022).

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Geographic disparities in cancer treatment refer to discrepancies in access to and quality of care based on a patient's geographic location. In Indonesia, these disparities are particularly evident when comparing the experiences of patients living in urban and rural areas(Laksono et al., 2023). These may be attributed to several factors, including the distribution of healthcare facilities, medical expertise, and financial resources as explained as follows:

1. Limited Availability of Cancer Treatment Facilities

One of the most significant challenges faced by Indonesian cancer patients is the uneven distribution of healthcare facilities. According to the World Health Organization, there is a stark contrast between the number of hospitals and doctors available in urban and rural areas. This disparity means that those living in rural regions often have to travel long distances to access specialized cancer care (Stockton et al., 2021).

2. Lack of Expertise and Specialized Services

Cancer treatment in Indonesia faces significant challenges, leading to delays and disparities in patient care. A majority of patients experience treatment delays due to both patient and provider factors, with many seeking alternative treatments before medical care (S. Gondhowiardjo, Hartanto, et al., 2021). The lack of specialized services and expertise is evident, with only 233 surgical oncologists serving a population of over 273 million (Gautama, 2022). This shortage contributes to late-stage diagnoses, with 68-73% of breast cancer patients presenting at advanced stages (Gautama, 2022). Gynecological cancer survivors report unmet care needs and deficient health care services, including short consultation times and unempathetic professionals (Afiyanti et al., 2021). Advanced cancer patients often choose complementary and alternative treatments over medical care initially, influenced by external sources and distrust in medical treatments (Deliana et al., 2019). These factors collectively contribute to

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the disparity in patients' responsiveness to therapy and highlight the need for improved cancer care infrastructure in Indonesia.

In addition to limited access to healthcare facilities, Indonesian cancer patients may also face challenges in finding healthcare professionals with the necessary expertise to provide optimal care. Oncologists, radiologists, and other specialists are more likely to be concentrated in urban areas, leaving rural patients with fewer options for consultation and treatment (Widjaja et al., 2022).

3. Financial Constraints and Access to Care

The cost of cancer treatment can be prohibitive, even in countries with relatively affordable healthcare systems like Indonesia. Patients in rural areas may face additional financial challenges due to limited access to insurance coverage and financial assistance programs. This can result in delayed diagnosis, inadequate treatment, or even the inability to seek care altogether (Septiono, 2023).

4. Inadequate Infrastructure and Support Services

Geographic disparities in cancer care also extend to the availability of essential support services, such as palliative care, psychological counseling, and support groups. These services are crucial for patients dealing with the physical, emotional, and social impacts of cancer. The lack of such resources in rural areas can exacerbate the challenges faced by cancer patients and their families (Putranto et al., 2017).

In addition, Indonesian patients with cancers, to some extent, experience transportation barriers. Numerous research studies have reported that the travel burden, which is determined by the length of time or distance traveled, can lead to diagnostic delays, and adversely affect treatment decisions for a range of common cancers (Ambroggi et al., 2015; S. Gondhowiardjo, Hartanto, et al., 2021; Turner et al., 2023; Widjaja et al., 2022). As aforementioned, the most pertinent goals of health policies are to increase patient satis-

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faction, safety, quality, and efficiency of healthcare. The patient living in underserved or rural areas may have limited access to specialized oncological care or cancer treatment centers. This condition will impact delayed diagnosis and treatment then lead to affect treatment effectiveness (S. Gondhowiardjo, Hartanto, et al., 2021; Widjaja et al., 2022).

5. Cultural and Linguistic Barriers

Cancer treatment often requires extensive communication between patients, healthcare providers, and support networks. Effective communication between patients and healthcare providers is essential for ensuring appropriate and effective cancer treatment (J. Li et al., 2020).

Patients from diverse cultural origins may encounter language barriers during interactions with healthcare providers, which could hinder their ability to completely understand cancer diagnosis, possible treatments, and prescription guidelines. Miscommunication or misunderstanding can lead to less than optimum treatment adherence and poorer results. In addition, doctors were perceived as being less engaged in forming an emotional bond and as communicating less biomedical, informative, and supportive communication statements during consultations or during visits with patients who were members of minorities or migrants from other countries(Ahmed et al., 2017; Paternotte et al., 2015). Consequently, patients from underrepresented or immigrant groups may experience stigma related to mental health problems or cancer, which could result in under use of supporting services that could enhance quality of life while undergoing treatments (Kane et al., 2019; Nyblade et al., 2019).

B. PROVIDER BIAS

Provider bias, which refers to the tendency of healthcare professionals to treat patients differently based on factors such as age, gender,

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ethnicity, or socioeconomic status, can have a significant impact on cancer treatment outcomes (Kale et al., 2023).

Healthcare provider bias significantly impacts patient care and outcomes, contributing to health disparities in various medical fields, including gynecologic oncology (Almirza et al., 2022; Torres et al., 2022). Implicit biases, which are automatic and unconscious attitudes, have been observed among healthcare professionals towards racial, ethnic, and socioeconomically disadvantaged groups (Maina et al., 2018; Torres et al., 2022). A systematic review of 37 studies found evidence of pro-White or light-skin bias among healthcare providers, with some studies showing associations between higher implicit bias and disparities in treatment recommendations, pain management, and empathy (Maina et al., 2018). In gynecologic oncology, providers have exhibited higher biases for cervical cancers, as measured by the Implicit Associations Test (D. M. Chase et al., 2021). These biases can affect patient-provider communication and potentially influence clinical outcomes (Maina et al., 2018). Addressing healthcare provider bias is crucial for improving patient outcomes and reducing disparities in the healthcare system (Almirza et al., 2022).

Provider bias can manifest in various ways that may negatively influence cancer treatment in Indonesia, for instances:

1. Delayed or Inadequate Diagnosis

Healthcare providers who exhibit bias may be less likely to consider a cancer diagnosis in certain patients, leading to delayed or inaccurate diagnoses. This can result in missed opportunities for early intervention and treatment, ultimately affecting the patient's prognosis (Cohen & Greaney, 2021; Wall et al., 2023)

This is a significant issue in Indonesia which contribute to the high burden of advanced-stage cancers. Studies show that 43.3% of breast cancer patients experience presentation delays of ≥3 months, while 64.7% face diagnosis delays of ≥1 month (Hutajulu et al.,

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2022). These delays are associated with more advanced disease stages. Similarly, a study at a national referral hospital found that 86% of cancer patients experienced treatment delays, with both patient and provider factors contributing (S. Gondhowiardjo, Hartanto, et al., 2021). Despite 30 years of progress, 68-73% of breast cancer patients are still present at their late stages (Gautama, 2022). Factors contributing to delays include lack of awareness, fear of treatment, complex referral pathways, and limited access to oncologists. To address these issues, Indonesia needs to increase the number of surgical oncologists, improve the referral system, and reform healthcare regulations (Gautama, 2022). These delays significantly impact cancer epidemiology and burden in Indonesia (S. Gondhowiardjo, Hartanto, et al., 2021).

2. Unnecessary or Ineffective Treatments

In some cases, provider bias may lead to the over-treatment or under-treatment of cancer patients. For example, a provider might recommend more aggressive treatment for a patient they perceive as having more social or economic resources, while withholding necessary treatment from those they believe cannot afford it or are not worth investing in (Kale et al., 2023; Mead et al., 2013).

3. Poor Patient-Provider Communication

Provider bias can create a hostile or dismissive environment, hindering effective communication between patients and healthcare professionals. This can lead to misunderstandings about treatment plans, patient non-adherence, and reduced trust in the healthcare system (H. S. Shah & Bohlen, 2023; Vela et al., 2022).

C. RACIAL AND ETHNIC DISPARITIES

Racial and ethnic disparities in healthcare are a complex issue, with multiple factors contributing to their emergence. One crucial aspect is the patient's individual attributes, which can influence their

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interactions with healthcare providers. For instance, minority patients may exhibit behaviors such as refusing recommended services, poor adherence to treatment regimens, and delayed seeking of care. These attitudes and behaviors can be shaped by a lack of cultural understanding between patients and providers, mistrust, misunderstandings, or prior negative experiences with healthcare systems. However, it is essential to recognize that patient-level differences are unlikely to be the primary drivers of healthcare disparities. While there may be variations in patient preferences and behaviors, these differences are relatively small and do not fully account for the observed disparities in healthcare receipt (Smedley et al., 2003).

Moreover, research has shown that racial and ethnic differences in healthcare utilization can also be attributed to factors beyond patient-level characteristics (Caraballo et al., 2022; J.-A. D. Chase et al., 2018). Some studies have demonstrated that overuse of clinical services is more common among white patients, which may contribute to disparities in discretionary procedures.

Research indicates persistent racial disparities in healthcare utilization, particularly between White and minority patients. White patients are more likely to receive clinical genetic testing (Carroll et al., 2019) and undergo various surgical procedures compared to Black patients, even when adjusted for insurance status (Best et al., 2021). Interestingly, overuse of preventive care and screening is often greater among socioeconomically advantaged patients, potentially leading to subsidization by disadvantaged groups within insured populations (Helfrich et al., 2019). These findings suggest that addressing healthcare disparities requires a nuanced approach, considering both underuse and overuse of services across different racial and socioeconomic groups, and implementing targeted de-implementation strategies to reduce low-value care while promoting equitable access to high-value interventions (Helfrich et al., 2019; Jackson & Gracia, 2014).

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D. GENETIC AND BIOLOGICAL FACTORS

Genetic and biological factors play a significant role in the disparate responses to cancer therapy across different populations. Studies have identified genes, gene families, and pathways associated with cancer racial disparities across multiple cancer types (Y. Li et al., 2020). For example, XKR9 gene expression was found to be significantly linked to overall survival in several cancers. Pharmacogenomic differences may explain some of these disparities, with ethnic variations in the frequencies of polymorphisms within cancer drug-related genes contributing to differences in drug disposition and sensitivity (O'Donnell & Dolan, 2009). Additionally, a favorable cancer immune phenotype has been associated with better prognosis and increased responsiveness to immunotherapies, although it remains unclear whether this is dictated by tumor genetics or individual genetic makeup (Bedognetti et al., 2015). Understanding these genetic determinants is crucial for personalizing cancer therapy and improving treatment outcomes across diverse patient populations (Maitland et al., 2006).

More superficially, research indicates significant racial and ethnic disparities in cancer incidence, mortality, and survival rates. African Americans and Native Hawaiians show higher lung cancer risk compared to other groups, particularly at lower smoking intensities (Stram et al., 2019). These disparities persist even when accounting for socioeconomic factors (Ward et al., 2004). Across various cancer types, African Americans, Hispanics, and other minority groups often present with more advanced stages at diagnosis, receive less definitive treatment, and have worse survival outcomes compared to Asian and non-Hispanic White patients (C. Zhang et al., 2020). Factors contributing to these disparities include differences in cancer risk behaviors, access to screening and early detection, treatment availability, and genetic variations (Schabath et al., 2016). While smoking remains a primary risk factor for lung cancer, the impact

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of smoking intensity on cancer risk varies among racial and ethnic groups, suggesting complex interactions between genetic and environmental factors (Stram et al., 2019). Compared to non-Hispanic Whites, Hispanics are more likely to develop stomach and cervical cancers. Non-Hispanic Whites, on the other hand, had lower mortality rates from stomach, liver, and cervical cancers than did Asians, Pacific Islanders, and Native Americans. The greatest total rates of breast cancer mortality across all racial and ethnic groups are found among Native Hawaiians (Shinagawa, 2000). African Americans, however, had a threefold higher risk of dying from cancer than did Asian/Pacific Islanders, American Indians, and Hispanics (Fu et al., 2009).

Racial differences in mortality have persisted, despite widespread reductions in the death rates of both African Americans and Whites. Compared to Whites, African Americans have often experienced smaller and less frequent reductions. Racial and ethnic disparities in cancer outcomes are often attributed to a more advanced state of disease at diagnosis in minority populations (Shavers & Brown, 2002). Based on the majority of medical research to date, it appears that Black-White inequalities in cancer outcomes are largely caused by inadequate cancer care rather than racial differences in tumor biology, response to treatments, or stage at presentation (Esnaola & Ford, 2012).

This genetic and biological factor is also well exemplified by the cases of nasopharyngeal carcinoma (NPC), which globally is an infrequent yet significant malignant disease that disproportionately affects certain regions and populations. While its prevalence is generally low, with rates typically below 1/100,000 in most parts of the world, it is a major public health concern in southern China and Southeast Asia. The Guangdong province in southern China, for instance, has the highest incidence of NPC globally (Adham et al., 2012). Intermediate incidence rates of this carcinoma have been observed in Southeast Asia, including Singapore, Malaysia,

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Vietnam, Taiwan, and the Philippines. Similarly, high incidence rates have been reported among indigenous populations in the Arctic region. In Africa, NPC is also prevalent, with intermediate incidence rates observed in countries such as Kenya and those in the Maghreb region. In Indonesia, NPC is ranking as the fourth most common tumor after cervical cancer, breast cancer, and skin cancer. It is the most common malignancy in the head and neck region and is 100% associated with Epstein-Barr virus (EBV) infection. The country's diverse population of over 225 million people makes NPC a major socioeconomic concern, with an estimated incidence rate of 6.2/100,000 or approximately 12,000 new cases per year. However, many cases go unreported due to limited medical awareness and a lack of hospital facilities and nationwide cancer diagnostic and registration systems (Adham et al., 2012).

But one might question how biological landscapes might affect the extent of the responsiveness of a patient. It is well learned that genetic and biological differences among various racial and ethnic groups can influence cancer susceptibility, progression, and treatment responsiveness. For example, some populations may have a higher prevalence of specific genetic mutations that affect how their bodies respond to certain chemotherapeutic agents or targeted therapies. Additionally, variations in immune system responses can impact the effectiveness of immunotherapies across different racial and ethnic groups.

One frontliner biological aspect is the diversity of human leukocyte antigen (HLA). HLA molecules play a critical role in the immune system, as they are responsible for presenting antigens (foreign substances) to immune cells, allowing the body to recognize and respond to pathogens, including cancer cells. HLA diversity across different populations can impact the effectiveness of cancer treatments, particularly immunotherapies, and contribute to responsiveness disparities among cancer patients (Pagliuca et al., 2022).

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1. HLA and Cancer Susceptibility

Genetic variations in HLA molecules can influence an individual's susceptibility to specific types of cancer. Certain HLA alleles may be associated with a higher risk of developing particular cancers, while others may offer protection (X. Li et al., 2009; C. Zhang et al., 2018).

The relationship between HLA class I and DNA analysis has been explored as a potential predictor of tumor development and breast cancer (BC) recurrence. It was consistently shown that HLA class I expression was downregulated in 32.5% of BC patients, which was significantly associated with lymph node involvement, TNM stage, lymphatic invasion, and venous invasion. Furthermore, patients with preserved HLA class I expression had a longer disease-free interval compared to those with deleted HLA class I (Kaneko et al., 2011).

The role of killer cell immunoglobulin-like receptors (KIRs) in BC has been investigated by analyzing the relationship between KIR genes and HLA alleles. Our study revealed that the presence of KIR2DL2 inhibitory receptors was significantly higher in BC patients compared to healthy controls. Notably, HLA-C2 and HLA-Bw4 showed no significant differences, while HLA-C1 was found to be more common in BC patients. These findings suggest that the KIR gene system may play a crucial role in BC development (Jobim et al., 2013).

Recent research has highlighted the importance of HLA class I-specific immunoglobulin-like receptors (KIRs) in controlling natural killer (NK) cell-mediated tumor cell elimination. In advanced BC patients, levels of KIR and HLA-ligand activating combinations were found to be higher. Furthermore, all patients with advanced cancer who had 2DS1 + C2 or 3DS1 + Bw4 had their corresponding iKIR homologs. These findings demonstrate that NK cells expressing iKIR to similar HLA ligands play a crucial role in the antitumor response (Ashouri et al., 2021).

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The significance of HLA class I and regulatory T cells (Tregs) in predicting chemotherapy response in early BC patients has been explored by (de Kruijf et al. 2010).. In support of this finding, a study by (Aboulaghras et al. 2024) showed that HLA class I and Tregs were strong predictors of chemotherapy response in early BC patients. Chemotherapy can effectively destroy tumor cells that retain HLA class I and Tregs, allowing cytotoxic T lymphocytes (CTLs) to attack them. Therefore, HLA class I and Tregs are valuable indicators of chemotherapy response in early BC patients (Aboulaghras et al., 2024). Unfortunately, reports on the association between HLA class I and cancer susceptibility are limited thus it is hard to draw a firm conclusion.

A recent study conducted in a cohort of 176 Caucasian women with early-onset breast cancer (BC) and 215 ethnically matched controls aimed to investigate the relationship between HLA alleles and BC susceptibility. The findings revealed that HLA DQB*03032 was absent in all early-onset BC cases, whereas it was present in 7% of controls. Similarly, the HLA DRB1*11 allele was overrepresented in controls (16.3%) compared to BC cases (3.5%). These results suggest that the HLA DQB*03032 and HLA DRB1*11 alleles may have a protective effect against BC development (Chaudhuri et al., 2000).

In a study conducted in Tunisia, the relationship between HLA class II alleles and susceptibility to BC was examined. The HLA-DRB1 and HLA-DQB1 loci were molecularly typed in 70 Tunisian patients with BC. The results showed a significant negative correlation between HLADRB1*07-DQB1*02 and BC incidence in the Tunisian population. This suggests that these alleles may be associated with a reduced risk of developing BC (Harrath et al., 2006).

Different profile was shown in Turkish population where certain alleles, such as HLA-DRB1*03, HLADQB1*02, HLA-DRB1*13, and HLA-DQB1*06, were associated with an excellent prognosis and may play a role in preventing BC development. Conversely, other

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alleles, including HLA-DRB1*03 and HLADRB1*04, were found to be associated with a poor prognosis. These findings highlight the importance of understanding the relationship between HLA alleles and BC susceptibility in different populations (Gun et al., 2012).

Speaking of the significance of HLA profile and some deadly fatal diseases, it is considerably well identified and known that the genetic landscape of Indonesia is characterized by a unique blend of influences from its geographical position and historical migration patterns. The HLA profile of the Indonesian population is remarkably similar to that of its South East Asian neighbors, with high frequency variations in HLA-B*15:02 and HLA-DRB1*12:02 being particularly notable among the Javanese, Moluccans, and Nusa Tenggara populations (Sanchez-Mazas et al., 2005). However, it is essential to note that not all Indonesian populations have been comprehensively typed for HLA variation, with the majority of studies focusing on West Javanese (Yuliwulandari et al., 2009, 2024).

Despite this limited scope, research has revealed that certain populations, such as the Yogyakarta and Mollucan people, exhibit distinct HLA profiles that differ from those found in other countries. For instance, the Yogyakarta population is characterized by a high frequency of DQA1*06:01, DQB1*03:01, and DRB1*12:02 alleles (X. Gao & Matheson, 1996), while Western Javanese individuals tend to have a higher frequency of HLA-A*2407 alleles (Yuliwulandari et al., 2009). These findings suggest that Indonesia has a unique genetic diversity that is shaped by its complex migration history (Pradana et al., 2020).

The genetic relationship between Indonesia and its neighboring countries is also noteworthy. A recent genome-wide association study (GWAS) revealed that Indonesia has a unique genetic diversity between different geographical regions. Furthermore, studies have shown that the closest ethnicity to the Indonesian population is the Malaysian and other South East Asian countries. This close genetic

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affinity is likely due to the shared migration history of these populations, with two distinct migration waves occurring in the region. The first wave of migration, which occurred around 40,000 years ago, involved the movement of people from the Indian subcontinent through the Indo-Malaysian archipelago. This group was later replaced by the Austronesian migration, which occurred around 6,000-5,000 years ago and led to the development of the Javanese culture in West Indonesia (Yuliwulandari et al., 2009, 2024).

The Indonesian population's specific HLA profile has yet to be thoroughly explored, particularly in the context of cancer development. However, a notable study by Zhao and colleagues in 2013 provides valuable insights into the relationship between *Helicobacter pylori* infection and carcinogenesis. Conducted in Mataram, Lombok, where the *H. pylori* infection rate stands at 11.2%, the study revealed a significant correlation between HLA-DQ variation and H. pylori susceptibility. Specifically, individuals carrying the DQB1*0401 genotype were found to be at higher risk of developing *H. pylori* infection compared to those with DQB1*0301 genotypes. In contrast, haplotypes of DQA1 or DQB1 did not demonstrate any association with *H. pylori* infection. The HLA class II molecules, comprising HLA-DP, HLA-DQ, and HLA-DR, play a crucial role in immune responses to pathogens, including bacteria and toxins. The study's findings may partly explain the low prevalence of *H. pylori* infection in Indonesia, which is consistent with previous reports from China. Moreover, the study highlights the importance of exploring other host factors, such as genetic polymorphisms and inflammatory cytokines, in addition to HLA-DQ genotypes. Notably, HLA-DQ genotypes have been linked to *H. pylori* infection and related diseases (Zhao et al., 2013). As H. pylori is a significant gastrointestinal pathogen associated with gastric cancer (Peek et al., 2000), it is reasonable to anticipate that HLA-DQ genotypes play a crucial role in carcinogenesis. While more comprehensive studies are

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needed to validate these findings across a broader range of Indonesian populations, the existing literature can guide our understanding of the importance of having a robust dataset on our own population.

2. HLA and Immunotherapy Responsiveness

The advent of checkpoint blockade immunotherapies has revolutionized the treatment of advanced-stage cancers, but only a minority of patients respond. A critical factor in determining immune checkpoint inhibitor (ICI) response is tumor mutational burden (TMB), which is a proxy for the number of tumor-derived neoantigens that can be presented on the cell surface by HLA molecules and subsequently recognized by cytotoxic T cells. Another genetic factor that determines ICI response is heterozygosity at the highly polymorphic HLA-I loci, which facilitates the presentation of a more diverse set of tumor antigens to T cells. The HLA-I genotype, consisting of a pair of alleles at each of the classic class I genes, exhibits marked interindividual variability in immunopeptidome diversity due to its peptide-binding properties and sequence divergence (Chowell et al., 2018).

Recent studies have shown that the HLA genotype shapes the landscape of oncogenic mutations observed in tumors, and that somatic loss of HLA-I is one possible mechanism by which tumors evade immune control (Chowell et al., 2018; Marty et al., 2017; McGranahan et al., 2017; Rosenthal et al., 2019). Motivated by these findings altogether, Chowell and colleagues hypothesized that the effect of HLA-I heterozygosity on response to ICIs may be modulated by the amount of sequence divergence between the peptide-binding domains of patient HLA-I alleles. They calculated the heterozygote advantage (HED) using HLA-I genotypes across multiple cohorts of patients with metastatic melanoma or non-small-cell lung cancer (NSCLC) treated with anti-CTLA-4 or anti-PD-1/-PD-L1 and showed that patients with high mean HED had improved overall survival after ICIs, with an independent effect of HED on survival

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when controlling for TMB and other genomic and clinical variables (Chowell et al., 2018).

Furthermore, they found that HED was associated with improved survival after ICIs in fully heterozygous patients from multiple cohorts, including patients with melanoma and NSCLC. A combined analysis of all cohorts revealed a negative relationship between mean HED and hazard ratio, indicating that an increase in mean HED corresponds to improved overall survival. Beyond survival, clinical response to ICIs was also associated with high mean HED in both fully heterozygous and non-fully heterozygous patients. These findings suggested that HLA-I heterozygosity, particularly when accompanied by high sequence divergence, may be an important determinant of response to ICIs in cancer patients (Chowell et al., 2018) that further will offer a paradigm shift in the understanding of the complex interplay between genetic and immunological factors in determining patient outcomes. The identification of high HED patients, who are more likely to respond to ICIs, can enable targeted interventions and optimized treatment regimens. For instance, patients with high HED may be prioritized for ICIs, while those with low HED may be more likely to benefit from combination therapies or alternative treatment approaches.

Furthermore, the understanding of HLA-I heterozygosity as a determinant of ICI response can inform the development of novel strategies to anticipate and overcome treatment resistance. By recognizing that patients with low HED may be more prone to resistance, clinicians can proactively implement strategies to mitigate this risk, such as modifying treatment regimens or incorporating additional therapeutic agents (Chowell et al., 2018). Additionally, the identification of genetic markers associated with high HED can enable early detection and intervention, potentially leading to improved patient outcomes and reduced morbidity (Daull et al., 2022; Z. Lu et al., 2021). The incorporation of HLA-I genotyping into clinical

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practice can also facilitate more accurate patient stratification and risk assessment, ultimately enhancing the overall efficacy of cancer treatment (Dhall et al., 2023; Hazini et al., 2021).

3. HLA and Personalized Cancer Vaccines

Personalized cancer vaccines aim to harness the power of the immune system to target specific cancer cells. These vaccines are designed to use a patient's HLA molecules to present tumor-specific antigens, stimulating a targeted immune response. HLA diversity can influence the effectiveness of personalized cancer vaccines, as patients with less diverse HLA profiles may have a limited repertoire of antigens that their immune system can recognize and attack(C. Wang et al., 2020; N. Xie et al., 2023).

The development of epitope-prediction methods has been marked by significant advancements in HLA class I-binding epitopes, with HLA class II-binding epitope prediction still in its infancy. The HLA class I peptide-binding groove has closed ends, which limits the presentation of peptides to CD8+ T cells. In contrast, the HLA class II peptide-binding groove has open ends, allowing for the binding and presentation of peptides of longer and more variable lengths. This complexity has led to the development of novel approaches to predict immunogenic HLA class II epitopes, such as the use of long peptides that encompass predicted HLA class I-binding CD8+ T cell epitopes (Andreatta et al., 2015; Bijker et al., 2007).

The incorporation of HLA-II profiling into neoantigen vaccine design is crucial for the development of personalized treatment strategies. Recent advances in HLA-II prediction have enabled the identification of HLA class II-presented epitopes, which can stimulate CD4+ T cell responses and promote antitumor immunity. The creation of a mono-allelic HLA expression system, known as mono-allelic purification with tagged allele construct (MAPTAC), has enabled the training of machine learning-based prediction algorithms to identify HLA class II-presented epitopes (Abelin et

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al., 2019). Furthermore, the update of the HLA class II-binding epitope-prediction algorithm NetHLA classIIpan has improved its ability to predict immunogenic HLA class II epitopes (Reynisson et al., 2020).

The incorporation of HLA-II profiling into neoantigen vaccine design is critical for optimizing the immunogenicity of neoantigen-based therapies. Additional factors, such as gene expression, RNA splicing, and proteosomal processing, can affect the ultimate immunogenicity of predicted epitopes. Moreover, neoantigen sequences with similarity to pathogen-derived epitopes can exhibit enhanced immunogenicity. A better understanding of these factors will enable the design of more effective therapeutic T cell vaccines (Blass & Ott, 2021).

In addition to computational approaches, tumour lysates can be used to induce neoantigen-specific immune responses. Autologous APCs, typically DCs, can be isolated from the patient and exposed to tumour lysates *ex vivo*, before being injected back into the patient with the aim of stimulating an immune response to TAAs or neoantigens (Harari et al., 2020). This approach circumvents the sequencing and computational analysis required for the identification of patient-specific neoantigens. Recent studies have demonstrated that tumour-lysate-based vaccine therapies can induce antitumour T cell responses, including neoantigen-specific CD8+ T cell responses. Therefore, the use of tumour-lysate-based approaches and/or antigen delivery via APCs merits further exploration (Tanyi et al., 2018).

Hitherto, the development of cancer vaccines has gained significant momentum in recent years, as researchers strive to harness the power of natural immunity to combat the disease. Therapeutic cancer vaccines, in particular, offer a promising approach due to their safety profile, specificity, and ability to elicit enduring immune memory (Antonarelli et al., 2021). The surge in early-stage clinical trials globally underscores the growing excitement around this field. However, significant challenges remain, including the complexity

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of identifying immunogenic neo-antigens, the intricacies of rapid manufacturing, and the difficulties of detecting clinically meaningful immune responses. Despite these hurdles, researchers are making progress, refining their approaches and leveraging advances in technology to overcome these obstacles (Fan et al., 2023).

One key area of focus is the identification of highly immunogenic neoantigens, made possible by the rapid progress in next-generation sequencing and computing power. Researchers are also exploring innovative vaccine technologies, including diverse expression formats, improved co-stimulation components, and prime-boost approaches. The selection of an optimal delivery system is critical to amplify antigen immunogenicity and facilitate the entry of the antigen and activation signal into APCs (Fan et al., 2023).

Ultimately, the goal of cancer vaccine research is to establish a tumor-specific cytotoxic T cell response that can effectively stimulate durable immunity in patients with cancer and prolong their survival. The convergence of innovative approaches, strategic candidate selection, and refined administration protocols holds the potential to revolutionize cancer treatment, paving the way for a new era of therapeutic cancer vaccines. As research continues to advance, we can expect to see the emergence of numerous effective therapeutic cancer vaccines (Bradford, 2024; Fan et al., 2023).

4. HLA and Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is a potentially curative treatment for some blood cancers and hematologic malignancies (Appelbaum, 1997; Bair et al., 2020). The success of this treatment depends on the compatibility between the donor's and recipient's HLA molecules, as mismatches can lead to graft-versus-host disease (GVHD) and reduced treatment efficacy. HLA diversity across different populations can impact the availability of suitable donors for patients in need of allogeneic transplantation (Petersdorf, 2017; C. Sweeney & Vyas, 2019).

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Indonesia has made significant progress in the field of transplantation, particularly in the context of cancer treatment. The country's first allogeneic and autologous bone marrow transplants (BMTs) were performed in 1987, marking the beginning of its involvement in BMT services. Since then, several hospitals have established their own BMT programs, including Dr. Kariadi General Hospital in Semarang, which has been a pioneer in the field (Santosa et al., 2021).

In 2012, Dr. Kariadi Hospital committed to establishing a modern BMT program, which involved developing a road map for BMT services, formalizing international partnerships, and increasing human resources capacity. The hospital's team has made significant strides in recent years, including performing 16 hematopoietic stem cell transplants (HSCTs) between 2012 and 2018 (Santosa et al., 2021).

The hospital's BMT program is led by a multidisciplinary team of experts, including hematologists, medical oncologists, dentists, cardiologists, pulmonologists, clinical pathologists, clinical microbiologists, infectious-disease specialists, psychologists, and psychiatrists. The team has developed a comprehensive approach to BMT, including cryopreservation of stem cells, and has implemented measures to ensure the safety and efficacy of the procedure (Santosa et al., 2021).

The hospital's BMT program has also been recognized for its commitment to quality and patient safety. The program has been accredited by international organizations and has received support from nonprofit organizations, including the Hematology and Thalassemia Foundation and the Indonesian Cancer Foundation (Santosa et al., 2021).

Despite the progress made, there are still challenges that need to be addressed. The hospital's BMT program faces financial constraints, which limit its ability to provide services to patients who

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need them. To address this challenge, the hospital is working with the Ministry of Health to improve access to healthcare services and resolve financial constraints (Santosa et al., 2021).

Another story in regard with the transplantation is the introduction of pediatric liver transplantation (LT) in Indonesia in 2006 that marked a significant milestone in the country's healthcare sector. Collaborating with Japanese experts, the program has made remarkable progress over the past four years, providing hope for those in need of LT. Currently, five hospitals in Indonesia have performed pediatric LT, with two active centers - Dr. Cipto Mangunkusumo Hospital (CMH) and Dr. Sardjito General Hospital. CMH, located in Jakarta, has been a pioneer in pediatric LT, performing its first living donor liver transplant (LDLT) in 2010 in collaboration with Zhejiang University, China (Oswari et al., 2020).

However, the program's progress was slow between 2010 and 2014, with only three transplants performed due to strict recipient selection criteria. The hospital only accepted recipients weighing over 10 kg during this period. In 2015, CMH began collaborating with the National Centre for Child Health and Development, Japan, led by Prof. Mureo Kasahara, which led to a significant increase in the number of LTs performed (Oswari et al., 2020).

Between 2010 and 2018, CMH had performed 45 pediatric LDLTs, with all donors being relatives, mostly parents. The hospital's team conducts thorough psychiatric and psychosocial assessments of potential donors before proceeding with the medical evaluation. The 1-year graft survival rate in 2018 was 88.9%, comparable to outcomes reported by the Japan Transplantation Society (Kasahara et al., 2013) and data from the United States (Venick et al., 2018).

The hospital's experience with pediatric LT has also highlighted challenges faced by patients in Indonesia, including delays in referral, severe malnutrition, and pre-existing infections. These factors can significantly impact patient outcomes and survival rates (Oswari et al., 2020).

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In terms of immunosuppression, the hospital faces challenges due to limited availability of immunosuppressants in the country. Despite these challenges, the team has made efforts to develop tailored immunosuppression regimens for patients (Oswari et al., 2020).

Indonesia's liver transplantation (LT) program has exclusively relied on living liver donors (LLDs) to date. Despite official approvals from religious and governmental authorities, deceased donor LT (DDLT) has not yet gained traction as a preferred source of donor organs (Jasirwan et al., 2020). This may be attributed to the lack of a comprehensive donor registration system, as well as limited public awareness of the LT program (A. N. L. Lalisang et al., 2023) .

Consequently, the only viable procedure in Indonesia has been LDLT, with its associated demands on transplant team skills, facility infrastructure, and material support. However, there is a significant knowledge gap regarding the characteristics of LLDs in Indonesia (A. N. L. Lalisang et al., 2023).

Gaining insights into the backgrounds and experiences of donors is crucial for several reasons. Firstly, it enables the development of a more effective LDLT program, which can inform policymaking at the government level. Secondly, it assists the national transplantation committee in creating national guidelines for donor selection criteria. Finally, it provides support to other centers seeking to establish their own transplantation services (A. N. L. Lalisang et al., 2023).

E. CULTURAL AND LANGUAGE BARRIERS

A culturally competent strategy that takes into account the language demands and cultural beliefs of the patients is necessary to address cultural and linguistic hurdles in cancer therapy (Khatri & Assefa, 2022; Nair & Adetayo, 2019). This entails hiring community health workers or patient navigators from a variety of backgrounds, provid-

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ing culturally competent training for healthcare professionals, and providing language interpretation services in addition to culturally appropriate educational materials. Healthcare systems can lower gaps in cancer treatment results and raise the standard of care for all patients, irrespective of their language or cultural background, by removing these obstacles (M. I. Patel et al., 2020; Ringborg et al., 2024).

To foster inclusive research, healthcare professionals and stakeholders must cultivate meaningful and enduring partnerships with diverse entities, including private and public organizations, academic and community practices, patients, caregivers, advocacy groups, and other organizations. This collaborative approach necessitates a profound understanding of the existing barriers to research participation in underrepresented communities and populations. To address this issue, innovative strategies have been developed, such as multimedia consent methods that incorporate concise text blocks, visual icons, and videos on smartphone-optimized Web interfaces, designed to be more accessible to participants from diverse cultural and linguistic backgrounds (Winkfield et al., 2017). The use of social media and patient-centered recruitment messaging has also gained popularity in recruiting patients for clinical research who may have traditionally been underrepresented. Furthermore, patient navigation, community health worker-led initiatives, and partnerships with community and advocacy organizations have been instrumental in improving inclusion in research. These efforts can help overcome well-known barriers to participation, such as transportation and childcare challenges (M. I. Patel et al., 2020).

To achieve these goals, it is essential to incorporate a range of strategies into research recruitment and retention efforts. Organizations must also provide and sustain research funding and infrastructure support to facilitate the attainment of equitable participant representation. Moreover, it is crucial to empower clinicians and stakeholders to achieve diverse representation in research through

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initiatives such as meetings and symposia (American Society of Clinical Oncology, 2017). To achieve the recommendations outlined in this section, a high-quality data management infrastructure is also necessary to support research activities, broaden the inclusion criteria of clinical trials, address financial barriers to participation, and promote access to research in underrepresented areas (M. I. Patel et al., 2020).

F. HEALTH LITERACY

Health literacy is a crucial concept that enables individuals to navigate the complex healthcare system, make informed decisions about their health, and access necessary services. It is not just about having knowledge, but also about possessing the skills and abilities to apply that knowledge. For instance, being able to critically evaluate health information, communicate effectively with healthcare providers, and navigate the system to access appropriate services (Coughlin et al., 2022).

Unfortunately, limited health literacy is a significant issue in the United States, with over one-third of adults struggling to access and utilize healthcare services. This has been linked to poor health outcomes, including poor self-management of chronic conditions, increased hospitalizations, and higher rates of mortality. Moreover, individuals with lower health literacy skills are at greater risk of developing long-term life-limiting health conditions and face more difficulty managing their medications (Coughlin et al., 2022).

The issue of poor health literacy is particularly concerning in the context of cancer diagnosis and treatment. Patients who lack health literacy may neglect their initial symptoms, leading to delayed diagnoses and suboptimal treatment outcomes. This is often attributed to a lack of understanding of their condition, as well as a lack of knowledge about treatment options and how to manage their care (PRAKARSA, 2023).

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In the case of head and neck cancer and oral cancer, studies have shown that patients' behavioral patterns play a significant role in delayed diagnoses and suboptimal treatment outcomes. For instance, patients may neglect seeking medical attention until their condition has deteriorated significantly due to a lack of understanding of their symptoms and the importance of seeking medical attention (Goy et al., 2009).

Upon arriving at health facilities, patients may encounter various barriers to optimal care, including inadequate hospital services, lack of transparency regarding treatment stages and referral procedures, and limited information provision. These challenges can hinder patients' ability to navigate the healthcare system effectively and make informed decisions about their treatment (PRAKARSA, 2023).

In addition to these challenges, patients may also face various forms of support during their care journey, including support from caregivers, family, and extended family networks, as well as community support and information from third-party sources. These forms of support can take various forms, including psychological support, practical assistance, financial support, material aid, and access to information about treatment options (PRAKARSA, 2023).

Interestingly, smoking, sedentary lifestyles, and inadequate consumption of fruits and vegetables are associated with low levels of health literacy. Low health literacy is also linked to misperceptions about cancer, a decrease in information seeking, and a decrease in the sense of control over cancer risks. Furthermore, there is a negative correlation between cancer fatalistic attitudes and cancer-related health literacy (Fernandez et al., 2016; von Wagner 2007) (Kobayashi et al., 2016; Gansler et al., 2005).

To address these issues, it is crucial to educate patients in order to increase their health literacy. Language comprehension skills are correlated with health literacy, particularly for patients who are mi-

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grants or are abroad. By empowering patients with knowledge and skills, we can improve their ability to understand their treatment options and adhere to treatment plans (Morris et al., 2013).

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CHAPTER VI
THE BIOLOGY OF LESS SURVIVED CANCERS

Numerous studies conducted in affluent nations have demonstrated consistent advancements in cancer survival rates over the last twenty years (Bütepage et al., 2022; Coleman et al., 2011; De Angelis et al., 2014; Stenbeck et al., 1995). Despite these improvements, disparities in survival rates among countries have remained a constant issue across various types of cancer, persisting to varying degrees. These variations have been viewed as indicators of the progress made in cancer treatment services, prompting policy revisions on a global scale. However, it is vital to evaluate the effectiveness of evolving cancer control strategies not only based on the enhancements in survival rates but also by considering trends in cancer incidence and mortality. This approach can provide valuable insights into the underlying biological, epidemiological, and clinical factors at play (Arnold et al., 2019).

Comparing international disparities in cancer survival rates is a complex task due to the multitude of potential factors that could contribute to these differences. Beyond variables like stage of diag-

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nosis and treatment methods that directly impact patient outcomes, other factors such as variations in cancer registration and classification practices can also influence survival rates. Moreover, disparities at the national and regional levels in aspects related to healthcare systems, cancer policies, and clinical procedures can play significant roles. Therefore, it is believed that public awareness and perceptions about cancer have minimal influence on the disparities in survival rates across countries (Arnold et al., 2019).

In Indonesia, efforts to manage and integrate data have been robust, but the overall data management practices in the country remain lacking. This has hindered the ability to effectively demonstrate the overall survival rate of Indonesian cancer patients. Furthermore, existing reports tend to focus on specific types of cancer and are often based on observations from different tiers of hospitals of public health facilities in the country (Deanasa et al., 2022; S. Gondhowiardjo et al., 2023; Labeda et al., 2022). This fragmented approach makes it difficult to consolidate the data and draw comprehensive conclusions about the nation's overall survival status. At a glance, the characteristics of Indonesian patient cohorts reveal a stark disparity in survival rates, with a significantly lower outcome compared to those reported in developed countries. The prognosis for Indonesian patients with cancer is poorer than that of their counterparts in developed nations (Deanasa et al., 2022; Sinaga et al., 2018).

In Indonesia, the mortality rates for certain types of cancer are significantly higher than their other counterparts, including lung, colorectal, and liver cancers have the highest mortality rates across all sexes (Globocan, 2020). The biology of these three will be elaborated in this Chapter to better understand their underlying causes.

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A. LUNG CANCER

Lung cancer is especially noticeable in smokers and people who have been exposed to both indoor and outdoor air pollution (C. Li et al., 2023; Y. Liu et al., 2023). This remarkably high smoking prevalence highlights the tremendous threat that lung cancer poses to Indonesia. Most Indonesians now consider smoking to be an integral part of their social and cultural lives (D. A. Ayuningtyas et al., 2021).

The proportion of tobacco-smoking men in Indonesia has skyrocketed, from 56.2% in 2000 to 76.2% in 2015. Indonesia lacks tobacco market-related policies as one of the nations that has not ratified the WHO Framework Convention on Tobacco Control (WHO FCTC). When considered collectively, these facts suggest that Indonesia has a major impact on the global incidence of tobacco-related illness(Holipah et al., 2020).

Around 69 million individuals in Indonesia smoke regularly, making it one of the nations with the largest percentage of smokers worldwide according to recent polls. Since 230 000 children under the age of ten and three million (9.1%) of children between the ages of ten and eighteen smoke habitually, concerns have been raised on the number of youngsters who smoke in Indonesia (Meilissa et al., 2022; Susilowati, 2010).

Lung cancer has been the leading cause of mortality for the past ten years, according to statistics from the Indonesian Social Insurance Administration Organization in 2016. Cancer is the second most prevalent health-care burden (Mahendradhata et al., 2017). With 34 783 new cases recorded in 2020, lung cancer accounted for 14.1% of all new cancer cases in Indonesian men of all ages, making it the most common disease to be diagnosed in men (Puspitaningtyas et al., 2021). Lung cancer incidence in men was predicted to be 19.4 per 100 000 persons. With 13.2% of all fatalities (or 30 843 deaths) due to cancer, lung cancer remains the most common

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cause of cancer-related mortality(International Agency for Research on Cancer (IARC), 2020). Furthermore, it was estimated that up to 64% of students who responded to the 2022 Outlook Data for Indonesian Student Smokers had parents who smoke (Aranditio, 2023). Lung cancer cases in Indonesia rank third (8.8%) among new cancer cases worldwide, behind breast cancer (16.6%) and cervical cancer (9.2%), according to GLOBOCAN 2020 data. Among men, lung cancer accounts for 14.1% of all cancer cases. With risks up to twenty times higher, smoking is still the leading cause of lung cancer(WHO, 2020).

Approximately 1 billion individuals worldwide—153 million women and 847 million men—used tobacco products in 2019. Of these tobacco smokers, 25 million were youths between the ages of 13 and 15. There are the greatest numbers of smokers in the Western Pacific Region (WPRO) and Southeast Asia Region (SEARO), with roughly 4.7 million and 6.4 million smokers, respectively. Indonesia is a major contributor to the region's number of smokers. According to a poll conducted by the Indonesia Ministry of Health (IMoH), the percentage of youths aged 10 to 18 who smoke has climbed from 7.2% in 2013 to 9.1% in 2018. The Global Youth Tobacco Survey (GYTS) conducted in Indonesia in 2019 revealed an even greater smoking prevalence of 19.2%. This fell well short of the government's 2019 goal of bringing the percentage of youth and teenage smokers down to 5.4%. The National Regulation No. 109 of 2012 (PP 109/2012) change has been processed by the Ministry of Health Republic Indonesia since 2018. The amended version addressed several issues, including the tobacco advertisement, promotion, and sponsorship (TAPS) restriction. Unfortunately, the amendment process was a mess, and in 2021 it was revoked (Megatsari et al., 2023).

The International Agency for Research on Cancer (IARC) has identified cigarette smoke as a complex mixture of over 7,000 compounds, with approximately 50 of these compounds proven to

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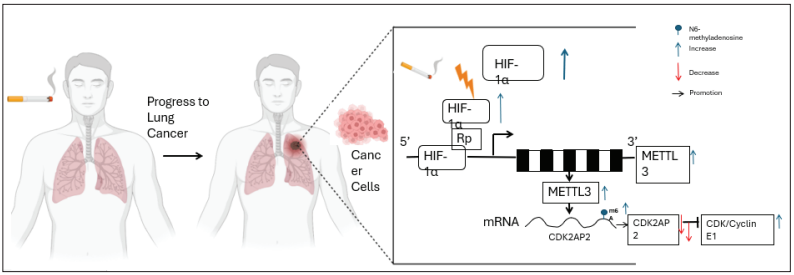
be carcinogenic. During the combustion process, tobacco smoke is comprised of various gaseous products and suspended particles (Omare et al., 2022). In 1997, Hoffmann published a seminal report on the composition of cigarettes and the changes in the composition of cigarette smoke, providing a detailed summary of the carcinogens present in cigarette smoke. The "Hoffmann analytes" are widely recognized by regulators worldwide as relevant to smoking-related diseases and comprise 82 substances deemed harmful. This list includes various substances such as PAHs, aromatic amines, N-nitrosamines, phenols, low-boiling point carbonyl compounds, and heterocyclic aromatic amines (Hoffmann et al., 1997). The IARC has thoroughly evaluated the well-documented risks to humans posed by 86 carcinogens found in cigarette smoke (T. Zeng et al., 2023).

Since the 1950s, the composition of cigarettes and cigarette smoke has undergone a significant transformation. In the United States, the average "tar" and nicotine yields of cigarettes have decreased dramatically. By 1992, these levels had dropped to 12 mg and 0.95 mg, respectively, from a peak of 38 mg and 2.7 mg in 1954. A similar trend was observed in the United Kingdom, where the decline was from approximately 32 mg "tar" and 2.2 mg nicotine to less than 12 mg "tar" and 1.0 mg nicotine per cigarette. The reduction in smoke yields was largely achieved through the introduction of filter tips, tobacco type selection, and the use of highly porous cigarette paper (Hoffmann & Hoffmann, 1997).

In addition, reconstituted tobacco, opened and cut ribs, and "expanded tobacco" were incorporated into the tobacco blend. This shift has also been accompanied by an increase in nitrate content in cigarette tobacco, particularly in countries where burley tobacco is used. In the United States, nitrate levels rose from 0.3-0.5% to 0.6-1.35%, enhancing tobacco combustion. While complete combustion reduces carcinogenic PAH, it also increases the generation of nitrogen oxides, which can form carcinogenic N-nitrosamines,

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such as tobacco-specific nitrosamines (TSNA) (Hoffmann & Hoffmann, 1997).



Source: Modified from (Y. Yang et al. 2023).

Figure 6.1 Cigarette smoking (CS) promotes NSCLC cell proliferation which leads to the progression of NSCLC

Researchers found that cigarette smoke exposure increased the proliferation of NSCLC cells, which was associated with cell cycle disturbances and the upregulation of specific proteins with m6A modification being the key player in the progression. The enzyme METTL3, which regulates m^{6}A modification, was elevated in NSCLC tissues of smokers. In contrast, downregulating METTL3 reduced the proliferation of NSCLC cells thus inhibited their ability to form colonies and migrate. In addition to this, the transcription factor HIF-1α, which is regulated by cigarette smoke, activated the transcription of METTL3, leading to increased m6A modification. It was revealed that HIF-1α was positively correlated with METTL3 levels in NSCLC tissues and that HIF-1α binding to the METTL3 promoter region was essential for its transcription. The study also identified a novel target gene, CDK2AP2, which was found to be downregulated in NSCLC cells. CDK2AP2 is a key regulator of the cell cycle G1/S transition, and its downregulation may contribute to the uncontrolled growth of tumor cells (Y. Yang et al., 2023). Overall, the study suggests that cigarette smoke play a critical role in the development and progression of NSCLC through the regulation

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of key cellular pathways. The findings highlight the importance of targeting these pathways in the development of effective therapies for this disease (Y. Yang et al., 2023).

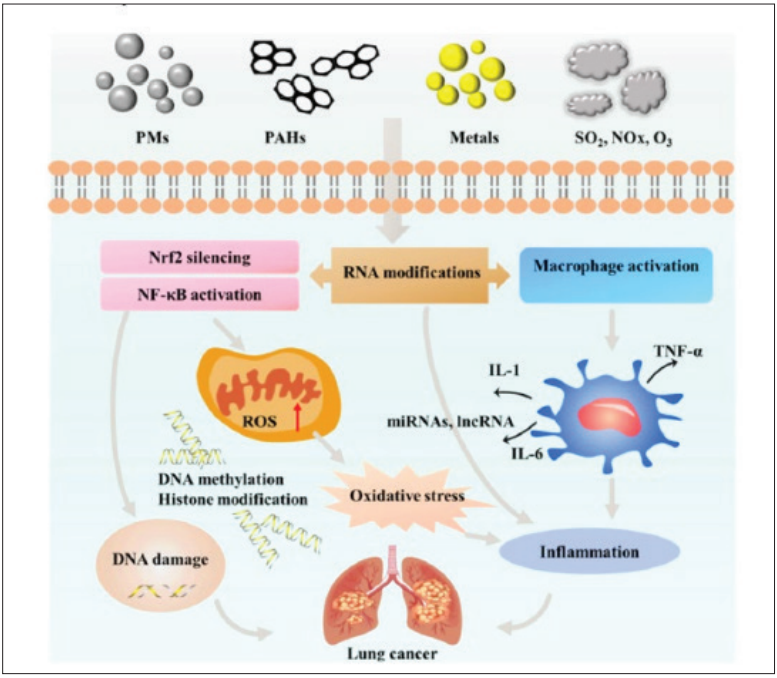
Indonesia's commitment to public health is often touted, but its failure to sign the Framework Convention on Tobacco Control (FCTC) raises concerns about its dedication to this cause. Despite the overwhelming majority of countries having ratified the FCTC, Indonesia remains one of only nine nations that have not taken this step. However, the government has implemented two key principles of the FCTC, namely, excise policy and pictorial health warnings, which are aimed at reducing cigarette consumption. The third principle, harm reduction, remains unaddressed (Audrine, 2020).

Indonesia's approach to reducing tobacco consumption has primarily been through regulatory measures and public awareness campaigns. The Health Law No. 23/1992 established the framework for regulating tobacco products, followed by subsequent government regulations that set standards for nicotine content, advertising, and production. These regulations were later revised and expanded to address specific concerns about tobacco use (Audrine, 2020).

In recent years, Indonesia has taken steps to strengthen its tobacco control measures. Health Law No. 36/2009 revised the 1992 law to focus on the impact of tobacco on public health. The law mandates restrictions on addictive substances, including tobacco products, and requires health warnings and smoke-free areas in various public spaces. Additionally, the government has enacted regulations to control the handling of materials containing addictive substances (Audrine, 2020).

The government's efforts to regulate tobacco products are crucial in reducing the negative impact of smoking on public health. However, more needs to be done to ensure that Indonesia's policies align with international standards and effectively address the nation's tobacco-related problems (Audrine, 2020).

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Source: Adapted from (Kusumawardani, Indraswari, and Komalasari 2023).
Figure 6.2 Mechanism of air pollution as a cause of lung cancer. Adapted from Kusumawardani et al (2023).

Lung cancer development and progression are heavily linked to exposure to air pollution. Several mechanisms are thought to contribute to this relationship, including the accumulation of oxidative stress, DNA damage, inflammation, alterations in metabolism, epigenetic changes, and disruptions to signal transduction pathways (Fig.6.2) (Kusumawardani et al., 2023).

Previous studies have investigated the impact of particulate matter $(PM)_{2.5}$ and PM_{10} on gene expression profiles. Despite differences in cell types, microarray platforms, and PM sources and doses, these studies consistently identified commonalities in the expression of genes and pathways involved in xenobiotic metabolism,

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immune response, inflammation, and oxidative stress (Gualtieri et al., 2012; Y.-C. T. Huang, 2013; H. Sun et al., 2012). Liu and colleagues in 2015 published a report which was in support of the aforementioned findings. They examined the effects of $PM_{2.5}$ on gene expression in human bronchial epithelial cells (HBE cells) and identified 13 protein-coding genes with significant changes in expression. These genes were primarily involved in xenobiotic metabolism and immunoregulatory or inflammatory pathways. In addition to protein-coding genes, they found aberrant expression of 138 microRNAs (miRNAs) in HBE cells exposed to $PM_{2.5}$. They identified miR-182 and miR-185 as target regulators of SLC30A1, SERPINB2, and AKR1C1, which are potential oncogenes. These genes have been shown to induce neoplastic transformation in NIH3T3 cells and are overexpressed in human lung cancer. Furthermore, they observed reduced levels of plasma miR-182 and miR-185 in human subjects exposed to high levels of $PM_{2.5}$ compared to those exposed to low levels of $PM_{2.5}$ (C. Liu et al., 2015). SLC30A1 is a zinc transporter that regulates intracellular zinc homeostasis. Overexpression of SLC30A1 may disrupt zinc homeostasis, leading to cell neoplastic transformation. SERPINB2 is a plasminogen activator inhibitor that is commonly expressed in many types of human cancer, including lung cancer. Their findings suggest that SERPINB2 can be induced by $PM_{2.5}$ and ectopic expression of this gene is implicated in neoplastic transformation in NIH3T3 cells. AKR1C1 is a member of the aldo/keto reductase superfamily that catalyzes the conversion of aldehydes and ketones to generate their corresponding alcohols. A previous study has shown that AKR1C1 and AKR1A1 play a crucial role in the metabolic activation of polycyclic aromatic hydrocarbons, a major component of PM2.5, which may contribute to the development of lung cancer (Penning, 2014). Additionally, studies have demonstrated that the AKR1C family, including AKR1C1, can induce neoplastic transformation in NIH3T3 cells, which is consis-

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tent with our findings. However, they were unable to induce tumor formation in nude mice with transformed NIH3T3 cells (Chien et al., 2009).

An analysis of SLC30A1, SERPINB2, and AKR1C1 levels in human lung cancer tissues from the TCGA database revealed aberrant expression of these genes in lung cancer compared to normal tissues. While these findings do not provide direct evidence that the aberrant expression of these genes is caused by $PM_{2.5}$ exposure, they do suggest a role for these genes in the development of lung cancer. Furthermore, it was also observed that the aberrant expression of these genes differs between lung adenocarcinoma and squamous cell carcinoma, suggesting that they may function differently in the carcinogenesis of different lung cancer subtypes (C. Liu et al., 2015).

Other than PM, polycyclic aromatic hydrocarbons (PAH) are also well identified as pulmonary carcinogenesis inducers. It involves multiple mechanisms. One such mechanism involves the activation of Cytochrome p450, family 1, subfamily A, polypeptide 1 (CYP1A1)/CYP1B1 enzymes, which form DNA adducts on key gene sequences, including p53, leading to the formation of lung tumors. In contrast, CYP1A2 is upregulated by PAH exposure, but its role in carcinogenesis is paradoxical, as it can also exhibit a protective effect. Moreover, PAH exposure induces epigenetic changes, including DNA methylation and non-coding RNA modifications, such as microRNA (miRNA) expression. These epigenetic alterations can lead to the downregulation of tumor suppressor genes, thereby promoting pulmonary tumorigenesis. Non-coding enzymes can also exhibit a protective effect by inhibiting oncogene expression and preventing tumor formation. Furthermore, PAH exposure has been linked to the activation of long interspersed nuclear elements (LINE), which can lead to genetic instability and tumor development. Additionally, histone modification induced by PAH exposure can result in proteins that promote DNA damage and inflammation. The histone modi-

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fication also contributes to pulmonary carcinogenesis by inducing the transcription of CYP1A1 and further exacerbating DNA adduct formation (Stading et al., 2021).

The occurrence of lung cancer in non-smokers remains a significant concern, as established environmental risk factors cannot be definitively linked to the majority of cases. This underscores the need for further epidemiological research to identify the underlying causes (Couraud et al., 2012). A crucial step in this direction is to investigate the role of heavy metals, such as arsenic (As), cadmium (Cd), chromium (Cr), and nickel (Ni), which have been implicated in the development of lung cancer (N.-W. Lee et al., 2022).

Cadmium (Cd), a ubiquitous environmental pollutant, is a potent carcinogen that can cause significant harm to humans. Exposure to Cd can occur through contaminated food or water, tobacco smoke, or polluted air (World Health Organization, 2010). Once ingested or inhaled, Cd can increase oxidative stress and stimulate the production of inflammatory cytokines (Navas-Acien et al., 2004). The potential carcinogenic effects of Cd are further underscored by its ability to modulate gene expression and signal transduction pathways (World Health Organization, 2010).

Cd has been observed to disrupt the DNA repair process, which is crucial for maintaining genomic integrity. Specifically, it appears to target proteins that contain zinc-binding structures, which are essential for the functioning of DNA repair proteins such as XPA, PARP-1, and p53. The exact mechanisms by which cadmium interacts with these proteins are not yet fully understood, but it is possible that it displaces zinc or reacts with thiol groups involved in zinc complexation or other critical positions (Hartwig, 2013).

In addition, Cd may also interfere with cellular redox regulation, potentially leading to an imbalance in reactive oxygen species (ROS) or altering the signaling pathways that rely on thiol groups. The combination of these mechanisms may contribute to a high

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degree of genomic instability in cells that have adapted to cadmium exposure, which is relevant not only for tumor initiation but also for later stages of tumor development (Hartwig, 2013).

The alarming rates of arsenic-induced lung cancer have sparked a surge of research into the underlying mechanisms of arsenic carcinogenicity (Ebert et al., 2011). A crucial aspect of this process is the biotransformation of arsenic, which leads to the formation of methylated conjugates and reactive oxygen species (ROS). This transformation plays a pivotal role in both genetic and epigenetic changes that contribute to carcinogenicity (D. J. Thomas et al., 2001). The competition for methyl groups between arsenic detoxification enzymes and DNA methyltransferases (DMTs) further exacerbates epigenetic abnormalities. Moreover, arsenic species directly modulate several oncogenic pathways, including EGFR, PI3K/AKT, and NRF2/KEAP1, which possess actionable targets for therapy in lung cancer (Hubaux et al., 2013).

Recent studies have shed light on the molecular mechanisms governing arsenic-related lung tumorigenesis. A comprehensive analysis of arsenic-related tumors and cell models at both genetic and epigenetic levels has revealed distinct characteristics that distinguish these tumors from other forms of lung cancer. Furthermore, the anti-tumoral effects of As2O3 in the treatment of acute promyelocytic leukemia (APL) provide valuable insights into the molecular effects of arsenic on the human body. In light of these findings, it is essential to deepen our understanding of the molecular mechanisms underlying arsenic-induced lung cancer. By doing so, we can uncover novel therapeutic targets and develop effective strategies to prevent and mitigate the toxic effects of arsenic exposure, particularly among populations chronically exposed to this hazardous substance (Hubaux et al., 2013).

Chromium is a ubiquitous element in the environment, existing in two distinct valence states: trivalent chromium (Cr III) and hexavalent chromium (Cr VI). Human exposure to this element can

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occur through both natural and industrial sources. While chromium III is remarkably less toxic than its hexavalent counterpart, both forms have been shown to pose significant health risks. Specifically, chromium III has been found to target the respiratory tract, leading to toxic effects similar to those caused by chromium VI. Interestingly, Cr III is an essential element for humans, whereas Cr VI is not. The body's ability to detoxify some amount of chromium VI into Cr III provides a glimmer of hope for mitigating the toxic effects of the former. Moreover, an overwhelming body of evidence has established that inhaled chromium VI is a proven human carcinogen, significantly increasing the risk of lung cancer (Rollinson, 1973; Yatera et al., 2018).

The carcinogenic properties of Cr VI have been extensively studied, with numerous studies demonstrating its mutagenic and genotoxic potential. *In vitro* assays have consistently shown Cr VI to be one of the most active agents in inducing genetic mutations and chromosomal damage. The element's ability to form adducts with DNA, including DNA-protein cross-links and cross-links with amino acids, underscores its potential to disrupt cellular processes (DesMarias & Costa, 2019).

Moreover, Cr VI has been shown to induce chromosomal damage, and the formation of oxidized DNA adducts, further supporting its role as a carcinogen. While the mutagenic effects of Cr VI are well-established, recent studies have also highlighted its potential to alter epigenetic programs and gene expression, which may contribute to its carcinogenic properties (DesMarias & Costa, 2019).

In addition to its mutagenic effects, Cr VI has been linked to changes in gene expression that reflect its toxic action. For example, it has been shown to activate antioxidant pathways, such as the Nrf2 pathway, which may play a role in its carcinogenicity. Furthermore, exposure to Cr VI has been linked to inactivation of DNA mismatch repair mechanisms, which may also contribute to its carcinogenic

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potential (DesMarias & Costa, 2019).

In contrast, industry-funded studies have sought to demonstrate a non-mutagenic mode of action for Cr VI. These studies have proposed alternative mechanisms for its carcinogenic effects, such as enhanced cell proliferation and non-mutagenic gene expression changes. However, these findings have been disputed by many experts in the field, who argue that the evidence for Cr VI's mutagenic effects is overwhelming and that there is no safe threshold for exposure (Nickens et al., 2010; Risks, 2008).

Nickel, a non-essential metal, has been identified as a significant environmental concern due to its widespread use in various industries, including the production of coins, jewelry, and medical devices (Salnikow & Zhitkovich, 2008). While epidemiological studies have established the carcinogenic properties of nickel compounds, the underlying mechanisms of nickel-induced carcinogenesis remain unclear. Some studies suggest that structural alterations in chromatin and epigenetic changes may be the primary events leading to nickel-induced carcinogenesis (Doll et al., 1970; Fletcher et al., 1994; A. C. Miller et al., 2001).

One of the key findings is that nickel sulfide particles can selectively target heterochromatin, leading to the silencing of genes by inducing DNA methylation (Y. W. Lee et al., 1995). This phenomenon has been observed both *in vitro* and *in vivo* studies, where changes in DNA methylation have been linked to the inactivation of gene expression. The mechanism by which nickel induces DNA methylation is still unknown, but it is thought to involve the ability of nickel to substitute for magnesium in the phosphate backbone of DNA (Y. W. Lee et al., 1995).

In addition to DNA methylation, other epigenetic changes induced by nickel include the loss of histone acetylation and increases in histone ubiquitylation. These changes have been observed in various cell lines and are thought to play a crucial role in nickel-induced

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carcinogenesis. Furthermore, pretreatment with histone deacetylase inhibitors has been shown to inhibit the ability of nickel to induce cell transformation, suggesting that gene silencing mediated by histone modification may be a key mechanism in nickel-induced carcinogenesis (Broday et al., 2000; H. Chen et al., 2006; Karaczyn et al., 2005; Klein et al., 1991).

Recent studies have also highlighted the role of chromatin damage in nickel-induced carcinogenesis. Nickel ions have been shown to bind to specific motifs on histone H3 and H2A, potentially disrupting the structure and function of the nucleosome. This binding can lead to the formation of oxidative DNA damage via Fenton-like mechanisms, resulting in carcinogenicity (Kasprzak et al., 2003).

The carcinogenic properties of heavy metals such as chromium, cadmium, arsenic, and nickel have led to a widespread recognition of their potential risks to human health (Tchounwou et al., 2012). As a result, almost all nations have implemented strict regulations to restrict the use of these metals in various industries. The regulatory landscape has been transformed to ensure that these toxic substances are used with caution and only when necessary (Arshad et al., 2020; International Labor Organization, 2004)

In recent years, there has been a significant shift towards the adoption of stricter regulations on the use of these heavy metals. Governments and international organizations have collaborated to develop and enforce guidelines that minimize the exposure of humans to these carcinogenic substances. The European Union's REACH regulation, for instance, has established strict guidelines for the use of heavy metals in consumer products and industrial processes (S. S. Epstein, 2005; The European Commission, 2024)

Similarly, many countries have implemented laws and regulations to restrict the use of heavy metals in various industries. In the United States, the Environmental Protection Agency (EPA) has established guidelines for the use of heavy metals in consumer prod-

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ucts and industrial processes (EPA, 2024). Canada has also implemented regulations to restrict the use of heavy metals in consumer products and industrial processes (Intertek, 2022).

m^6A

RNA can have epigenetic changes, one of which is N6-methyladenosine (m^6A). By altering the RNA molecules' destiny, this chemical mark added to them controls the expression of genes. Methyltransferase "writers" and demethylase "erasers" control this reversible posttranscriptional RNA change. The ability of various "readers" to identify and bind to m^6A-modified RNAs determines their destiny. The significance of m^6A methylation alteration in controlling the course of cancer has led to a recent surge in research on the subject (Z. Liu, Gao, et al., 2023).

The lung cancer screening program in Indonesia thus far solely targets those who are most at risk, in contrast to population-based screening programs for breast, cervical, and colon cancer, which target all individuals of a given age and gender, regardless of any risk factors. Finding particular biomarkers unique to lung cancer is a rapidly emerging alternative to lung cancer screening. The use of blood-borne biomarkers, which some refer to as "liquid biopsies," to track advanced stage lung cancer has grown in popularity. These biomarkers can identify circulating proteins, nucleic acids, or tumor cells. One instance is the identification of particular circulating microRNAs, including miRNA21, which has been demonstrated to exist in lung cancer cell lines and tissue, and let7 miRNA, which is downregulated in lung cancer tissue. Analysis of exhaled breath has been suggested as another noninvasive technique. One sensitive method for identifying volatile organic compounds (VOCs) in lung cancer patients'

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exhaled breath is ion mobility spectrometry; pilot research has demonstrated that patients' VOCs may be readily identified from controls (Andarini et al., 2023).

B. LIVER CANCER

Globally, hepatocellular carcinoma (HCC) is the second most common cause of cancer-associated mortality. It is the most prevalent primary liver cancer, and the prognosis and result are not good. It is the third most frequent cancer in males and the seventh most prevalent in women, with a considerably greater incidence in men. Eastern and Southeast Asia had the highest incidence rates, with age-standardized ratios of 31.9 and 22.2 per 100 000 population, respectively (Jasirwan et al., 2020). Based on the most recent WHO data released in 2020, Indonesia had 19,721 liver cancer deaths, or 1.17% of all fatalities. With an age-adjusted death rate of 8.53 per 100,000 people, Indonesia is ranked 43rd globally. According to the IARC, out of all gastrointestinal malignancies, alcohol use accounts for 37% of liver cancer cases. The Indonesian liver cancer treatments market is expected to develop at a compound annual growth rate (CAGR) of 17.6% from 2022 to 2030, when it is expected to reach a value of $64.3 million from $17.58 million in 2022. A small number of domestic pharmaceutical companies, including Taiho Pharmaceutical, Eisai, and Chugai Pharmaceutical, dominate the Indonesian market for liver cancer therapies. The Indonesian market for liver cancer therapeutics is divided into categories based on the types of cancer and the types of treatments available. The rising incidence of liver cancer as well as the expensive and unfavorable side effects of some liver cancer treatments are some of the key factors influencing this market(Modhia, 2023).

A study which retrieved retrospectively from medical records of 157 liver cancer patients divided into three disease categories: 1)

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compensated cirrhosis (CC), 2) decompensated cirrhosis (DC), and 3) hepatocellular carcinoma (HCC) from January to December 2020 from a large referral hospital in Yogyakarta, Indonesia evaluated the medical cost caused by liver cancers from their perspective and experience. The direct medical expenditures per patient by stage of liver cancer multiplied by the total number of patients yielded the anticipated national medical costs. An estimated US$3.8 million would be spent on direct medical expenses related to liver cancer in 2020. The primary factor influencing the expense of treating liver cancer at every stage was the cost of surgery. The anticipated yearly direct medical costs per patient for CC, DC, and HCC are US$20,339, $24,784, and $26,538 correspondingly. These costs are directly correlated with the severity of the disease. Obviously, patients with liver cancer bear a heavy financial cost(Kristina et al., 2021).

Etiology of Liver Cancer

1. Hepatitis B Infection

Hepatitis B infection continues to be the leading risk factor for HCC, particularly in Asian nations, where over half of all HCC cases occur. The hepatitis B virus, in addition to producing cirrhosis, is a major factor in the development of HCC. Research conducted in vitro has demonstrated that the integration of the hepatitis B virus into host DNA can activate oncogenes. Liver cancer can also occur in chronic hepatitis B carriers who do not exhibit symptoms of cirrhosis. Patients with chronic HBV in East Asia are reported to have an incidence of 3.7 per 100 person-years for those with compensated cirrhosis and 0.2 per 100 person-years for chronic HBV carriers(Samant et al., 2020).

2. Nonalcoholic Fatty Liver Disease (NAFLD)

The metabolic syndrome, which includes obesity, dyslipidemia, and type 2 diabetes, manifests as NAFLD. The more severe type of

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NAFLD known as NASH (non-alcoholic steatohepatitis) is characterized by inflammation and can lead to cirrhosis and the eventual development of HCC. About 25% of people worldwide are estimated to have NAFLD; the rates are highest in South America (31%) and the Middle East (32%), followed by Asia (27%), the US (24%), and Europe (23%), with the lowest rates in Africa (32). Furthermore, NASH is quickly rising to the top of the global list of causes of chronic liver disease. From NASH-cirrhosis, the risk of developing HCC might vary from 2.4% to 12.8%. Relative risks for diabetes and HCC have been found to be 2.0–2.5, regardless of other risk factors(Samant et al., 2020).

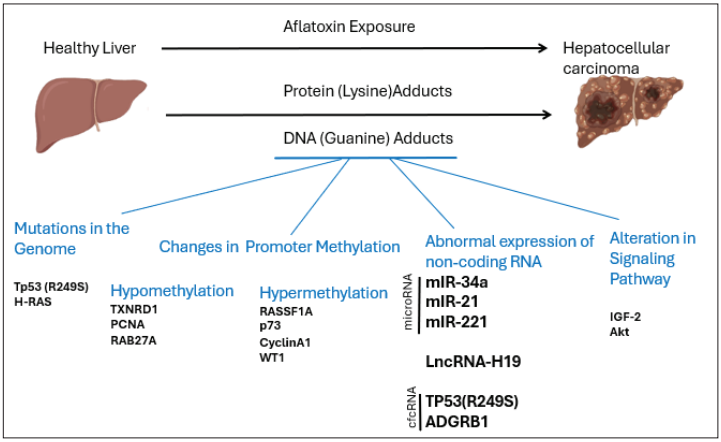
3. Environmental Toxins

Certain environmental and occupational factors may also contribute to the development of HCC. These include working with polycyclic aromatic hydrocarbons (PAHs) at work, being exposed to aflatoxin, and ground water poisoning from industrial waste. Fungal contamination of food or water is the main source of aflatoxin production. Among liver carcinogens, aflatoxin B1 is the strongest. Aflatoxin B1 and HBV positively interact with regard to the risk of HCC. It has been estimated that between 4.6-28.2% of HCC cases are related to aflatoxin exposure. Employees who are often exposed to organic solvents such as toluene and xylene are at a higher risk of developing HCC(Samant et al., 2020).

Histone modifications like acetylation and methylation, DNA methylation variations, and non-coding RNAs—which are essential for controlling and expressing genes—are examples of epigenetic modifications. HCC results from aflatoxins' modification of these crucial regulatory systems (Figure 6.3) (Mungamuri & Mavuduru, 2020).

It has been demonstrated that aflatoxins alter nucleosome occupancy and encourage methylation of the CpG islands close to the promoters. Zhu et al. used the MSP approach to analyze the

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Source: Modified from (Mungamuri and Mavuduru 2020).

Figure 6.3 Epigenetic modifications in the fflatoxin-induced HCC

methylation status of 92 cancer-associated genes in patients with liver cancer. Seven genes' promoters (MAGEA1, ASPH, OXCT, MTHFD2, SRP72, ENO3, and MDFI) were found to have decreased methylation in their study, whereas 25 other promoters (RASSF1A, GSPT1, SALL3, OCT6, CFTR, AR, p73, Cyclin A1, MYOD1, p16IN-K4a, ABO, DBCCR1, ITGA9, IRF7, LRP6, PENK, WT1, CDH13, DKC1, CSPG2, GALR2, p57KIP2, MT1A, HIC1, and CAT) exhibited increased methylation status in comparison with healthy individual profiles(J. De Zhu, 2005).

Other than affecting the DNA methylation, high exposure to aflatoxins can also alter the histone modification mechanisms causing HCC(Chappell et al., 2016). After binding to DNA at CpG sites, aflatoxin releases proteins like MeCP2, which in turn attracts enzymes that change histones, like histone deacetylases (HDAC), condensing the chromatin to prevent the transcription of genes. For the start of gene expression, histone acetylation and deacetylation are also indispensable. Transcription of a gene is activated when an acetyl group is introduced because it weakens the histone-DNA

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bond. A class of enzymes known as histone acetyl transferases is responsible for acetylation, while HDACs are responsible for deacetylation. HDACs are categorized into four groups according to where they work, and there are 12 total (HDAC1 through HDAC11 plus Sirtuins). Chromosomes become relaxed when amino acid tails are acetylated. The binding transcription factors (TF) to DNA can enhance the expression of genes. Gene expression is suppressed by deacetylation because it firmly packs the nucleosomes and prevents transcriptional factors from binding to DNA(L. Ma et al., 2014; N. Zhao et al., 2016).

HDAC8 suppression results in increased expression of the p53 gene, acetylation of lysine 382 of the p53 gene, and reduction of HCC cell growth. It has also been demonstrated that inhibiting HDAC8 increases the rate of apoptosis in HCC cells, making it a promising target for therapy. While H3 lysine9 or lysine14 acetylation (H3K9Ac and H3K14Ac) and H3 lysine4 methylation (H3K4me) are commonly thought of as activation marks, modifications such histone H3 lysine9 methylation (H3K9me) or lysine27 methylation (H3K27me) are typically regarded as repressive marks(Hayashi et al., 2014; Kanno et al., 2012).

The TP53 - R249S mutation is used to evaluate the involvement of aflatoxin in the development of HCC at the population level. When compared to the control group, HCC patients have a substantial elevation in circulating DNA levels containing the R249S mutation. This p53 hotspot mutation causes aberrant cell division. It was discovered that aflatoxin-induced HCC was caused by mutations in ADGRB1, an orphan G-protein-coupled receptor. It is feasible to stratify the susceptibility of developing HCC from the exposure extent to aflatoxin by detecting alterations in the circulating DNA (Mungamuri & Mavuduru, 2020; W. Zhang et al., 2017).

The first systemic medication that has been shown to improve patients' chances of survival for those with advanced-stage HCC was

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sorafenib in 2008. No other medication has been able to outperform sorafenib for almost ten years. But in the previous five years, a lot of progress in systemic medicines has been made to address the lack of available effective treatment choices. Following successful phase III clinical trials, a number of medications have been approved for use in clinical settings. These medications include immune checkpoint inhibitor atezolizumab in combination with bevacizumab, a monoclonal antibody that targets the vascular endothelial growth factor, and lenvatinib, regorafenib, cabozantinib, and ramucirumab. With so many options available, clinical decision making requires knowledge of each drug's safety profile, clinical evidence, and patient features and preferences (Hasan et al., 2023).

C. COLORECTAL CANCER (CRC)

Colorectal cancer (CRC) has emerged as a significant global health concern, with approximately 1.9 million new cases and 0.9 million deaths reported in 2020 alone (WHO, 2023). In Indonesia, CRC is a growing health problem, ranking second in incidence among men and fourth among women, with a mortality rate of 12.8 per 100,000 adult population and a mortality rate of 9.5% among all cancer cases (The International Agency for Research on Cancer, 2020).

Recent studies have shown that CRC incidence in Indonesia has been increasing, particularly among younger age groups. A significant shift has been observed in the age trend, with cases now developing at a younger age (Khairina et al., 2018). A European study revealed a substantial increase in CRC before the age of 50, with the highest growth rate occurring among individuals aged 20-29 years (Vuik et al., 2019).

However, some guidelines suggest start screening at an earlier age, such as 45 years old, due to the severity of the disease and its increased incidence in younger subjects. The American Cancer Society

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recommends started screening at 45 years old, citing the potential for better prevention outcomes in this age group (Rex et al., 2017).

The stage at which CRC is diagnosed plays a crucial role in determining mortality rates. The Surveillance, Epidemiology, and End Results (SEER) Program reports that only 37.5% of CRC cases are diagnosed at an early stage (stage I), resulting in a 5-year relative survival rate of 90.6%. In Indonesia, there is currently no national consensus on CRC screening guidelines, and public awareness regarding cancer screening is still low (Purnomo et al., 2023; Werdhani, 2019).

To improve early diagnosis and reduce mortality rates, a new strategy is needed to increase community participation in CRC screening. Primary health care centers (Puskesmas) play a vital role in prevention, screening, and addressing various health problems. By involving these centers in CRC screening initiatives, we can increase public participation and reduce the financial burden of treatment costs (Purnomo et al., 2023).

Etiology of CRC

The rising incidence of early-onset colorectal cancer (eoCRC) is a pressing concern that demands a thorough understanding of its underlying causes. Genetic and familial risk factors are crucial areas of investigation, as they significantly contribute to the development of this disease. Hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis are the most common inherited forms of CRC (Sinicrope, 2018). Lynch syndrome, resulting from germline mutations in DNA mismatch repair genes, is associated with a staggering 80% lifetime risk of CRC, often manifesting with microsatellite instability. Familial adenomatous polyposis, caused by mutations in the adenomatous polyposis coli gene, is characterized by early-onset adenomatous polyps, leading to a nearly 100% lifetime risk if left untreated (Menon et al., 2024).

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In addition to these well-established syndromes, other genetic conditions such as MutYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and Li-Fraumeni syndrome have also been linked to an increased risk of eoCRC (Yoshida et al., 2017). Moreover, mutations in BRCA1 and BRCA2 genes, traditionally associated with breast and ovarian cancers, have been implicated in eoCRC. Somatic mutations in tumor protein 53, Kirsten rat sarcoma viral oncogene homolog, and adenomatous polyposis coli genes are also common in eoCRC, suggesting potential pathogenesis pathways (Thota et al., 2021).

While most studies suggest that having a first-degree relative with CRC significantly increases the risk, especially if diagnosed at a young age, research is not entirely consistent. A recent cross-sectional study by Abou-Zeid et al. found that family history criteria and pathologic features of tumors in young Egyptian patients do not differ significantly from those in older patients, implying that they may share a similar etiology. This raises questions about whether hereditary risk factors are indeed the primary driver of this atypical pattern of eoCRC in Egyptian patients (Abou-Zeid et al., 2017).

The relationship between dietary habits and the development of early-onset colorectal cancer (eoCRC) is a crucial area of investigation. A diet characterized by a high consumption of red and processed meats, refined grains, and sugary beverages, and a low intake of fruits, vegetables, and whole grains has been linked to an increased risk of eoCRC (Chapelle et al., 2020). Conversely, diets rich in fiber, such as the Mediterranean diet, have been associated with a reduced risk, likely due to their impact on gut microbiota and reduced levels of pro-inflammatory compounds (Jones et al., 2017). A comprehensive case-control study by Puzzono et al. examined the dietary habits and lifestyle factors of individuals with eoCRC, compared to age-matched healthy controls, and identified processed meat, dairy products, and smoking as significant risk fac-

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tors for eoCRC (Puzzono et al., 2022). Multiple studies have since corroborated this finding, highlighting the importance of a balanced diet in reducing the risk of eoCRC. The American Cancer Center emphasizes that a high intake of red and processed meat can lead to DNA damage caused by toxic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons (PAH), increasing the risk of colon cancer (Adigun et al., 2023).

In addition to dietary factors, substance use, particularly tobacco and alcohol consumption, contributes significantly to the risk of eoCRC. Smoking has been shown to increase the risk of eoCRC, with the intensity and duration of smoking playing a crucial role (N. A. Khan et al., 2015). The carcinogenic compounds present in cigarette smoke, including aromatic amines, nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons, are thought to be responsible for this increased risk. Meanwhile, moderate to heavy alcohol consumption (≥ 20 g/day) has been recognized as a risk factor for eoCRC due to the carcinogenic effects of acetaldehyde, a metabolic product of ethanol (Rosato et al., 2013). These lifestyle-related risk factors, combined with increasing sedentary behavior, underscore the need for targeted public health interventions focusing on lifestyle modifications to curb the rising trend of eoCRC. Based on the evidence available, it is evident that smoking and alcohol cessation can significantly reduce the risk of eoCRC (Adigun et al., 2023).

In addition, body mass index (BMI) and family history of other cancers were deemed to have a significant correlation in the development of colorectal cancer. Specifically, individuals with a family history of other malignancies are at a higher risk of developing colorectal cancer (Henrikson et al., 2015). A meta-analysis has demonstrated a substantial correlation between the incidence of CRC and family history of CRC in first-degree relatives (O'Sullivan et al., 2022). Notably, Wilkinson's study suggests that individuals

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with a first-degree relative diagnosed with CRC or advanced adenoma should undergo colonoscopy every 5-10 years from age 40 to 50 or perform stool immunochemical testing at intervals of every 1-2 years (Wilkinson et al., 2019). Furthermore, a study conducted on the Swedish Family-Cancer Database, which analyzed over 1.8 million cancer patients and 200,000 CRC cases, has consistently found familial associations between CRC and other cancers (H. Yu et al., 2017). This profile was also seen in Indonesian cohort where obesity and CRC were positively correlated (Purnomo et al., 2023). A meta-analysis has shown that approximately 11% of CRC cases can be attributed to overweight and obesity in Europe, with an increased risk of colon cancer in men by 30-70% and less consistent association in women (Bardou et al., 2013). Obesity is linked to CRC through various mechanisms, including nutrition, adipokines and hormones, inflammation, gut microbiota, and bile acids (P. Ye et al., 2020).

The analysis of genome-wide imputation in an Indonesian population highlights the need for a reference panel tailored to the region. While the 1000 Genomes Project has samples from Vietnam, genetic markers specific to Indonesians may not impute well due to the lack of representation (GenomeAsia100K Consortium, 2019). Several previously identified colorectal cancer-associated single nucleotide polymorphisms (SNPs) replicated in our study. Notably, the rs7758229 variant within SLC22A3 on chromosome 6 was initially identified and subsequently replicated in a Japanese population (Cui et al., 2011), but not in a Chinese population (L. Zhu et al., 2013). This highlights the importance of understanding variation in SLC22A3 and its role in colorectal cancer. SLC22A3 encodes for OCT3, an organic cationic transporter involved in neurochemistry and oncology (Cui et al., 2011; Grisanzio et al., 2012; Yokoo et al., 2008).

Intergenic variant rs11255841 on chromosome 10 was identified in a European ancestry GWAS and replicated in a Japanese study and meta-analysis (Schmit et al., 2019; Tanikawa et al., 2018;

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Whiffin et al., 2014). This SNP is associated with an increased risk of colorectal cancer, with an odds ratio of 2.2 in a study by Yusuf and colleagues and the results were published quite recently in 2021. The team conducted a groundbreaking genome-wide association study to identify and discover colorectal cancer risk factors. They gathered questionnaires and collected blood samples from 162 individuals with colorectal cancer admitted to several hospitals, being Wahidin Sudirohusodo Hospital, Hasanuddin University Hospital, Ibnu Sina Hospital, Akademis Hospital, Grestelina Hospital, Stella Maris Hospital, and Hikmah Hospital. They also established a control group of 193 healthy individuals, frequency-matched by age, sex, and ethnicity to ensure a robust comparison. The region on chromosome 15 near SCG5 and GREM1 has been flagged in multiple GWAS. They replicated associations for rs4779584, rs11632715, and rs73376930. Interestingly, the smallest p-value was rs10083612 within an intron of SCG5, suggesting a potential role for SCG5 in colorectal cancer. SCG5 and GREM1 are adjacent genes that have been implicated in polyposis syndromes associated with colorectal cancer. GREM1 is a proangiogenic factor and has been found to be upregulated in cancer-associated stromal cells. The duplication of SCG5 and GREM1 has been linked to hereditary mixed polyposis syndrome and tumorigenesis. Two previously identified colorectal cancer markers replicated in our study: rs6936461 and rs9497673, both located in the intronic regions of STXBP5-AS1 on chromosome 6. These SNPs have the potential to alter splicing of the gene, which may contribute to colon carcinogenesis. STXBP5-AS1 is a long non-coding RNA gene that has been implicated in various signaling pathways involved in cancer development. Its expression is altered in breast cancer and may play a role in predicting patient prognosis (Yusuf et al., 2021).

This study's significance lies in its representation of an often-overlooked population, shedding light on the genetic and environmental factors that contribute to colorectal cancer risk in In-

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donesia and potentially informing future research and prevention strategies (Yusuf et al., 2021).

Colorectal Cancer

Breaking News: Indonesia Launches Groundbreaking Colorectal Cancer Diagnostic Kit

In a significant milestone, Bio Farma, a leading pharmaceutical company in Indonesia, has launched BioColomelt-Dx, a revolutionary PCR kit with High Resolution Melting (HRM) analysis for the detection of genetic disorders in colorectal cancer patients. This breakthrough product has obtained marketing authorization from the Indonesian Ministry of Health and is set to transform the way doctors diagnose and treat colorectal cancer (Biofarma, 2022).

The launch event, held at the Dharmais Cancer Hospital in Jakarta, was attended by prominent government officials, including the Minister of Health, Budi G Sadikin, and the Head of the Goods/Services Procurement Policy Institute (LKPP), Abdullah Azwar Anas. The event marked a significant achievement in Indonesia's healthcare sector, with BioColomelt-Dx being the first diagnostic kit to obtain marketing authorization from the Ministry of Health (Biofarma, 2022).

The kit is capable of detecting genetic disorders that occur in colorectal cancer patients, providing doctors with critical information to determine the most effective treatment plan. Moreover, it can also be used for screening Lynch syndrome, a hereditary condition that increases the risk of developing various types of cancer (Biofarma, 2022).

Dr. Soeko W Nindito D.MARS, Director of Dharmais Cancer Hospital, emphasized the importance of early detec-

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tion and prevention, stating that BioColomelt-Dx will be more efficient and effective in detecting colon cancer. The Head of LKPP also expressed his support for the innovation, highlighting its potential to strengthen Indonesia's domestic industry and contribute to the country's economic growth (Biofarma, 2022).

In his address, the Minister of Health praised the discovery of DNA technology and its potential to revolutionize disease diagnosis and treatment. He expressed hope that Indonesian scientists will continue to push boundaries and develop innovative products that benefit the country's health sector (Biofarma, 2022).

Honesti Basyir, President Director of Bio Farma, reaffirmed the company's commitment to collaborating with stakeholders and contributing to the development of domestic products. He emphasized that Bio Farma's production has a Domestic Component Level (TKDN) of over 50%, ensuring national independence in providing medical devices (Biofarma, 2022).

This milestone achievement marks a significant step forward in Indonesia's healthcare sector, demonstrating the country's capability to develop innovative products that can rival international standards. As Indonesia strives for health independence, BioColomelt-Dx is poised to play a crucial role in improving patient outcomes and reducing reliance on imported medical devices (Biofarma, 2022).

D. PANCREATIC CANCER

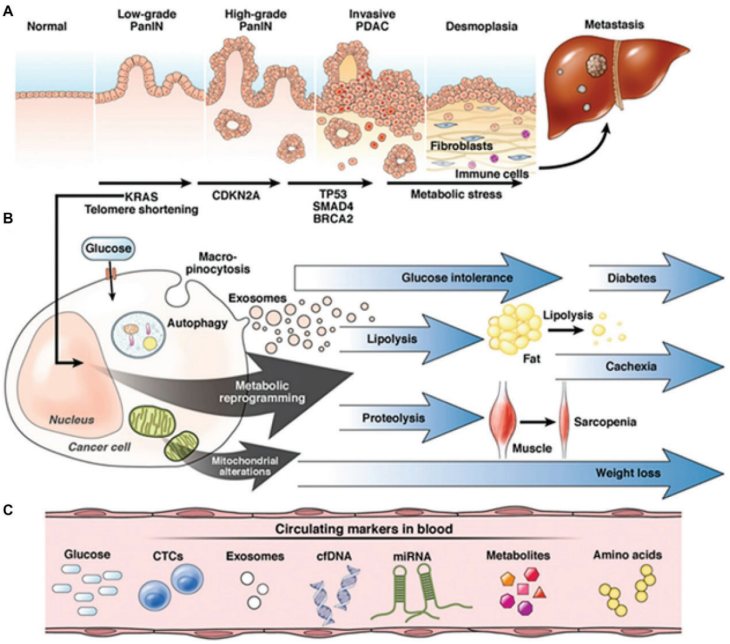
In Indonesia, pancreatic cancer ranks as the eleventh leading cause of cancer-related deaths in 2020. However, in the USA, pan-

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creatic cancer is the second most common cause of cancer-related deaths after lung cancer. Pancreatic carcinoma is quite high on the list of murderers due to its extreme aggressiveness, while being far less frequent than the other cancers. The multistep carcinogenesis of pancreatic cancer begins with Pancreatic Intraductal Neoplasia (PanINs IA, IB, II, and III) and culminates in an invasive neoplastic lesion. The fact that pancreatic cancer prevalence varies by nation further highlights the critical role that environmental variables play in the disease's development (Rikarni, 2021). the major cause of pancreatic cancer in Indonesia can be attributed to lifestyle factors such as unhealthy diets, physical inactivity, tobacco and alcohol consumption (Renaldi et al., 2020). Public health initiatives and educational programs aimed at promoting a healthier lifestyle and early detection of disease are crucial in mitigating this growing health concern.

The deadly characteristic of pancreatic cancer is its ability to spread quickly to distant organs and the lymphatic system. Pancreatic cancer patients have a high death rate due in part to the absence of effective chemotherapies and the presence of occult or clinical metastases at the time of diagnosis. One of the most innately drug-resistant cancers is pancreatic cancer, and one of the main reasons for treatment failure in this disease is the tumor's resistance to chemotherapeutic drugs. Following a phase III trial in 1997 that showed a modest survival advantage of this agent over 5-FU (median survival 5.65 versus 4.41 months, respectively), gemcitabine became the standard chemotherapy drug for patients with advanced pancreatic cancer. Surprisingly, however, this treatment also improved alleviation of disease-related symptoms (Iovanna et al., 2012).

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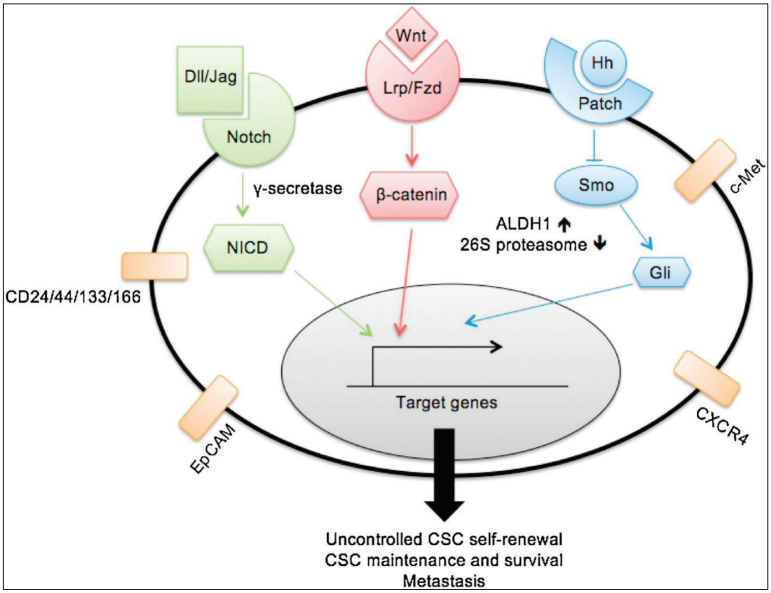
Source: adapted from (Ulanja et al. 2022).

Figure 6. 4 Pancreatic adenocarcinoma (PDAC) progression.

Shown in Figure.6.4, (A) low-grade pancreatic intraepithelial neoplasia (PanIN) marks the initial step in the progression from normal pancreatic cells to pancreatic ductal adenocarcinoma (PDAC). Subsequent mutations driven by KRAS, CDKN2A, TP53, SMAD4, and BRCA2 propel this progression toward high-grade PanIN and ultimately invasive PDAC. Characteristic features of PDAC include a pronounced desmoplastic reaction and active immune cell-fibroblast interactions, which promote epithelial-mesenchymal transition and facilitate metastasis. (B) The classic symptoms associated with PDAC—diabetes, cachexia, and sarcopenia—arise from downstream effects of KRAS-induced metabolic reprogramming and mitochondrial alterations. (C) Early detection efforts may benefit from analyzing cell-free DNA (cfDNA), enabling the identification of metabolic abnormalities at initial stages of carcinogenesis. .(Ulanja et al., 2022).

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CSCs are a tiny subset of cancer cells that can self-renew and give rise to the various lineages of cancer cells that make up the tumor. Though recent research has shown their involvement in the processes leading to invasion and metastasis in a variety of cancer types, including PDAC, CSCs are still thought to be the primary driver of cancer genesis and initiation (Giovannetti et al., 2017).



Source: adapted from (Giovannetti et al. 2017).

Figure 6.5 Important proteins and signaling mechanisms controlling the metastatic potential of pancreatic CSCs.

In pancreatic cancers, the Notch, Hh, and Wnt pathways are crucial for maintaining the phenotype of CSCs. Recent data indicates that they are also necessary to support PDAC's ability to migrate. Additionally, subpopulations of PDAC cells that exhibited metastatic ability have been linked to intracellular markers like ALDH1 and surface markers of pancreatic CSCs such c-Met, CXCR4, CD24, CD44, CD133, and EpCAM(Figure 6.5) (Giovannetti et al., 2017).

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In Indonesia, poor results led to the abandonment of pancreaticoduodenectomy in the 1960s; overall surgical mortality was between 25 and 35%. However, by the end of the 20th century, operative mortality had dramatically dropped to less than 5%, and some facilities reported 0% mortality on a hundred pancreaticoduodenectomy resections. Good patient selection, a multidisciplinary team approach, the surgeons' experience, good skill, and aggressive action against complications were all contributing factors to the declining fatality rate. The number of patients with periampullary tumors is strongly correlated with survival, morbidity, and surgical mortality (T. J. M. Lalisang et al., 2004).

Furthermore, data from (T. J. M. Lalisang, Simanjuntak, and Philippi 2004) clearly shows that the mortality was significant in the initial period due to a lack of experience and a careless selection of cases; four surgical deaths occurred in the first 12 patients, with sepsis following pancreatic leakage accounting for the majority of these deaths. Out of the final 19 patients, one died because of protracted shock that was improperly handled both during and after the procedure. 48 hours following the procedure, the patient passed away. The mortality was decreasing with increasing experience.

Pancreatic leakage was one of the deadly consequences that could cause mortality in the majority of the patients. According to recent studies, pancreatic leaks occurred between 6-25% of the time, and between 26% and 40% of these leaks directly contributed to the patient's death. Shown in Lalisang and colleagues' study, four pancreatic leaks in the first and second periods ended in sepsis and multiple organ failure (MOF), but the leak in nine of the final eight individuals spontaneously repaired with proper drainage. Surgery is required for the last patient because of a high-output pancreatic fistula. Because of this experience, they have regularly installed draining tubes around the pancreatic jejunostomy anastomosis to ensure proper drainage. Another effective strategy against morbidity

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was aggressive surgical intervention. The researchers did not give the patients somatostatin or octreotide. To reduce the occurrence of leaks, they must enhance the pancreatic anastomosis technique. Three cases of delayed gastric emptying were successfully treated with oral erythromycin and a prolonged nasogastric tube (T. J. M. Lalisang et al., 2004).

E. CERVICAL CANCER

There are 102.5 million women in Indonesia who are over the age of 15 and at risk of cervical cancer. According to current estimates, 21003 women lose their lives to cervical cancer each year, along with 36633 women receiving a diagnosis. In Indonesia, cervical cancer is the second most common type of cancer among women overall and among women aged 15 to 44 in particular. At any given moment, 4.0% of women in the general population are thought to be infected with cervical HPV-16/18, and HPVs 16 or 18 are responsible for 87.0% of invasive cervical cancer cases(Information Centre on HPV and Cancer (ICO/IARC), 2023).

The inability of a comprehensive population-based pre-cervical cancer lesion detection system, coupled with low public awareness and education regarding the disease's occurrence, contribute to the high incidence of cervical cancer in developing nations, despite the fact that the disease is preventable and curable if detected early enough in the patient's precancerous lesions (Agustiansyah et al., 2021; Y. Xie et al., 2017). Epidemiological studies indicate that a number of factors affect the chance of developing cervical cancer and genital HPV infection. Together with the cancer-associated HPV strains, a number of other variables also have a role in cervical cancer risk (Agustiansyah et al., 2021; Y. Xie et al., 2017; zur Hausen, 2002).

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1. Etiology of Cervical Cancer

As one of the leading causes of morbidity and mortality among women worldwide, understanding the etiology of this cancer is of essence for developing effective strategies not only to prevent, but also to diagnose, and ultimately to treat every impacted patient.

Individual lifestyle factors significantly influence susceptibility to cervical cancer. Research has consistently demonstrated a link between tobacco smoke and cervical cancer, attributed to the suppression of the immune response and the carcinogenic properties of tobacco (Y. T. Ma et al., 2011; MacLaughlan et al., 2011). Moreover, the use of hormonal contraceptives has been shown to increase the risk of cervical cancer due to elevated HPV gene expression (Ghanem et al., 2011).

Early onset of sexual activity (Mekonnen & Mittiku, 2023; Plummer et al., 2012; Xavier-Júnior et al., 2017) and multiple sex partners are also recognized as independent risk factors for abnormal cytology and cervical cancer (Y. Huang et al., 2020; Z.-C. Liu et al., 2015). Women who contract multiple HPV types are more susceptible to developing cervical cancer, as these viruses can interact synergistically. In fact, a recent study discovered a strong correlation between multiple HPV types and cervical intraepithelial neoplasia and cervical cancer (Y. Huang et al., 2020; Z.-C. Liu et al., 2015).

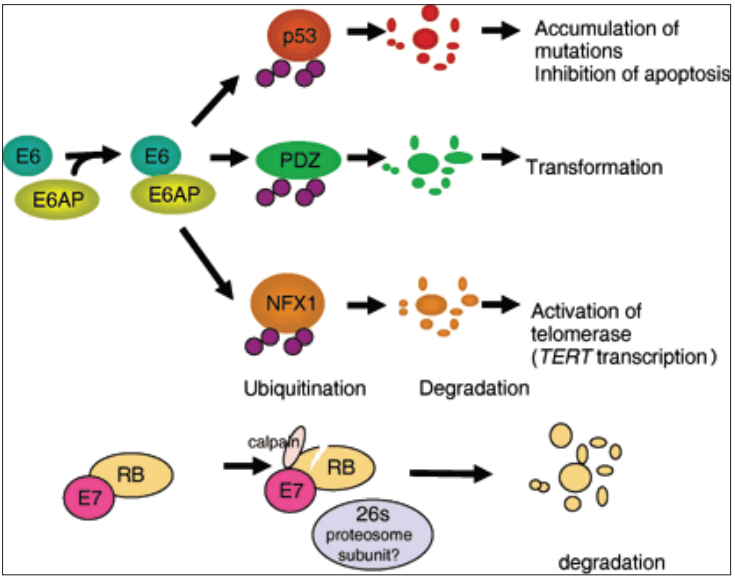
The presence of co-infections with other pathogens has also been found to play a critical role in cervical disease progression. For instance, co-infection with *Chlamydia trachomatis* (CT) has been linked to an increased risk of cervical intraepithelial neoplasia and abnormal cytology compared to patients without CT infection (Safaeian et al., 2010; H. Zhu et al., 2016). Furthermore, Human immunodeficiency virus (HIV) infection has been shown to significantly increase the risk of invasive cervical cancer due to HIV-induced immunosuppression and the synergistic interaction between HIV and HPV (Diarra & Botha, 2017; Stelzle et al., 2021).

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As such, it is essential to consider individual lifestyle factors and potential co-infections when assessing an individual's risk of developing these diseases.

2. HPV-Induced Cervical Cancer Mechanism

The primary drivers of HPV-induced cervical cancer have been identified as the HPV viral oncogenes E6 and E7. Increasing expression of these oncogenes has been seen in invasive tumors and a subset of high-grade lesions, most likely as a result of viral DNA integration into the host cell genome. A frequent occurrence in the carcinogenesis of human cells is the inactivation of the tumor suppressor p53 and/or retinoblastoma protein (pRb). The E6 and E7 HPV oncogenes interact with these tumor suppressors, preventing them from doing their intended functions (Narisawa-Saito & Kiyono, 2007).



Source: Taken from (Narisawa-Saito and Kiyono 2007).

Figure 6.6 The roles of E6 and E7 proteins in papillomavirus-induced carcinogenesis.

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The tumor suppressors p53 and retinoblastoma protein (pRb) can be rendered inactive by the high-risk human papillomaviruses (HPV) E6 and E7 proteins, respectively. The E6 protein can form ternary complexes with p53 to ubiquitinate it, even though it cannot attach to p53 directly. Instead, it can bind to a cellular ubiquitin ligase called E6AP. In addition, the E6 protein performs tasks unrelated to p53 inactivation. It's probable that ubiquitin ligase E6AP plays a significant role in p53 degradation as well as telomerase activation and E6-induced cell transformation. Recent research has revealed that E7 stimulates the calcium-activated cysteine protease calpain to cleave pRb at the C-terminal, and that this cleavage is necessary for E7 to next stimulate the proteasomal degradation of pRb. The majority of E7's biological activities are accomplished by pRb family protein inactivation (Figure 6.6) (Narisawa-Saito & Kiyono, 2007).

Elimination Plan for Cervical Cancer

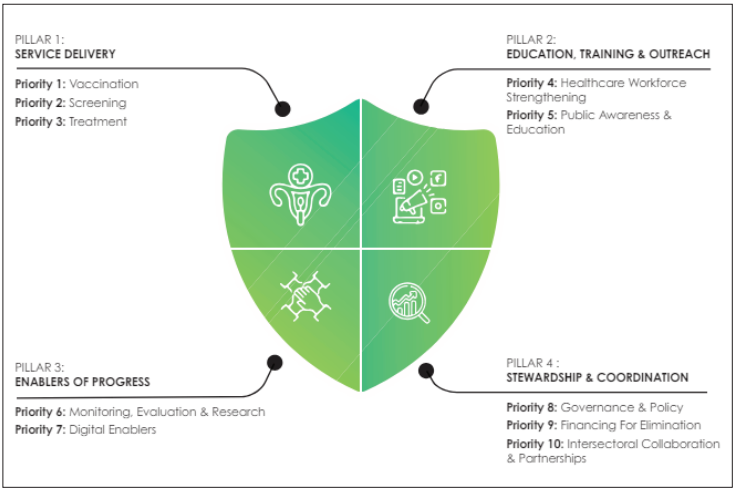
The vision to eliminate cervical cancer set by the Indonesian government is:

Indonesia aspires to become a nation where cervical cancer is eliminated as a public health concern. Together, as a united Indonesia, we envision a future where cervical cancer is a disease of the past, and every women – across all socio-economic demographics - can live a healthy life free from its threat.

The Elimination Plan, which is based on this vision, is composed of four action pillars (Figure 6.7): (1) service delivery; (2) outreach, education, and training; (3) important progress enablers; and (4) governance and policy. These pillars provide the groundwork for particular priority areas and related strategies and activities to "leapfrog" Indone-

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sia toward cervical cancer elimination through strong local and national leadership, evidence-based programming, and multi-stakeholder collaboration(Ministry of Health of Republic of Indonesia, 2022).



Source: Taken from (Ministry of Health of Republic of Indonesia 2022).
Figure 6.7 Four pillars of action in the The National Cervical Cancer Elimination Plan for Indonesia (2023-2030).

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CHAPTER VII
NOVEL APPROACHES IN CANCER THERAPY PLATFORM

The term "anticancer therapy" describes a range of medical practices and methods used in the treatment of cancer. Anticancer therapy's main goal is to eradicate cancer cells and stop their proliferation while sparing healthy cells from harm. Consequently, this course of treatment preserves the patient's general quality of life while managing symptoms. The selection of anticancer therapy is influenced by the kind, stage, and location of the cancer as well as the health of the particular patient(Krzyszczyk et al., 2018). Conventional anticancer medicines, including radiation therapy, hormone therapy, chemotherapy, and surgery, have been the mainstay of cancer treatment for many years(Tannock, 1998).

Despite their demonstrated effectiveness, traditional anticancer therapies do have some disadvantages. These limitations include(Debela et al., 2021) the following: 1) inability to target cancer cells selectively, harming healthy cells and tissues in the process; 2) the potential for cancer cells to become resistant to chemotherapy and radiation over time, reducing the long-term efficacy of these ther-

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apies; 3) the potential for chemotherapy drugs to cause side effects such as fatigue, nausea, hair loss, and weakened immune system, and 4) the quality of life of a patient can be greatly affected by traditional treatments because of the side effects and stress associated with undertaking arduous procedures. Therefore, new strategies for anticancer treatments are required that can target cancer cells directly while causing the least amount of harm to healthy tissues and limiting side effects.

In this chapter, we are going to delve further into progressions that have been made on some considerably novel approaches in cancer therapy realm that include:

A. GENE THERAPY

Gene therapy at first was centered on rare (orphan diseases) mediated by deleterious monogenetic defects. It explains the introduction of functional genes into a patient's body to supersede disease-inducing genes in such a way that the disease can be controlled from the genomic level hence drugs, radiation and surgery are no longer necessary(Goswami et al., 2019a). Gene therapy offers both complete treatment and disease or disorder prevention for disease like monogenic (Prakash et al., 2016) and cardiovascular diseases (Prondzynski et al., 2019), immunodeficiency and cancers for which typical medications or antibodies are hardly responded as excellently as expected (Goswami et al., 2019b; Hidai & Kitano, 2018).

The concept of gene therapy was initially proposed by Edward Tatum in 1966 who highlighted the central role of nucleic acids in biology and genetics upon which metabolic diseases, developmental defects, virus infection and carcinogenesis were seen to be interconnected phenomena. Moreover, he pointed out that aberrancy from normality was attributed to changes in normal sequences of molecular biology which bridge gene to enzyme (Tatum, 2010). Tatum repurposed viruses for genetic therapy and this largely influences

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the direction of therapy. Hitherto, there have been more than 3000 clinical trials registered under this platform. Although it is an undeniably incredible journey, gene therapy contributed to a few adverse outcomes due to off-target effects, cytotoxicity, transmissibility as well as immune response against the viral vector itself. However, this does not reduce their advantage as vectors for gene therapy because virtually human cells are potential for genetic manipulation. Viruses, on the other hand, show specificity in infecting cell types render them superior for gene delivery (Goswami et al., 2019b).

The history of gene therapy can be divided into four phases, as shown in **Fig** 7.1.

A wide range of items are used in cancer gene therapies, such as plasmids, bacterial, viral, and genetically modified human cells. Before moving on, it is helpful to briefly review the main categories of cancer gene therapy products, as each class of these products has different challenges during the manufacturing and testing stages (Byrnes et al., 2014).

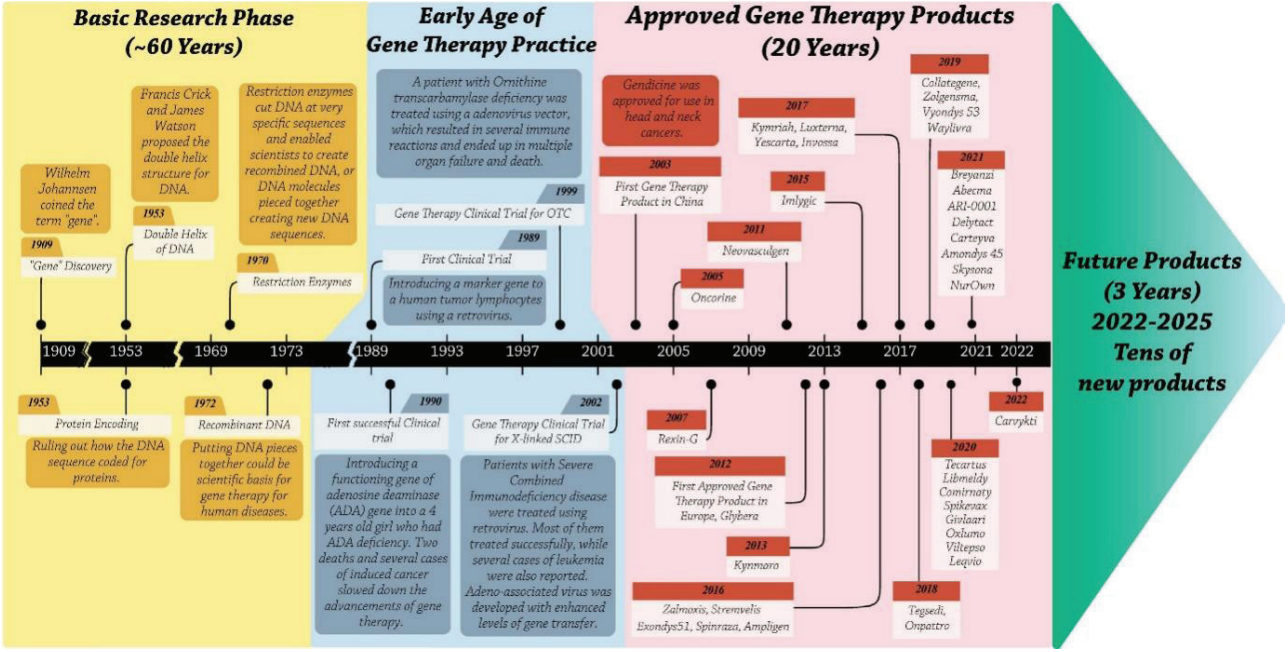
1. Nonreplicating Gene Therapy Vectors In In Vivo Setting

   The foreign transgene in certain cancer gene therapies has both direct and indirect anticancer activity, including pro-inflammatory, pro-angiogenic, pro-cytocidal, and prodrug-converting properties. Sometimes the transgene is the tumor antigen itself, meant to elicit a particular effector response. A transgene is a synthetic DNA fragment that has been adapted to fit into a recipient's genome. For high-resolution observations, it furthermore expresses a marker that may be observed experimentally in certain cell types or cellular structures (Mosimann & Zon, 2011).

2. Replication-Competent Gene Therapy Vectors

   Given their remarkable capacity for replication in transformed cells, viruses are commonly used as vectors for gene therapy. These viruses could be modified further to make them more

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Source: Taken from (Arabi, Mansouri, and Ahmadbeigi 2022).

Figure 7.1 Historical timeline of gene therapy.

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capable of reproducing in tumor cells or to prevent them from reproducing in non-tumor cells. These goods are commonly known as oncolytic viruses. If they express a transgene as well, they are classified as gene treatments (Z. Zhao et al., 2022).

3. Cell therapies that are genetically modified ex vivo

   Additionally, the genomes of cultured human cells can be altered by the use of gene therapy vectors. The subject (in this case, patients) is then given these cells. The concept is effectively shown by the production of T lymphocytes expressing both tumor-associated and tumor-specific antigens. Moreover, antigen-presenting cells (APCs), which are primarily dendritic cells (DCs), can be genetically modified to express the antigen in a vaccine-like manner (Edwards & Passineau, 2015).

There are some gene therapy platforms implemented to combat cancers, including:

1. Gene Replacement Therapy

Gene replacement therapy is a revolutionary approach in the field of medicine that holds immense promise for treating various diseases, including cancer. In this method, the focus is on substituting defective or missing genes in cancer cells with healthy, functional ones. The ultimate goal is to restore normal cellular function and limit cancer progression(Cesur-Ergün & Demir-Dora, 2023).

Gene replacement therapy aims to rectify these genetic abnormalities by introducing a healthy, functional copy of the missing or defective gene into the cancer cells. This can be achieved through various techniques, including viral vectors, non-viral vectors, and direct gene transfer methods (Pandey & Balekar, 2018).

Viral vectors are one of the most commonly used methods in gene replacement therapy. They involve modifying a virus to carry the healthy gene of interest. The modified virus is then introduced into the patient's body, where it selectively targets cancer cells and

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delivers healthy genes. The virus's natural ability to infect cells is harnessed for therapeutic purposes, making it an efficient method for gene delivery (Bezeljak, 2022).

Non-viral vectors, on the other hand, include various techniques such as liposomes, nanoparticles, and electroporation. These methods do not rely on viruses to deliver the healthy gene but instead use other carriers to transport genetic material into the target cells. This approach is considered safer than viral vectors, as it reduces the risk of immune responses and potential side effects associated with viral infections(Kaneda & Tabata, 2006).

Direct gene transfer methods involve the physical introduction of healthy genes into cancer cells. This can be achieved through various techniques, such as microinjection or gene gun, where tiny gold particles coated with the healthy gene are shot into the cells (Bleiziffer et al., 2007).

Once the healthy gene is successfully introduced into the cancer cells, it can either replace the defective or missing gene or work alongside it, depending on the specific therapeutic strategy. This restoration of normal gene function can lead to several beneficial outcomes (Das et al., 2015), such as:

(1) Restoring the ability of cancer cells to undergo programmed cell death (apoptosis), which can help control uncontrolled cell growth.
(2) Enhancing the immune system's ability to recognize and eliminate cancer cells.
(3) Inhibiting the production of growth factors and other molecules that promote cancer progression.
(4) Restoring the function of tumor suppressor genes, which play a crucial role in preventing cancer development.

Despite its promising potential, gene replacement therapy for cancer faces several challenges, including the difficulty in targeting

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specific cancer cells without affecting healthy cells, maintaining the stability of the introduced gene, and ensuring long-term therapeutic effects. However, ongoing research and advancements in gene editing technologies, such as CRISPR/Cas9, are continuously improving the safety and efficacy of gene replacement therapy (Jain et al., 2024).

2. Suicide Gene Therapy

Suicide gene therapy is an innovative and promising approach in the field of cancer treatment. It involves the introduction of a specific gene into cancer cells, which, when activated, triggers the death of these cells while leaving the healthy cells unharmed. This targeted approach offers several advantages over traditional cancer treatments, such as chemotherapy and radiation therapy, which often cause damage to healthy cells and tissues (Zarogoulidis et al., 2013).

The core concept behind suicide gene therapy is the selective elimination of cancer cells using a genetically modified agent. This agent, often a virus or a plasmid, carries a gene that is capable of inducing cell death in cancer cells. The most commonly used suicide gene is the herpes simplex virus thymidine kinase (HSV-TK) gene, which has been successfully employed in various clinical trials (Jiao et al., 2004).

When the suicide gene is introduced into cancer cells, it is incorporated into the cell's DNA and becomes a part of the cell's genetic makeup. The gene remains dormant until it is activated by a specific trigger. This activation can be achieved through the administration of a prodrug, which is a harmless compound that is converted into a toxic substance only within the cancer cells expressing the suicide gene (Zarogoulidis et al., 2013).

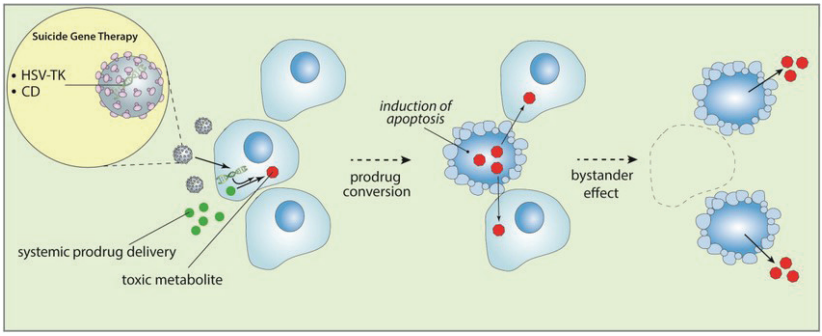
Once the prodrug is administered, it is selectively taken up by the cancer cells carrying the suicide gene. Inside these cells, the prodrug is metabolized into a toxic substance by the enzyme produced by the suicide gene. This toxic substance then causes the cancer cells

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to undergo programmed cell death, or apoptosis, without affecting the healthy cells (Springer & Niculescu-Duvaz, 2000).

The development of suicide gene therapy has been driven by the need for more targeted and less toxic cancer treatments. Moreover, suicide gene therapy can be combined with other cancer treatments, such as surgery, chemotherapy, and radiation therapy, to enhance their effectiveness. This combination therapy can help to eliminate cancer cells that may have been missed during surgery or that have become resistant to conventional treatments (Zarogoulidis et al., 2013).

One example of this approach is the use of TNF-related apoptosis inducing ligand (TRAIL) as an apoptosis-inducer, which has been shown to kill a wide range of tumor cells while having low toxicity on normal cells(Dai et al., 2015; Zhong et al., 2019).



Source: Taken from (Okura, Smith, and Rutka 2014).
Figure 7.2 Strategy for suicide gene therapy.

The aim of suicide gene therapy strategy is to increase the delivery of toxic metabolites to tumor cells and result in efficient cell death (Figure 7.2). Initially, a gene encoding a prodrug-activating enzyme is delivered by a tumor-targeting viral vector. Subsequent systemic administration of an inactive prodrug results in generation of a toxic metabolite and cell death of the transduced cells and

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non-transduced bystander tumor cells (bystander effect) only at the tumor site(Okura et al., 2014).

3. Gene Silencing Therapy

This approach can be done by blocking the expression of small RNA molecules, such as small interfering RNA (siRNA) or microRNA, that can be used to silence specific genes that promote cancer growth (Mirzaei et al., 2021). Thus, the growth of cancer cells can be slowed or halted. Melanoma cells treated with antisense oligonucleotides targeting the *c-myc* gene showed a reduction in cell growth rate (Chana et al., 2002). Disruption of K-*ras* gene in colorectal cancer by antisense RNA leads to apoptosis and tumor growth suppression both in vitro and in vivo in animal models (Nakano et al., 2001; Réjiba et al., 2007).

B. ONCOLYTIC VIROTHERAPY

Oncolytic viruses are designed to selectively infect and destroy cancer cells. These viruses can also activate the immune system, causing it to detect and fight cancer cells(Kooti et al., 2021). The most common example of this approach is the delivery of *Herpes Simplex Virus* (HSV)-thymidine kinase (TK) to treat patients with prostate cancer or malignant glioma (Fukuhara et al., 2010; J. Wang et al., 2004; J. Zeng et al., 2021).

Apart from offering the targeted treatment for cancer, gene therapy can also be personalized based on the genetic profile of the patient's tumor, leading to tailored treatments for individual patients. Successful gene therapy can cause long-lasting or permanent alterations in cancer cells, resulting in a sustained anticancer impact (S. R. Kumar et al., 2016; L. Wang et al., 2023).

Despite significant advantages over traditional cancer therapy, gene therapy in cancer treatment confronts major constraints, such as: 1)ensuring the properly functioning cell following therapeutic

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gene delivery, 2) safety concerns over whether gene therapy can trigger immunological responses or have unforeseen effects for other genes, 3)ethical and regulatory considerations regarding the need for strict regulatory monitoring since gene therapy entails manipulating the fundamental building blocks of life, 4)gene therapies can be expensive, limiting their accessibility to certain patient populations (Brenner et al., 2013; Das et al., 2015; Heo, 2002).

C. CANCER IMMUNOTHERAPY

Cancer immunotherapy has emerged as a groundbreaking approach in the fight against cancer. By harnessing the power of the immune system, this innovative treatment strategy aims to improve the effectiveness of cancer treatments, reduce side effects, and ultimately save lives. In this article, we will delve into the significance of cancer immunotherapy and its potential to revolutionize the way we combat this devastating disease (Y. Zhang & Zhang, 2020).

Cancer immunotherapy involves using the body's immune system to identify, attack, and eliminate cancer cells. Unlike traditional cancer treatments, such as chemotherapy, radiation, or surgery, immunotherapy does not directly target the tumor itself. Instead, it stimulates the immune system to recognize cancer cells as foreign invaders and destroy them. This has shown promising results in various clinical trials, with some patients experiencing complete remission. More importantly, this is encouraging for patients with advanced or metastatic cancers, where traditional treatments have limited success (S. Tan et al., 2020).

Cancer immunotherapy has shown promising results in improving patient outcomes globally, but its implementation in Indonesia faces challenges. In Indonesia where pediatric cancer survival rates remain low, with only 48.8% 5-year survival for high-risk acute lymphoblastic leukemia, CAR T-cell therapy is proposed as a potential solution to enhance the treatment although cost and infrastructure

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remain barriers (Azhar & Aisyi, 2024). For triple-negative breast cancer (TNBC), PD-1/PD-L1 inhibitors have shown promise, but treatment guidelines are lacking (Purwanto et al., 2020b).

As research continues to advance, we can expect to see further improvements in treatment efficacy, personalization, and patient outcomes. In the years to come, cancer immunotherapy may very well become a cornerstone of cancer care, transforming the way we approach and overcome this devastating disease.

Different immunotherapy modalities function in various ways. Certain immunotherapy treatments assist in preventing or delaying the growth of cancer cells by the immune system. Others aid in the immune system's destruction of cancer cells or prevent the disease from spreading to other regions. The diverse forms of immune treatment consist of:

1. Cancer Vaccines

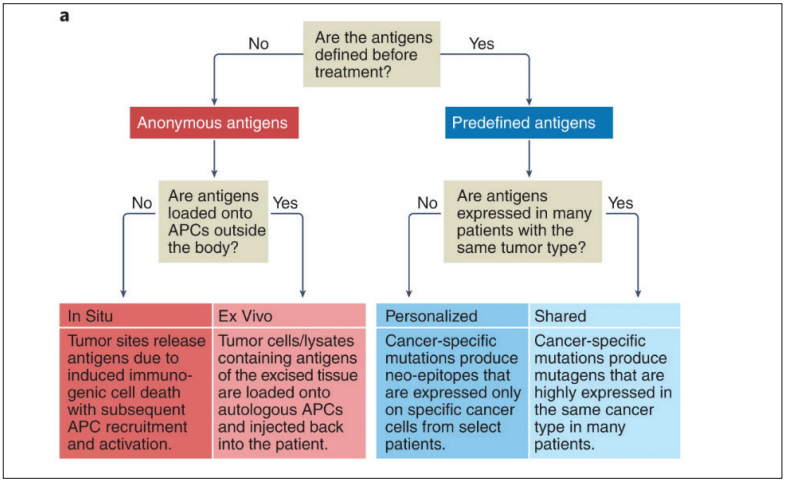
Cancer vaccines are biological agents designed to stimulate the immune system to recognize, target, and eliminate cancer cells or prevent their development. They work by either boosting the body's natural defenses against specific cancer types or teaching the immune system to identify cancerous cells as foreign invaders. Cancer vaccines can be preventive, targeting high-risk individuals to prevent cancer occurrence, or therapeutic, aiming to treat existing cancers by enhancing the immune response against them. The development of effective cancer vaccines is an important area of cancer research, as they have the potential to significantly improve cancer prevention and treatment outcomes (Petkar et al., 2023).

One active cancer immunotherapy treatment now under clinical development is the whole cell cancer vaccination. This strategy is predicated on the idea that tumor cells will produce several tumor antigens for immune recognition and will contain proteins expressed in the patient's cancerous lesions. Because it can be time-consuming,

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expensive, and technically tough to harvest patient-specific tumor cells, developing vaccine platforms based on autologous tumor cells has proven to be challenging. Using cell lines as an allogeneic vaccination strategy has been an alternative. In this approach, it is anticipated that the patient's tumor contains antigens expressed by the cell lines, which will trigger immune recognition (Ramirez-Montagut, 2015).

Cancer vaccine is thought to be promising for the immunotherapy of solid tumors is the cancer vaccination. Tumor antigens, which can be given as entire cells, peptides, nucleic acids, etc., are used by the cancer vaccine to elicit anti-tumor immunity. The optimal cancer vaccines would be able to stimulate humoral immunity as well as cellular immunity, surpassing the immunological suppression found in tumors(J. Liu et al., 2022).



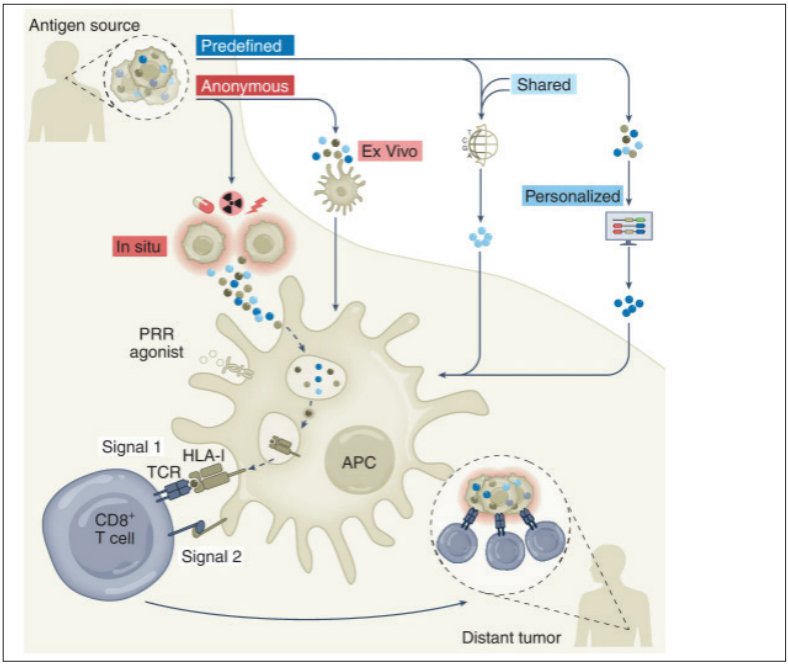
Source: Taken from (M. J. Lin et al. 2022).

Figure 7.3 The scheme of a four-vaccine type.

For predetermined vaccines, antigens must be identified using either shared or individualized computational analysis of tumor biopsies or pooled features across tumor types (Figure 7.3 and Figure

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7.4). Anonymous antigen vaccines have the ability to colocalize antigens with APCs either directly at the tumor site (*in situ*) or in the lab (*ex vivo*) (Lin et al., 2022).



Source: Taken from (M. J. Lin et al. 2022).

Figure 7.4 Four schemes of vaccination types based on the characteristics of TAA: TAA's known characteristics (predefined versus anonymous), the patient's tumor expression type (shared versus personalized), and the way in which APCs interact with and load TAAs.

The Food and Drug Administration (FDA) has approved two cancer vaccines hitherto:

1. Provenge (sipuleucel-T): Approved in 2010, Provenge is a first-of-its-kind cancer vaccine designed to treat advanced prostate cancer. It is made from a patient's own immune cells, which are modified to target prostate cancer cells (Anassi & Ndefo, 2011; Cheever & Higano, 2011).

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2. Talimogene Laherparepvec (T-VEC): Approved in 2015, T-VEC is a genetically engineered herpes simplex virus that has been modified to target and kill cancer cells, primarily in the treatment of melanoma. It is also known as an oncolytic virus (Bommareddy et al., 2017; Harrington et al., 2015).

While these are the only two cancer vaccines approved by the FDA, research is ongoing for other potential cancer vaccines targeting various types of cancer. In Indonesia, cancer vaccines are not as widely used as they are in some developed countries. However, some cancer treatment centers in Indonesia may use cancer vaccines, particularly for specific cases or in combination with other therapies. The availability of cancer vaccines in Indonesia may depend on the hospital or treatment center, and they might not be as readily accessible as in other countries.

Studies show high parental acceptance of HPV vaccination (96.1%), despite low awareness and knowledge about HPV and cervical cancer (Jaspers et al., 2011). However, barriers to implementation include high costs, fear of side effects, and concerns about vaccination locations (Jaspers et al., 2011). The Indonesian government has initiated pilot projects for free HPV vaccination in some areas, but nationwide implementation requires further adjustments and support (D. Ayuningtyas & Sutrisnawati, 2018). The nonavalent HPV vaccine, which protects against nine HPV types, has the potential to accelerate cervical cancer elimination (Hidayat & Reynaldi, 2023). To achieve the WHO's 90-70-90 strategy for cervical cancer elimination by 2030, Indonesia aims to vaccinate girls in grades 5 and 6 of elementary school (Purwito, 2023). Success of this program requires support from all stakeholders and efforts to increase community acceptance.

In relation to the national HPV immunization initiative, achieving a high level of vaccine uptake in Indonesia could lead to a future where women who have been vaccinated might not require frequent

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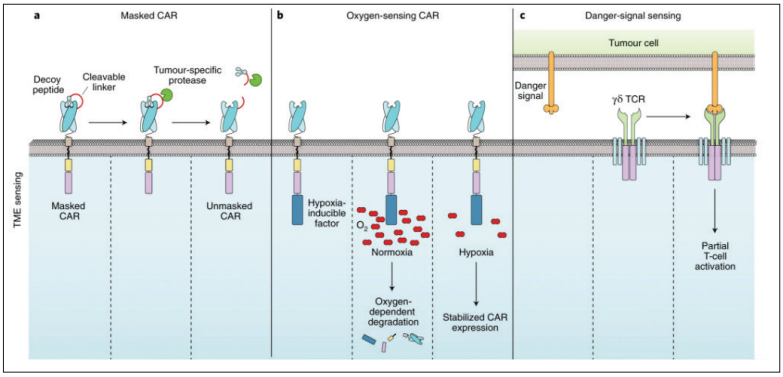
screenings. The main challenge here is effectively tracking those vaccinated during their elementary school years (specifically in the 5th and 6th grades), as the necessity for screenings typically arises several years later. Given the strong protective capabilities of the vaccine, it is plausible that the number of necessary screenings could be limited to three over a lifetime—possibly at ages 30, 40, and 60. However, this assertion needs to be supported by larger-scale studies that utilize HPV DNA testing. In Indonesia, screenings could be integrated with the HPV vaccination process, yet it's crucial that vaccination does not depend on the completion of screening. This approach will ensure that both vaccination and screening rates improve concurrently (Hidayat & Reynaldi, 2023).

In order to meet the 2030 SDGs, the Indonesian government is dedicated to reducing morbidity, mortality, and disability brought on by diseases that can be prevented by vaccination. In order to improve health services in the nation, the Ministry of Health prioritizes strengthening and expanding health services with a focus on preventive and promotive efforts. One way to achieve this is by adding new vaccines to the national immunization program, such as the HPV vaccine. The government is dedicated to creating a more robust and innovative system. A Joint Decree of Four (four) Ministers— Ministers of Education, Culture, Research and Technology, Health, Religion, and Home Affairs of the Republic of Indonesia— was issued in 2022. The decree dealt with the implementation of improving the health status of students, stating that elementary schools, madrasahs, and other equivalent institutions must guarantee that every student has received all necessary vaccinations, including the HPV vaccine. Thus, the successful implementation of HPV vaccination integrated with The Month of School Child Immunization (Bulan Imunisasi Anak Sekolah, BIAS) as one of the School Health Efforts (UKS) depends greatly on the role played by local government and the school sector (Indonesia Communication Team, 2023).

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2. Chimeric Antigen Receptor (CAR)- T Cell Therapy

Treatment with chimeric antigen receptor (CAR)-T cells has been revolutionary because of the extraordinarily potent and long-lasting therapeutic responses it has generated. CARs are artificially created receptors that work to reroute lymphocytes, usually T cells, so they can identify and destroy cells that express a particular target antigen. Strong anti-tumor responses and robust T cell activation are the outcomes of CAR binding, which occurs independently of the MHC receptor, to target antigens produced on the cell surface. The US Food and Drug Administration (FDA) approved anti-CD19 CAR-T cell therapy in 2017 due to its exceptional efficacy against B cell malignancies (Sterner & Sterner, 2021).



Source: Taken from (Labanieh, Majzner, and Mackall 2018).

Figure 7.5 Engineering CAR-T Cells with Protease-Activated, Oxygen-Sensing, and γδ TCR-Based Mechanisms for Tumor-Specific Targeting

Additionally, CAR safety modules can be engineered to selectively activate CAR-T cells at the tumor location, giving the immune system spatial control over targeting (Fig.7.5). To accomplish this, masked CARs incorporate an inhibitory peptide that is attached extracellularly by a cleavable linker. This peptide reversibly inhibits the scFv and maintains the T cells in an inactive state until they arrive at the tumor microenvironment (Han et al., 2017).

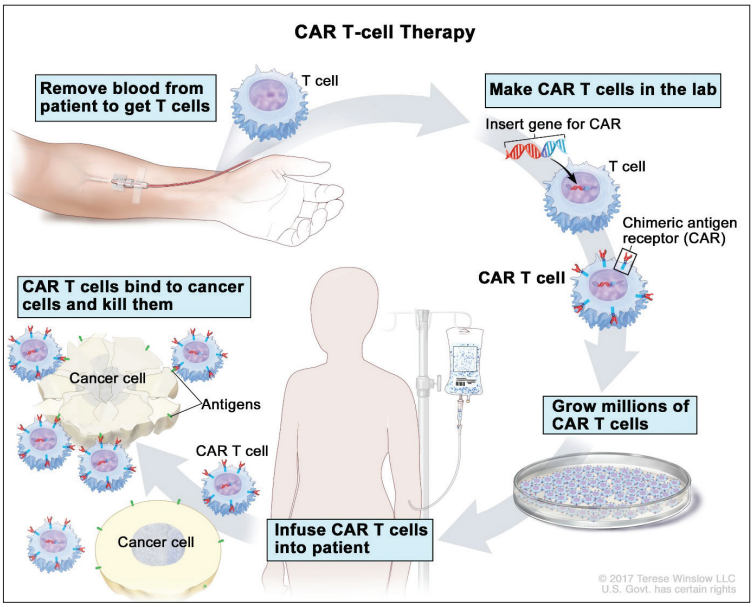
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Once there, locally secreted proteases specifically cleave the inhibitory peptide, revealing the CAR and preparing it to target tumor cells. One study found that when targeting the epidermal growth-factor receptor (EGFR) in a murine xenograft model, a masked CAR was as effective as non-masked CARs. However, since the single-chain fragment variable (scFv) used was derived from cetuximab, which has little cross-reactivity with mouse EGFR, more research is needed to show that the strategy reduces on-target and/or off-tumor effects(Mamot et al., 2012).

One such aspect of the tumor microenvironment that may be explored further for context-dependent CAR activation is the hypoxic environment, brought on by insufficient tumor vascularization. By designing a CAR with oxygen-sensitive domains that degrades in normoxic settings but stabilizes in hypoxic ones, this property has been capitalized on (Juillerat et al., 2017). Despite the poor surface expression of this construct and the system's restricted dynamic range, it shows that the idea of integrating microenvironmental sensors into T cells can allow for control over their behavior(Labanieh, Majzner, and Mackall 2018).

The Food and Drug Administration (FDA) has approved six CAR T-cell therapy platforms since 2017 for the treatment of blood malignancies, including multiple myeloma and some types of leukemia and lymphomas (Figure 7.6). Though these treatments are highly anticipated, only less than half of the patients who receive them go on to live long-term. The fact that they are expensive—more than $450,000 in the case of the most recently approved CAR T-cell therapy—has also drawn criticism (NIH NCI, 2022).

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Source: Taken from (NIH NCI 2023).

Figure 7.6 Process of CAR T-Cell Therapy: Isolation, Engineering, and Reinfusion of Modified T Cells to Target Cancer

Table 7.1 FDA-Approved CAR T-Cell Therapies

FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

Adapted from (NIH NCI, 2022)

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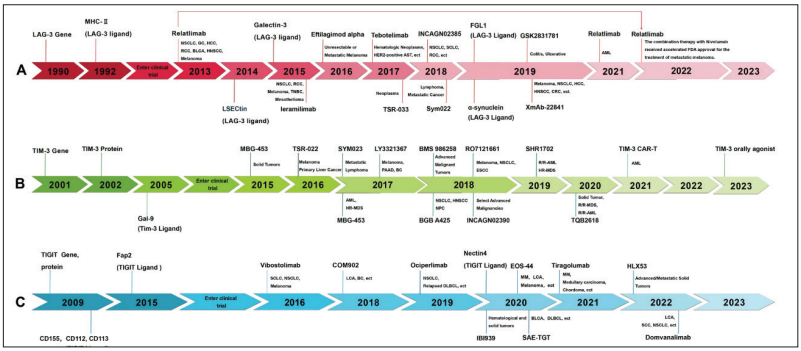
The approximate cost of $450,000 USD for CAR T-cell therapy is a significant financial burden for many people worldwide, with Indonesians are no exception. This high price is primarily due to the complex and specialized process involved in creating personalized treatments for each patient. The therapy requires a combination of advanced scientific research, cutting-edge technology, and extensive clinical trials (Gajra et al., 2022; Hwang et al., 2024). In Indonesia, the majority of the population relies on government-subsidized healthcare or private insurance for medical treatment. Unfortunately, CAR T-cell therapy is often not covered by these insurance plans, leaving patients to bear the full cost of the treatment out-of-pocket. This financial barrier makes it nearly impossible for most Indonesians to access this potentially life-saving treatment (Prasetya, Layyinah, Maftuchan, et al., 2023b).

Moreover, the high cost of CAR T-cell therapy also raises concerns about equitable access to healthcare. While this treatment is groundbreaking and could offer hope to cancer patients, its exorbitant price tag means that only a select few who can afford it will have the opportunity to benefit from it (Cliff et al., 2023). This situation highlights the need for more affordable and accessible cancer treatments, as well as improved healthcare policies and insurance coverage in countries like Indonesia.

3. Immune Checkpoint Inhibitors (ICIs)

The use of immune checkpoint inhibitors has gained significant traction, particularly since the FDA initially approved ipilimumab for the treatment of melanoma. Several immune checkpoints, such as CTLA-4, PD-1, LAG-3, and TIGIT, have been studied for a variety of cancer types during the past few decades (Figure 7.7). To reflect their role as gatekeepers of immunological responses in physiological conditions, they are termed after "immune checkpoints".

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Source: Taken from (Cai et al. 2023).

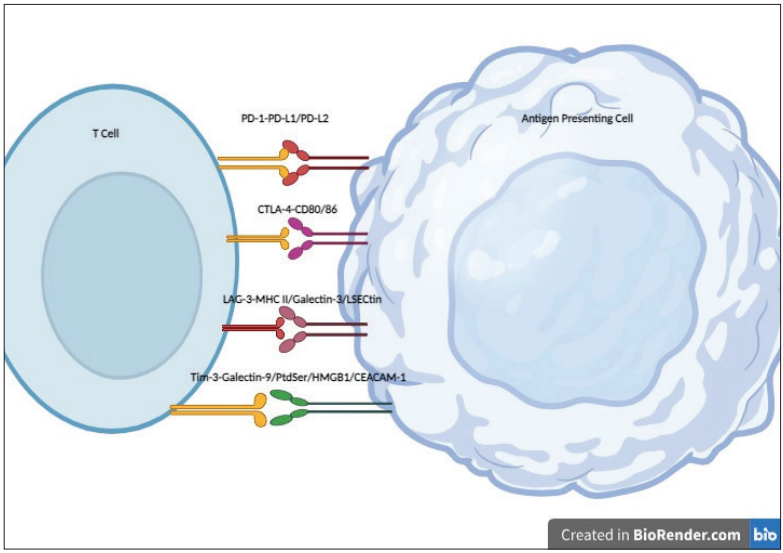
Figure 7.7 The chronology of A.LAG-3, B.TIM-3, and C.TIGIT antibody development and discovery.

Notes: AML: Acute Myelocytic Leukemia; AST: Advanced Solid Tumors; BC: Breast Cancer; BLCA: Bladder Cancer; BLCA: Bladder Cancer; CAR-T: Chimeric Antigen Receptor T Cell Immunotherapy; CRC: Colorectal Cancer; DLBCL: Diffuse Large B cell Lymphoma; ESCC: Esophageal Squamous Cell Carcinoma; Fap2: Fibroblast activation protein 2; FGL-1: Fibrinogen-like protein 1; Gal-9: Galectin-9; GC: GC; HCC: Hepatocellular Carcinoma; HNSCC: Head and neck squamous cell carcinoma; LCA: Lung cancer; LSECtin: Liver and lymph node sinusoidal endothelial cell C-type lectin; MDS: Myelodysplastic Syndromes; MHC-II: MHC class II; MM: Multiple Myeloma; NPC: Nasopharyngeal Carcinoma; NSCLC: Non-small Cell Lung Cancer; OV: Ovarian Cancer; PAAD: Pancreatic Cancer; RCC: Renal Cell Carcinoma; SCC: Squamous Cell Carcinoma; SCLC: Small Cell Lung Carcinoma; TNBC: Triple-Negative Breast Cancer(Cai et al., 2023).

The receptors use mono-tyrosine signaling patterns, such as immunoreceptor tyrosine-based switch motif (ITSM) and immunoreceptor tyrosine-based inhibitory motif (ITIM), to transmit inhibitory signals. As surface molecules, their ability to bind to their cognate receptor can be prevented by blocking antibodies. This is

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the big idea of developing immune checkpoint blockade (Nurlaila, 2022).



Source: Taken from (Nurlaila and Pambudi 2024).

Figure 7.8 Immune Checkpoint-based Immunotherapy (ICIs)

Immune checkpoint inhibitors currently represent the predominant immunotherapeutic modalities utilized in clinical practice, predicated on the mechanism of obstructing the interaction between these checkpoint molecules and their respective ligands (Figure 7.8). The most extensively used immune checkpoint pathway in clinical cancer immunotherapy is programmed death (PD)-1/programmed death ligand (PD-L)1. PD-1 (also known as CD279) is a type I transmembrane glycoprotein with a single extracellular immunoglobulin variable domain, a transmembrane region, and a cytoplasmic domain that contains immunoreceptor tyrosine-based switch motif (ITSM) and immunoreceptor tyrosine-based inhibitory motif (ITIM). The dominant ligand of PD-1, PD-L1 (also called

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CD274 or B7-H1), is a member of the B7 family and is expressed by immune cells, macrophages, DCs, mast cells, T cells, B cells, normal tissue cells, and aberrant tumor cells. When PD-1 binds to PD-L1 on the surface of immune effector cells, like T cells, its cytoplasmic ITIM and ITSM can be phosphorylated, which then draws in Src homology 2 domain-containing tyrosine phosphatase 2 (SHP2) to further suppress T cell receptor (TCR) signaling transduction (Meng et al., 2024).

Unlike CD28, CTLA-4 does not generate a stimulatory signal when it binds to B7, but it is a CD28 homolog with a significantly higher binding affinity for B7. Consequently, the costimulatory signal that CD28:B7 binding typically provides may be inhibited by this competing binding. The activation or anergy of a T cell is dependent on the ratio of CD28:B7 binding to CTLA-4:B7 binding. Additionally, there is evidence to suggest that the stimulatory signals from CD28:B7 and TCR:MHC binding may be counteracted by inhibitory signals that are produced when CTLA-4 binds to B7. Some theories about the mechanisms underlying these inhibitory signals include direct inhibition at the TCR immunological synapse, suppression of CD28 or its signaling pathway, or enhanced T cell mobility that results in a reduced capacity to engage with APCs(Buchbinder & Desai, 2016).

T cell immunoglobulin and mucin-domain containing-3 (Tim-3) protein is involved in the regulation of the immune response and immune tolerance. It contributes to the depletion of CD8+T cells and is expressed on Th1, Th17, monocytes, dendritic cells, and macrophages. Additionally involved in efferocytosis is the TIM-3 protein. Its capacity to bind particular ligands, which open up metabolic pathways, is a crucial characteristic. These comprise high mobility group protein 1 (HMGB-1), phosphatidylserine (PtdSer), cancer-embryonic antigen cell adhesion molecule 1 (CEACAM1), and galectin-9 (Gal-9)(Acharya et al., 2020).

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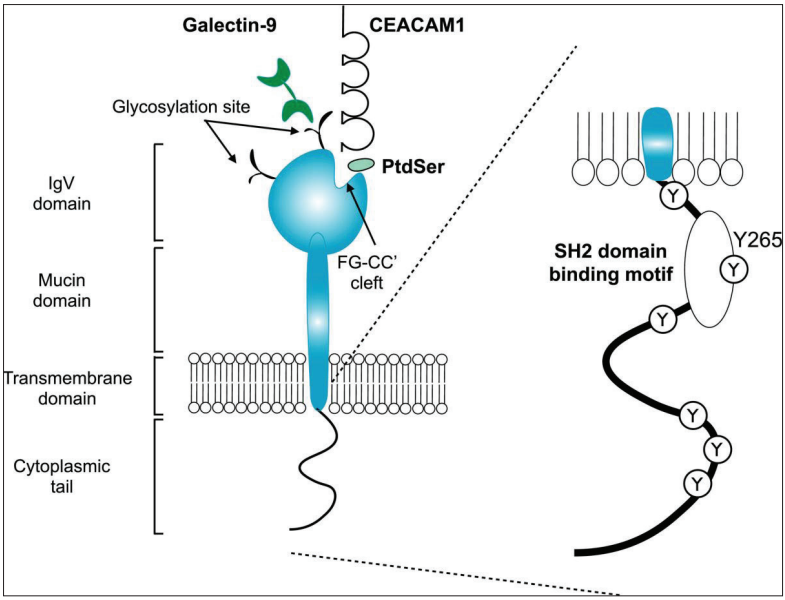
Some studies have demonstrated that the binding of Gal-9 to Tim-3 causes intracellular calcium flow to cause Th1 cell death, ultimately leading to apoptosis(H. Chen et al., 2024; Gooden et al., 2013; Lhuillier et al., 2015; Pang et al., 2024). As a result, Th1 and Th17 responses are suppressed, and immunological tolerance is induced. By forming a heterodimer with Tim-3, CEACAM1 also develops immunological tolerance. They have the ability to bind in both cis- and transforms, which control immunological tolerance and have a role in the depletion of CD8+ T cells. PtdSer is another ligand of Tim-3, and it binds to it via F and G β strands (FG loops) in the IgV domain.

The highly conserved IgV domain has a FG loop and a CC′ loop and is composed of two antiparallel β-sheets with four cysteines in the variable region. Normally, these loops are situated at opposite ends of the IgV domain; however, the CC′ loop in Tim-1, -3, and -4 proteins is orientated closer to the FG loop, resulting in the formation of a distinct ligand-binding pocket and determining receptor–ligand interaction. The phosphorylation of tyrosine residues in the cytoplasmic tail is essential for Tim-3 signaling; however, the downstream signaling pathways in T cells are not as well understood (Zeidan et al., 2021b).

TIM-3 ligands have been discovered as galectin-9, phosphatidylserine (PtdSer), high-mobility group box 1 (HMGB1), and carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1) (Figure 7.9). The glycosylation sites of the IgV domain allow Galectin-9 to bind to TIM-3, while the FG-CC cleft can be the site of PtdSer and CEACAM1 ligation. Six tyrosine residues and one Src homology 2 (SH2) binding motif may be found in the cytoplasmic tail of TIM-3 (Kikushige, 2021).

On the other hand, phosphorylation of certain tyrosine residues by (ITK) IL2 Inducible T Cell Kinase is triggered by galectin-9 and/or CEACAM1 ligation to the IgV domain of Tim-3, leading

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Source: Taken from (Kikushige 2021).

Figure 7. 9 Tim-3 (human T-cell immunoglobulin and mucin domain containing 3) and its ligands' molecular structure.

to the release of BAT3. Afterwards, FYN can be called to the same area. BAT3 and FYN may thus engage in competition for binding to Tim-3's cytoplasmic tail. By interacting with phosphoproteins linked to glycosphingolipid-enriched microdomains1 (PAG1), FYN has been demonstrated to inhibit T-cell receptor (TCR) activation. Thus, Tim-3-ligand-induced FYN-recruitment is one potential route of T cell inhibitory signaling mediated by TIM-3. Moreover, TIM-3 colocalizes with the receptor phosphatases CD45 and CD148 at the immunological synapse, and inhibiting TIM-3 has been demonstrated to improve the development of functional immunological synapses in human T cells(Kikushige, 2021). There is also a soluble version of Tim-3 that does not include the mucin and transmembrane domains and may be detrimental to the T-cell-mediated immunological response(Zeidan et al., 2021b).

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Table 7.2 Completed phase 3 clinical trials of immune checkpoint inhibitor medications across a range of cancer types.

Disease	Code	NCT Number	Enrolment	Arms	Follow-up	Median PFS/RFS	Median OS	PMID
Untreated unresectable stage III or IV melanoma	---	NCT00324155	681	A: Ipilimumab 10 mg/kg (Q3W, -22 weeks) + Dacarbazine 850 mg/m^2 (Q3W, -22 weeks) B: Dacarbazine 850 mg/m^2 (Q3W, -22 weeks)	5-year	--	A: 11.2 months B: 9.1 months	25713437
Complete resection of high-risk stage III melanoma	EO-RTC-18071	NCT00636168	1211	A: Ipilimumab 10 mg/kg (Q3W, -3 years) B: Placebo	5-year	A: 27.6 months B: 17.1 months	--	27717298
Unresectable or metastatic melanoma	---	NCT01515189	831	A: Ipilimumab 10 mg/kg (Q3W, 4 doses) B: Ipilimumab 3 mg/kg (Q3W, 4 doses)	5-year	--	A: 15.7 months B: 11.5 months	32503946
Untreated, unresectable or metastatic melanoma	Check-Mate-066	NCT01721772	418	A: Nivolumab 3 mg/kg B: Dacarbazine 1000 mg/m^2	5-year	A: 5.1 months B: 2.2 months	A: 34.8 months B: 20.5 months	32997575

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
Unresectable or metastatic melanoma	KEY-NOTE-006	NCT01866319	834	A: Pembrolizumab 10 mg/kg (Q2W, -24 months) B: Pembrolizumab 10 mg/kg (Q3W, -24 months) C: Ipilimumab 3 mg/kg (Q3W, 4 doses)	5-year	A + B: 8.4 months C: 3.4 months	A + B: 32.7 months C: 15.9 months	31345627
Previously treated advanced or metastatic squamous cell NSCLC	Check-Mate-017 Check-Mate-057	NCT01642004 NCT01673867	854	A: Nivolumab 3 mg/kg or 480 mg B: Docetaxel	5-year	---	A : 11.1 months B: 8.1 months	33449799
Previously treat-ed NSCLC	KEY-NOTE-010	NCT01905657	1034	A: Pembrolizumab 2 mg/kg (Q2W, -2 years) B: Pembrolizumab 10 mg/kg (Q3W, --2 years) C: Docetaxel 75mg/m^2	5-year	---	A + B: 11.8 months C: 8.4 months	34048946
Previously untreated stage IV, programmed cell death ligand 1 (PD-L1) strong express-ing NSCLC	KEY-NOTE-024	NCT02142738	305	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	5-year	A: 7.7 months B: 5.5 months	A: 26.3 months B: 13.4 months	33872070

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
PD-L1 strong expressing NSCLC	KEY-NOTE-042	NCT02220894	1274	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	5-year	---	A: 16.4 months B: 12.1 months	36306479
Locally ad-vanced or meta-static NSCLC	OAK	NCT02008227	1225	A: Atezolizumab 1200 mg B: Docetaxel 75 mg/ m^2	2.25-years	---	A: 13.8 months B: 9.6 months	27979383
Stage IV non-squamous NSCLC	Impow-er-130	NCT02367781	723	A: Atezolizumab+ Nab-Paclitaxel+ Carbo-platin B: Nab-Paclitaxel+ Carboplatin	Median 18.5 months	A: 7.0 months B: 5.5 months	A: 18.6 months B: 13.9 months	31122901
PD-L1 selected, chemotherapy naïve stage IV NSCLC	Impow-er-110	NCT02409342	572	A: Atezolizumab B: Chemotherapy	Median 15.7 months	A: 7.2 months B: 5.5 months	A: 20.2 months B: 13.1 months	32997907
Extensive-dis-ease small cell lung cancer	Impow-er-133	NCT02763579	403	A: Atezolizumab 1200mg +EP B: Placebo +EP	Median 22.9 months	---	A: 12.3 months B: 10.3 months	31959349

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
	CASPIAN	NCT03043872	987	A: Durvalumab+ Tremelimumab+ EP B: Durvalumab +EP C: EP	Median 25.1 months	---	B: 12.9 months C: 10.5 months	33285097
	AS-TRUM-005	NCT04063163	585	A: Serplulimab +EP B: Placebo +EP	Median 12.3 months	A: 5.7 months B: 4.3 months	A: 15.4 months B: 10.9 months	36166026
Advanced or metastatic (medically or surgically unresectable) clear-cell renal cell carcinoma	Check-Mate-025	NCT01668784	821	A: Nivolumab 3 mg/kg B: Everolimus	5 -year	---	A: 25.8 months B: 19.7 months	32673417
Metastatic or lo-cally advanced/ unresectable urothelial carci-noma	KEY-NOTE-045	NCT02256436	542	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	Median 27.7 months	---	A: 10.1 months B: 7.3 months	31050707

Buku ini tidak diperjualbelikan

Disease	Code	NCT Number	Enrolment	Arms	Follow-up	Median PFS/RFS	Median OS	PMID
Locally advanced or metastatic urothelial bladder carcinoma	IMvigor-211	NCT02302807	931	A: Atezolizumab B: Chemotherapy	Median 33 months	---	A: 8.6 months B: 8.0 months	33902955
Advanced renal cell carcinoma	CLEAR	NCT02811861	1069	A: Lenvatinib 20 mg +Pembrolizumab 200 mg B: Sunitinib 50 mg	Median 26.6 months	A: 23.9 months B: 9.2 months	---	33616314
Unresectable advanced or recurrent esophageal cancer	ATTRACTION-3	NCT02569242	419	A: Nivolumab 240 mg B: Docetaxel/ Paclitaxel	Minimum 17.6 months	---	A: 10.9 months B: 8.4 months	31582355
Advanced/metastatic adenocarcinoma and squamous cell carcinoma of the esophagus that have progressed after first-line standard therapy	KEYNOTE-181	NCT02564263	628	A: Pembrolizumab 200 mg (Q3W, -2 years) B: Chemotherapy	16 months	---	A: 9.3 months B: 6.7 months	33026938

Buku ini tidak diperjualbelikan

Disease	Code	NCT Number	Enrolment	Arms	Follow-up	Median PFS/RFS	Median OS	PMID
Stage IV mismatched repair deficient or microsatellite instability-high colorectal carcinoma	KEYNOTE-177	NCT02563002	307	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	44.5 months	A: 16.5 months B: 8.2 months	No significant difference	35427471
Recurrent or metastatic head and neck squamous cell cancer	CheckMate-141	NCT02105636	361	A: Nivolumab 3 mg/kg B: Cetuximab/ Methotrexate/ Docetaxel	1-year	---	A: 7.5 months B: 5.1 months	27718784
	KEYNOTE-040	NCT02252042	495	A: Pembrolizumab 200 mg (Q3W, -2 years) B: Cetuximab/ Methotrexate/ Docetaxel	2-year	---	A: 8.4 months B: 6.9 months	30509740
	KEYNOTE-048	NCT02358031	882	A: Pembrolizumab 200 mg (Q3W, -2 years) B: Pembrolizumab 200 mg (Q3W, -2 years) + Chemotherapy C: Cetuximab + Chemotherapy	Median 45 months	---	A: 14.9 months B: 14.7 months C: 10.8 months	36219809

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Disease	Code	NCT Number	Enrolment	Arms	Follow-up	Median PFS/RFS	Median OS	PMID
Squamous cell carcinoma Recurrent or metastatic, platinum-refractory cervical cancer	EMPOWER	NCT03257267	608	A: Cemiplimab 350 mg B: Chemotherapy	Median 18.2 months	---	A: 12.0 months B: 8.5 months	35139273
Persistent, recurrent, or metastatic cervical cancer	KEYNOTE-826	NCT03635567	617	A: Pembrolizumab 200 mg (Q3W, -2 years) + Chemotherapy B: Placebo + Chemotherapy	Median 22 months	A: 10.4 months B: 8.2 months	A: 53.0-54.4% B: 41.7-44.6%	34534429
Previously untreated metastatic triple-negative breast cancer	Impassion130	NCT02425891	902	A: Atezolizumab + Nab-Paclitaxel B: Placebo + Nab-Paclitaxel	Median 18.8 months	---	A: 25.4 months B: 17.9 months (PD-L1 postive)	34272041
Previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer	KEYNOTE-355	NCT02819518	882	A: Pembrolizumab 200 mg (Q3W, -2 years) + Chemotherapy B: Placebo+ Chemotherapy	Median: 44.1 months	---	A: 23.0 months B: 16.1 months	35857659

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
Triple-negative breast cancer	KEY-NOTE-552	NCT03036488	1174	A: Pembrolizumab 200 mg (Q3W, -2 years) + Chemotherapy B: Placebo+ Chemo-therapy	Median: 39.1 months	A: 84.5% B: 76.8%	---	35139274
PD-L1- selected, chemotherapy naïve stage IV NSCLC	Impos-er-110	NCT02409342	572	A: Atezolizumab B: Chemotherapy	Median: 15.7 months	A: 7.2 months B: 5.5 months	A: 20.2 months B: 13.1 months	32997907
Extensive-dis-ease small cell lung cancer	Impos-er-133	NCT02763579	403	A: Atezolizumab 1200mg + EP B: Placebo + EP	Median: 22.9 months	---	A: 12.3 months B: 10.3 months	31959349
	CASPIAN	NCT03043872	987	A: Dunvalumab+-Tremelimumab + EP B: Dunvalumab + EP C: EP	Median: 25.1 months	---	B: 12.9 months C: 10.5 months	33285097
	AS-TRUM-005	NCT04063163	585	A: Serplulimab + EP B: Placebo + EP	Median: 12.3 months	A: 5.7 months B: 4.3 months	A: 15.4 months B: 10.9 months	36166026

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
Advanced or metastatic (medically or surgically unresectable) clear-cell renal cell carcinoma	Check-Mate-025	NCT101668784	821	A: Nivolumab 3mg/kg B: Everolimus	5-year	---	A: 25.8 months B: 19.7 months	32673417
Metastatic or locally advanced/ unresecctable urothelial carcinoma	KEY-NOTE-045	NCT02256436	542	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	Median: 27.7 months	---	A: 10.1 months B: 7.3 months	31050707
Locally advanced or metastatic urothelial bladder carcinoma	IMvig-or-211	NCT02302807	931	A: Atezolizumab B: Chemotherapy	Medi-an: 33 months	---	A: 8.6 months B: 8.0 months	33902955
Advanced renal cell carcinoma	CLEAR	NCT02811861	1069	A: Lenvantinib 20mg +Pembrolizumab 200mg B: Sunitinib 50 mg	Median: 26.6 months	---	A: 23.9 months B: 9.2 months	33616314

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Disease	Code	NCT Number	Enrol-ment	Arms	Fol-low-up	Median PFS/RFS	Median OS	PMID
Unresectable advanced or recurrent esoph-ageal cancer	ATTRAC-TION-3	NCT02569242	419	A: Nivolumab 240mg B: docetaxel/Pacitaxel	Mini-mum: 17.6 months	---	A: 10.9 months B: 8.4 months	31582355
Advanced/met-astatic adeno-carcinoma and squamous cell carcinoma of the esophagus that have progressed after first-line standard therapy	KEY-NOTE-181	NCT02564263	6280	A: Pembrolizumab 200 mg (Q3W, -2 years) B: Chemotherapy	16 months	---	A: 9.3 months B: 6.7 months	33026938
Stage IV mis-matched repair deficient or microsatellite instability-high colorectal carci-noma	KEY-NOTE-177	NCT02563002	307	A: Pembrolizumab 200 mg (Q3W, -35 doses) B: Chemotherapy	44.5 months	A: 16.5 months B: 8.2 months	No sig-nificant ddiffer-ence	35427471

Notes: *NSCL* non-small cell lung cancer, *RP* carboplatin or cisplatin plus etoposide, *CCRT* concurrent chemoradiation therapy, *Q2W* once every 2 weeks, *Q3W* once every 3 weeks, *PFS* progression-free survival, *RFS* recurrence-free survival, *OS* overall survival.

Source: Modified from(Q. Sun et al. 2023).

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Apart from the four ligands listed before, there has also been evidence of direct interaction between Tim-3 and retinoic acid-inducible gene I (RIG-I), a member of the (RIG-I)-like receptor family. In particular, Tim-3 blocks the expression of RIG-I in macrophages via STAT1, encourages RIG-I ubiquitination and destruction via the action of the E3 ligase RNF-122, and ultimately suppresses the generation of type I interferon (IFN) and antiviral activity. Sabatolimab, the first anti-Tim-3 monoclonal antibody, was created for use in solid tumor therapy. It functions by preventing Tim-3 from attaching to its ligands, PtdSer and Gal-9. Over 33 Tim-3 mAbs have been tested as cancer immunotherapies in clinical trials to date(Cai et al., 2023).

Tumor-infiltrating lymphocytes (TILs) from several solid tumors, such as melanoma, glioma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), breast cancer (BC), gastric cancer (GC), lymphoma, and leukemia, have been found to overexpress lymphocyte activation gene-3 (LAG-3) (Cai et al., 2023). LAG-3 is a type I transmembrane protein with four Ig-like domains termed domain 1 (D1) to domain 4 (D4). LAG-3's extracellular region and CD4, which likewise consists of four Ig-like domains, have an amino acid homology of about 20%. Furthermore, in the majority of species, the LAG-3 gene is situated next to the CD4 gene. Therefore, it is most likely that gene duplication is how these genes developed. In contrast to their shared extracellular areas, LAG-3 and CD4's intracellular regions don't really resemble each other (Maruhashi et al., 2020).

Unlike other checkpoint molecules that become an impediment to activated T cell proliferation, T cells lacking LAG-3 precisely display faulty growth. This was noted in an *in vitro* setting. As LAG-3 has a greater affinity for MHC class II than CD4, the CD4:MHC class II complex may be disrupted if LAG-3 is present. This was not the case, though, according to an experiment by Workman and

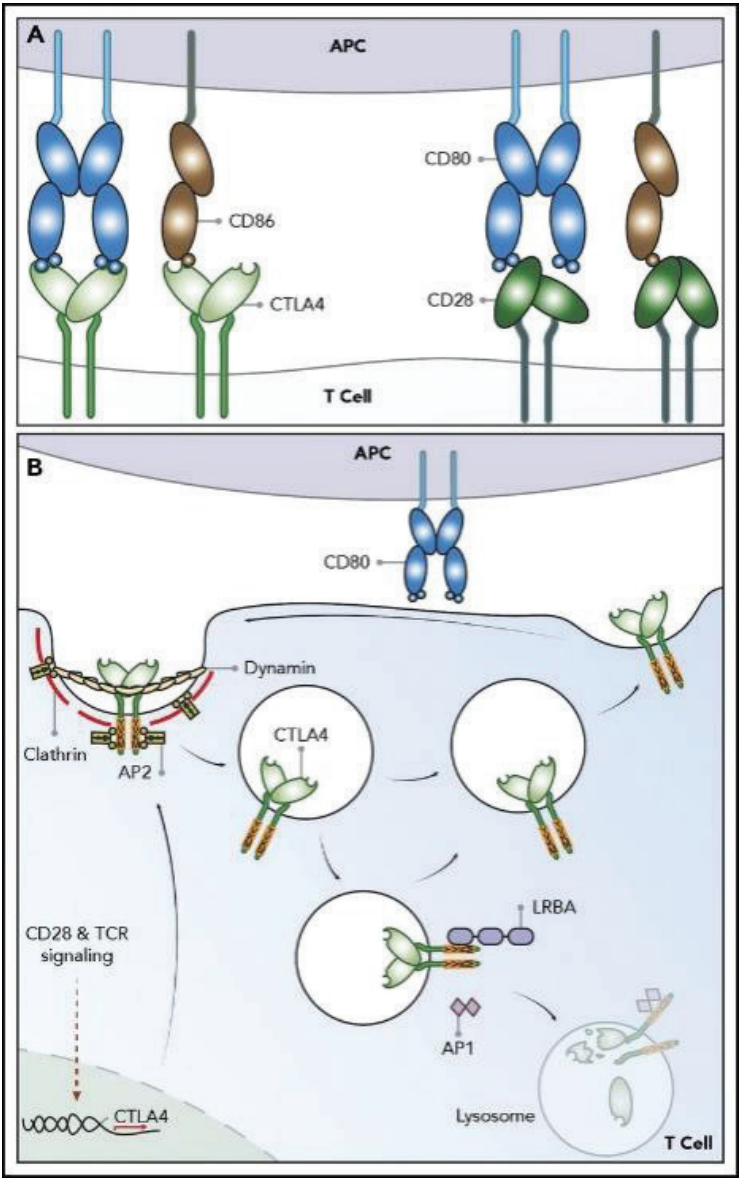
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Vignali in which OT-II-TCR mice were pre-crossed with a pair of transgenic mice that had a knock-out mutant of LAG-3. The OT-II-TCR is an MHC class II-restricted TCR that binds to chicken ovalbumin residues 323–339. Workman and Vignali discovered that LAG-3 had no effect on the interaction between CD4 and MHC class II (Nurlaila, 2022).

The inhibitory receptor CTLA-4, which is mostly produced by T lymphocytes, is a member of the CD28 immunoglobulin subfamily. The antigen-presenting cells' surface is usually home to its ligands, CD80 and CD86, which can bind to either CTLA-4 or CD28 to produce a co-inhibitory or costimulatory response, respectively. T-cell homeostasis and self-tolerance are vitally regulated by CTLA-4 due to its damping impact. Cell-intrinsic mechanisms, which impact T-cells that express CTLA-4, and cell-extrinsic mechanisms, which impact secondary cells, are the two categories in which CTLA-4's inhibitory actions fall. The past ten years of research have demonstrated that CTLA-4 primarily functions in a cell-extrinsic manner through its rivalry with CD28, its ability to trans-endocytose CD80 and CD86, and its direct tolerogenic effects on the contacting cell(Van Coillie et al., 2020).

As shown in Figure.7.10, two ligands, CD80 and CD86, are shared by the CTLA-4 and CD28 receptors. Both receptors bind to CD86, a monomeric ligand with lesser affinity, and CD80, a dimeric ligand with higher affinity. When it comes to CD80, CTLA-4 is more ardent and has a greater affinity than CD86. The relative affinities go from high to low and from left to right, b) T cell-expressed CTLA-4 exhibits strong endocytic activity. CTLA-4 is either induced after T-cell activation through CD28 and TCR signaling, or it is produced constitutively in Treg. When the ligand is not present, CTLA-4 is primarily located inside of cells after clathrin-mediated endocytosis, which is facilitated by CTLA-4's interaction with the AP2 protein. The fast internalization of CTLA-4 is facilitated by the binding of

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Source: Taken from (Rowshanravan, Halliday, and Sansom 2018).

Figure 7.10 The Biology of CTLA-4.

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the AP2 (μ2 subunit) to the tyrosine-based (YVKM) motif of the cytoplasmic domain. Additionally, it has been discovered that the LRBA and AP1 proteins bind to the YVKM motif on CTLA-4, thereby imposing distinct fates on the protein. While AP1 may mediate CTLA-4 trafficking to lysosomal compartments, where it is subsequently degraded, LRBA may promote CTLA-4 recycling to the plasma membrane(Rowshanravan et al., 2018).

With a 10-to 100-fold higher affinity than CD28, CTLA-4's competitive binding of B7 proteins is the most extensively documented mechanism of suppression. T-cells are thus devoid of CD28-mediated activation signals. After binding B7 proteins, CTLA-4 has also been shown to inhibit proximal T-cell receptor (TCR) signaling, disrupt the central supramolecular cluster (c-SMAC) within the immunological synapse, and transendocytose B7 molecules from the surface of APCs. These mechanisms further deprive T-cells of stimulatory signaling. Since the genetic deletion of CD28 prevents the catastrophic lymphoproliferation seen in CTLA-4–/– mice, it is widely believed that the disruption of CD28 signaling is the primary mechanism by which CTLA-4 works (Oyewole-Said et al., 2020).

After these well-known ICIs were widely available, a new checkpoint was discovered: T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif (ITIM) domain (TIGIT), which is sometimes referred to as WUCAM, VSTM3, or VSIG9. There are ongoing clinical trials involving anti-TIGIT or anti-TIGIT plus anti-PD-1 combos. In patients with advanced lung cancer, tiragolumab, a TIGIT-targeted antibody, recently failed to reach the endpoint, although showing promise in a few clinical trials (P. Zhang et al., 2024).

In addition to memory T cells, Tregs, follicular helper cells, and NKT cells, TIGIT is produced on activated conventional αβ T cells. In contrast to CD226 for malignancies, TIGIT is co-expressed with PD-1 on human and mouse tumor-infiltrating CD8+ T cells and

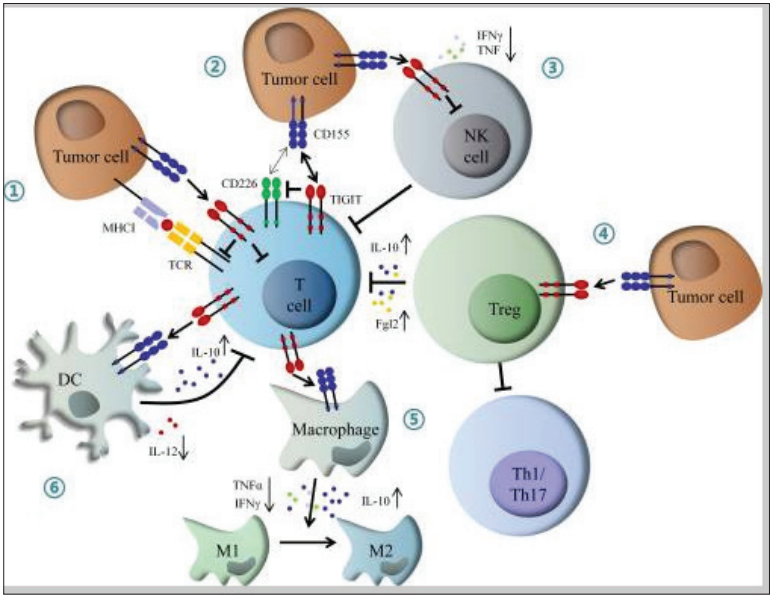
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is expressed dimly by naive T cells. Furthermore, TIGIT is further elevated in the tumor microenvironment and is strongly expressed in peripheral blood Tregs from both cancer patients and healthy donors (Joller et al., 2014).

TIGIT's ligands consist of CD112 and the poliovirus receptor (PVR), which is also referred to as CD155, Necl-5, and Tage4. PVR is the high-affinity cognate receptor of TIGIT. Moreover, TIGIT engages in ligand competition with CD96 (TACTILE) and CD226 (DNAM-1). Research has demonstrated that TIGIT has the highest affinity for CD155, as evidenced by its ability to successfully prevent CD155 from binding to either CD96 or CD226. Notably, TIGIT can directly cis-bind to CD226 to inhibit its homo-dimerization, preventing CD226 from binding to CD155 to perform a co-stimulatory role, in addition to competing with CD226 for ligands(W. Tang et al., 2023).

Despite the hopeful success of therapeutic strategies targeting TIGIT in hematological malignancies, over-activated T cells can cause immune-related adverse events (irAEs) that can lead to multiple organ dysfunction and a poor prognosis. Two patients experienced adverse events (irAEs) in the first phase of the anti-TIGIT antibody vibostolimab research. One of which was a severe skin response and the other an adrenal insufficiency. Additional phase 1 research with the combination of anti-PD-1 antibody tislelizumab and anti-TIGIT antibody ociperlimab in advanced solid tumors revealed that 15 out of 26 patients experienced adverse events (irAEs), with three of those cases being severe (grade ≥3). The CITYSCAPE trial also found that skin rash was the most common adverse event (irAE) in 69% of patients treated with anti-TIGIT antibody tiragolumab and anti-PD-L1 antibody atezolizumab. Pancreatitis, hypothyroidism, colitis, and diabetes were the next most prevalent irAEs(Jin et al., 2022).

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Source: Taken from (Jin et al. 2022).

Figure 7.11 Mechanism of inhibitory role of TIGIT in immunoregulation.

The immunoregulation-inhibiting mechanism of TIGIT. The intracellular inhibitory signals that are transmitted by TIGIT's interaction with CD155 directly decrease the TCR signal and the function of effector T cells (Figure 7.11). By preventing CD226 homodimerization and reducing IFN-γ production, TIGIT suppresses T cell activation triggered by CD226. Lastly, TIGIT directly causes NK cell fatigue, which aids in CD8+ T cell inactivation. By increasing IL-10 and Fgl2, as well as inhibiting Th1 and Th17 cells, TIGIT improves Tregs-mediated effector T cell failure. Increased IL-10 and decreased IFNγ and TNFα allow TIGIT to facilitate macrophage transition from pro-inflammatory M1 to anti-inflammatory M2 phenotype. Through aberrant cytokine production mediated by DCs, TIGIT impairs T cell activity(Jin et al., 2022).

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Table 7.3 Ongoing clinical trials targeting TIGIT in hematological malignancies.

NCT number	Agent	Treatment	Tumor type	Phase
NCT05315713	Tiragolumab	Combined with mosunetuzumab ± atezolizumab (Anti-PD-L1 mAb) Monotherapy	r/r-DLBCL r/r-FL	Phase 1/2
NCT04045028	Tiragolumab	Combined with rituximab Combined with daratumumab ± atezolizumab	r/r-B-NHL r/r-MM	Phase 1
NCT05267054	Ociperlimab (BGB A1217)	Combined with rituximab Combined with tislelizumab (anti-PD-1 mAb)	r/r-DLBCL	Phase 1/2
NCT04150965	BMS-986207	Combined with pomalidomide and dexamethasone	r/r-MM r/r-HL	Phase 1/2
NCT05005442	Vibostolimab (MK7684A)	Combined with pembrolizumab (anti-PD-1 mAb)	r/r-B-NHL r/r-MM	Phase 2
NCT04354246	CM902	Monotherapy Combined with COM701 (anti-PVRIG mAb)	MM	Phase 1
NCT04254207	SEA-TGT	Monotherapy Combined with sasanlimab (anti-PD-1 mAb)	cHL DLBCL PT-CL-NOS	Phase 1

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NCT number	Agent	Treatment	Tumor type	Phase
NCT04772989	AB308	Combined with zimberelimab (anti-PD-1 mAb)	DLBCL MM	Phase 1
NCT05289492	EOS-448	Monotherapy Combined with iberdomide ± dexamethasone	r/r-MM	Phase 1/2

Source: modified from Jin et al., 2022.

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CHAPTER VIII
AGING ADDS VOLUME IN CANCER EMERGENCE

Because of the world's current demographic condition, which includes a low birth rate, rising average life expectancy, and an increase in the population of seniors and older people, our era is known as the age of ageing. An important indicator of the global population aging process is the notable rate of growth of the proportion of people over 60 and older worldwide compared to other age groups. Therefore, the proportion of the global population that is 60 years of age or older was 962 million in 2017, or 13%. Every year, the proportion of people over 60 in the world increases by 3%. UN estimates indicate that there will be 3.1 billion individuals on the earth who are 60 years of age or older by 2030. Numerous international sources of data demonstrate that industrialized countries have a significant propensity toward a dynamic increase in the total population structure's number of individuals over 80, with the share of this population group seeing a sharp rise in care needs. This percentage is expected to rise from 70 million to 401 million between 2000 and 2050. Japan and other European nations, such as Germany, Italy, Sweden, and

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Greece, are thought to have the highest demographic aging rates; the population 65 and older comprises individuals from 18 to 21% (Khavinson et al., 2020).

Indonesia is home to 273.5 million people, making it the fourth most populous country in the world. About 10% of Indonesians, or 25.9 million people, were over 60 in 2019. The working-age population in Indonesia is beginning to outnumber "dependants" who are either over 65 or under 15 years old. This is known as the "demographic dividend" period, which the country is currently entering. Meeting the demands of an aging population has grown in importance as a matter of national public policy in recent years. Given that by 2050, one-third of Indonesians are expected to be over 60, millions of people will be at risk of poverty as they age since many will not have sufficient additional income (from pensions or savings) to maintain their standard of living(Ministry of Health, 2019). Moreover, aging is a significant risk factor for a variety of chronic human diseases, including cancer. Consequently, the growing number of elderly persons contributes to the increase of cancer patients (Berben et al., 2021; Laconi et al., 2021).

As people age, their bodies gradually deteriorate and their risk of developing several diseases rises. Specifically, it has long been known that the incidence and fatality rate of cancer rises exponentially with age. A deeper comprehension of the connection between aging and cancer is crucial given the growing aging population. Furthermore, differences in malignancies between younger and older individuals have also been noted. For example, older patients with ovarian cancer have a worse prognosis than younger patients with breast cancer, which tends to be more aggressive and associated with a lower survival rate (Chatsirisupachai et al., 2022).

Numerous investigations have uncovered unique molecular traits of tumors in connection to age in a range of cancer types, including colorectal(Siegel, Wagle, et al., 2023; Spáčilová et al., 2018),

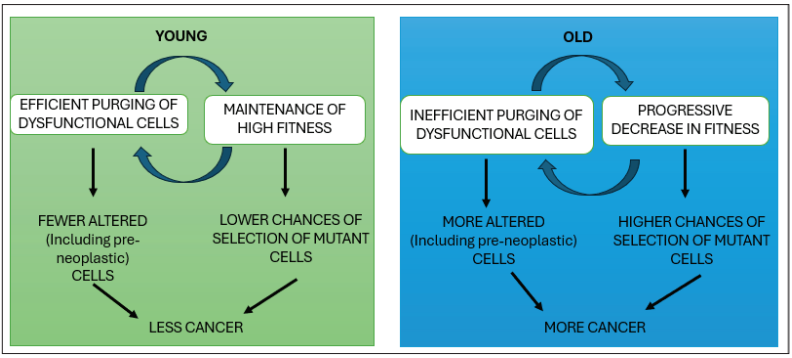
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prostate (Bechis et al., 2011; Pettersson et al., 2018; Stangelberger et al., 2008), and breast cancers(Benz, 2008; Gu et al., 2020; Lemij et al., 2022). However, only a few molecular data categories and one cancer type were examined at a time in these analyses. Four independent studies have conducted pan-cancer analysis to reveal the genomic, transcriptome, and epigenomic trends linked with aging. Age-related molecular change patterns may indicate variations in the oncogenic pathways according to the patient's age (Chatsirisupachai et al., 2022).

Ageing and cancer are still two biological processes whose complexity has so far eluded easy explanations. Nonetheless, several discoveries in both domains appear to converge on fundamentally shared features and start to illuminate the mechanisms underlying the long-standing correlation between aging and cancerous disease. Given that some of these clones are pre-neoplastic, the widespread presence of aberrant clonal expansions in old tissues demonstrates a direct biological relationship between the aged phenotype and cancer risk (Laconi et al., 2020).

Three parameters were proposed to be related to aged tissues' clonogenic propensity. First, due to inadequate maintenance during the traditionally post-reproductive periods, tissue microenvironments deteriorate with age; second, the competitive fitness of the majority of the tissue initially declines; and third, a concomitant relative inability to clear altered (dysfunctional) cells that is attributed to the reduced competitive fitness of certain tissue. These changes work in concert to create a feedforward system that will probably favor the formation of modified cell clones with adaptive mutations, some of which may be carcinogenic. The potential for evolution-minded strategies for cancer prevention and treatment is highlighted by our growing understanding of the factors that contribute to the genesis and progression of cancer(Laconi et al., 2020).

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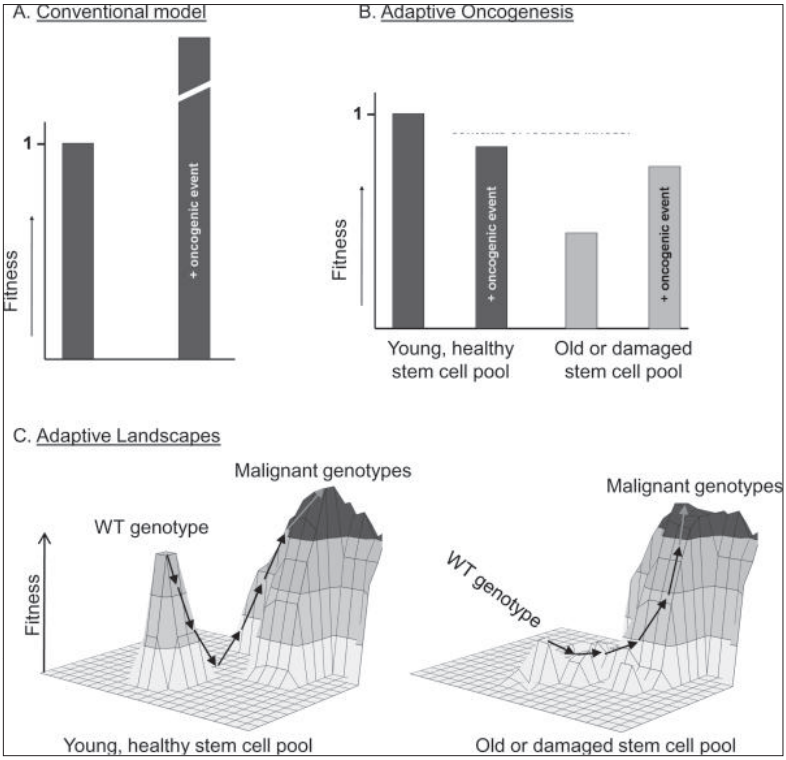
Source: Modified from (Laconi, Marongiu, and DeGregori 2020).

Figure 8.1 Modulations of Age-Related Tissue Microenvironments and Their Influence on Carcinogenesis Dynamics.

Throughout reproductive ages, quality-control mechanisms guarantee the preservation of cell fitness (YOUNG; left panel) (Figure 8.1). This maintenance is caused by the efficient elimination of changed cells as well as the minimal likelihood that these cells will be selected in a landscape of young, healthy tissue. These two systems support one another. In contrast, post-reproductive ages see a decline in quality-control mechanisms (OLD, right panel). This reduction suggests that when more modified cells proliferate, the possibility of their selection rises when clones carry mutations that are advantageous in the environment of older tissues. Reductions in cellular fitness and ineffective removal of modified cells reinforce each other once more(Laconi et al., 2020).

The prevailing theory states that clonal selection results from oncogenic events that typically increase cellular fitness. Therefore, it is thought that the existence of oncogenic mutations restricts the onset and spread of cancer. On the other hand, DeGregori argued that long-lived multicellular organisms have developed populations of highly adapted stem cells, both to maintain a tissue effectively and to counteract the evolution of somatic cells. Stabilizing selection should

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Source: Courtesy of (DeGregori 2011).

Figure 8.2 Comparion of Adaptive Oncogenesis with the Conventional Model of Cancer Initiation.

As illustrated in Figure. 8.2A, the Traditional Oncogenic Model posits that oncogenic events are predominantly advantageous, with their occurrence dictating the initiation of tumorigenesis. In contrast, Figure. 8.2B reflects the Adaptive Oncogenesis framework, which suggests that within a population of healthy, well-maintained stem and progenitor cells, phenotypic modifications—whether genetic or epigenetic—are infrequently beneficial. According to this model, oncogenic alterations that confer increased cellular fitness are

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typically selected for only in contexts where aging, environmental stressors, or accumulated cellular damage diminish the functional capacity of the stem/progenitor cell compartment (DeGregori, 2011).

Furthermore, the adaptive stem cell populations are proposed to exist across a spectrum of physiological states, including young, healthy individuals as well as elderly or previously exposed to carcinogenic stressors. The diversity of potential genetic and epigenetic variants within these populations is represented along the X and Y axes, respectively, highlighting the dynamic heterogeneity and plasticity inherent in stem cell evolution under varying biological contexts.Fitness is represented via the Z axis. Little arrows point to epigenetic or mutational alterations that may result in cancer. These changes have a significant impact on cellular fitness in a population of immature, healthy stem cells, but much less of an impact on a pool of damaged stem cells (DeGregori, 2011).

A. AGE-RELATED SOMATIC MUTATION BURDEN IN TUMORS

With an estimated rise of 0.077 mutations per megabase per year, older age is linked to greater somatic mutations (single-nucleotide variations and minor insertions/deletions) in most cancer types(-Jaiswal et al., 2014; C. H. Li et al., 2022; Risques & Kennedy, 2018). This age-related rise in mutation load is mostly driven by spontaneous deamination of 5-methylcytosine to thymine (C>T) transitions, often known as the "clock-like" mutational signature(Mealey et al., 2021; Poulos et al., 2017; Spisak et al., 2023). Moreover, older people have a higher likelihood of having DNA damage repair markers. In both prostate and melanoma, the mutational signature linked to APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like family) cytidine deaminase activity rises with age(J. Gao et al., 2018; Pecori et al., 2022).

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Furthermore, somatic copy-number changes (SCNAs) also rise with age in addition to somatic mutations. Certain cancer types, such as low-grade glioma, endometrial, ovarian, and prostate cancers, showed a strong positive correlation between SCNA level and age (Chatsirisupachai et al., 2022; C. H. Li et al., 2022). Nevertheless, in sarcoma alone, a study discovered a favorable correlation between SCNAs and age. This disparity may result from the 50-year-old limit used to distinguish between elderly and younger individuals, in contrast to other research that included age in their statistical model as a continuous variable(Chatsirisupachai et al., 2022; C. H. Li et al., 2022).

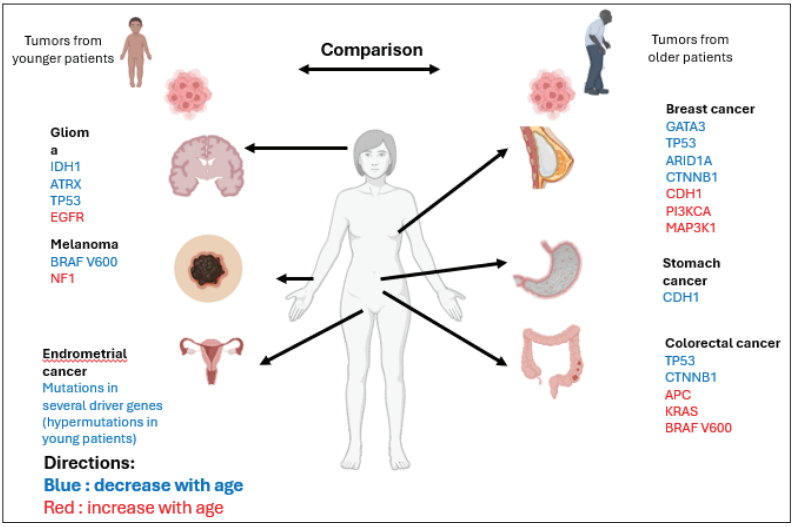
Tumors in older people typically have a higher concentration of clonal mutations, or mutations that appear early in the tumor's evolution(C. H. Li et al., 2022). This finding may be explained by the accumulation of somatic mutations with aging that take place prior to carcinogenesis, as has been recently shown in the majority of human tissues that are not malignant(Kakiuchi & Ogawa, 2021; W. Lee et al., 2021). To have a better understanding of the influence of age on the evolution of cancer, more research is required to clarify the ways in which age influences clonal and sub-clonal mutations in cancer (Chatsirisupachai et al., 2022).

B. AGE-RELATED DIFFERENCES IN SOMATIC MUTATION OF CANCER DRIVER GENES

Certain driver genes are more likely to be mutated in younger or elderly people. One well-known illustration of this is the significantly increased frequency of mutations in younger glioma patients' tumor protein p53 (TP53), alpha thalassemia/mental retardation syndrome X-linked gene (ATRX), and isocitrate dehydrogenase 1 (IDH1). The IDH-mutant subtype is linked to these mutations (Ceccarelli et al., 2016; Chatsirisupachai et al., 2022; C. H. Li et al., 2022; Y. Shah et al., 2021). One study indicated that mutations in ATRX are an

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age-dependent prognostic biomarker for low-grade glioma; such mutations are associated with a poor result in younger individuals but with better survival in older patients(C. H. Li et al., 2022). Conversely, the IDH-wild-type subtype linked with copy-number losses of chromosome 10 (PTEN) and gains of chromosome 7 (EGFR) is higher in older glioma patients(Chatsirisupachai et al., 2022; Körber et al., 2019; C. H. Li et al., 2022).



Source: Modified from (Chatsirisupachai, Lagger, and de Magalhães 2022).

Figure 8.3 Age-associated variations in the cancer genome.

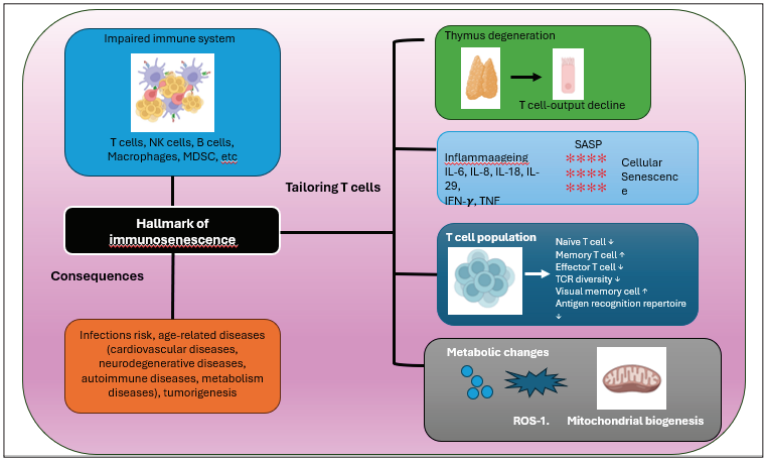
The image displays examples of cancer driver genes with age-associated trends in somatic mutations (Figure 8.3). Driver genes that are highlighted in blue are those that have mutations more frequently in younger patients, whereas those that are highlighted in red are more frequently mutated in older patients. Note that this is not an exhaustive list of somatic mutations associated with aging in cancer driver genes (Chatsirisupachai et al., 2022).

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C. HOW AGING AFFECTS THE IMMUNE SURVEILLANCE

How ageing affects immune surveillance

Neoplasms are linked to innate and adaptive immune dysfunction that accompanies aging (known as immunosenescence). As an organism ages, it typically develops an inflammatory state known as "inflammaging," which is characterized by increased expression of pro-inflammatory markers. This persistent inflammation is thought to be the main risk factor for age-related illnesses and is a common phenomenon associated with immunosenescence. Notable characteristics of immunosenescence include dysregulated metabolism, epigenetic modifications, thymic involution, and an imbalance in the ratio of naïve to memory cells. Immune cells undergo early senescence due to disruptions in T-cell pools and prolonged antigen stimulation. Senescent immune cells also exhibit a proinflammatory phenotype associated with their senescence, which intensifies inflammation(Z. Liu, Liang, et al., 2023).



Source: Taken from (Zaoqu Liu et al. 2023).

Figure 8.4 Characteristics of immunosenescence and cancer.

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Immunosenescence brought about changes in several immune cell subsets. Significant alterations occurred in T-cell subpopulations, including aberrant T-cell metabolism, a reduction in T-cell production correlated with aging owing to thymic degeneration, variations in the ratio of T subpopulations, and a chronic low-grade inflammatory environment mediated by senescence-associated secretory phenotype (SASP). Interferon-γ (IFN-γ), interleukin-6, IL-8, IL-18, IL-29, myeloid-derived suppressor cells, NK cells, natural killer cells, ROS (reactive oxygen species), TCR T-cell receptor, and TNF (tumor necrosis factor) are examples of interferon-γ and interleukin-related molecules(Z. Liu, Liang, et al., 2023).

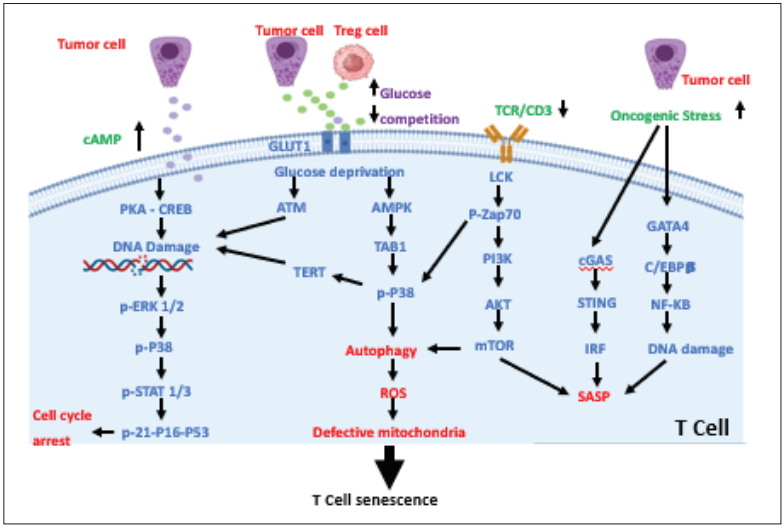
The process of immunosenescence includes multiple cellular regulatory mechanisms as well as the restructuring of organs. As a result, immune system function declines, which makes older people less able to respond appropriately to vaccinations or diseases. Determining the signs and features of immunosenescence is essential to investigating its relevance and influence, especially in age-related illnesses and here it is delineated in Figure 8.4.

In general, as people age, their risk of malignant tumors rises. Scientists think immunosenescence may be a significant factor in the tumoral process in addition to the accumulation of genetic abnormalities. The elderly group had a greater probability of tumorigenesis(Laconi et al., 2020; White et al., 2014). The age distributions of one hundred distinct cancers led them to the conclusion that the immune system might be a major factor in the formation of malignancies(Palmer et al., 2018). A phenotypic investigation on 57 women (16–91 years old) with mammary epithelial cells showed that the accumulation of progenitor and lumen cells with aging may raise the risk of carcinogenesis(Vatter et al., 2018).

Numerous investigations have demonstrated that immune system dysfunction in the elderly can lead to tumor progression and T cell senescence, as evidenced by an increase in the percentage of

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regulatory T cells (Tregs) and tumor-associated macrophages (H. Chen et al., 2023; Jagger et al., 2013; Ohue & Nishikawa, 2019). Figure 8.5 depicts the chemicals and pathways connected to T cell senescence in the tumor microenvironment (TME). According to a number of research, endogenous cyclic adenosine monophosphate (cAMP) produced from tumors suppresses effector T cells specific to the tumor in a hypoxic microenvironment, causing T cell senescence (M. Huang et al., 2024; X. Liu et al., 2020; J. Ye et al., 2014).



Source: Modified from (Lian et al. 2020).

Figure 8.5 T cell senescence-related signaling pathways.

The PKA-CREB signaling pathway can be triggered by tumor-derived cAMP, which then causes DNA damage and T cell senescence. Competition by T cells for glucose causes ATM-related DNA damage, opens the P38 and ERK1/2 pathways, and interacts with STAT1/3 to cause aging and T cell cycle arrest. TERT is downregulated when the P38 pathway is activated, which damages DNA. Senescent T cells can develop ROS generation, mitochondrial malfunction, and autophagy induction by downregulating TCR

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signaling, which can also activate the P38 pathway and inhibit the PI3K-AKT-mTOR signaling pathway. Higher SASP molecule secretion is a result of DNA damage caused by the GATA4-C/EBPβ signaling pathway. The cGAS-STING signaling pathway likewise causes an increase in SASP molecule secretion(Lian et al., 2020).

Furthermore, by generating cAMP, tumor cells trigger the PKA-CREB and P38 pathways, damaging T cell DNA and inducing T cell senescence(A. Gao et al., 2021; M. Huang et al., 2024). Similar to this, glucose competition causes ATM-related DNA damage, activates the p38 and ERK1/2 pathways, and collaborates with STAT1/3 to cause aging and T cell cycle arrest (L. Li et al., 2019; J. Ye et al., 2014). DNA damage and T cell senescence can also result from the activation of ATM and AMPK pathways brought on by glucose. In this scenario, AMPK activates p38 by attaching to the TAB1 protein and suppressing the telomerase reverse transcriptase gene (Lanna et al., 2014).

p38 activates p53, p21, and p16 to impede the advancement of the cell cycle. Furthermore, anaerobic glycolysis is the energy source of choice for aged T cells, which leads to mitochondrial malfunction and elevated production of reactive oxygen species (ROS)(Lian et al., 2020). The induction of T cell senescence is also significantly influenced by the NF-κB, C/EBPβ, and cGAS-STING pathways. Moreover, by preventing the generation of senescent T cells and tumor-specific T cells *in vitro* and *in vivo* and counteracting their inhibitory effect, the activation of Toll-like receptor 8 (TLR-8) signaling in tumor cells can improve antitumor immunity(Goronzy & Weyand, 2019).

Age-related alterations in T cell metabolism inside the TME are also tightly linked to tumor invasion and metastasis in the senescent microenvironment. Melanoma in elderly patients may have more invasive and distantly metastasis-prone melanoma cells due to ECM rearrangement brought on by alterations in Hyaluronan

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and Proteoglycan Link Protein 1(Ecker et al., 2019). Additionally, the fibroblasts' enhanced secretion of age-related sFRP2 encouraged the angiogenesis and spread of melanoma cells(Kaur et al., 2016).

D. STRATEGY OF CANCER TREATMENT FOR ELDER PATIENTS IN INDONESIA

The concept of biological age has been introduced to characterize the processes of aging, which is distinct from chronological age. This notion is essential in understanding the complexities of aging, particularly in elderly cancer patients. According to (Vitiello et al. 2020), biological age is contingent upon an individual's functional reserve, personal attributes, and physical performance. The importance of considering biological age in healthcare is evident in the development of geriatric oncology, which emphasizes the significance of providing tailored care to older adults with cancer.

Geriatric oncology has gained attention in Indonesia due to the country's aging population, advancements in cancer care, and the need for specialized care to address the unique healthcare needs of elderly cancer patients. Research has shown that elderly patients with cancer face various challenges, including comorbidities, functional decline, and treatment tolerability (Kanesvaran & RoyChowdhury, 2017). A comprehensive geriatric assessment (CGA) is essential in identifying these challenges and developing individualized care plans (Aggarwal et al., 2023).

Indonesia's demographic shift, with an increasing number of elderly citizens. According to the Central Statistics Agency (BPS) of Indonesia, the population aged 60 years and above is projected to reach 22.4 million by 2025, accounting for 11.3% of the total population (N. R. Sari et al., 2023). This underscores the need for tailored approaches to address their specific healthcare needs, including cancer care. The country's healthcare system is evolving, and there is a growing interest in acquiring the necessary skills and knowledge

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to provide better care for this vulnerable population (Outlaw et al., 2022; Pathi et al., 2023; Tejawinata, 2013).

Studies have highlighted the importance of assessing elderly patients' pre-treatment status prior to starting any form of treatment, as well as evaluating psychosocial factors such as education level, family support, and mental health (Sutandyo et al., 2015). Moreover, geriatric oncology emphasizes the need for palliative care to be included in the care of elderly cancer patients whose condition prevents them from benefiting from therapeutic techniques (Given & Given, 2008). As awareness and understanding of geriatric oncology continue to grow, it is expected that this field will play an increasingly important role in improving cancer care for older adults in Indonesia (Tejawinata, 2013).

The healthcare system's response to cancer in older adults is often inadequate, with patients receiving less potent medication, fewer treatment options, and limited access to clinical trials. This disparity is evident in the limited use of chemotherapy, hormone therapy, and radiation therapy in older women with breast cancer (Muss et al., 2007). Moreover, advanced cancer patients are often excluded from clinical trial participation and directed to smaller centers for treatment plans or second opinions (Given & Given, 2008). In contrast, some older patients may still benefit from anticancer therapy, particularly those with good health (Townsley et al., 2006). However, for those whose condition prevents them from benefiting from therapeutic techniques, palliative care should be a priority. This includes providing support, assistance with decisions, and encouragement to communicate with doctors (Given & Given, 2008).

To address these challenges, the Indonesian government can implement several measures to improve their strategy for dealing with older patients suffering from cancer. This includes enhancing the healthcare system and contributing to a more inclusive and compassionate society. The key is to reevaluate treatment goals and direct

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patients and their families towards palliative care, where they can receive the necessary support and guidance. By taking these steps, the Indonesian government can help ensure that older patients receive the best possible care, regardless of their age or health status.

The Indonesian government can implement several measures to improve their strategy for dealing with older patients suffering from cancer. These initiatives will not only enhance the healthcare system but also contribute to a more inclusive and compassionate society. Here are some expectations for the Indonesian government's efforts:

1. Enhanced Healthcare Infrastructure

   The government should invest in upgrading cancer treatment facilities, especially those designed to cater to the unique needs of elderly patients (Muhamad, 2024). This includes well-equipped hospitals, clinics, and specialized cancer centers with trained professionals (Mahendradhata et al., 2017).

2. Comprehensive Insurance Coverage

   The government should expand insurance coverage to include cancer treatments for older patients. This will help reduce financial burdens on patients and their families, ensuring that they receive the necessary care without worrying about the cost (Raharja et al., 2023).

3. Awareness and Education Campaigns

   Launching public awareness campaigns to educate people about the early signs of cancer and the importance of regular checkups for older adults can lead to early detection and better treatment outcomes (Croager et al., 2018; Saab et al., 2021).

4. Specialized Training for Healthcare Professionals

   In Asian nations—including Indonesia—family caregivers typically remain by the patient's side all the time. Usually, they are ready to offer any kind of palliative care that is required. Most family caregivers are ill-prepared to deal with the difficulties

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of helping a patient who is unable to perform activities of daily living while they are staying at home (Purba et al., 2023). Asian patients could also feel more at ease asking their own family for assistance. When family caregivers require additional information, they can consult the handbook, which includes thorough explanations and illustrations. It was revealed that health professionals used this as an additional tool in similar treatments that simply used manuals. Medical personnel reported that they were more at ease using their own methods of information sharing and discussed a range of experiences they had with palliative care. As a result, the effectiveness of an intervention may differ based on the innovations created by medical professionals (Kristanti et al., 2017).

5. Palliative Care and Support Services

   Only 1% of terminal cancer patients in Indonesia are receiving palliative care at this time (RI Ministry of Health, 2022). As long as a patient has a professional or informal caregiver present, palliative care can be given at an advanced referral health facility or at home. The Decree of the Minister of Health (Keputusan Menteri Kesehatan, KMK) number 812 of 2007 and the National Guideline for Palliative Cancer Program 2015, which largely focuses on professional caregivers or healthcare workers, explain the policies governing palliative care in Indonesia. On the other hand, family members can also be extremely important in the role of informal caregivers, helping patients deal with the range of difficulties that follow a cancer diagnosis (PRAKARSA, 2023).

6. Age-Friendly Policies

   Implementing age-friendly policies and guidelines in healthcare settings will help create an environment that is more accommodating to the needs of older patients. This includes accessible facilities, patient-centered care, and respect for the dignity and

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autonomy of elderly patients (Fatmah et al., 2019; Ministry of Health, 2019).

By implementing these measures, the Indonesian government can significantly improve its strategy for dealing with older patients suffering from cancer, ensuring better healthcare, quality of life, and overall well-being for this vulnerable population (Anurogo et al., 2024; Utami, 2024).

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CHAPTER IX
INTERVENTION STRATEGIES FOR CANCER TREATMENT IN INDONESIA

The narrative of cancer management in Indonesia stands as a testament to the resilience of the human spirit, the power of compassion, and the relentless pursuit of a better tomorrow. This chapter invites us to embark on a journey through the intricate landscape of healthcare in Indonesia, where we will witness the triumphs and challenges faced by those who dedicate their lives to fighting this formidable foe. As we delve into these pages, we are reminded of the interconnectedness of our world and the importance of unity in addressing global health issues. Through the lens of cancer management in Indonesia, we are given a unique opportunity to appreciate the strength of the human spirit and the indomitable will to overcome adversity. This chapter will not only touch our hearts but also inspire us to work together towards a future where no one has to face cancer alone.

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A. NATIONAL ACTION PLANS

Cancer is a type of disease that is considered by most people to be scary because the death rate from this disease is quite high. In order to remind the dangers of cancer and increase public awareness of the prevention of this disease, the world sets February 4 every year as cancer day. Cancer can be said to be a "lifestyle disease" that can be prevented by adopting a healthy lifestyle and staying away from risk factors for developing cancer (such as smoking habits, being a passive smoker, drinking alcohol, obesity, unhealthy eating patterns). WHO also states that 43% of cancer can be prevented (Redaksi Sehat Negeriku, 2015).

Concerning the intricacy of cancer treatment, the Indonesian government established the National Cancer Control Committee (NCCC). The history of the NCCC can be traced back to several key events and initiatives started in early 2000s where the Indonesian government began to acknowledge the increasing burden of cancer on the country's healthcare system. This led to a growing awareness of the need for a coordinated and strategic response to cancer control. In 2005, the Indonesian government founded the Indonesian National Cancer Institute (Lembaga Nasional Kanker Indonesia or INCI) under the Ministry of Health. The primary objective of INCI was to serve as a central institution for cancer research, prevention, control, and treatment. Two years later in 2007, the Indonesian government launched the National Cancer Control Action Plan (NCCAP). This plan aimed to reduce the cancer burden in the country by focusing on prevention, early detection, treatment, and palliative care. To ensure the effective implementation of the NCCAP, the Indonesian government established the National Cancer Control Committee (NCCC) through a decree of the Minister of Health number HK.02.02/MENKES/389/2014, issued on October 17, 2014. This decree aimed to ensure the safety, efficacy, and quality of medical devices in the country. It also established a framework

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for the registration, licensing, and post-marketing surveillance of medical devices (NCCC, 2020). The decree was later amended by the Minister of Health of the Republic of Indonesia through Decree Number HK.01.07/MENKES/14/2017, issued on January 9, 2017. This amendment introduced updates and improvements to the previously established guidelines. The primary purpose of the amendment was to align the medical device regulation in Indonesia with international standards and best practices(NCCC, 2020). Some key changes introduced by the 2017 amendment include:

1. Clarification of the classification of medical devices and the corresponding regulatory requirements.
2. Updates to the registration and licensing processes for medical devices, including the introduction of a Unique Device Identification (UDI) system.
3. Strengthened post-marketing surveillance requirements to ensure the ongoing safety and efficacy of medical devices in the market.
4. Establishment of a more efficient and transparent system for the assessment and approval of medical devices.
5. Enhanced collaboration with international regulatory bodies and organizations to promote global harmonization in medical device regulation.

Following the decree of the Minister of Health number HK.02.02/MENKES/389/2014, issued on October 17, 2014, which emphasizes the importance of national unity in addressing cancer, all sectors in Indonesia can contribute to this effort in various ways, from public awareness campaigns to healthcare services and community initiatives.

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1. NGO initiatives

As a prominent non-profit organization, the Indonesian Cancer Foundation (ICF) has been at the forefront of promoting cancer care through a multifaceted approach. With a mission to enhance community awareness and participation in cancer care, the ICF has established a robust network of 114 branches across Indonesia, making it the largest cancer foundation network in the country. Recognizing the significance of multisectoral collaboration in cancer care, the ICF engages with various stakeholders, including professional organizations, NGOs, and private sector entities, both nationally and internationally (Eng et al., 2023).

In a unique partnership with the government, the ICF has strong ties with the governor's office, enabling it to work closely with local authorities to address cancer care needs. By filling the gap between government health care programs and community needs, the ICF has played a vital role in providing comprehensive cancer care services (Eng et al., 2023).

Since its inception in 1995, the ICF has received international palliative care training and established home hospice care programs to improve cancer patients' quality of life and dignity at the end of life. In accordance with WHO guidelines for home-based palliative care, the ICF has developed a team of healthcare professionals and volunteers to provide care to vulnerable patients at home. Over the past 12 years, the ICF has served over 621 patients, with 79% of them passing peacefully at home after receiving palliative care services from the ICF team (Eng et al., 2023).

In addition to direct patient care services, the ICF has also implemented WHO guidelines for community-based palliative care by conducting public education and socialization programs in conferences. Furthermore, the ICF has provided palliative care training for caregivers, volunteers, and healthcare professionals in 10 provinces since 2015, with a total of 2,353 participants receiving training. Some

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of these training courses have been joint collaborations with local health districts and international foundations (Eng et al., 2023).

In addition to ICF, one NGO entity is the Indonesia Cancer Care Community (ICCC), which has set its sights on creating a comprehensive hub for cancer education, information dissemination, and patient support. By bridging the gap between individuals affected by cancer and their loved ones, ICCC aims to empower individuals to take proactive steps towards their health by providing accessible information and education on cancer and its early detection. Furthermore, the organization seeks to develop a network of skilled professionals and dedicated volunteers who are committed to providing compassionate care to cancer patients, offering emotional support and practical assistance during their journey (ICCC, 2024).

These organizations, along with others, are working together to advocate for better cancer care policies, increased government funding for cancer research and treatment, and improved access to healthcare services for all Indonesians. By raising awareness about cancer prevention, early detection, and treatment options, they are helping to reduce the burden of the disease on individuals and the healthcare system.

2. Public Involvement

The annual Jakarta Goes Pink event, initiated by Lovepink community, is set to return on October 9 at Altira Business Park in North Jakarta. This year's event features a 5- and 10-kilometer charity run, alongside local celebrities, breast cancer warriors, and survivors, to raise awareness about early screening for cancer. The event aims to attract 1,500 runners and 3,500 fun walk participants, with registration open until September 17. Alternatively, participants can opt to make a donation instead, starting from Rp 50,000 (US$4), which will support the charity run. The event also features a fun walk with Lovepink ambassador Chelsea Islan and celebrity Dian Nitami, breast screening, a pop-up market, and Pink Attire Award.

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The event is part of the government's efforts to promote public awareness about cancer detection. According to the Health Ministry's Director of Prevention and Control of Non-Communicable Diseases, Eva Susanti, the ministry involves various elements in society in pushing an active public participation in the movement of early detection for cancer. The ministry has prepared equipment and human resources to support this initiative and has also continued to socialize early cancer detection-related activities through various social media platforms and direct outreach.

In addition to these efforts, the government has equipped 10 thousand community health centers with ultrasound equipment to detect breast cancer since 2022. The government is also striving to eliminate cervical cancer by providing HPV immunization and HPV DNA testing. Furthermore, the government is treating lung cancer by installing CT scans in 514 hospitals in 514 districts and cities, and colon cancer by providing colonoscopy equipment in 514 hospitals.

By supporting events like this and encouraging healthy lifestyles, we can work towards reducing the incidence of cancer in Indonesia (Nasution, 2024; Wira, 2016).

3. Corporate Social Responsibility (CSR)

Several corporations have demonstrated their commitment to Corporate Social Responsibility (CSR) by supporting cancer treatment and care for Indonesian patients. Two exemplary cases are MNC Peduli and Patra Jasa.

MNC Peduli, through its "1 Million Masks for Cancer Fighters" program, has donated 20,000 masks with medical standards to the Indonesian Child Cancer Foundation to support cancer fighters, particularly children. The donation was handed over at the Dharmais Cancer Hospital in Jakarta, where it was received by the Chairwoman of the Indonesian Child Cancer Foundation. The program aims to distribute masks to various shelter homes and hospitals that treat cancer.

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In addition, Patra Jasa has aided the Indonesian Cancer Foundation, donating cash to support a lung cancer early detection program and stoma bags for 100 people. This initiative is part of Patra Jasa's CSR efforts to celebrate Pertamina's 65th Anniversary. The assistance was handed over by the Corporate Secretary team to representatives from the Indonesian Cancer Foundation.

These CSR initiatives demonstrate the importance of corporate involvement in supporting cancer treatment and care in Indonesia. By providing vital resources and assistance, MNC Peduli and Patra Jasa are helping to alleviate the burden on cancer patients and their families, contributing to a more compassionate and inclusive society (MNC Group, 2024; Patra Jasa, 2022).

B. REGULATION OF ANTICANCER TREATMENTS

According to the observation from ASEAN Cost in Oncology (ACTION) in eight countries (Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, and Vietnam) from 2012-2014, approximately 78% of cancer patients experience poverty that ultimately results in death. The number of Indonesian cancer patients administered to the hospitals through national health insurance (NHI) was 702,207 in 2014 alone. In 2015, there were 1,257,230 cases of cancer; in 2016, there were 1,308,061 cases. For NHI users who had cancer, the managing body of social insurance in health (BPJS Kesehatan) paid Rp1.5 trillion in medical costs in 2014. The expenses incurred by cancer patients escalated further, reaching Rp 2.2 trillion in 2015 and Rp 2.3 trillion in 2016 (Pratama et al., 2019).

According to the Ministry of Health, BPJS Kesehatan is responsible for managing around 7.6 trillion in financing for cancer treatment in 2019 and 2020. It is envisaged that by offering the benefit package to the community, out of pocket (OOP)'s impact on medical expenses paid by cancer patients and their families will be lessened. Since JKN was made available in 2014, when total health

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expenditures totaled 56.43 trillion rupiah, the percentage of OOP in Indonesia has decreased as of 2019. Just that, with a maximum percentage of 20%, this statistic still does not exceed WHO guidelines (Prasetya, Layyinah, Putri, et al., 2023).

It is indeed concerning that the financial burden of cancer treatment costs paid by BPJS Indonesia is significant. To address this issue effectively, a more integrated and comprehensive re-strategizing approach should be implemented. This could involve exploring new avenues for cost reduction, such as promoting preventive measures, encouraging early detection, and collaborating with healthcare providers to optimize treatment methods. Additionally, fostering partnerships with research institutions and pharmaceutical companies to develop more affordable and effective cancer therapies could also help alleviate the financial burden on BPJS Indonesia. By focusing on these strategies, we can work towards a more sustainable and equitable healthcare system for cancer patients in Indonesia.

While it is true that Indonesia has implemented the National Social Health Insurance (BPJS Kesehatan) to address healthcare costs, the high cost of treatment remains a significant barrier for many Indonesians. BPJS aims to provide affordable and accessible healthcare for the population, but certain limitations and challenges persist.

The coverage of BPJS Kesehatan may not be comprehensive for everyone. Some services and treatments might not be fully covered or may have limitations on the number of treatments or visits allowed. This can lead to out-of-pocket expenses for patients, especially those with chronic or complex medical conditions (PRAKARSA, 2023). The affordability of BPJS contributions might be a challenge for non-wage earners. Although the premiums are designed to be progressive, based on income levels, some individuals may still struggle to pay their contributions regularly (Mediana, 2024). This can result in gaps in coverage and limited access to healthcare

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services.c. The quality of healthcare services and infrastructure in Indonesia can also impact the effectiveness of BPJS Kesehatan. Limited access to quality healthcare facilities, particularly in rural and remote areas, can make it difficult for people to benefit from the insurance program (National Team for the Acceleration of Poverty Reduction, 2015).

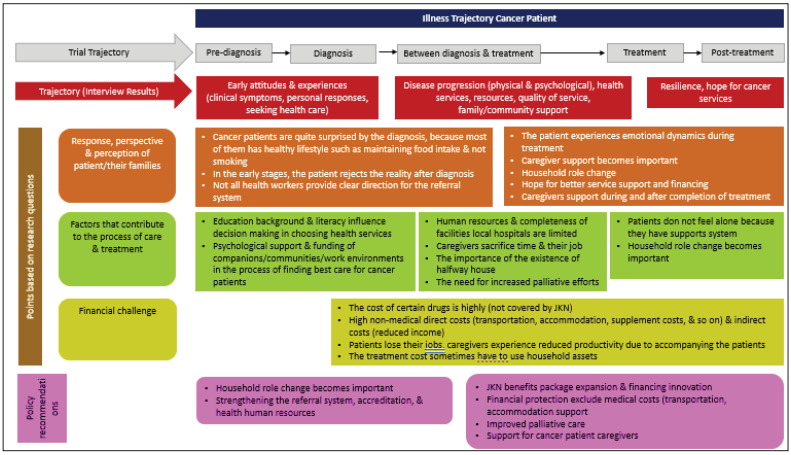
C. MANAGEMENT OF CANCER TREATMENTS IN INDONESIA

In accordance with Law No. 40/2004 concerning the national social security system, which aimed to transition the nation towards Universal Health Coverage (UHC), the government appointed the Social Security Administrative Body (BPJS) to oversee the national health insurance program in Indonesia. The National Team for The Acceleration of Poverty Reduction (2015) stated that the goal of the National Health Insurance Scheme (JKN), which went into effect on January 1, 2014, is to attain UHC by 2019. The JKN team created the prospective payment method known as INA-CBGs (Indonesian – Case Base Groups) tariff rates for the healthcare payment system at the hospital level. The healthcare payment is determined by the CBGs code based on the patient's diagnosis of the illness; expenditures incurred by the patient for individual health services are not taken into account (Mboi, 2015).

Hospital payment options are as follows: prospective payment methods and retrospective payment methods. The retrospective payment technique is a way to pay for the health services that patients receive. It bases payment on the number of services rendered; the more services rendered, the more money that must be paid. Fee For Services (FFS) is one instance of a retrospective payment arrangement. When paying for medical services, a prospective payment method is used when the total cost is known before the services are rendered. The global budget, case-based payment, capitation, and

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per diem are a few instances of prospective compensation(Waters & Hussey, 2004). It is well grasped that Every financing scheme has pros and cons, thus there is no such thing as a flawless financing scheme. Denmark, the UK, and Thailand are a few examples of nations that use capitation; Australia, Hungary, and the US are examples of nations that use case-based payment; and Germany, Korea, and Taiwan are examples of nations that use fee-for-service payment methods.



Source: Modified from (Prasetya, Layyinah, Putri, et al. 2023).

Figure 9.1 Illness Trajectory results of field data analysis

Analysis of Medical Cost for Cancer Treatments

Many interventions are available for the treatment of cancer. Radiation therapy, chemotherapy, targeted therapy, and surgery are the four mainstays. A patient has to be admitted to the hospital, either in their local region or at a referral hospital in a different city in order to receive treatment or medical action (such as cycles of chemotherapy or radiation). Though medical procedures and treatment can be received by patients in their homes, in certain cases and clinical

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conditions, cancer patients need to be referred to a higher-level hospital or referral hospital for more comprehensive care and access to subspecialties better suited to tackle cancer cases (Figure 9.1). This results in significant out-of-pocket expenses for patients and companions. This results in significant personal costs (OOP) for patients and their companions for things like accommodation and meals (apart from hospital nutrition services). Land travel expenses (including drivers or tolls), airline, motorbike taxi, and ship expenses are all included in the cost of transportation. It was reported that patients who do not reside in Jakarta must pay hefty transportation expenses, which can amount to up to seven million rupiahs for a single treatment (Prasetya, Layyinah, Putri, et al., 2023).

As per the findings of the interviews, the monthly transportation expenses incurred by a cancer patient often amount to at least IDR 5,000,000. A number of factors contribute to the high cost, including the unequal distribution of healthcare facilities and the dearth of cancer specialists in the area, which force patients to pay extra to go to other locations, like Jakarta. Furthermore, the results of the interviews indicate that certain medications and supplements—like Avastin, for example—are not covered by BPJS Kesehatan, which is particularly problematic for patients with high stages and necessitates additional expenses for them (Prasetya, Layyinah, Putri, et al., 2023). Avastin was formerly limited to use in the benefit package to treat metastatic colorectal cancer. Nevertheless, this medication is not cost-effective and may reduce the effectiveness of the JKN system because the therapeutic advantages are not great enough, and the cost is too high (Kristin et al., 2021).

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Table 9.1 Healthcare Costs for Stage IIB-IIIB Cervical Cancer Patients' Treatment.

Average cost	Chemoradiation	Radiotherapy
	(USD)	(USD)
Outpatient services	7.33	10.82
Inpatient services	69.01	4.7
Emergency	1.17	1.13
Medical doctor visit	20.77	4.11
Laboratory	142.46	86.19
Radiology	48.54	42.8
Radiation oncologist consultation	55.6	53.76
Radiotherapy	2792.24	2717.53
Medical consumables	25.38	11.21
Chemotherapy drug	40.18	0
Non chemotherapy drug	28.44	12.12
Average cost per patient	**3231**	**2944**

Source: Adapted from (Puspitasari et al., 2021)

The mean expenses per patient for radiotherapy and chemoradiation were $2944 and $3231, respectively. Chemoradiation has more adverse effects than radiation, yet it was a more successful treatment than radiotherapy. With an increment cost-effective ratio (ICER) of $48.60 per percent complete ratio (CR), chemoradiation will cost $48.60 for every percent increase in CR if it is used in place of radiotherapy(Puspitasari et al., 2021). The expenditures of radiation, hospital stays, lab work, and chemotherapy medications were the main factors affecting the ICER. The cost of radiation therapy had the greatest impact on the ICER; for patients receiving chemoradiation, it accounts for over 86% ($2792/$3231) of the overall therapy

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cost, and for those receiving radiotherapy alone, it accounts for over 92% ($2717/$2944). Thus, radiation will be more economical if its cost could be decreased. The cost of laboratory testing for chemoradiation is $164.46 / $86.19, or 1.64 times more than the cost of testing for radiotherapy alone. The fourth biggest factor influencing the ICER was the cost of the chemotherapeutic medications. This is due to the fact that the chemotherapy drug used in chemoradiation, as per national standards, is given to patients with IIB-IIIB cervical cancer for radiosensitization, requiring lower dosages of the drug during treatment and making it more affordable than standard chemotherapy. However, individuals who had radiotherapy do not have to pay for chemotherapy medications, so that expense also came into play (Puspitasari et al., 2021).

D. IMPLEMENTATION OF NOVEL APPROACH IN CANCER IMMUNOTHERAPY

Checkpoint inhibitors are a type of cancer treatment that has gained significant attention in recent years due to their potential to improve the survival rates of patients with various types of cancer. In Indonesia, the use of checkpoint inhibitors is gradually increasing as more cancer patients and healthcare providers become aware of their benefits.

Checkpoint inhibitors work by targeting specific proteins on the surface of cancer cells, which helps the immune system recognize and attack the cancer more effectively. These drugs are usually administered intravenously or as oral medications. Some of the most common checkpoint inhibitors include pembrolizumab, nivolumab, and ipilimumab (Kong et al., 2023).

In Indonesia, the use of checkpoint inhibitors is primarily focused on treating advanced or metastatic cancers, such as melanoma,

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non-small cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma. However, their use may vary depending on the availability of specific drugs and the individual patient's condition (Sekarutami & Handoko, 2019).

The availability and cost of checkpoint inhibitors in Indonesia can be a limiting factor for their widespread use. These drugs are often expensive and may not be covered by the national health insurance program. As a result, many patients may not have access to these treatments, especially those in rural areas or with limited financial resources. Moreover, checkpoint inhibitors are often patented by pharmaceutical companies, which can lead to high prices due to exclusive rights to manufacture and sell the drugs. In some cases, the Indonesian government may negotiate lower prices for these medications, but these agreements can take time and may not always result in affordable access for all patients.

E. FUTURE DIRECTION OF CANCER TREATMENT IN INDONESIA

Recent studies highlight the challenges and future directions for cancer treatment in Indonesia. Chemotherapy remains a primary treatment modality, but its side effects, particularly anticipatory nausea, can lead to treatment discontinuation in 27% of patients (Hamdani & Anggorowati, 2019). Various interventions, including hypnotherapy, progressive muscle relaxation, and acupressure, have shown promise in managing these side effects (Hamdani & Anggorowati, 2019). Chemotherapy's impact on patients' daily activities is also a concern, necessitating further investigation (Evangelista et al., 2020). For specific cancers like nasopharyngeal carcinoma, which has a high incidence in Indonesia, tailored treatment guidelines are crucial (Bossi et al., 2020). Improving access to radiation therapy is vital, especially for cervical cancer treatment, as highlighted by the World Health Organization's goals (Lin et al., 2023). However,

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resource limitations in low-middle income countries like Indonesia pose significant challenges to providing comprehensive cancer care, including radiation therapy (Lin et al., 2023).

The future direction of cancer treatment in Indonesia is expected to focus on the following key areas:

1. **Improved access to advanced treatments**

   The Indonesian government and healthcare providers are working towards expanding access to advanced cancer treatments, including adoptive T cell therapy, immunotherapy, targeted therapy, and personalized medicine. This will help ensure that patients have access to the most effective and suitable treatments for their specific cancer types.

2. **Integrating traditional and alternative medicine**

   Indonesia has a rich history of traditional and alternative medicine, which may hold potential for cancer treatment. Integrating these practices with modern oncology could lead to innovative, holistic approaches to cancer care.

   Integrating traditional and alternative medicine for cancer in Indonesia is an ongoing effort to provide comprehensive and holistic healthcare options for cancer patients. In Indonesia, traditional medicine, also known as Jamu, has been practiced for centuries and is deeply rooted in the country's culture. Alternative medicine, on the other hand, refers to treatments and practices that are not part of conventional or mainstream medicine.

In Indonesia, the local context and regional and international obligations are inextricably linked to the plans and measures taken to prevent and control cancer. NAP for Cancer Control 2020–2024 was created with these linked ideas in mind. In a decentralized system, outcome-based health program provision is offered in four areas (S. Gondhowiardjo, Permata, et al., 2021):

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1) community empowerment
2) equality and universal health coverage
3) cross-sector involvement and stakeholders, and
4) community empowerment.

In order to achieve shared objectives in the next five years and over the long term in the next fifteen, the NCCAP 2020–2024 employs a strategic approach that considers a number of determinants. This approach theoretically has the potential to produce synergistic interactions between approaches at the individual and population levels. These shared objectives are to reduce the number of cancer cases among Indonesians, increase cancer survivorship, and improve the quality of life for cancer patients(S. Gondhowiardjo, Permata, et al., 2021).

Cancer Vaccination

In order to meet the 2030 SDGs, the Indonesian government is dedicated to reducing morbidity, mortality, and disability brought on by diseases that can be prevented by vaccination. In order to improve health services in the nation, the Ministry of Health prioritizes strengthening and expanding health services with a focus on preventive and promotive efforts. One way to achieve this is by adding new vaccines to the national immunization program, such as the HPV vaccine.

Girls in the fifth grade of elementary schools receive the first dose of the HPV vaccination (or 11 years old for children not enrolled in school), while girls in the sixth grade

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of primary schools receive the second dose (or 12 years old) (Figure 9.2). Through the events of School Children Immunization Month, or BIAS, this vaccination is administered to children who attend school. At least 90% of the population must receive the HPV vaccine in order to hasten the decline in cervical cancer-related morbidity and mortality. Therefore, for this initiative to be successful, cooperation from all policy makers, associated industries, and societal segments is crucial(Indonesia Communication Team, 2023).



Source: Taken from https://setkab.go.id/en/health-ministry-expands-free-hpv-vaccination-coverage/

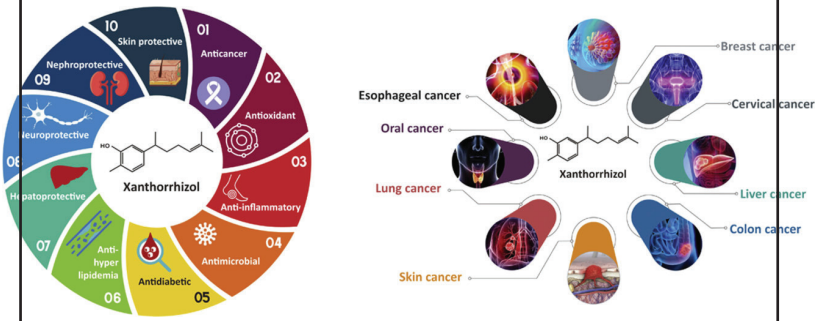
Figure 9.2 Vaccination for elementary school students

JAMU

The traditional herbal medication known as jamu has been used for many years in the Indonesian community to treat and preserve health. Although modern medicine is becoming more and more prominent in Indonesia, jamu is still quite popular both in urban and rural regions. Jamu is being developed by herbalists and transformed into phytopharmaceuticals, based on its historic usage, as a logical type of ther-

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apy. Jamu has gained potential advantages in both the therapeutic and financial domains (Sekarutami & Handoko, 2019).



Source: Taken from (Simamora et al. 2022).

Figure 93 Anticancer properties of Xanthorrhizol

Xanthorrhizol (XTZ), in addition to curcumin, is a sesquiterpene or bisabolene that can be found in different Curcuma species, particularly in the rhizome essential oil.of *C. xanthorrhiza,* that is often referred to as Java turmeric or temulawak in Bahasa (Figure 9.3) (Simamora et al., 2022).

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ABBREVIATIONS

AKT	Protein kinase B
AMPK	5'-adenosine monophosphate (AMP)-activated protein kinase
APC	Adenomatous polyposis coli
APOBEC	apolipoprotein B mRNA editing enzyme catalytic polypeptide-like family
ARID1A	AT-Rich Interaction Domain 1A
ATM	ataxia-telangiectasia mutated
ATRX	alpha thalassemia/mental retardation syndrome X-linked gene
Bcl-2	B-cell lymphoma 2
bFGF	basic fibroblast growth factor
BM	base membrane
BPS	Badan Pusat Statistik) central statistics agency
BRAF V600	B-Raf proto-oncogene serine/threonine kinase) V600 mutations
C/EBPβ	CCAAT/enhancer binding protein β
CAGR	compound annual growth rate
CAM	cell adhesion molecules
cAMP	cyclic adenosine monophosphate

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CAR	chimeric antigen receptor
CC	compensated cirrhosis
CD3	cluster of differentiation 3
CDH1	cadherin 1
CDH1	Cadherin-1 or Epithelial cadherin (E-cadherin)
CDK	cyclin dependent kinases
CDK2AP2	cyclin-dependent kinase 2-associated protein 2
cfDNA	cell-free DNA
CGA	comprehensive geriatric assessment
cGAS	cyclic GMP-AMP (cGAMP) synthase
CSC	cancer stem cell
CSE	cigarette smoke extract
CTNNB1	Catenin β-1
DC	decompensated cirrhosis
DNA	deoxyribo nucleic acid
ECM	extracellular matrix
ECM	extracellular matrix
ECs	endothelial cells
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
ER	endoplasmic reticulum
FCTC	Framework Convention on Tobacco Control
G1	gap 1
G2	gap 2
GATA 4	GATA Transcription factor 4
GATA	GATA Transcription factor
GLUT-1	Glucose transporter 1
GO	geriatric oncology
GSK	glycogen synthase kinase
GVHD	graft-versus-host disease
GYTS	Global Youth Tobacco Survey
H3K4me	H3 lysine4 methylation
H3K9me	H3 lysine9 methylation

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HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HDAC	histone deacetylases
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papilloma virus
IARC	International Agency for Research on Cancer
IDHI	isocitrate dehydrogenase 1
IFN-γ	interferon-γ
IL-18	interleukin-18
IL-29	interleukin-29
IL-6	interleukin-6
IL-8	interleukin-8
ImoH	Indonesia Ministry of Health
IRF	interferon regulatory factor
KMK	decree of the Minister of Health
KRAS	Kirsten rat sarcoma
LCK	lymphocyte cell-specific protein-tyrosine kinase
LEF	lymphoid enhancer factor
M	mitosis
m6A	N6-methyladenosine
MAP3K1	Mitogen-Activated Protein Kinase1
miRNA	microRNA
mTOR	mammalian target of rapamycin
NAFLD	Nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NF1	Neurofibromatosis type 1
NF-κB	nuclear factor κ-light-chain-enhancer of activated B cells
NSCLC	non-small cell lung cancer
p16	protein-16
p21	protein-21
PADC	pancreatic adenocarcinoma

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PAH	polycyclic aromatic hydrocarbons
PanIN	pancreatic intraductal neoplasia
p-ERK1/2	phospo- extracellular signal-related kinase ½
PI3KCA	phosphatidylinositol-45-bisphosphate 3-kinase catalytic subunit α
PI3Ks	phosphatidylinositol 3-kinases
PKA-CREB	protein kinase A - cAMP response element-binding protein
p-P38	phospo-protein-38
p-STAT 1/3	phospo-signal transducer and activator of transcription 1/3
PTEN	phosphatase and tensin homolog
PUMA	p53 upregulated modulator of apoptosis
p-ZAP70	phospo-ζ-chain-associated protein kinase 70
Rb	retinoblastoma
RNA	ribonucleic acid
ROS	reactive oxygen species
ROS	reactive oxygen species
RTKs	receptor tyrosine kinases
S	synthesis
SASP	senescence-associated secretory phenotype
SCNAs	somatic copy-number changes
SEARO	Southeast Asia Region
sFRP2	secreted Frizzled related protein 2
SH	Src-homology-2
STATs	signal transducers and activator of transcription
STING	stimulator of interferon (IFN) genes
TAB 1	TGF-β activated kinase 1 (MAP3K7) binding protein 1
TAPS	tobacco advertising promotion and sponsorship
TCF	T cell factor
TCR	T-cell receptor
TERT	telomerase reverse transcriptase

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TF	transcription factors
TLR-8	Toll-like receptor-8
TME	tumor microenvironment
TME	tumour microenvironment
TNF	tumor necrosis factor
TP53	tumor protein p53
UN	United Nations
VEGF	vascular endothelial growth factor
VOC	volatile organic compounds
WHO	World Health Organization
WPRO	Western Pacific Region

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GLOSSARY

Adherence compliance with the medication regimen.

Adjuvant Therapy additional treatment after primary therapy is given

Adoptive T Cell Therapy immunotherapy that utilizes a patient's own T cells.

Adenocarcinoma a type of cancer that starts from your gland (e.g., lung, colon).

Aerobic Glycolysis (Warburg Effect) a glycolysis process where cancer can get its energy by converting glucose to lactate in the presence of oxygen.

Aflatoxin a toxic substance produced by mold (mycotoxin).

Alkylating Agents a class of chemotherapeutic drugs that inhibit DNA transcription by adding alkyl groups to DNA, resulting in cross-linking that halts replication and triggers apoptosis in rapidly diving tumor cells.

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Alopecia Hair loss that can occur as side effect of chemotherapy and radiation therapy.

Angiogenesis The formation of new blood vessels from pre-existing vessels, which allows for tumor progression.

Angiogenic Switch Time-restricted event during tumor progression where pro-angiogenic factors outweigh anti-angiogenic ones, enabling the shift from dormant, avascular cell growth to an expanding, vascularized and ultimately malignant tumor.

Antigen Any substance that provokes an immune response to produce antibodies against it.

Antimetabolites A class of chemotherapeutic agents that interfere with DNA/RNA synthesis by acting as structural analog that block normal metabolic pathway.

Apoptosis A form of programmed cell death that removes damaged cells, but when it doesn't function properly, those cells can survive and multiply uncontrollably, leading to cancer development.

Asbestos A group of naturally fibrous minerals that are resistant to heat and corrosion, and they are carcinogenic, increase the risk for some types of cancer.

Autocrine Growth Stimulation The ability of cancer cells to produce and to respond to their own

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growth factors, allowing continuous self-driven proliferation.

B7 (CD80/CD86) Co-stimulatory ligands for CD28 (in positive T-cell co-stimulation) or CTLA-4 (in negative T-cell co-stimulation).

Balanitis Xerotica Obliterans (BXO) A chronic inflammatory condition of the foreskin and glans penis that increases the risk of developing penile cancer.

Balanoposthitis Inflammation of the glans and foreskin.

Basement Membrane (BM) A physical and biological barrier to tumor cell metastasis, separating epithelial tissue from deeper tissue.

Batson's Plexus A network of valveless veins in the body that connect pelvic and thoracic vessels to the intraspinal veins; they can provide a channel for the spread of cancers of the colon, rectum, and prostate to the spine.

BCL-2 B-cell lymphoma 2 protein normally regulate apoptosis, but when overexpressed it blocks apoptosis, allowing cancer cells to survive and proliferate, and resist chemotherapy.

BH3-Only Proteins Initiators of apoptosis.

Bone Marrow Suppression (Myelosuppression) A condition where the bone marrow doesn't produce enough blood cells due to chemotherapy or radiation therapy.

BPJS Kesehatan / JKN Indonesian national health insurance.

Busulfan An alkylating chemotherapy agent,

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	which work by damaging DNA and blocking cancer cell division, used mainly to treat certain blood cancers such as chronic myelogenous leukemia.
Cachexia	Cancer-related muscle and fat loss. A complex and serious metabolic wasting syndrome, which causes significant unintentional loss of skeletal muscle mass, along with loss of body fat.
Cancer Burden	Health and economic impact of cancer. The effect of cancer on the population as a whole, including incidence and mortality
Cancer Hallmarks	Core traits enabling tumor survival. The biological abilities of cancer cells that occur during tumor development, which allow them to multiply and spread.
Cancer Incidence	New cases. The number of new cancer cases discovered in a given time period.
Cancer Prevalence	New cases vs. total cases. The total number of people diagnosed with cancer and still alive at a later date.
Cancer Microenvironment (TME)	Surrounding cells, ECM, signals. The ecosystem of non-cancerous cells and structures that interact with the tumor, such as fibroblasts, blood vessels, and immune cells.

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CAR-T Therapy	Engineered T cells targeting antigens. Type of cancer immunotherapy that modifies the patient's genetic makeup to prevent and treat cancer.
Carcinogen	A Substance capable of causing cancer.
Carcinogenesis	Process of tumor formation. The formation of a cancer.
CD4 Cell Count	a number showing T helper cells expressing CD4 on their protein surface. This number represents how badly HIV infects a patient's immune system.
$CD4^+$/$CD8^+$ T Cells	protein found on the T-cell surface. These two can differentiate between Helper (CD4) vs. cytotoxic (CD8) T cells.
CD44 / CD147	protein surface found in cells that helps tumor invasion/metabolism.
CDH1	Gene encoding E-cadherin. A gene that codes for the production of E-cadherin.
CDK (Cyclin-Dependent Kinase)	Cell cycle enzymes. An enzyme that is important for regulating the cell cycle, works by forming a complex with another protein, namely cyclin.
Cemiplimab / Nivolumab / Pembrolizumab	AntiPD-1 therapies. PD-1 protein is expressed on the T-cell surface, which will interact with PDL-1 as a negative co-stimulating T-cell
Chemotherapy	Cytotoxic drug treatment. Cancer treatment with cytotoxic drugs or

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	with the use of chemical substances.
Chlorambucil	Alkylating chemotherapy for CLL/ lymphoma. Prescription chemo-therapy and immuno-suppressive drugs to treat cancers in the blood and lymphatic systems.
Cori Cycle	Lactate is recycled to glucose. Lactate metabolism during anaerobic glycolysis is transported to the liver.
Cytarabine (Ara-C)	Pyrimidine analog causing chain termination. Chemotherapy drugs are categorized as pyrimidine nucleoside analogs and antimetabolites.
Cytoreductive Surgery	Mass-reducing tumor surgery. Procedure to remove cancerous tumors in the abdominal cavity.
DALYs	Disease burden measure (death + disability). The overall measure of disease in a population.
Dendritic Cells (DCs)	a type of antigen-presenting cell (APC) found in the immune system
DHFR	Enzyme inhibited by methotrexate. Important enzymes that catalyze the reduction of dihidrofolat to tetrahidrofolat.
DNA Adducts / DNA Chain Termination	Carcinogen or drug-induced DNA damage. DNA molecules that have undergone chemical transformation, such as carcinogens
Drug Resistance	Reduced response to therapy. Cancer cells no longer respond to drugs designed to kill or inhibit them.

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Driver Genes	Mutated genes driving cancer. Mutations of genes lead to the development of cancer.
Early Detection	Finding disease early for better outcomes. Initial screening process that allows for timely treatment.
Early-Onset Cancer	Cancer <50 years. Cancer is detected in adults under 50 years of age, generally around 18 to 49 years of age, which is found in a younger age group when compared to the usual age associated with this cancer.
ECM	Structural support network. Computerized system that analyzes and evaluates machine work.
Electron Transport Chain (ETC)	ATP generation in mitochondria. Protein complex on the membrane that transfers electrons from the donor molecule to the acceptor molecule through a redoks reaction.
EMT	Transition increasing invasiveness. Emergency Medical Technician, a person trained in providing emergency medical care to patients.
Endothelial Cells	Vessel-lining cells for angiogenesis. Cells that consist of blood vessels, lymph vessels and the heart.
EORTC QLQ-C30	Cancer quality-of-life tool. The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire 30, which is used to measure the quality of life of cancer patients.

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Epigenetics	modifications in gene activity without altering DNA sequence, but still affect how cells interpret and express those genes.
Executioner Caspases (3/7)	Enzyme that trigger apoptosis in cancer cells.
Fibrosis	Formation of excess connective tissue causing stromal hardening and scar formation.
Fludarabine	Purine analog chemotherapy to treat B-cell chronic lymphocytic leukemia.
Frizzled	Part of the wnt pathway receptor; when abnormally activated are associated with many cancer hallmarks.
Gallstones	A hardened deposits of digestive fluid (components of bile) that cause irritation in gallbladder; a major risk factor of gallbladder cancer.
GAPDH	Glyceraldehyde-3-phospahte dehydrogenase; glycolytic enzyme that is overexpressed in cancer cells and correlated with aggressive malignant of the cancer cells.
GBM (Glioblastoma)	Aggressive and common type of malignant brain tumor.
G1/S Transition	Cell cycle checkpoint between growth and synthesis cell cycle.
Gene Editing/Silencing	targeted modification of genes to disable or remove genes that promote tumor growth, or to activate genes that suppress it.
Gemcitabine	Nucleoside analog chemotherapy drug that slows or stops the growth of

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	cancer cells by interfering with DNA formation.
Geographical Disparities	Regional cancer differences.
Glutaminolysis	Metabolic process of breaking down glutamine for fuel and to build new molecules for growth.
Glutaminase	Enzyme that converts glutamine into glutamate.
GPR81	G-protein-coupled receptor that is activated primarily by lactate; tumor-promoting receptor in breast cancer progression.
Growth Factors	Diffusible signaling proteins that stimulate cell growth, differentiation, survival, inflammation, and tissue repair.
GSK	Glycogen Synthase Kinase; protein kinase that can be a tumor promoter and a tumor suppressor depending on the cancer type.
HBV/HCV	Hepatitis B virus and hepatitis C virus, which are linked to cancer.
HDI	Human Development Index, indicators tied to cancer trends.
SDI	Socio Demographic Index, indicators tied to cancer trends.
HIF-1α	Hypoxia-inducible factor 1-alpha; a key protein that enable tumor cells survive and grow in low-oxygen environments.
HIV	Human immunodeficiency virus, which attacks $CD4^+$ T cells.

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Hormone Therapy	Hormone-modifying cancer treatment.
Hypopharynx	Rare and aggressive malignancy originates in the region between oropharynx and the esophageal inlet (lower throat behind voice box).
Immune Checkpoint Inhibitors (ICIs)	A type of cancer therapy that block proteins used by cancer cells to evade the immune system.
Immunotherapy	Immune-activating cancer treatments.
Incidence	Number of new cases of disease in a specific population over a period of time.
Integrins / Selectins	Cell adhesion molecules that promoting tumor progression and metastasis.
iNOS	inducible nitric oxide synthase; enzyme responsible for nitric oxide production and is expressed only in response to specific stimuli.
Ipilimumab	CTLA-4 inhibitor. This receptor is found in T-cells, which will bind to CD80 in APCs during negative co-stimulation of T-cells
Inflammaging	An age-related increase in the levels of pro-inflammatory markers in blood and tissues.
Lactate / Lactate Shuttle	Biological process that transfer lactate from one cell or tissue to another for use as energy or a signaling molecule.
Latency Period (Cancer)	Interval time between exposure to a carcinogen and tumor development.

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LDH (LDHA/LDHB)	Lactate dehydrogenase is a crucial enzyme for tumor metabolism. LDHA converts pyruvate to lactate, supporting rapid cancer cell growth and survival in harsh tumor environment. LDHB convert lactate back to pyruvate, suppressing tumor progression and serving as a marker of malignancy.
Left-Sided CRC	Colorectal cancer that starts in the lower part of the colon, including the descending colon, sigmoid colon, and rectum.
LVI	Lymphovascular invasion; tumor emboli present within the lymphatic or blood vessels near the primary tumor.
PNI	Perineural invasion; tumor emboli spread into the tissue surrounding a peripheral nerve.
Lymphadenectomy	Surgical procedure in which lymph nodes are dissected, and a sample of tissue is checked under a microscope for signs of cancer.
Lymphoproliferative Disorders	A type of lymphoid blood cancer characterized by the abnormal and uncontrolled proliferation of lymphocyte.
Malignant Tumor	Cancerous tumor; It develops when abnormal cell grows, multiply and spread to other parts of body (invasive, metastatic growth).

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MCT1/MCT4	Monocarboxylate transporter 1 and 4; highly expressed proteins which play a crucial role in tumor growth and spread by transporting lactate, protons, and other metabolites.
Melphalan / 6-MP	Alkylating chemotherapy agents that works by damaging cancer cell DNA that stops the cancer cells from dividing and kills them.
Metabolic Reprogramming	The process where cancer cells alter their metabolic pathways to support rapid growth and survival.
Metastasis	Distant spread of the disease. Usually, this term is used in cancer.
Microtubules / Spindle Fibers	Hollow, tube-like structure made of tubulin proteins that are part of the cell's cytoskeleton; useful for maintaining cell shape, intracellular transport, and chromosome segregation during mitosis and meiosis.
MMPs	Matrix metalloproteinases; family of enzymes that break down proteins in the extracellular matrix (ECM).
mTOR / mTORC1	Key protein kinase that regulate cell growth, metabolism, and survival in response to nutrients, energy and growth signals; mTORC1 is the most studied mTOR complexes that promotes cell growth and proliferation.
NAFLD	Nonalcoholic fatty liver disease; a condition in which fat builds up in

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	liver
NASH	Nonalcoholic steatohepatitis; a type of NAFLD characterized by inflammation and liver damage
Nanocarrier Drug Delivery	Medical approach in which tiny carriers at the nanoscale (usually 1-100 nanometers in size) are used to deliver drugs directly to specific cells, tissues, or organs.
Neutrophil Infiltration	Neutrophils, a type of white blood cell, move from the bloodstream into tissues.
Nrf2 Pathway	Nuclear factor erythroid - related factor 2; cellular defense mechanism that helps protect normal cells or malignant cells from oxidative stress
Oncogene	Mutated form of a normal gene that may cause cancer.
Opportunistic Infection (OI)	Infection caused by pathogens that usually do not affect healthy individuals but can cause disease in immunocompromised people.
Organ-Sparing Therapy	Treatment or therapy that aims to treat disease, while preserves the structure and function of the affected organ.
Oxidative Phosphorylation	Mitochondrial production of ATP or energy via electron transfer to oxygen through the electron transport chain.
Palliative Care	Specialized medical care focuses on relieving symptoms and improving quality of life, rather than curing the disease.

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PD-1/PD-L1	Immune checkpoint proteins are involved in T cell negative co-stimulation. PD-1 found in T-cells, while PD-L1 is found in APCs
Phimosis/ Penile SCC	Medical condition for a foreskin that is too tight to retract over the head of the penis, and is associated with an increased risk of penile squamous cell carcinoma.
Personalized Therapy	a medical approach that customizes treatment to an individual's specific characteristics, such as their genetic profile, tumor type or biomarker; also known as precision medicine.
PKM2	Pyruvate Kinase M2; a glycolytic enzyme that is over expressed in many cancer cells to help them generate energy and metabolic intermediates to sustain growth.
Pleural Effusion	A build-up of fluid in the lining of the lungs.
Primary Vaginal Cancer	Rare type of cancer originates in the cells of the vagina
Pyrimidine Analog	chemotherapy drugs that mimics the structure of natural pyrimidine nucleotides, interfering with DNA/ RNA synthesis, leading to cell cycle arrest and cell death.
Radical Cholecystectomy	Surgical procedure to remove the gallbladder and surrounding tissues for gallbladder cancer.
Radiotherapy	cancer treatment that uses high-energy radiation to kill cancer cells

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	and shrink tumors by damaging their DNA.
RARECARE	European surveillance project for monitoring rare cancers, which established a definition for these cancers and provided epidemiological data.
Regulatory T Cells (Tregs)	T cells that act as immunosuppressive.
Reverse Warburg	A phenomenon when cancer cells stimulate nearby stromal cells to generate energy-rich metabolites that the cancer cells use for growth.
Risk Factor	Condition that increases the likelihood of developing a disease or health problem.
ROS	Reactive molecules causing cell damage. This substance can be produced inside the phagolysosome of a macrophage.
Self-Sufficiency in Growth Signals	The ability of tumor to grow without relying on normal external growth signals, also known as tumor autonomous signaling.
SCC (Squamous Cell Carcinoma)	type of skin cancer originating from squamous epithelium that line the skin, respiratory tract, and other organs.
STATs / ERK / STAT5	Signaling pathways that regulate cell growth, survival, and differentiation; when it is dysregulated, as in cancer cells, it promotes tumor develpoment.

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Stem Cell Transplantation	Bone marrow replacement procedure in which healthy stem cells are infused into the body.
TACC3	Protein component of the centrosome axis which affect mitosis and regulate chromosome stability and are involved in tumor development and progression.
Targeted Therapy	Cancer treatment that uses substances to attack specific molecules that are involved in cancer cell growth and survival (molecular-targeting drugs).
TCA Cycle	A cyclic series of enzymatically catalyzed reactions inside mitochondrial matrix that generates energy (ATP) and key metabolic intermediates.
Temozolomide	An alkylating chemotherapy drug to kills brain tumors by damaging their DNA and stopping their growth.
Thyroid Cancer	A type of treatable endocrine cancer that develops in the thyroid gland.
TIGIT	Immune checkpoints that suppress immune response, allowing tumors to evade immune attack, can be found on T cells and NK (natural killer) cells.
LAG-3	Immune checkpoints that suppress immune response, allowing tumors to evade immune attack, can be found in T cells, regulatory T cells, and NK cells.

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Total Laryngectomy Surgical procedure to remove the entire larynx (voice box).

Tumor Suppressor Genes Genes preventing uncontrolled growth, repair DNA damage, and trigger cell death when needed.

Unlimited Replicative Potential The ability of cancer cell to divide themselves indefinitely also known as replicative immortality.

Urothelial Carcinoma Common form of bladder cancer, a cancer that starts from urothelial cells found in the urinary tract.

VEGF Main angiogenesis driver.

Wnt Signaling Signaling pathway important for tissue development and homeostasis; when it is upregulated, as in cancer cells, it can cause excessive cell growth, survival, and metastasis.

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ABOUT THE AUTHORS

Ika Nurlaila

As an alumnus of the University of Birmingham, where she earned her PhD in Cancer Immunology and Immunotherapy, she has had the privilege of cultivating a profound fascination with the intricate dynamics of cancer biology. Her academic journey was marked by a series of milestones, commencing with her undergraduate studies in Biology at the Department of Biology, Brawijaya University. During this formative period, she had the opportunity to secure a student research grant from the Technological Professional Skill Development Project and later emerged victorious in the prestigious Youth Researcher Competition held by LIPI in 2004. These experiences not only honed her research skills but also instilled within me a deep-seated passion for exploring the molecular mechanisms underlying cancer development and progression. Currently, as a research scientist at the Research Center for Vaccine and Drugs (PRVO), she is vigorously pursuing her dream projects, which revolve around identifying and characterizing cancer-specific antigens, mapping multiomics profiles of breast cancer in Indonesia, and reformulating cancer immunotherapy platforms tailored to the

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unique genetic-molecular landscape of the Indonesian population.

Dwi Wahyu Indriati

Dwi Wahyu Indriati is a distinguished lecturer at the Faculty of Vocational Studies, Universitas Airlangga, where she specializes in Medical Laboratory Technology. Moreover, she is a researcher at the Research Center for Global Emerging and Re-emerging Infectious Disease, Institute of Tropical Disease, Universitas Airlangga. With a Doctoral Degree in Physiological Science from the National Institute for Physiological Science, The Graduate University for Advanced Studies in Japan, Dr. Indriati has established herself as an expert in her field. Her fascination with molecular and cellular mechanisms dates back to her undergraduate studies in Biology at Brawijaya University. Upon joining Airlangga University, her research focus shifted to infectious diseases caused by pathogenic microbes, with a particular emphasis on antimicrobial resistance detection, alternative therapy using natural products, and rapid detection methods involving antigen or antibody production. Dr. Indriati's ultimate goal is to contribute valuable solutions to the detection and treatment of infectious diseases through her research.

Dwi Wahyu Indriani

As a researcher at the Research Center for Vaccines and Drugs, National Research and Innovation Agency of the Republic of Indonesia (BRIN), Dr. Dwi Wahyu Indriani has established herself as an expert in the field of physiological science. Having earned her doctorate from the National Institute for Physiological Science at Japan's prestigious Graduate University for Advanced Studies, Dr. Indriani has developed a unique blend of expertise in cellular and disease processes, underpinned by her molecular biology knowledge gained during her undergraduate studies in biology. Her research endeavors have thus far focused on developing disease models using experimental animals to elucidate the mecha-

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nisms underlying disease onset, which has been facilitated by her rigorous training in *in vivo* experimentation. Building upon this foundation, Dr. Indriani is currently conducting extensive in vitro experiments, followed by comprehensive *in vivo* studies, to investigate the therapeutic potential of Indonesian herbal plants as novel drug candidates. Her work has the potential to contribute significantly to the development of innovative treatments for various diseases, ultimately enhancing public health outcomes in Indonesia and beyond.

Asri Sulfianti

Asri Sulfianti, a researcher at the Research Center for Vaccine and Drugs, National Research and Innovation Agency, Republic of Indonesia (BRIN), has dedicated over a decade to pioneering groundbreaking research in the development of novel drugs and biopharmaceutical products. Holding a master's degree in biomedical sciences from the University of Indonesia, Asri's research trajectory has been marked by a consistent focus on vaccine development, with a particular emphasis on biopharmaceuticals. From 2014 to 2020, Asri made significant contributions to the Dengue National Consortium in Indonesia, spearheading the development of a virus-like particle vaccine specifically designed to combat Indonesian dengue virus strains. This endeavour showcased her expertise in vaccine development and her ability to tackle complex scientific challenges. In 2020, she expanded her scope by joining the HPV Vaccine Consortium, where she played a key role in investigating the interactions between LI HPV45-based vaccine candidates and prevalent HLA types in the Indonesian population. Since 2019, Asri has been an active member of the monoclonal antibody research group, applying her knowledge and skills to generate high-quality antibodies. As a recipient of the prestigious Endowment Fund for Higher Education (LPDP), she is poised to take the final step towards achieving her ultimate academic goal.

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Sri Ningsih

Dr. Sri Ningsih is a prominent researcher at the Research Center for Pharmaceutical Ingredients and Traditional Medicine, a prestigious institution within the National Research and Innovation Agency, Republic of Indonesia (BRIN). Holding a Ph.D. in Biomedical Sciences from the University of Indonesia, she has established herself as an expert in the development of herbal medicines for degenerative diseases. Her research has focused on the pharmacodynamics and toxicity studies of these medicines, with a particular emphasis on their potential to treat conditions such as gout, high blood glucose levels, and dyslipidemia. Furthermore, Dr. Ningsih has fostered collaborations with local enterprises to apply her research findings, thereby contributing to the development of standardized herbal medicines that can benefit the public. Her work has far-reaching implications for the development of alternative treatments and highlights her dedication to advancing the field of traditional medicine in Indonesia.

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Cancer remains one of the most formidable public health challenges and the second leading cause of mortality worldwide. Beyond its intricate biological etiology and shifting global epidemiological patterns, the fight against cancer is complicated by profound disparities in healthcare access, diagnostic delays, and variable therapeutic responsiveness, particularly in developing nations such as Indonesia.

Cancer Conundrum: The Etiology, Global Trends, and National Response delivers a comprehensive exploration of carcinogenesis mechanisms—including the Warburg effect, cellular hallmarks of cancer, and tumor microenvironment dynamics—alongside conventional and cutting-edge therapeutic platforms such as gene therapy, oncolytic virotherapy, and immunotherapy. By bridging fundamental molecular oncology with Indonesia's national health landscape and clinical strategies, this book serves as a vital reference for researchers, healthcare professionals, oncologists, and policymakers committed to transforming cancer management

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