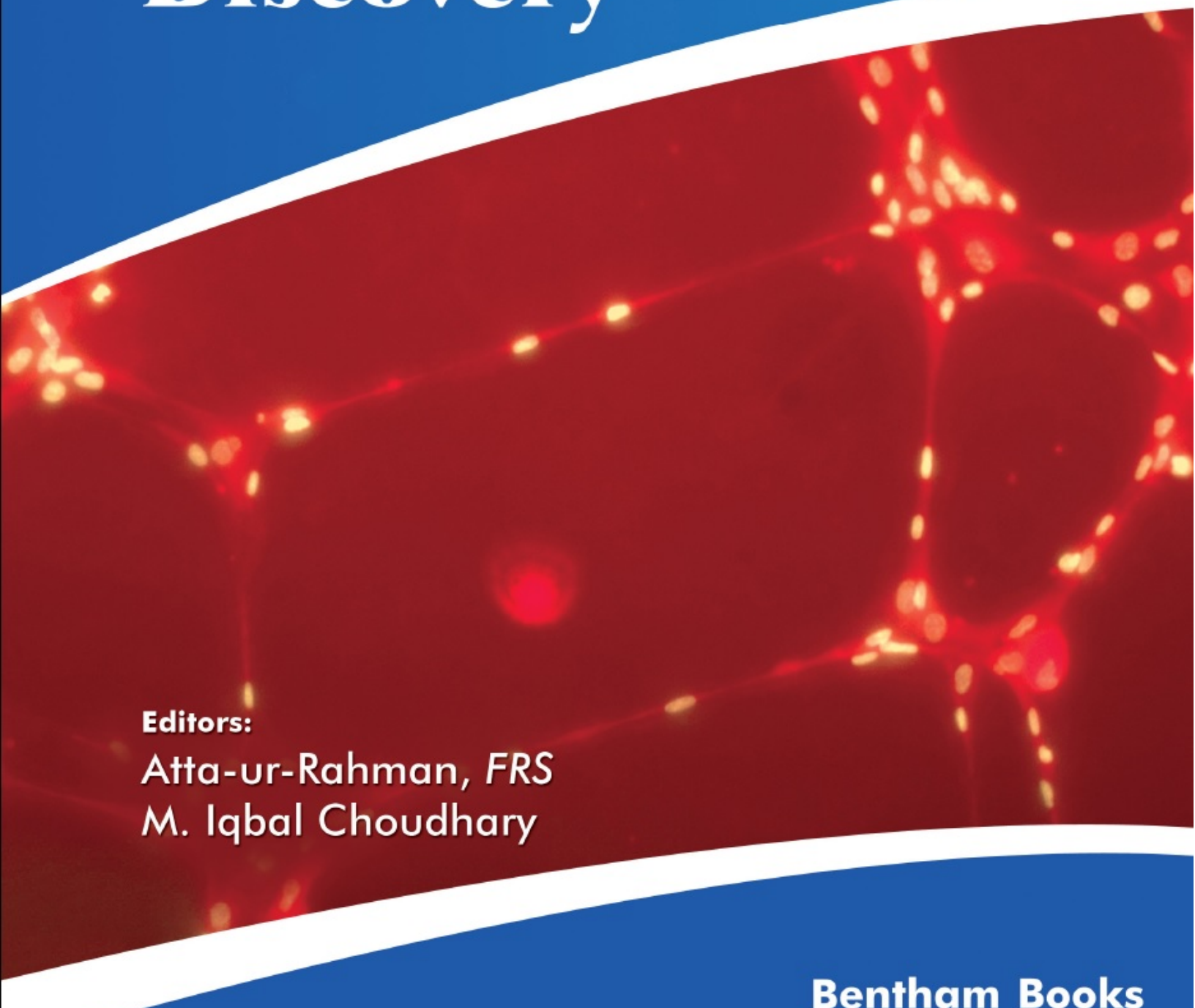
# Frontiers in Anti-Cancer Drug Discovery



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# Frontiers in Anti-Cancer Drug Discovery

**(*Volume 11*)**

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## Frontiers in Anti-Cancer Drug Discovery

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# PREFACE

Despite tremendous development in our understanding of different types of cancer at biochemical and genetic levels, prevention, diagnosis, and treatment is still far from perfect. Based on the histopathological heterogeneity and remarkable genetic complexities of cancer, research on this disease has emerged as a truly interdisciplinary science. From biomarker identification for diagnosis and diseases progression monitoring to personalized treatment, the research is spread over a wide range of fields and disciplines. This book series "*Frontiers in Anti-Cancer Drug Discovery*" is, therefore, aimed to provide comprehensively written review articles on carefully selected topics in this important field. Volume 11 of the book series contains five (5) chapters covering target identification to new classes of anticancer therapies, each contributed by eminent experts.

The review contributed by Neri *et al.* focusses on the importance of targeting phosphoinositide 3 kinases (P13Ks), their downstream mediator Akt and the mammalian target of rapamycin (mTOR) as targets for drug discovery against the acute lymphoblastic leukemia (ALL). They have included examples of small molecular inhibitors of P13Ks/Akt/mTOR as targeted drug candidates. Javed *et al.* have reviewed recent researches on polymeric nanomedicine for the treatment of breast cancers. The results of preclinical studies on polymeric nanomedicines in terms of target specificity, improved bioavailability and safety *via* their passive and active modes of action arepresented. Lung cancers (non-small cell lung cancer and small cell lung cancer) are among the most aggressive cancer types with high mortality. Gabrani *et al.* review recent developments in the treatment of lung cancers, including EGFR tyrosine kinase inhibitors (TKIs), inhibitors of imbalance microRNA, and immunotherapy. Saima *et al.* have contributed a comprehensive chapter on the recent advancements in the applications of self-nonemulsifying drug delivery system (SNEDDS) for cancer chemotherapeutics. SNEDDSs offer improved bioavailability and greater tolerability as oral anticancer drug delivery vehicles. Last but not the least, Jain *et al.* focus on exciting advances in novel targeting approaches for the prevention, diagnosis and treatment of cancers. This includes theranostics based systems for diagnosis coupled cancer therapies.

The above review articles by prominent researchers in the field of cancer research directed towards anticancer drug discovery should be of great interest to research scholars. We are grateful to all the authors for their excellent and scholarly contributions to the 11th volume of this internationally acclaimed ebook series. The Editorial team of Bentham Science Publishers deserves appreciation for the efficient processing and timely management of this publication. The coordination and liaison by Ms. Fariya Zulfiqar (Manager Publications), under the leadership of Mr. Mahmood Alam (Director Publications) is gratefully acknowledged. We also hope that like the previous volumes of this book series, the current compilation will also receive wide readership, and appreciation.

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CHAPTER 1

# PI3K/Akt/mTOR Pathway in Acute Lymphoblastic Leukemia Targeted Therapies

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**Abstract:** Acute Lymphoblastic leukemia (ALL) comprises a subset of different hematologic neoplasms characterized by impaired proliferation of immature lymphoid cells in bone marrow and peripheral blood. Pediatric patients have experienced treatment success with 5- year overall survival rates approaching 90%, whereas ALL adult patients are associated with poorer survival. Therefore, the development of new targeted therapeutic protocols constitutes a primary need. Phosphoinositide 3-kinases (PI3Ks) and their downstream mediators Akt and mammalian target of rapamycin (mTOR) represent the main components of the PI3K/Akt/mTOR signaling network. It is a key regulatory signaling cascade which drives proliferation, survival and drug-resistance of cancer cells, and it is frequently up-regulated in the different T- and B-ALL subtypes. Serious and irreversible late effects from conventional therapy are a growing issue for leukemia survivors, both for adult and pediatric patients. Therefore, the need to develop targeted and personalized therapy protocols for the treatment of leukemias is mandatory. Recent diagnostic tools allow to design therapeutic protocols with increased target specificity towards PI3K/Akt/mTOR axis that represents a critical target for cancer therapy. This chapter will focus on how this pathway could constitute a paradigm for the development of therapeutic strategies and how effective the recent pharmacological Small Molecule Inhibitors (SMIs) can suppress leukemic cell growth.

**Keywords:** Acute Lymphoblastic Leukemia, Apoptosis, Autophagy, Cytotoxicity, PI3K/Akt/mTOR, Proliferation, Signal transduction, Small Molecule Inhibitors (SMIs), Survival, Targeted Therapies, Tyrosine Kinase Inhibitors (TKIs).

## INTRODUCTION

Neoplastic diseases such as solid tumors and leukemia hematological disorders

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contribute significantly to morbidity and mortality of the population worldwide [1 - 4]. Whereas, some cancers show declining incidences in part due to effective prevention programs, others such as ALL are increasing in incidence. This is in part due to the fact that as life expectancy is increasing, in parallel some ALL incidence increases as well.

Development of new targeted treatment strategies aiming to increase cure rates and to decrease side effects is essential to take care of this patient population. Fundamental bases for such developments are a complex knowledge on oncogenesis, and more specifically on leukemogenesis [5, 6]. Aberrantly activated signaling pathways have been identified in different cancer models leading to the development of specific drugs, targeted therapies and ameliorated cure rates.

An example of aberrantly activated signaling pathways or receptors that could contribute to the oncogenesis mechanism is, in colon cancer cells, the Epidermal Growth Factor Receptor (EGFR). This receptor is responsible for the activation of RAS/RAF/MAPK pathway [7]. Subsequently, EGFR inhibitors and anti-EGF antibodies were developed, improving treatment outcomes. Similarly, in renal carcinoma, abnormal activation of receptor tyrosine kinases has been identified, leading to an abnormal activation of the VEGF/RAF/RAS pathway [8]. Other multikinase inhibitors, such as Regorafenib for colon cancer or Cabozantinib for renal carcinoma and hepatocellular carcinoma, have been developed with the aim to increase survival and quality of life [9 - 11].

It has been reported that in ALL, and especially in the T-ALL subtype, the EGFR pathway inhibition enhanced anticancer drugs induced cell death [12]. But another signaling pathway that displays constitutive activation in ALL, leading to uncontrolled production of malignant cells and driving chemotherapy resistance is the PI3K/Akt/mTOR signaling network. PI3K/Akt/mTOR is one of the most frequently aberrant activated pathway, and the inactivation of the tumor suppressor gene Phosphatase and tensin homolog (PTEN) represents one of the causes of this network stimulation [13 - 16], thereby giving the cancer cell a survival advantage. Indeed, literature data indicate that genetic alterations in components of PI3K/Akt/mTOR network have a close relationship with the development of ALL, thereby contributing to leukemogenesis, and these evidences highlighted the importance of developing new targeted therapies against this signaling network, with the aim to better predict favorable outcomes in acute leukemia patients. In chronic myeloid leukemia (CML), activation of this pathway is correlated to BCR-ABL tyrosine kinase, found also in 25% of adult ALL and less in ALL childhood. Treatment of ALL adults is more difficult than in pediatric patients due to the higher frequency of this chromosome rearrangement, including also the development of a recently characterized

subtype, Philadelphia (Ph)-like ALL, with high expression of signaling tyrosine kinases, resulting in stimulation of Abl and the Janus kinase (JAK) signal transducer of activation (STAT) pathway (Jak/Stat) pathways [17]. As PI3K signaling is considered to be one of the decisive pathways for the transformation potential of BCR-ABL, and that it may play a role in causing one of the tyrosine kinase inhibitor (TKI) resistance, that is imatinib, the pharmacological combination of more than one targeted cascade inhibitor is necessary, as well as the association of drugs targeting the same pathway at multiple levels. Pediatric patients have better prognosis because of minimal residual disease (MRD) monitoring and the intensification of more targeted treatments that, in association also with recent PI3K/Akt/mTOR inhibitors, could overcome glucocorticoid (GC) treatment resistance, frequently observed in ALL pediatric patients.

The importance of targeting this signaling network will be discussed in this chapter, together with a detailed profile of the most recent PI3K/Akt/mTOR inhibitors, also known as SMIs, tested in preclinical and recent clinical studies for the treatment of ALL.

## Acute Lymphoblastic Leukemia

ALL is a malignant hematological disorder characterized by aberrant expansion and diffusion in blood and bone marrow of lymphoid progenitor cells. ALL is the most frequent cancer identified in children [18].

Based on morphology and cytogenetic profiles, two different types of ALL have been identified: B-acute lymphoblastic (B-ALL) and T-acute lymphoblastic (T-ALL).

The uncontrolled growth of B-cell precursors represents the main feature of B-ALL subtype [19] that, due to the differentiation level, can be classified as pro-B, common, precursor B (pre-B), and mature B-cell ALL.

T-ALL is an invasive blood neoplasm characterized by aberrant proliferation of transformed T-cell precursors, and accounts for approximately 15% and 25% of pediatric and adult ALLs, respectively [20 - 22]. The most specific surface marker for lymphoblastic T-cell is represented by CD31, others T-cell markers such as CD1a, and CD2-CD8 are differently expressed and are strictly dependent on the T-cell differentiation degree [23]. A novel subtype of T-cell ALL, ETP T-ALL, has recently been described [24], and is capable to differentiate into both T-cell and myeloid lineages. Indeed, these lineages share high similarities in the myeloid leukemic stem cells gene expression profiles [23]. Concerning the frequency, in children ETP-ALL has been reported to be present in 11% to 16% of T-ALL, while in adults ETP-ALL frequency ranges from 7,4% to 17% of T-ALL [25].

# CHAPTER 2

# Polymeric Nanomedicines in Treatment of Breast Cancer: Review of Contemporary Research

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**Abstract:** Among various types of cancers, breast cancer is one of the most frequent and major reasons of cancer death among women worldwide. It has the ability to spread to different organs of the body and develop metastases. Till date, chemotherapy is the most common option for the treatment of breast cancer. However, chemotherapy is not a very successful strategy to cure breast cancer and has decreased the survival rates according to the different breast cancer reports. The inability to deliver a specific drug to the target tissue/cell that causes toxicity to the normal healthy tissue/cell is the primary concern in the chemotherapy. Most of the chemotherapeutic drugs used in conventional chemotherapy have low aqueous solubility and high pre-systemic metabolism; therefore, they are biologically less available to the target location and affect normal healthy tissues/cell as well. Since the last decades, the development of nanoparticle technology has opened a new option in the successful treatment of breast cancer due to the various unique advantages offered by this nanoplatform. Among them, polymeric nanomedicines become the promising choice as the effective drug delivery system and provide great potential in the management of breast cancers as per the outcome of different preclinical studies. Polymeric nanomedicines may exhibit their anticancer efficacy either *via* passive or active targeting approach. Polymeric nanomedicines can be actively targeted by its surface conjugation to the breast cancer-specific targeting ligands. Active targeting of the nanomedicines has the ability to deliver the specific drug to the target site, therefore, healthy cells remain unaffected by active targeting. Moreover, polymeric nanomedicines have also been exploited in breast cancer treatment through gene therapy. This chapter summarizes the extensive literature of preclinical findings on polymeric nanomedicines exploited in the treatment of breast cancer.

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**Keywords:** Breast Cancer, Chemotherapy, Polymeric Nanomedicine, Targeted Delivery, Ligand, Preclinical Studies.

## INTRODUCTION

Human bodies are made up of more than $10^{14}$ cells, and cancer can begin with one single cell or a group of cells that have mutations in them. The cell division and growth of cells are regulated by signals produced by the cells, and when such signals are faulty, then there is an uncontrolled, unregulated cell growth, which if unchecked by the immune system, leads to the formation of a lump or a tumor. There are more than two hundred types of cancers, classified according to the tissue and cell type of initial tumor. Cancer is known to be the major cause for human death worldwide and is a global pandemic as per the American Cancer Society, and according to the WHO, cancers account for more than 13% of all deaths each year, and this number is expected to reach 45% by 2030. Breast cancer is the most common cancer in women and is the second most common cancer overall. The American Cancer Society estimates about 271,270 new cases and 42,260 deaths in 2019 in the United States alone [1]. Around the globe, it affects more than 2.1 million women every year and is the leading cause of cancer-related deaths in women. Breast tissue consists of fat, duct, connective tissue, and glandular tissue. Breasts develop as a response to estrogens, progesterone, and other hormones such as growth hormone and insulin. Breasts grow mainly during puberty and in lactating women and during pregnancy. Breast cancer is majorly the carcinomas (adenocarcinomas) of epithelial cells lining the milk ducts. Early detection of breast cancer has improved the rate of survival, however, the current mortality rates remain high [2]. While the hallmarks of cancer are many, but from a pharmaceutical science perspective, the challenge is to make the existing few therapies that we have more effective. Chemotherapy remains one of the mainstays in our possible therapies in the fight against cancer. Polymeric nanomedicines are a pragmatic way forward to treat breast cancers as they offer specific targeting to different tumors, modifications and alterations in the nano device.

## CHALLENGES IN TREATMENT OF BREAST CANCER

Cancers as such are a complex disease, and amongst different forms of cancers, the breast cancer is a severe complex and heterogeneous disease where there are multiple tumor entities which have different clinical behaviors and have distinct histological patterns. Breast cancers usually metastasize into the lungs, liver, lymph, and brain, a significant number of women lose their lives as a result of metastatic breast cancer. Different types of breast special cancers such as basal-like carcinoma, Mucinous carcinoma, neuroendocrine carcinoma, micropapillary

carcinoma, papillary carcinoma, medullary carcinoma, acinic cell carcinoma constitute about 25% of breast cancers. The World Health Organization recognizes the existence of more than 18 different types of invasive breast cancers based on their histological type. Such a complex disease needs a multidisciplinary approach for its treatment and novel targets are being identified in these breast special cancers [3]. Breast cancer is defined based on the expression of receptors such as the HER-2 (Human Epidermal Growth Factor Receptor-2), ER (Estrogen Receptor) and PR (Progesterone Receptor). To target these receptors or any other targets, chemotherapy, hormonal therapy and radiotherapy seem to be a better choice of treatment, however, these are conventional methods which have only been able to kill differentiated cells but not able to completely remove the tumors [4].

Radiotherapy uses a high level of radiation and regresses the tumor growth in combination with chemotherapy and kills cells that are unseen during the surgery, preventing a recurrence. However, due to the high levels of radiation, there can be mild to severe side effects such as itching, peeling, soreness of the skin, loss of sensation in the breast tissue, and at the end of the treatment it may leave the skin weepy and moist [5]. Hormonal therapy, on the other hand, either adds or blocks hormones, female hormones play a role in the development of some breast cancer types mainly the estrogen and the progesterone, and hormonal therapy either lowers the levels of female hormones or completely blocks them thereby, preventing the development and growth of cancer cells. Tamoxifen a SERM (Selective Estrogen Receptor Modulator) has been commonly used in breast cancers since it is an anti-estrogen; it completely blocks the attachment of estrogen on the breast cancer cells' ER receptors. However, there are limitations with Tamoxifen as it increases the chances of resistance and also puts one at the risk of uterine cancer. Other agents which block the estrogen production such as Anastrozole causes bone fractures and joint pain [6].

Conventional dosage forms of chemotherapeutic agents lack selectivity in targeting and also cause cytotoxicity by non-targeted cells. Chemotherapy is given as either adjuvant or neoadjuvant chemotherapy, which is used after surgery to remove undetected breast cancer cells and before surgery to regress the tumors, which can be further removed by lumpectomy. Literature suggests that chemotherapy works best in a combination of different drugs and these come with side-effects such as the increased risk of infections, hair-loss, easy bleeding (because of the lesser number of platelets) mouth sores, nausea, vomiting and loss of appetite [7].

Another major limitation in the treatment of breast cancer is special types of breast cancers which are highly complex such as the basal-like breast cancer and

CHAPTER 3

# Treatment of Lung Cancer in the New Era

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**Abstract:** The most frequent cancer related deaths have been associated with lung cancer. The subtypes, Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancers (SCLC), respond to chemical drugs and radiotherapy. NSCLC (60%) express membrane epidermal growth factor receptor (EGFR). The cell signalling pathway induced by EGFR has been attributed as a key reason for lung cancer progression. There are many FDA approved drugs available for the treatment which primarily includes EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, or EGFR neutralizing antibody, necitumumab. However, the reports suggest that EGFR can undergo further mutation in tyrosine kinase domain which makes the cells resistant to the ongoing treatment. Alternate signalling pathways may get activated accompanied by epithelial mesenchymal transition and imbalanced microRNAs that contribute towards resistance. Epigenetic changes in lung cancer also offer dynamic targets for cancer therapy. The agents targeting epigenetic changes can be combined with chemotherapy or other-directed therapy so that effective dose and hence toxicity is reduced with enhanced efficacy. Micro-RNAs are the largest class of the gene regulators that regulate the cancer genes. Inhibiting or replacing the cancer-causing miRNAs can be potential targets for cancer treatment. Researchers have also worked on immunotherapy drugs like nivolumab, pembrolizumab and atezolizumab, which reverse the inhibitory mechanism of the immune response. New findings from recent trails provide an optimistic perspective on the progress towards the better treatment of lung cancer.

**Keywords:** EGFR, Epigenetic, Immunotherapy, miRNA, PD-1/PDL-1, T790M mutation.

## INTRODUCTION

Lung cancer or lung carcinoma is defined as the uncontrolled proliferation of normal lung cells due to the genetic damage and it has the capacity to invade the neighboring tissues and metastasize the various cells of the body. Lung Cells sometimes behave abnormally and do not grow; these changes may lead to nonca-

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ncerous tumors like hamartoma and papilloma. On the other hand, some changes that develops into cancerous behaviour with the ability to metastasize to different organs [1]. Today, in the 20th century, lung cancer is reported for the most deaths at the worldwide level and ranked high in both incidence and mortality. Lung cancer is subdivided into two forms: Non-Small Cell Lung Cancer (NSCLC) and Small-Cell Lung Cancer (SCLC) where NSCLC are considered as the most prevalent form. Lung Cancer was considered a rare disease till the beginning of the 19th century whereas, thereafter increased incidents of lung cancer cases have been linked to rising in cigarette consumption worldwide [2]. Cigarette or tobacco contains benzo[a] pyrene, nicotine-derived nitrosamine ketone, 1, 3-butadiene and radioisotope of polonium-210, polonium among which at least 73 known carcinogens are identified and are the main reasons for lung cancer. Apart from smoking, the inheritance of gene polymorphism, radiations, asbestos and air pollution have also been found to be the major reasons for lung cancer [3].

The genetic DNA damage and epigenetic changes affect the cellular normal function, proliferation, repair, and apoptosis [4]. Molecular alterations in phosphoinositide 3-Kinase (PI3K)/Protein kinase B also known as AKT/mammalian target of rapamycin (mTor) pathways have been linked to lung cancer. Certain biomarkers like ProGRP (pro-gastrin-releasing peptide), CEACAM (carcinoembryonic antigen), EPCAM (epithelial cell adhesion molecule) and CYFRA 21-1 (cytokeratins) have been reported for their use in the diagnosis of lung cancer. Successful chemotherapy regimens were developed in 1970 after that new chemotherapy drugs for NSCLC include paclitaxel, docetaxel, vinorelbine, and gemcitabine [5]. Patients that were found with genomic aberrations are benefitted with the molecular targeted therapies. Some of the current therapies have been listed in Fig. (**1**). Epidermal Growth Factor Receptor (EGFR) overexpression has been predominantly linked to NSCLC lung cancer and has been related to poor survival and increased metastasis. Gefitinib and Erlotinib are the first generation reversible inhibitors that can completely block the adenosine triphosphate (ATP) binding site of EGFR and also inhibit the activity of tyrosine kinase. Unfortunately, there are many types of cancer that acquire resistance mutations and stop responding to the drugs. Although new drugs have been developed which are sensitive to the mutated versions of the EGFR, there is still a need to explore more compounds and drugs which could be effective against lung cancer [6].

## SMALL MOLECULE-BASED INHIBITORS

The discovery and optimization of small molecule inhibitors for the treatment of human diseases have been the major focus of the pharmaceutical industry for more than a century. Small-molecule kinase inhibitors are being intensively

pursued as new anticancer therapeutics. Broadly, there are three categories of inhibitors that are mentioned in Table **1**. Currently, there are some of the known kinase inhibitors that target the ATP binding site with the kinase activation loop in the active (Type 1) or inactive (Type 2) conformations [19].

**Table 1. Recent FDA approved drugs used for the treatment of Non-small cell lung cancer [7].**

| S.No | Name of Inhibitor | Year of Approval | Mechanism of Action | References |
|---|---|---|---|---|
| **First Generation Inhibitors** | | | | |
| 1. | Crizotinib (Xalkori) | March 11, 2016 | An anti-cancer drug for Anaplastic lymphoma kinase (ALK) or ROS1 (c-ros oncogene-1) positive metastatic NSCLC. | [8] |
| 2. | Erlotinib Hydrochloride (Tarceva) | May 14, 2013 | It competes for the ATP binding site of EGFR and further inhibits phosphorylation of tyrosine kinase. | [9] |
| 3. | Gefitinib (Iressa) | May 5, 2003 | It blocks the ATP binding site which in turn inhibits the tyrosine kinase activity of EGFR. | [10] |
| **Second Generation Inhibitors** | | | | |
| . 4. | Dacomitinib (Vizimpro) | September 27, 2018 | Dacomitinib is used for the first-line treatment for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. | [11] |
| 5. | Afatinib Dimaleate (Gilotrif) | January 12, 2018 | Afatinib is used to treat metastatic NSCLC where tumors have non-resistant EGFR mutations. | [12] |
| 6. | Alectinib (Alecensa) | November 6, 2017 | Alectinib is used as an oral drug to block the activity of ALK to treat NSCLC. | [13] |
| 7. | Ceritinib (Zykadia) | May 26, 2017 | Ceritinib is used for the treatment of ALK-positive metastatic NSCLC. | [14] |
| 8. | Brigatinib (Alunbrig) | April. 28, 2017 | 1nhibitor for metastatic NSCLC having alteration in ALK gene. | [15] |
| **Third Generation Inhibitors** | | | | |
| 9. | Lorlatinib (Lorbrena) | November 2, 2018 | ALK-positive metastatic NSCLC resistant to crizotinib/ alectinib or ceritinib. | [16] |
| 10. | Osimertinib Mesylate (Tagrisso) | March 30, 2017 | Irreversible inhibitor, targets metastatic EGFR T790M mutation harboring NSCLC. | [17] |
| 11. | Olmutinib (Olita) | May 2016 | Irreversible TKI binds tyrosine kinase domain of mutant EGFR. | [18] |

# CHAPTER 4

# Oral Administration of Cancer Chemotherapeutics Exploiting Self-Nanoemulsifying Drug Delivery System: Recent Progress and Application

**Javed Ahmad[1], Farooq Ali Khan[2], Mohammad Zaki Ahmad[1], Showkat Rasool Mir[3], Noor Alam[4]** and **Saima Amin[5,*]**

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**Abstract:** The delivery of cancer chemotherapeutics has shifted dramatically in the last two decades from parenteral to oral administration. Improved patient compliance, drug tolerability, ease of administration, and potential effectiveness for oral therapy relative to intravenous administration have appeared as the main reasons to use cancer chemotherapeutics through the oral route of administration. However, most of the cancer chemotherapeutics show very poor oral absorption due to the drug's physicochemical characteristics, stability, and biological barrier (multidrug efflux proteins: P-glycoproteins) present in the GI tract. With advanced research in homolipids and heterolipids as excipients, lipid-based formulations were exploited to enhance the oral efficacy of poorly absorbable cancer chemotherapeutics in recent years. Self-nanoemulsifying drug delivery system (SNEDDS) is the highly developed strategy of emulsion dependent drug delivery systems and relies on the GI fluids for the formation of nanoemulsion inside the *in vivo* system. The advancement in the field of biocompatible lipid and their derivatives in addition to finding on pharmaceutical excipients such as oil, surfactants, co-surfactants having P-gp modulating potential further extend the interest in SNEDDS for delivery of cancer chemotherapeutics through oral administration. This chapter provides a comprehensive discussion about contemporary advancement in the application of SNEDDS for oral delivery of cancer chemotherapeutics.

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**Keywords:** Cancer Chemotherapeutics, Nanoemulsion, Oral Absorption, P-Glycoproteins, SNEDDS.

## INTRODUCTION

Cancer is a disease that occurs after numerous mutagenesis steps, permitting cancerous cells to develop uncontrollably [1]. Cancer is a leading cause of global mortalities. The cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. The diagnoses estimated for different cancers are: cancer of lung (2.1 million), breast (2.1 million), colorectal (1.8 million), prostate (1.3 million), and stomach (1.0 million) [2]. Breast cancer is the most common form of cancer in women globally and is rising mainly in developing countries where most of the cases are diagnosed in later stages [3]. The recent data from the World Health Organization suggests a 45% increase in the deaths caused due to cancer by 2030, of which 70% would be in developing countries like India [2]. Owing to these figures, there is a growing concern to treat this deadly disease. Presently, the technologies have made huge development but accurate therapy is still a challenge. Existing cancer treatments can be widely classified into two groups: cytotoxic therapies and molecular targeted drug delivery [4, 5]. Except for a few cancer types, where the treatment involves hormonal therapy or immunotherapy, cytotoxic agents remain the major form of chemotherapy for cancer [6]. Cytotoxic agents are a diverse class of compounds that are used in cancer therapy as they are toxic to cells that grow and divide quickly. Due to the fast growth and proliferation of cancerous cells, they are favorably killed by these agents. The preferred routes of administering these cytotoxic agents are through intravenous bolus or infusion, usually in the form of a drug solution. They have been used for a long time and the development of several multi-drug treatment regimens improved their clinical success. However, there is still the case of treatment failure [7, 8]. There is often an enormous and erratic protein binding of cytotoxic agents with body tissue and serum protein when given through traditional mode, only a small portion of the cytotoxic agents reach the tumor site [9]. This generally reduces the therapeutic efficacy and increases the systemic toxicity of the drug. Cytotoxic agents are supposed to kill only the cancer cells; however, they also end up killing noncancerous cells such as the ones which quickly divide, *e.g.* bone marrow cells. There is a regular occurrence of normal tissue toxicities even when the dose of anticancer agents remains standard. The significant challenge to effective cancer treatment is the poor drug specificity in terms of biodistribution and also at the cellular levels. The patients' quality of life and the overall life expectancy relates directly to the targeting ability of cytotoxic agents. Systemic administration through intravenous bolus or infusion sometimes leads to side effects which can be at times so intense, that the patient has to discontinue

the therapy, even before the drug could kill cancer cells [10]. There is an evolution of new anticancer agents and also the development of new methods to effectively administer old drugs.

## ANTICANCER ORAL THERAPY

In oncology, medicines as chemotherapy are mostly delivered intravenously contrasting the majority of biomedical disciplines [11, 12]. There has been a dramatic shift in the administration of chemotherapeutic agents, they are now been given orally differing from the traditional parenteral route. However, the administration of cancer chemotherapeutics has shifted remarkably in the past 15 years from parenteral to oral administration [13, 14]. During recent times, the therapeutic trends have been observed by a continuous growth in the availability of oral cytotoxic drugs with >20 oral anti-cancer drugs presently approved for application in the United States and Europe [15 - 17]. It has mostly been the preference of patients to choose oral therapy relative to intravenous administration simply because of ease of administration and home-based therapy. It is also required that the toxicities associated with oral therapy should not be higher than intravenous therapy and the efficacy should be the same. Improved compliance, tolerance, ease of administration, and potential efficacy for oral therapy relative to intravenous administration have appeared as the major cause to use cancer chemotherapeutics through oral delivery. Compliance is vital for oral therapy because it decides the dose-intensity of the therapy and eventually efficacy and toxicity of the therapy. A lot of surveys indicate that maximum patients favor oral therapy to intravenous therapy [18 - 20]. Liu and group found that 89% of patients favor oral therapy rather than intravenous. It is primarily for the convenience of a home-based therapy (57% of patients), thereby escaping the insertion of a venous catheter (55% of patients) [18]. Other reasons were the negative earlier experiences with intravenous administration and a lesser access rate to the oncology service. The oral administration of cytotoxic agents provides longer drug exposure when compared to intermittent intravenous infusion. The drug exposure is dependent on exponential factors which are concentration and time. A drug with shorter $t_{1/2}$ achieves better exposure time when given as a nonstop infusion. The exposure time has profound effects on drug toxicities and efficacy. An added advantage of oral chemotherapy is the decrease in the utilization of various resources for inpatient and ambulatory care services. There is also an improved quality of life with oral chemotherapy. Despite their numerous advantages for convenience and patient compliance, there are however potential challenges with the oral use of chemotherapeutic agents, which clinicians are desired to be aware of and take necessary steps to circumvent them or mitigate them [21 - 23]. Lastly, keeping in mind the rising prices of anticancer therapy,

# CHAPTER 5

# Targeting Approaches for the Diagnosis and Treatment of Cancer

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**Abstract:** Cancer is a multi-factorial disease that necessitates a multi-modality therapeutic approach to accomplish a favorable outcome. Recently, theranostic based systems have been introduced for the diagnosis coupled cancer therapy. The development of targeted novel drug/gene delivery approaches for safe and efficacious treatment of cancer is an emerging arena that includes liposomes, nanoparticles, nanoemulsion, gene therapy, immunosuppressant therapy, herbal bioactive loaded nanocarriers and stimuli sensitive systems (pH, temperature, ultrasound, redox potential, hypoxia and magnetic). Advancements in molecular biology have rendered a wide range of targeting moieties (ligands) and a meticulous understanding of the cancer biology is under extensive exploration for the selection of appropriate targets for cancer treatment. The outcomes of various clinical studies of nanocarriers depict an improvement in the anticancer efficacy and reduction in side effects. This chapter is an assemblage of advances in the novel targeting approaches that enable the cancer prevention, prediction, diagnosis and treatment.

**Keywords:** Cancer, Diagnosis, Liposomes, Nanocarriers, Nanoparticles.

## INTRODUCTION

Tumor growth is a dynamic and complex process. Several factors such as complex angiogenesis, suppression of apoptosis, uncontrolled proliferation, escape from growth suppressor, increased invasion and metastasis, altered metabolism and evaded immune destruction may be involved in tumor growth and

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dissemination [1, 2]. The tumor microenvironment (TME) consists of different cellular and non-cellular elements. The TME contains various non-malignant cells such as immune cells, bone marrow derived cells, inflammatory cells, extracellular matrix and tumor vasculature cells like cancer associated fibroblasts, endothelial cells and pericytes [3]. The stromal cells are recruited and stimulated by cancer cells. Stromal cells activate the biological signals and enhance the growth of fibroblasts which synthesize the chemokines, growth factors and adhesion molecules. The tumor stroma plays an important role in tumor metastasis and increases the capability to invade another cell. The cancerous cells are hypoxic in nature. Diffusion-limited hypoxia is caused due to restricted tumor vasculature since the tumor cells are distant from closest capillary as compared to the healthy cells (>100 μm) [4]. Due to the variation in oxygen delivery in blood vessels of tumor cells and oxygen consumption by cancer cells, there is a variation in their distance from blood vessels at which hypoxia occurs. Hypoxic condition in cancer cells causes stimulation of genes (hypoxia inducible factors 1 mediated) that are linked with angiogenesis process and cell survival. Such gene expressions may cause enhanced cell proliferation with modulated biochemical pathways which may resist the drug delivery [5]. Hypoxic areas of tumor cells have a reduced nutrient supply like glucose and amino acids. This is since cancer cells frequently utilize glycolysis to produce lactate in order to attain energy needed for cell survival and proliferation instead of oxidative metabolism, which efficiently leads to the generation of $CO_2$ and carbonic acid. Reduced metabolism and clearance of these acidic components cause low interstitial pH, which is another feature of tumors [6, 7]. Nanotechnology has been the area of interest over the last decade for developing precise carrier as it offers numerous benefits to overcome the limitations of conventional drug delivery system [8, 9]. It is a very promising platform for the treatment and diagnosis of cancer because it enters into the cells at molecular level. The nanotechnology is divided into different types like passive targeting, active targeting and stimuli responsive targeting. In case of passive targeting, the nanoparticles are preferentially retained into the tumor due to enhanced permeability and retention effect whereas in active targeting, the drug is preferentially delivered to the site of action [10]. Nanoparticles can be designed through various modifications such as changing their size, shape, chemical and physical properties, and so forth, to program them for targeting the desired cells. The nanocarriers are anchored with some ligands or antibodies for active targeting of drug. The target moiety facilitates the recognition of nanocarriers either by ligand receptor interaction or antibody-antigen recognition [11]. Nanocarriers have three basic components (i) chemotherapeutic agents (ii) targeting agents (ligand or antibody) and (iii) carriers (liposomes, nanoparticles, niosomes, dendrimers, *etc*.) [12 - 14]. Nanocarriers are usually made up of natural and synthetic polymers and lipids [15]. Accelerated

clearance of nanocarriers from blood by reticulo-endothelial system uptake is the major drawback of novel drug delivery. Various approaches have been investigated to avoid the RES uptake and prolong the retention of nanocarriers in blood. The surface of nanocarriers is coated with hydrophilic polymers like polyethylene glycol (PEG), poloxamers, polysaccharides and poloxamines to avoid the elimination of carriers from opsonization. This phenomenon is known as "cloud" effect [16, 17]. The TME displays some unique features which can be used for active targeting of drug to the cancer cells. Cancer cells overexpress some receptors which can be utilized for active drug targeting. The ligands can be conjugated with nanocarriers which selectively bind to the receptor on tumor cells and internalized by receptor mediate endocytosis. Numerous studies are carried out to investigate interaction between ligand and receptor utilized for clinical use [18]. Further, stimuli sensitive nanocarriers came forth with recent advancements in nanotechnology. Several stimuli sensitive drug delivery systems have been used for the treatment of cancer like pH sensitive, temperature sensitive, photo sensitive, magnetic field responsive and hypoxia responsive drug delivery systems. They are made by stimuli responsive materials which change their properties in response to variations in the environment. They selectively release the drug in the presence of external or internal stimuli [19, 20]. The emerging growth of nanotechnology provides the opportunity to develop the multifunction delivery systems that allow the simultaneous detection, diagnosis, and treatment of tumor [21]. The theranostic system containing both diagnostic agent and drug in a single carrier can monitor the localization of drug at a specific site, visualize their biodistribution and assess therapeutic efficacy [22]. Ideal theranostic systems should: (i) localize into the cancer cells, (ii) visualize the biochemical and morphological changes of tumor cells, (iii) selectively deliver the drug to the target site without affecting the normal cells and (iv) be safe and biodegradable [23, 24].

## DIAGNOSIS TECHNOLOGY

"Theranostics" is a new pharmaceutical strategy merging both diagnosis and treatment in a single delivery system. The theranostic nano-carrier contains therapeutic agents and diagnostic entities in a single system like liposomes or nanoparticles which monitor the treatment efficiency by proper imaging of disease and beneficial for more precise treatment of various complex diseases (Fig. **1**). The field of theranostic is uprising after the development of nanotechnology based carriers like nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes. It is one of the most potential approaches for targeting the cancer and providing the individualized treatment for cancer patients [25 - 27].

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## PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.

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