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Utilization of Synthetic Drugs in Cancer: Preclinical and Clinical-based Evidence

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1.1 Introduction

Cancer is a multifaceted pathological condition that begins with a single abnormal cell and can spread through tissue invasion, uncontrolled growth, and the formation of new blood vessels [1, 2]. It can appear in different tissues and cause various types of cancer [3]. Cancer, a relentless disease, remains a leading cause of mortality and a substantial barrier to global longevity [4]. Among various cancers, breast cancer stands as the most prevalent malignancy in women. According to GLOBOCAN 2020, breast cancer has surpassed lung cancer as the leading cause of cancer incidence worldwide, with an estimated 2.3 million new cases diagnosed in 2020, accounting for 11.7% of all cancers [5]. Approximately 200 distinct neoplasms are categorized as rare malignancies due to their exceedingly low incidence. These rare cancers occur at a rate of approximately 15 cases per 100 000 individuals in the United States and a significantly lower rate of 6 cases per 100 000 individuals in Europe [6]. In the year 2022, India experienced a projected 1461 427 new occurrences of

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cancer cases, translating to a crude incidence rate of 100.4 per 100 000 individuals. A stark epidemiological reality emerges: a significant proportion of the population, approximately one in nine, is destined to encounter a malignant diagnosis during their lifetime. A disconcerting trajectory is projected, with a 12.8% increase in the incidence of neoplastic disease anticipated in the year 2025 relative to the year 2020 [7]. Paradoxically, the collective incidence of these rare cancers surpasses that of any individual, more common cancer type. The past decade has witnessed substantial progress in the management and treatment of cancer, particularly with the advent of immune-based therapies [8]. Four prominent immune-based treatment modalities have emerged: immune-checkpoint inhibitors, macrophage therapy, chimeric antigen receptor (CAR) T-cell therapy, and neo-antigen-based therapies. Despite the availability of numerous chemotherapeutic agents, the development of drug resistance poses a significant challenge. Understanding the intricate molecular mechanisms underlying this resistance is crucial, as they contribute to the failure of traditional therapies [9]. These mechanisms encompass a diverse array of processes, including enhanced drug efflux, reduced drug influx, alterations in drug targets, increased DNA repair capacity, heightened drug extrusion mediated by multidrug resistance efflux transporters, intrinsic genetic and epigenetic variations in drug-metabolizing enzymes, evasion of cellular senescence, tumor heterogeneity, ATP-dependent drug resistance, P-glycoprotein-mediated drug resistance, receptor kinase-mediated drug resistance, and mechanisms that impede apoptosis [10]. Given the complexity of these mechanisms, there is an urgent need for the identification and development of novel compounds that can effectively target these pathways while exhibiting reduced toxicity. Ten million people died from cancer in 2020, out of an estimated 19.3 million cases. By 2040, 28.4 million new cases are expected to occur [11]. Because of this, new, effective medications are needed, and it is crucial to understand the distinctive characteristics of existing treatments.

1.1.1 Cancer Biology and Pathophysiology

Cancer development, regardless of its histological type, seems to follow a common pathophysiological process that affects the body as a whole. Through the analysis of numerous scientific studies and research findings, it can be claimed that malignant tumors arise not only due to genetic damage within the cells but also due to the suppression of the body's antitumor immunity [12]. Our immune system normally detects and eliminates cancer cells, but sometimes it becomes suppressed [13]. This suppression is a natural response, but when it becomes excessive, it develops an alarming pathological condition [14]. In this state, the immune system can no longer effectively combat the growing tumor, allowing cancer to develop and progress [15].

Carcinogenesis is a multistep process wherein a carcinogenic agent induces genetic alterations in stem cells, initiating a cascade of events that ultimately leads to tumorigenesis. The initial phase, termed initiation, involves the introduction of a mutagen, a substance capable of inducing DNA damage. This genetic insult can predispose cells to neoplastic transformation. Subsequently, a promoter agent stimulates the proliferation of these initiated cells, accelerating tumor growth. A compound possessing both initiating and promoting properties is classified as a complete carcinogen [16].

The two-stage model of carcinogenesis postulates a sequential process involving initiation and promotion. In the initiation phase, carcinogenic agents, or initiators, interact with cellular DNA, inducing irreversible genetic mutations [17]. These initiators, often metabolically activated by endogenous enzymes, can transform normal cells into preneoplastic cells. Subsequently, in the promotion phase, promoters stimulate the proliferation of these initiated cells. Unlike initiators, promoters do not directly alter DNA but rather activate specific signaling pathways that drive cell growth and division. Promoters can be classified as specific or nonspecific, depending on their mode of action [18]. Specific promoters interact with cell surface receptors, while nonspecific promoters influence gene expression through more generalized mechanisms. The carcinogenic potency of a promoter is dose-dependent, with low doses often insufficient to induce tumorigenesis [19]. In experimental models, repeated exposure of initiated tissue to a promoting agent can result in the formation of benign tumors, such as papilloma's. While many of these benign lesions may regress upon cessation of promoter exposure, a subset can undergo malignant transformation. This process of malignant progression, as described by Leslie Foulds, is characterized by a series of genetic and phenotypic alterations [20]. These alterations, including aneuploidy and changes in cellular morphology and biochemistry, contribute to the acquisition of invasive and metastatic properties.

1.1.2 Nanomedicine in Cancer Treatments

Cancer has long been one of humanity's most formidable challenges. From ancient herbal remedies to modern radiation therapy, the battle against cancer has been shaped by continuous scientific discovery. Now, we find ourselves in the era of nanomedicine, a cutting-edge field that combines nanotechnology with healthcare to revolutionize cancer treatment. Nanomedicine allows for ultra-precise interventions, enabling drugs to be delivered directly to tumors while sparing healthy tissue [21]. This precision opens new possibilities for treating cancer, with the potential to reduce side effects and improve patient outcomes, driving excitement and innovation across the medical community. Nanomedicine, by manipulating matter at the nanoscale, has revolutionized the

oncologic paradigm, offering a distinct advantage over conventional therapeutic modalities. While conventional chemotherapeutic agents exhibit systemic distribution, often resulting in deleterious effects on healthy tissues, nanomedicine enables targeted drug delivery, maximizing therapeutic efficacy by concentrating agents within the neoplastic milieu while minimizing systemic toxicity. Furthermore, nanomedicine enhances the therapeutic index of antineoplastic agents through modifications that optimize pharmacokinetics, including augmented solubility, prolonged circulation, and controlled release within the tumor microenvironment. This approach also facilitates personalized oncology by enabling the design of nanoparticles that target specific molecular markers expressed by individual neoplasms [22].

Clinical validation of numerous nanomedicine-based therapeutic modalities has substantively demonstrated the transformative potential of this emergent paradigm in the oncologic domain. A salient exemplar is liposomal doxorubicin (Doxil), a nanomedicine approved for the management of mammary carcinoma [23]. Doxorubicin, a chemotherapeutic agent of considerable potency, exhibits a spectrum of adverse sequelae encompassing cardiotoxicity. Encapsulation of doxorubicin within a liposomal matrix comprised of lipidic vesicles attenuates its inherent toxicity, thereby facilitating the administration of augmented dosages with a concomitant diminution in adverse event profiles. Another instance of clinical success is exemplified by nanoparticle albumin-bound paclitaxel (Abraxane), approved for the management of metastatic mammary carcinoma and pancreatic adenocarcinoma [24]. Paclitaxel, a chemotherapeutic agent of considerable efficacy, encounters limitations in its therapeutic delivery owing to its paucity of aqueous solubility. Abraxane circumvents this constraint by conjugating paclitaxel to albumin nanoparticles, augmenting its aqueous solubility and facilitating enhanced delivery to neoplastic tissues. This novel formulation has demonstrated superior therapeutic efficacy and a reduced incidence of adverse events compared to conventional paclitaxel formulations [25].

Nanomedicine is bringing about breakthroughs in cancer treatment, offering several potential benefits that could change the landscape of oncology care. Key advantages include:

***Early Detection*:** Nanotechnology plays a crucial role in the early detection and diagnosis of cancer. Nanoparticles can be designed to detect biomarkers associated with cancerous growths, leading to earlier intervention and better survival rates [26].

***Precise Treatment*:** One of the most exciting aspects of nanomedicine is its ability to deliver treatments directly to cancerous cells and tissues, bypassing healthy cells. This level of precision minimizes damage to healthy tissues, reducing side effects often associated with traditional cancer treatments like chemotherapy and radiation [27, 28].

***Personalized Therapy*:** Nanomedicine allows for the customization of therapies tailored to the specific characteristics of a patient's tumor. By leveraging the molecular and genetic features of both the tumor and the individual patient, treatments can be optimized for better efficacy [29].

***Reduced Toxicity*:** Traditional cancer treatments often come with significant side effects due to their lack of specificity. Nanomedicine can significantly reduce these side effects by concentrating the treatment in cancerous areas, sparing healthy tissue from unnecessary damage, and minimizing toxicity [28].

***Improved Patient Outcomes*:** By offering more precise and targeted therapies, nanomedicine has the potential to improve overall patient outcomes. With enhanced drug delivery and the ability to customize treatments, patients are more likely to experience better responses and recoveries from cancer treatment [30].

1.1.2.1 Applications of Nanomedicine in Cancer Treatment

Nanomedicine is already being applied in various aspects of cancer care, from drug delivery to imaging and immunotherapy. ***In drug delivery***, nanomedicine aims to enhance the precision, efficacy, and safety of treatments by utilizing nanoscale carriers that can target specific tissues, penetrate biological barriers, and release drugs in a controlled manner. Nanomedicine, a rapidly evolving field, has made significant strides in revolutionizing cancer therapy [31]. One of its most prominent applications lies in the domain of drug delivery. Nanoparticles, meticulously engineered carriers, can encapsulate therapeutic agents and deliver them directly to tumor sites. This targeted approach, bypassing systemic circulation, enables the delivery of higher drug concentrations to the cancerous tissue, thereby enhancing therapeutic efficacy while minimizing systemic toxicity [32]. Notable examples include Food and Drug Administration (FDA)-approved drugs like Doxil and Abraxane, which leverage nanoparticle technology to improve the delivery of anticancer drugs to breast and ovarian cancer cells. ***Cancer imaging*** plays a crucial role in the diagnosis, staging, treatment planning, and monitoring of cancer. Advanced imaging techniques provide detailed visualizations of tumors, enabling clinicians to determine the extent of disease, assess treatment efficacy, and detect recurrences. Beyond drug delivery, nanomedicine plays a pivotal role in cancer imaging [33]. By incorporating imaging agents into nanoparticles, researchers can track the delivery of therapeutic agents and monitor treatment responses in real time. This dual functionality empowers clinicians to make informed decisions regarding treatment adjustments as needed. Magnetic nanoparticles, for instance, have been employed in lung cancer imaging, enhancing the sensitivity of magnetic resonance imaging and facilitating precise monitoring of tumor behavior during therapy [34]. ***Immunomodulation*** therapy is a cornerstone of modern oncology, leveraging the body's immune system to recognize and eliminate cancer cells. Unlike conventional treatments such as

chemotherapy and radiation, which directly target cancer cells, immunomodulation therapy enhances the immune system's ability to detect and combat malignancies. Nanomedicine also extends its influence to the tumor microenvironment (TME), a complex interplay of cells and extracellular matrix components [35]. By manipulating elements within the TME, nanomedicine can modulate the immune response, enabling the immune system to recognize and eradicate cancer cells more effectively. This approach is particularly crucial in overcoming the immunosuppressive nature of tumors, which often evade immune detection [36]. ***CAR T-cell therapy*** is another groundbreaking application of nanomedicine which is in the realm of CAR T-cell therapy. Nanoparticles can be utilized to construct CAR on the surface of circulating T cells, thereby enhancing their ability to target and destroy cancer cells. This precise engineering of T cells holds immense potential for more effective immunotherapies against cancers such as leukemia and lymphoma [37].

1.1.3 Evolution of Synthetic Anticancer Drugs from Ancient Beliefs to Modern Medicine

The origins of oncology, the study of cancer, can be traced back to ancient civilizations (Table 1.1). Evidence of bone tumors has been found in the fossilized remains of prehistoric animals, suggesting that cancer is not a modern disease. Ancient Egyptians, as early as 3000 BC, documented cases of breast cancer and described surgical interventions [38]. However, their understanding of cancer was rooted in mystical beliefs, attributing the disease to divine retribution [39]. The Greek physician Hippocrates, in the 5th century BC, proposed a more scientific explanation for cancer. He believed that tumors arose from an imbalance of bodily humors, particularly an excess of black bile [40]. This humoral theory, later refined by Galen, dominated medical thought for centuries [41]. The 18th century marked a turning point in the history of oncology. Researchers began to recognize the link between environmental factors and cancer. Percivall Pott's observations on scrotal cancer in chimney sweeps highlighted the role of occupational exposure in carcinogenesis [42]. The 19th century witnessed significant advancements in the understanding of cancer. Rudolf Virchow, often called the "father of cellular pathology," proposed that cancer arises from abnormal cell growth. This cellular theory revolutionized the field of oncology, leading to the development of more effective treatments [43]. In the 20th century, the development of chemotherapy and radiation therapy significantly improved cancer treatment outcomes. More recently, the advent of targeted therapies and immunotherapy has opened up new avenues for cancer treatment. Today, oncology is a rapidly evolving field. Researchers are using advanced technologies, such as genomics and proteomics, to identify new targets for cancer therapy. By understanding the molecular mechanisms underlying cancer, scientists are developing more precise and effective treatments.

Table 1.1 Summary of key milestones in the development of synthetic anticancer drugs.

Era	Event/Discovery	Drug/Technology	Description	Reference
Before 1900s: early work	Chemist Paul Ehrlich coined the term "chemotherapy" and used animal models to screen for anticancer drugs	N/A	Ehrlich's work laid the foundation for chemotherapy as a treatment modality for cancer.	[44]
1940s: initial discoveries	First breakthroughs in synthetic anticancer drugs	First breakthroughs in synthetic anticancer drugs	A nitrogen mustard alkylating agent, mechlorethamine was the first approved chemotherapy drug (1949).	[45]
1949	A nitrogen mustard alkylating agent, mechlorethamine was the first approved chemotherapy drug (1949)	Aminopterin (precursor to methotrexate)	Proven effective in treating childhood leukemia, marking a pivotal shift toward synthetic therapies.	[45]
1950s: drug development	Modifications to nitrogen mustard chemicals to increase efficacy and tumor cell targeting	Melphalan, chlorambucil	These derivatives of nitrogen mustard were designed to be more effective at entering tumor cells.	[46]
1960s–1980s: chemotherapy expansion	Development of chemotherapy regimens that target cancer cells more selectively	Methotrexate, cyclophosphamide	Methotrexate (1948) and cyclophosphamide (1950s) became core components of modern cancer regimens.	[47]
1975s–1990s: monoclonal antibodies	Development of monoclonal antibodies as targeted cancer therapies	Rituximab, trastuzumab	Monoclonal antibodies can target specific cancer cell markers, increasing precision in treatment.	[48]
2000s: advances in synthetic biology	Emerging field that uses biological systems to design and construct drugs for cancer therapy	Synthetic biology	This innovative approach allows for the production of complex biologics and targeted therapies.	[49]

1.2 Synthetic Pharmaceutical Anticancer Drugs

The development of synthetic pharmaceutical anticancer drugs marks a significant milestone in the fight against cancer, revolutionizing the treatment landscape and offering renewed hope to millions of patients worldwide. These chemically engineered compounds have been designed to either stop the division of cancer cells or prevent their proliferation, helping to shrink tumors and improve patient outcomes. As cancer research advances, these drugs play a crucial role in the ongoing battle against various forms of cancer. The evolution of synthetic anticancer therapeutics represents a remarkable journey from serendipitous discovery to precision medicine. This transformative odyssey commenced in the early 20th century with the accidental observation of the cytotoxic properties of mustard gas [50]. This serendipitous finding led to the development of nitrogen mustards, the first generation of chemotherapeutic agents ushering in the era of synthetic anticancer therapy [51]. Although effective, these early agents lacked specificity, indiscriminately targeting rapidly dividing cells, resulting in significant systemic toxicity. Subsequent decades witnessed the refinement of these agents and the development of novel classes, including alkylating agents, antimetabolites, and vinca alkaloids, which exhibited greater selectivity for cellular division processes [52]. The elucidation of DNA's structure in the mid-20th century, coupled with advancements in molecular biology, revolutionized the landscape of anticancer drug discovery [53]. Cancer, once considered a monolithic disease, was increasingly recognized as a genetic disorder, characterized by aberrant molecular pathways. This paradigm shift led to the identification of critical molecular targets involved in tumorigenesis and progression. The emergence of targeted therapies, exemplified by the tyrosine kinase inhibitor imatinib, marked a significant milestone. Imatinib specifically inhibits the BCR-ABL fusion protein, a key driver of chronic myeloid leukemia (CML), demonstrating the power of precision medicine [54]. Concomitantly, preclinical research methodologies, including high-throughput screening and animal models, were refined to enable the efficient evaluation of drug efficacy and toxicity. Synthetic chemists, armed with a deep understanding of molecular interactions, designed and synthesized compounds with enhanced selectivity and potency, minimizing off-target effects and reducing collateral damage to healthy tissues. The transition from preclinical research to clinical development involves a rigorous and multiphased process. Phase I clinical trials prioritize safety, determining the maximum tolerated dose and assessing the pharmacokinetic profile of the investigational drug in human subjects [55]. Phase II trials focus on evaluating the drug's efficacy in specific cancer types, while Phase III trials conduct large-scale comparative studies to assess the new drug's efficacy relative to standard-of-care therapies [56]. Regulatory agencies, such as the FDA and European Medicines

Agency (EMA), play a crucial role in ensuring the safety and efficacy of novel therapeutics through a stringent approval process. The successful clinical development and subsequent widespread adoption of synthetic anticancer drugs, including cisplatin, paclitaxel, and doxorubicin, have significantly improved patient outcomes [57]. In recent decades, the convergence of genomics, proteomics, and computational biology has accelerated the pace of drug discovery. Synthetic drugs are now being designed to target specific genetic alterations, such as epidermal growth factor receptor (EGFR) mutations in lung cancer or Breast Cancer (BRCA) mutations in breast cancer [58]. The integration of synthetic chemistry with nanotechnology has led to the development of advanced drug delivery systems, enabling targeted release of therapeutic agents and minimizing systemic toxicity. Moreover, immunotherapy, although not purely synthetic, has been augmented by synthetic small molecules that modulate the immune response, expanding the therapeutic armamentarium against cancer [59]. The detailed description of synthetic anticancer drugs along with the mechanism of action toward specific types of cancer is represented in Table 1.2.

***Methotrexate*:** Methotrexate, a pioneering chemotherapeutic agent introduced in the mid-20th century, has solidified its position as a cornerstone in cancer treatment. Preclinical studies in the 1940s demonstrated its potent antiproliferative effects in leukemia models, laying the groundwork for its subsequent clinical application. By the 1950s, clinical trials in pediatric acute lymphoblastic leukemia unequivocally established methotrexate's therapeutic efficacy, culminating in its FDA approval [60]. Today, methotrexate remains an integral component of treatment regimens for a diverse range of cancers, including leukemia, breast cancer, and osteosarcoma. Methotrexate exerts its therapeutic effects by inhibiting the de novo synthesis of tetrahydrofolate, a critical cofactor involved in the production of purines and thymidylate, essential building blocks for DNA replication and cell proliferation. The widespread availability of methotrexate as a generic medication has significantly contributed to its global impact, with an estimated market value of approximately $350 million in 2023. This remarkable drug continues to transform the treatment of cancer and autoimmune diseases, saving countless lives worldwide.

***Cisplatin*:** The serendipitous discovery of cisplatin in the 1960s marked a turning point in the field of oncology. Initially investigated for its antibacterial properties, researchers were astounded by its potent antitumor activity, particularly against solid tumors, notably testicular cancer. Preclinical studies provided compelling evidence of its efficacy, paving the way for its evaluation in clinical trials. The results were groundbreaking, transforming testicular cancer from a life-threatening disease to a highly treatable condition [61]. In 1978, the FDA granted approval for cisplatin, solidifying its position as a cornerstone of cancer

Table 1.2 Description of synthetic anticancer drugs utilized to treat multiple types of cancer [95, 96].

Drug name	Type	Primary uses	Mechanism of action
Capecitabine	Synthetic chemotherapeutic agent	Colon cancer, gastrointestinal cancers	Metabolized into 5-fluorouracil, which inhibits thymidylate synthase, halting DNA synthesis
Fluorouracil	Synthetic chemotherapeutic agent	Colon cancer, breast cancer, solid tumors	Inhibits thymidylate synthase, preventing DNA synthesis and cell division
Oxaliplatin	Platinum-based chemotherapy drug	Colon cancer, gastrointestinal cancers	Forms DNA crosslinks that prevent DNA replication and division
Paclitaxel & docetaxel	Synthetic chemotherapy drug	Breast, ovarian, and non-small cell lung cancers	Stabilizes microtubules, preventing their disassembly, which is necessary for cell division
Irinotecan	Synthetic chemotherapy agent	Colon cancer (particularly metastatic or recurrent)	Inhibits topoisomerase I, leading to DNA damage and cell death
Cabazitaxel	Semisynthetic taxane derivative	Metastatic hormone-refractory prostate cancer	Stabilizes microtubules, similar to paclitaxel, effective in taxane-resistant cancers
Neopeltolide	New synthetic anticancer agent	Investigational; potential for a variety of cancers	Disrupts cancer cell division, though mechanisms are still under study
Cisplatin	Platinum-based chemotherapy drug	Testicular, ovarian, bladder cancers	Forms DNA crosslinks, inhibiting cell division
Daunorubicin	Anthracycline antibiotic	Leukemia	Interferes with DNA/RNA synthesis, preventing cancer cell proliferation
Doxorubicin	Anthracycline antibiotic	Breast cancer, lymphoma, solid tumors	Intercalates into DNA, inhibiting transcription and replication
Etoposide	Plant-derived drug	Various cancers, including lung and testicular cancers	Inhibits topoisomerase II, preventing DNA repair and triggering cancer cell death

chemotherapy. Today, cisplatin remains a widely used generic drug, with a global market value estimated at approximately $450 million in 2023.

***Doxorubicin*:** A potent chemotherapeutic agent derived from the bacterium Streptomyces, has revolutionized cancer treatment since its isolation in the 1960s. This anthracycline antibiotic exerts its cytotoxic effects by intercalating with DNA and inhibiting topoisomerase II, thereby disrupting cellular replication and inducing apoptosis. Preclinical studies demonstrated doxorubicin's broad-spectrum antitumor activity against both solid tumors and hematological malignancies [62]. Subsequent clinical trials confirmed its efficacy in treating breast cancer, lymphomas, and sarcomas, leading to FDA approval in 1974. Today, doxorubicin remains a cornerstone in the treatment of these cancers and others, such as ovarian cancer, offering hope to countless patients. With a global market value exceeding $1 billion in 2023, doxorubicin continues to play a vital role in the fight against cancer.

***Imatinib*:** This tyrosine kinase inhibitor selectively targets the aberrant BCR-ABL fusion protein, a key driver of CML pathogenesis. Has revolutionized the treatment of CML and ushered in the era of precision oncology. Preclinical studies demonstrated imatinib's remarkable ability to inhibit the growth and proliferation of CML cells with minimal impact on healthy cells, promising a therapeutic approach with reduced toxicity. Subsequent clinical trials yielded astonishing results, with imatinib inducing significant disease remission and improving patient survival [63]. The FDA's approval of imatinib in 2001 marked a watershed moment in cancer therapy. With the advent of generic formulations, the global market for imatinib is estimated to reach $3 billion in 2023, underscoring its enduring impact on patient care. Imatinib not only represents a beacon of hope for CML patients but also symbolizes a paradigm shift in the development and application of targeted therapies.

***Paclitaxel*:** The discovery of paclitaxel, a remarkable compound derived from the bark of the Pacific yew tree, marked a significant milestone in cancer therapy. In the 1960s, scientists were captivated by paclitaxel's unique ability to stabilize microtubules, a crucial component of the cellular cytoskeleton. This mechanism of action disrupts cell division, leading to cell death. Preclinical studies demonstrated paclitaxel's potent antitumor activity, particularly against ovarian and breast cancers [64]. Subsequently, clinical trials confirmed their efficacy, culminating in FDA approval in 1992. As of 2023, paclitaxel remains a cornerstone of cancer treatment, with a global market value exceeding $3.5 billion, underscoring its critical role in combating this devastating disease.

***Tamoxifen*:** Originally developed as a contraceptive agent, tamoxifen has undergone a remarkable transformation into a first-in-class selective estrogen receptor modulator (SERM) for the treatment of breast cancer [65]. Early preclinical investigations revealed tamoxifen's potent antiestrogenic properties, sparking

interest in its potential as a therapeutic agent for hormone receptor-positive breast cancer [66]. Clinical trials subsequently demonstrated tamoxifen's efficacy in improving survival outcomes, leading to its FDA approval in 1977. As of 2023, tamoxifen maintains a global market value of approximately $600 million, highlighting its enduring significance in the management of breast cancer.

***Rituximab*:** A groundbreaking monoclonal antibody, marked a significant milestone in cancer therapy by targeting the CD20 antigen expressed on the surface of B lymphocytes. Preclinical studies demonstrated rituximab's potent ability to induce B-cell depletion, leading to its evaluation in clinical trials for non-Hodgkin lymphoma (NHL). The remarkable efficacy of rituximab in treating NHL led to its FDA approval in 1997, ushering in a new era of targeted cancer therapy [67]. As of 2023, rituximab maintains a substantial global market value of approximately $7 billion, although the emergence of biosimilars is poised to impact its revenue stream. Nonetheless, rituximab remains a pivotal therapy in the treatment of B-cell malignancies.

***Trastuzumab*:** A revolutionary monoclonal antibody known as Herceptin, has transformed the treatment paradigm for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. By specifically targeting the HER2 receptor, which is overexpressed in a subset of breast cancers, trastuzumab disrupts critical signaling pathways, leading to tumor cell death. Early preclinical studies demonstrated the potent antitumor activity of trastuzumab, setting the stage for clinical trials that revealed significant improvements in survival outcomes for patients with HER2-positive disease. The FDA approved trastuzumab in 1998, marking a pivotal moment in the history of cancer therapy [68]. Despite the emergence of biosimilars, trastuzumab continues to be a cornerstone treatment, generating substantial revenue of approximately $6 billion globally in 2023, solidifying its enduring impact on the lives of countless patients.

***Bevacizumab*:** A monoclonal antibody targeting vascular endothelial growth factor, has revolutionized cancer therapy by inhibiting angiogenesis, the process by which tumors form new blood vessels to sustain their growth and metastasis. Extensive preclinical research demonstrated bevacizumab's potent antiangiogenic activity, leading to significant tumor regression and reduced metastatic potential. Clinical trials in colorectal cancer further validated bevacizumab's efficacy, resulting in a notable improvement in progression-free survival [69]. The FDA approved bevacizumab in 2004, marking a significant advancement in cancer treatment. As of 2023, bevacizumab maintains a global market value of approximately $7 billion, underscoring its critical role in contemporary oncology.

***Pembrolizumab*:** Marketed as Keytruda, it is a revolutionary immunotherapy that targets the programmed death 1 (PD-1) immune checkpoint. By inhibiting this checkpoint, pembrolizumab unleashes the full potential of T cells, enabling them to recognize and eliminate cancer cells more effectively. Preclinical studies demonstrated pembrolizumab's potent antitumor activity in cancers that exhibit immunogenic properties. Clinical trials in patients with melanoma, lung cancer, and head and neck cancer yielded remarkable results, with significant improvements in response rates and overall survival [70]. The FDA approved pembrolizumab in 2014, marking a significant milestone in cancer immunotherapy. As of 2023, Keytruda has achieved global sales of $24 billion, solidifying its position as one of the world's top-selling drugs.

***Nivolumab*:** A monoclonal antibody targeting the PD-1 immune checkpoint, has emerged as a powerful weapon in the arsenal of cancer immunotherapy. By disrupting the PD-1/programmed death ligand 1 (PD-L1) interaction, nivolumab liberates the immune system to recognize and eliminate tumor cells more effectively. Preclinical studies demonstrated nivolumab's potential to reverse immune suppression, paving the way for its evaluation in clinical trials. In patients with melanoma and lung cancer, nivolumab has shown significant clinical benefit, leading to improved survival outcomes. The FDA approved nivolumab in 2014, marking a significant advancement in cancer treatment [71]. As of 2023, nivolumab has achieved global sales of approximately $10 billion, solidifying its position as a pivotal therapy in modern oncology.

***Erlotinib*:** A potent tyrosine kinase inhibitor, targets the EGFR, a critical signaling pathway implicated in the development and progression of various cancers, particularly non-small cell lung cancer (NSCLC). Preclinical studies demonstrated erlotinib's efficacy in inhibiting EGFR-driven tumor growth, paving the way for its clinical evaluation. Subsequent clinical trials confirmed erlotinib's significant clinical benefit in patients with EGFR-mutated NSCLC, leading to its FDA approval in 2004 [72]. With the expiration of its patent, the market for erlotinib has transitioned to a generic landscape. Despite this, the drug continues to have a substantial impact on patient care, with a global market value of approximately $1.5 billion in 2023.

***Lenalidomide*:** A novel thalidomide derivative, has emerged as a potent immunomodulatory agent with antiangiogenic properties. Preclinical studies demonstrated lenalidomide's efficacy in targeting multiple myeloma, a hematological malignancy characterized by uncontrolled proliferation of plasma cells. Clinical trials further validated lenalidomide's ability to improve survival outcomes in patients with relapsed or refractory multiple myeloma, leading to its FDA approval in 2005 [73]. As of 2023, lenalidomide has achieved significant commercial

success, generating global sales of approximately $12 billion, solidifying its position as a pivotal therapy in the treatment of multiple myeloma.

***Sorafenib*:** A multi-kinase inhibitor targeting key signaling pathways such as vascular endothelial growth factor receptors (VEGFR) and Raf kinase, has emerged as a potent therapeutic agent in the treatment of advanced cancers. Preclinical studies demonstrated sorafenib's ability to inhibit tumor growth and angiogenesis, particularly in models of hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). Subsequent clinical trials confirmed sorafenib's efficacy in prolonging survival and improving quality of life for patients with these advanced cancers. The FDA approved sorafenib in 2005, marking a significant advancement in the treatment of these challenging diseases [74]. As of 2023, sorafenib maintains a global market value of approximately $3 billion, underscoring its enduring impact on patient care.

***Gefitinib*:** A targeted therapy designed to inhibit EGFR mutations, has revolutionized the treatment of NSCLC. Preclinical studies demonstrated gefitinib's potent antitumor activity in EGFR-driven NSCLC models. Subsequent clinical trials confirmed their efficacy, leading to remarkable improvements in progression-free survival for patients with EGFR-mutated NSCLC. The FDA approved gefitinib in 2003, providing a much-needed therapeutic option for patients with this aggressive disease [75]. While the global market for gefitinib was valued at $1.8 billion in 2023, the emergence of generic alternatives has increased access to this life-saving therapy.

***Carboplatin*:** A platinum-based chemotherapeutic agent, was developed as a less toxic alternative to cisplatin while maintaining potent antitumor activity. Preclinical studies demonstrated carboplatin's efficacy in inhibiting tumor cell growth and proliferation. Subsequent clinical trials confirmed carboplatin's comparable efficacy to cisplatin, with a more favorable toxicity profile. The FDA approved carboplatin in 1989, making it a valuable addition to the chemotherapeutic armamentarium [76]. As of 2023, carboplatin remains a widely used generic drug, with a global market value of approximately $300 million, underscoring its enduring role in cancer treatment.

***Oxaliplatin*:** A standout among platinum-based drugs, has made waves in the fight against colorectal cancer in preclinical trials, proving its effectiveness in various models. Its journey from the lab to the clinic has been remarkable, with clinical trials revealing notable survival benefits for patients with metastatic colorectal cancer. This success story culminated in FDA approval in 2002 [77]. As of 2023, oxaliplatin maintains a global market value of approximately $1.5 billion, underscoring its enduring role in cancer therapy.

***Docetaxel*:** An innovative semisynthetic taxane, plays a crucial role in stabilizing microtubules within cells. Preclinical studies have demonstrated its impressive activity, surpassing that of paclitaxel. Its efficacy was confirmed through

rigorous clinical trials in both breast and prostate cancer, ultimately leading to its approval back in 1996 [78]. Fast forward to 2023, and the global market for this powerful drug has reached around $2 billion, highlighting its significant impact in the realm of cancer treatment.

***Topotecan*:** A potent topoisomerase I inhibitor, was developed to address the challenge of drug resistance in ovarian and lung cancers. Preclinical studies demonstrated topotecan's efficacy in overcoming resistance mechanisms and inducing tumor cell death. Subsequent clinical trials confirmed topotecan's clinical benefit in patients with relapsed ovarian cancer and small cell lung cancer, leading to FDA approval in 1996 [79]. As of 2023, topotecan remains a valuable therapeutic option, with a global market value of approximately $800 million, primarily driven by generic formulations.

***Bortezomib*:** Recognized as the first proteasome inhibitor, has played a significant role in advancing treatment options for multiple myeloma. Initial preclinical studies highlighted its noteworthy capacity to induce apoptosis in cancer cells, which laid the foundation for its subsequent clinical development. As clinical trials progressed, bortezomib demonstrated considerable survival benefits, garnering the attention and endorsement of the medical community. This culminated in its FDA approval in 2003 [80]. By 2023, bortezomib achieved impressive global sales, reaching $2 billion, thereby reinforcing its position as an essential component in the arsenal against cancer.

***Cabozantinib*:** Stands out as a powerful multitasker in the fight against cancer, specifically targeting key kinases like MET and VEGFR. Preclinical studies have revealed its impressive potential against aggressive tumors, paving the way for its clinical journey [81]. In trials, cabozantinib showcased remarkable efficacy in treating medullary thyroid and RCC, earning its well-deserved approval in 2012 [82]. Fast forward to 2023, and this innovative treatment has generated around $1.5 billion globally, highlighting its significant impact on cancer care.

***Axitinib*:** A robust VEGFR inhibitor, was specifically designed to tackle RCC. Early preclinical studies revealed its impressive ability to impede angiogenesis, the process that fuels tumor growth. The results were so promising that clinical trials later validated its effectiveness in treating advanced renal cancer, leading to its FDA approval in 2012 [83]. Fast forward to 2023, and Axitinib is estimated to be making waves in the global market, valued at around $800 million.

***Abiraterone*:** Is a synthetic steroid that targets CYP17A1, a crucial enzyme involved in the production of androgens. In preclinical studies, it has shown remarkable potential in suppressing the growth of androgen-driven prostate cancer. The results were so promising that clinical trials conducted on metastatic prostate cancer highlighted significant survival benefits. As a result, this innovative treatment gained FDA approval in 2011 [84]. Fast forward to 2023, and Abiraterone has generated an impressive $3 billion globally.

***Capecitabine*:** An oral prodrug of 5-fluorouracil (5-FU), was developed to improve the pharmacokinetic profile and therapeutic efficacy of 5-FU while reducing the need for intravenous administration. Preclinical studies demonstrated that capecitabine is selectively activated in tumor tissues by the enzyme thymidine phosphorylase, which is overexpressed in many cancer cells. Rigorous preclinical testing assessed capecitabine's safety and efficacy before its progression to clinical trials [85]. Initial phase I and II clinical trials established capecitabine's activity against colorectal and breast cancer, demonstrating promising tumor response rates and manageable side effects. Phase III clinical trials further validated capecitabine's non-inferiority to 5-FU/leucovorin in metastatic colorectal cancer and confirmed its efficacy in metastatic breast cancer, particularly in combination with docetaxel [86]. As of 2023, capecitabine is widely available as a generic medication, with a global market value of approximately $2 billion.

***5-Fluorouracil (5-FU)*:** A synthetic pyrimidine analog, emerged in the mid-20th century as a cornerstone in the evolution of cancer chemotherapy. Its mechanism of action, centered on the inhibition of thymidylate synthase, a crucial enzyme in DNA synthesis, was elucidated through meticulous biochemical investigations [87]. Early clinical trials highlighted its efficacy against a spectrum of solid tumors, notably colorectal carcinoma. Over the ensuing decades, 5-FU solidified its position as an indispensable component of therapeutic regimens for a myriad of malignancies, including colorectal, head and neck, and breast cancers, often in conjunction with other cytotoxic agents [88]. Recognizing the limitations associated with its intravenous administration, researchers developed innovative prodrugs like capecitabine, designed to circumvent these challenges. Today, 5-FU, widely available as a generic medication, continues to play a pivotal role in global cancer care, with an estimated market value exceeding half a billion dollars in 2023.

***Cabazitaxel*:** A semisynthetic taxanes derivative, was developed to overcome the limitations of traditional taxanes like docetaxel. Preclinical studies revealed its potent ability to bind microtubules, thereby inhibiting their depolymerization. This mechanism of action proved effective even in cancer cells that had acquired resistance to other taxanes-based therapies [89]. Initial clinical trials, including phase I and II studies, established the safety and efficacy of cabazitaxel in patients with castration-resistant prostate cancer (CRPC). The landmark Phase III TROPIC trial provided definitive evidence of cabazitaxel superiority over mitoxantrone in the treatment of CRPC patients who had progressed after docetaxel therapy [90]. Its global market value was estimated at $500 million in 2023.

***Cyclophosphamide*:** A derivative of nitrogen mustard, was introduced in the 1950s as an alkylating agent [91]. Preliminary studies demonstrated its extensive

cytotoxic properties, while initial clinical trials validated its effectiveness against Hodgkin lymphoma, breast cancer, and leukemia [92]. Its prodrug characteristics enable targeted activation within tumor cells through cytochrome P450 enzymes. Cyclophosphamide continues to be an essential medication in chemotherapy protocols such as CHOP for lymphomas. Commonly available in generic form, its market valuation reached $1 billion in 2023.

***Ifosfamide*:** Is intriguing structural analog of cyclophosphamide, developed with the intent of enhancing its efficacy in combating cancer and addressing treatment resistance in challenging cases [93]. Comprehensive preclinical studies have demonstrated its considerable antitumor effects, while clinical trials have underscored its effectiveness against various malignancies such as sarcomas, testicular cancer, and lymphomas [94]. As with many potent therapies, ifosfamide is associated with certain risks, including neurotoxicity and bladder toxicity. To mitigate these side effects, it is frequently administered alongside means, which helps improve safety for patients. In spite of these challenges, ifosfamide plays a significant role in combination therapies for sarcomas and other cancers. With a global market valuation of approximately $800 million in 2023, it remains an essential component in the ongoing battle against cancer.

1.3 Challenges Faced in Early Drug Development

The journey of synthetic drug development, especially for complex diseases like cancer, has historically been fraught with numerous challenges (Table 1.3). These early-stage difficulties not only hindered progress but also shaped the drug discovery landscape. Below is an exploration of some key challenges faced during the initial stages of drug development, including the inherent complexities and their implications for the pharmaceutical industry [97].

***Lack of selectivity and toxicity*:** One of the primary challenges in early drug development was the lack of selectivity in early drugs. These drugs often targeted both cancerous and healthy cells, leading to severe side effects. Immune suppression, hair loss, and organ damage were some of the debilitating consequences [98]. This issue highlighted the need for more precise therapies that could specifically target cancer cells without harming surrounding healthy tissues.

***Complexity of cancer biology*:** The complexity of cancer biology added another layer of difficulty. Understanding how tumors grew, mutated, and spread was essential for developing effective treatments. However, researchers struggled to

Table 1.3 Representation of challenges in early drug development [109–111].

Challenges	Descriptions
Lack of selectivity and toxicity	Early drugs harmed both cancerous and healthy cells, leading to severe side effects such as immune suppression and organ damage.
Complexity of cancer biology	Understanding tumor biology and mutation patterns was difficult, hindering drug design.
Long timelines	The preclinical and clinical phases take years, delaying the availability of drugs to patients.
High costs	Developing new drugs costs billions, encompassing R&D, testing, and regulatory compliance.
High failure rates	90% of drugs fail in clinical trials due to efficacy or safety concerns.
Use of animal models	Animal models do not always predict human responses accurately, leading to potential failures in clinical trials.
Patient recruitment	Recruiting enough patients for trials is time-consuming, and costly, and can limit the trial's success.
Regulatory framework	Strict regulations ensure safety but can also delay drug approval processes.
Target identification & validation	Identifying and validating effective drug targets is challenging due to the complexity of disease biology.
Study design	Improper study design can lead to inaccurate or inconclusive results, increasing the risk of trial failure.
In-house development vs. outsourcing	In-house development is costly, while outsourcing to CROs may reduce control over the development process.

grasp the intricate biological processes behind tumorigenesis, making it difficult to design drugs that could specifically target these processes. Overcoming this challenge required significant advances in molecular biology and oncology [99].

***Drug development timelines*:** The drug development process is notoriously long. The preclinical phase can take between 3 and 6 years, and clinical trials often extend this timeline significantly. The prolonged timelines result in delayed drug availability for patients and contribute to the high costs associated with drug development. Researchers must also account for the time

spent on regulatory approvals and additional testing before a drug can be marketed [100].

***High costs*:** The financial burden of drug development is another significant hurdle. The cost of developing a new drug can range from approximately $985 million to over $2.8 billion. These high costs stem from research and development, preclinical and clinical testing, and compliance with regulatory frameworks. Pharmaceutical companies must balance these costs with the need for profitability, often resulting in high prices for new medications [101].

***High failure rates*:** Failure rates in early drug development are alarmingly high, with nearly 90% of drugs that enter clinical trials failing to reach the market. These failures are often due to safety concerns, lack of efficacy, or unforeseen complications arising from clinical trials. While these failures provide valuable lessons, they also contribute to the overall time and cost involved in bringing new drugs to market [102].

***Use of animal models*:** Animal models are frequently used in the early stages of drug discovery to predict how a drug will perform in humans. However, these models are not always reliable. Differences in biology between animals and humans can lead to inaccurate predictions, meaning that drugs that work well in animal models may not be effective or safe for humans [103]. This issue has led to ongoing debates about the relevance of animal testing in drug development.

***Patient recruitment*:** Recruiting enough patients to generate statistically significant data for clinical trials is a time-consuming and expensive process. Patient recruitment can be especially difficult in specialized areas, such as cancer, where patient populations may be limited or geographically dispersed [104]. The challenge is compounded by issues like patient consent, eligibility criteria, and retention throughout the lengthy trial periods.

***Regulatory framework*:** Pharmaceutical companies must adhere to strict regulatory guidelines set by government agencies, such as the FDA or EMA. The regulatory framework is designed to ensure drug safety and efficacy, but it can also create delays in the approval process [105]. Navigating these regulations is a complex and costly part of drug development.

***Target identification and validation*:** Effective drug development requires a deep understanding of disease biology, including the identification and validation of drug targets. This step is crucial to ensure the drug's specificity, minimize toxicity, and improve its therapeutic index. However, understanding disease mechanisms and identifying appropriate molecular targets can be challenging due to the complexity of biological systems [106].

***Study design*:** Designing a well-structured study is essential for generating reliable and reproducible data. Poor study design can lead to inconclusive

results, missed opportunities, and increased risk of failure in later phases of development [107]. This can be particularly challenging when studying novel diseases or therapies, as researchers may lack the necessary baseline data to guide the design process.

***In-house development vs. outsourcing*:** Developing drugs in-house can be prohibitively expensive, requiring significant investment in infrastructure, personnel, and resources. Alternatively, outsourcing to Clinical Research Organizations (CROs) can reduce costs and provide expertise [108]. However, outsourcing can come with challenges, including communication barriers, misaligned goals, and reduced control over the development process.

1.4 Conclusion

Cancer, defined by unregulated cellular proliferation, has posed significant challenges throughout history. While ancient cultures acknowledged its presence, a transformative understanding and approach to its treatment didn't materialize until the 20th century. The introduction of synthetic pharmaceuticals has marked a pivotal shift in oncologic therapy, facilitating more targeted and efficacious interventions. This chapter highlighted the complex molecular underpinnings of tumorigenesis, delving into the roles of oncogenes, tumor suppressor genes, and the tumor microenvironment in facilitating cancer progression. We also explored the burgeoning domain of nanomedicine, which employs nanotechnology to devise innovative drug delivery mechanisms aimed at enhancing targeted therapy for malignancies. A historical context surrounding cancer treatment is presented, tracing the lineage of synthetic drugs from archaic medicinal practices to contemporary pharmacotherapy. Key milestones in the advent of anticancer agents has emphasized, including the discovery of cytotoxic compounds, the advent of targeted therapies, and the advancements in immunotherapy. The emergence of synthetic anticancer drugs signifies a major achievement in modern oncological practice. These agents precisely target molecular pathways integral to cancer cell growth and survival, thereby improving therapeutic efficacy while minimizing adverse effects. However, challenges such as drug resistance and systemic toxicity persist. To counteract these obstacles, researchers are investigating cutting-edge strategies, including targeted therapies, immunotherapeutic modalities, and integrative combination regimens. Personalized medicine stands out as a transformative approach in oncology, aiming to customize treatments based on the distinct genetic and molecular profiles of individual tumors. By deciphering the unique genomic landscape of a neoplasm, clinicians can optimize therapeutic selections and

closely monitor tumor response and disease progression. In summary, the progression of cancer treatment from ancient practices to sophisticated modern strategies highlights the relentless endeavor to discover and refine effective therapies. Synthetic pharmaceuticals have fundamentally influenced this trajectory, enabling targeted, effective interventions. Nevertheless, ongoing investigative efforts are crucial to surmount the limitations inherent in current therapies and pave the way for innovative solutions in oncology.

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