**INSIGHT INTO THE TARGETS AND DRUG DEVELOPMENT AGAINST LUNG CANCER**

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**INTRODUCTION**

Lung cancer is the leading cause of death among men and women, which accounts for 350 deaths per day United States in 2022[1]. It is generally subdivided into a small cell (SCLC) and non-small cell lung cancer (NSCLC) types. The absence of sensitive tests for early diagnosis of lung cancer and ineffective treatment regimens for locally and advanced metastatic disease is the root cause of increased lung cancer prevalence[2, 3].With the broad endeavors for tobacco awareness education, development of imaging, and consolidated treatment modalities, it was observed a 5 year endurance pace of lung cancer improved by 12% (in 1977) to 16% (in 2007) [1]. Although lung cancer is diagnosed at an early stage, then complete resection might help improve 5-year survival by 67%[4]. Thus, we can conclude that early diagnosis of lung cancer disease by sensitive screening test may be used as a crucial strategy to improve the prognosis of affected lung cancer patients and reduce mortality incidence[5]. Over 80% of lung cancer cases in the Western world are attributable to smoking, and progress in smoking cessation has resulted in decreases in incidence and mortality. Continued smoking, as well as further risk factors such as occupational exposure to asbestos and combustion fumes, as well as environmental exposure to arsenic and air pollution, remain major contributors in the developing world. Lung cancer is divided based on the cell of origin into small-cell lung (SCLC) and non-small-cell lung cancers (NSCLC), the latter of which is further divided. According to the 2015 WHO classification, the most common types of lung cancer include adenocarcinoma (cancer of glandular cells), squamous cell carcinoma (SCC), and neuroendocrine cancers such as small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), and carcinoid [6]. Carcinoid tumorstumours are cancers of well-differentiated neuroendocrine cells (Kulchitsky cells), while SCLC also arises from poorly differentiated neuroendocrine cells, resulting in rapid metastasis, and poorly responseive to therapy, and poor prognosis. Squamous cell and small cell cancers are more likely to be centrally located and associated with a history of smoking, especially among men. Adenocarcinoma is more likely to arise in women and those without a smoking history, they arise peripherally, and test positive for targetable driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), BRAF, and ROS1. Receptor tyrosine kinase small molecule inhibitors against these mutations, as well as immunotherapies such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, have in recent years replaced or supplemented chemotherapy in eligible patients [7].

**Screening of Lung Cancer**

Several useful screening tools are exploited for early detection of lung cancer patients, including chest X-ray (CXR) or computed tomography (CT) employed with or without sputum sampling, LDCT, circulating DNA and RNA, serum biomarkers, CTC, exosomal microRNA will be reviewed further.

***CXR***

In the early 1980s, numerous randomized control trials have been performed using plain CXR and sputum cytology at Mayo clinic. In the randomized trial of high-risk patients, 9211 contributors were selected from 10,933, aged over 45 to CXR and sputum cytology assigned as the control group versus repeated CXR and sputum cytology analysis for a span of 6 years. Studies suggest 206 cases were diagnosed with lung cancer, and 160 cases were in the control group with significantly improved screening for early diagnosis and 5- year survival of lung cancer patients. Although statistically, studies do not demonstrate disease-specific mortality difference among the two studied groups from lung cancer, this remains in the case with the follow-up extended to over 20 years[8–12].

The MSKLP and JHLP is a randomized trial of participants aged more than 40 years was done annually where analysis of CXR in the presence (screening group) or absence (control group) of sputum cytology was checked every four months. In the MSKLP study, 10,040 participants were enrolled, and 144 cases were diagnosed in both groups, but no difference was observed in overall survival, stage distribution, and disease-specific mortality amongst the two groups [8, 9][13, 14]. In the JHLP study, 10,382 participants and around 194 cases with affected lung cancer were reported in the screening group, whereas 202 were in the control group. Similar to the MSKLP trial, the JHLP study did not show any difference in overall survival or disease-specific mortality amongst the two groups [15–17].Two studies were done at Johns Hopkins and Memorial Sloan-Kettering cancer centers that involved 10,000 participants each, compared plain CXR in the presence and absence of sputum cytology. In patients who developed lung cancer accomplices with dual screening, nearly 20% were diagnosed by cytology alone (most probably early-stage squamous cell carcinomas). However, there seems to no difference in mortality by adding cytology screening [14, 17].

**Low Dose CT Screening**

CT is more effective than CXR as it offers a more detailed image of the chest and is more helpful in diagnosing cancer. Although, it is mostly accepted that the radiation dose of LDCT, which is approximately 1000 times greater than CXR, is too high to assist the early diagnosis of lung cancer to exceed radiation exposure danger. Hence, until CT was approved at lower radiation doses, there was a reestablished appetite for lung cancer screening. LDCT generally has 22% of effective radiation dose when compared to standard CT. LDCT screening reflects the risk of radiation prompting cancer, which was recently estimated by a Milan study that screened 4 per 10,000 patients with a radiation dose of follow up PET CTs for patients with a positive LDCT scan (carrying high radiation doses). Adjusting this risk against the advantages of screening, the authors related to this study suggested that LDCT can be viewed as safe. However, alternative protocols have been suggested to reduce the usage of PET CTs in the screening tool to mitigate the risks of radiation exposure.

**Selecting the Target Population**

Screening of lung cancer needs to target those who are likely to at high risk of lung cancer. As such, screening of never smokers was found to be ineffective.

**Bronchoscopy**

Bronchoscopy is the widely used diagnostic tool, firstly performed by Gustav Killian of Freiburg, Germany, in 1887[18], employing endobronchial ultrasound (nodal staging of the lung cancer) [19, 20]. Bronchoscopy is commonly used for indicating tissue sampling and determining the degree of lung cancer [21]. Several diagnostic accessories can be introduced by the working channel of the flexible bronchoscope. These accessories include brushes, biopsy forceps, needles, and an immense role in diagnosing and staging lung cancers. Their combined effect has significantly improved in obtaining pulmonary biopsies, specifically of ever-smaller lesions. Computed tomography (CT) has emerged as the current cornerstones of imaging techniques [22]. Autofluorescence bronchoscopy (AFB) profited by perceiving that the emission spectrum of the bronchial mucosa under blue light fluctuates when dysplastic or carcinomatous lesions develop[23, 24].

**Liquid Biopsies**

Liquid biopsies or blood-borne biomarkers is gaining much attention for monitoring the advanced stage lung cancers. Liquid biopsies include circulating proteins, circulating nucleic acid, or circulating tumor cells (CTCs). The limitation lies in its sensitivity and specificity for the early diagnosis of lung cancer[25].

**Circulating miRNAs in Lung Cancer Diagnosis**

MicroRNAs (miRNAs) are key regulators of gene expression, which act through translational inhibition or degradation of mRNA targets. Fluctuation in miRNA expression is implicated in the pathogenesis of many cancers [26]**.** One such example includes let7 miRNA, which is down regulated in lung cancer tissue, whereas increased expression results in inhibiting lung cancer cell lines [27]. Studies indicate that the exosome arising from the cancer cells [28] raises the probability of distant signalling and preparing the niches for metastatic spread, a prospering research field. The potential for miRNA analysis with improve defficacy of lung cancer screening programs has been exploited. Boeri et al. [29]examined miRNA expression in plasma from the patients in the LDCT lung screening study [30] for identifying differentially expressed miRNAs before the development and diagnosis of lung cancer. Involving circulating miRNAs in early diagnosis appears to illustrate a promising tool for detection of NSCLC, but well-designed, independent, and high-powered validation studies are now essentially required to qualify their use.

**Antibodies in lung cancer detection**

It is well-known that the genetic aberration involved in the process of carcinogenesis leads to different expressions of ‘self-antigens’ either by inappropriate expression of tissue-specific proteins (neo-antigens) the products of non-synonymous gene mutations[31]. These tumor antigens are found to be at the interface amongst the immune system and developing cancers, arising through the malignant process [32], consequently offers the probability of exploitation as an early detection biomarkers. The association between the immune system and cancer is generally complex, and the literature focuses on the roles of cytotoxic T cells [33]. However, it has long been predicted that the humoral immune system may be dysregulated, resulting in autoantibodies that can be associated with biomarker discovery [34].Several studies reveal the association of antibodies with the occurrence of lung cancer. The first was p53 antibodies, which exist in around 12% of lung cancer patients (including SCLC and NSCLC)[35]. Certainly, the capacity that those may want to hold become underscored by using the emergence of p53 antibodies before radiologically demonstrable lung cancers[36] associated with lung cancer, which may limit its utility in large screening programs.

**ctDNA in lung cancer detection**

DNA is assumed to enter plasma either passively by cell death (apoptosis or necrosis) or by the secretion from living cells. Part of this cell-free DNA in cancer patients rises from the tumor and produces circulating tumor DNA (ctDNA) fraction [36]. The efficacy of ctDNA in lung cancer was validated in an NSCLC study, where mutations were recognized to form a library for detecting mutations related to NSCLC. Sensitivity and specificity of around 85% and 96%, respectively, were attained in a validation cohort of healthy controls and patients of NSCLC. ctDNA was generally detectable in all the late-stage NSCLC cases and only 50% of the early-stage cases[37]. The total amount of ctDNA has been validated by quantifying the human telomerase (hTERT) gene. Using this approach, NSCLC patients had elevated circulating levels than sex/ age/smoking matched controls [38]. Recent clinical ctDNA utility lies within the personalization of ctDNA assays, which rely on biopsy-derived genomic landscapes, and consequently monitor patient response and promising resistance to treatment regimens and tumor evolution [39]. Common lung cancer mutations like in p53 can be used; however, they are also observed in patients of smoking history without lung cancer, confounding specificity [40]. Additionally, there is emergent growth evidence for broad genetic mosaicism in the healthy tissue, including the mutations present in the genes with a prominent role in cancer [41]. Although the sensitivity of candidate gene analysis with droplet digital PCR-based strategies is higher, a broad panel of genetic mutations will be more informative on tumor presence due to the sensitivity of next-generation sequencing increases.

**Circulating tumor cells in lung cancer detection**

As the aggressive cancers grow and develop, cell subpopulations attain altered phenotypes and progress to motile, invading surrounding tissue and gain access in the bloodstream through various mechanisms, namely epithelial to mesenchymal transition [42], vasculogenic mimicry [43], and cell cooperation [44]. These so-called CTCs are mainly heterogeneous and are hypothesized to harbor the large subset of cells responsible for developing distant metastases [45]. Lending credence to this view within the lung cancer area, CTCs arising from SCLC patients be tumourigenic in mice, developing explants that re-capitulate precisely the response to the treatment observed in the original patients [46]. There are various methodological strategies for detecting CTCs [47], and intrinsically they have a promising emerging role as both a quantitative and qualitative biomarker of cancer burden.With the help of using various methods of CTC detection is seemingly to yield dividends in early detection. Isolation of epithelial tumor cells (ISET) by size detected CTCs in around 50% of NSCLC patients before radical treatment, different to 39% with cell search. The combination of the two techniques resulted in seeing 69% of patients [48].One another alternative study makes use of a ligand PCR method for quantifying CTCs. After immune-depletion of leukocytes and erythrocytes, cells were labelled by a ligand for folate receptor (FOLR1) conjugated toward an oligonucleotide, allowing quantification by mean of real-time PCR. This approach results in demonstrable CTCs in 8 of 10 stage I/II NSCLC patients tested and generally overall a sensitivity of around 82% and specificity of 93% for the diagnosis of stage I–IV NSCLC patients versus controls [49]. The technical hurdle for using CTC analysis is the infrequent occurrence of CTCs in advanced late-stage patients comparative to the overwhelming number of blood cells within the sample. CTC heterogeneity feature confounds marker dependent capture, and all the CTCs are not more massive than the blood cells, posing confounders rely on size-based methods. Furthermore, any CTC enrichment step suffers from cell loss. Novel approaches, including the elevated definition-single cell analysis platform, is more suitable for early detection as all the cells in the sample can be easily assessed by using a flexible panel of markers, and the cells can be imaged and physically be picked for single-cell molecular analysis for confirming tumor origin [50].

**Sputum analysis**

Initial studies of lung cancer screening by sputum cytology were found to be unsatisfactory. Although, there is renewed interest in investigating sputum by automated cytometric and new molecular techniques. One such example is the multi-center UK trial Lung SEARCH, where COPD patients were randomized to a yearly sputum cytology/cytometry or no screening. Patients that inferpositive cytology/cytometry receive thoracic CT and AFB [51]. Also, microRNA has been measured in sputum for early detection. One study proceeded on lung squamous cell carcinoma, a panel of three miRNAs, i.e. mir-205, mir-210, and mir-708 had a diagnostic sensitivity and specificity of around 72% and 95% respectively, of differentiating patients with squamous cell carcinomas from controls. There has also been keen interest in merging DNA mutational analysis to sputum for early detection of lung cancer (reviewed in [52]). Interestingly, one retrospective study associating sputum samples done before the histological detection of lung adenocarcinoma found that the KRAS mutations could be identified in the sputum of around 5 out of 11 patients, with KRAS positive tumors in between 1 month and four years before the clinical diagnosis[53].

**Exhaled breath analysis**

As an absolutely non-invasive and readily accessible patient sample, exhaled breath offers a promising emergent screening tool. In respiratory medicine, exhaled nitric oxide is now recommended by NICE to diagnose asthma [54].There have also been several interesting studies done by using exhaled breath for lung cancer detection. Perhaps the most captivating involved training dogs to easily distinguish breast and lung cancer patients from controls based on volatile components (VOC) in the breath samples taken on the silicone oil-coated polypropylene soaked cotton wool. In a double-blinded validation cohort, specificity and sensitivity were both 99% [55]. However, a recent study done with a similar design and sample size had around the sensitivity of 71% and specificity of about 93% for canine detection of lung cancer[56]. Ion mobility spectrometry offers a necessary sensitive means of detecting volatile compounds in the exhaled breath. The study of pilot patients with lung cancer was distinguished readily from controls-Cyranose 320 comprising of black carbon polymers that alter electrical resistance in response to VOCs' adsorption. Comparing healthy controls to lung cancer patients, a ‘small print’ for cancer was produced in a training cohort, which had a sensitivity and specificity of 71% and 92%, respectively, in an independent validation cohort [57].

**Treatment of lung cancer**

Studies of molecular and cellular biology of lung cancer have gradually led to discovering

The circuit diagram of pathways and the molecules driving cells to full grown lung cancer. These studies comprise the identification of genetic and epigenetic changes of particular molecules causing the activation of signalling pathways crucial in carcinogenesis. Some of these fluctuations involve well-known oncogenes and tumor suppressor genes. In search of targeted therapies, special attention is required to be paid to identifying the single or multiple genes that these lung cancer cells essentially required for their malignant phenotype and survival.These are often considered as “oncogene addictions”[58]. In lung cancer, commonly activated oncogenes may include MYC, KRAS, MET, CCND1, EGFR/HER1/ERBB1, HER2/ERBB2, EML4-ALK fusion, CDK4, and BCL-2 [59]. These targeted treatments yield longer progression-free survival, high response rates, and prolonged overall survival than the traditional cytotoxic chemotherapies[60–62].

**EGFR pathway inhibitors**

Several clinicopathologic features are related to the frequency of EGFR mutations and gene amplification, including adenocarcinoma histology, female sex, never-smoking history, and East Asian ethnicity. These features have been observed to have more than 50% probability with EGFR TK domain mutation [63]. Of note, a subset of patients with NSCLC having mutant EGFR likely do not respond to TKIs, and a “second” TK domain mutation, i.e., T790M, is associated with acquired drug resistance [64, 65]. Although EGFR mutation patients seem to have a dramatic response to the EGFR TKI therapy, protein overexpression and EGFR amplification have been associated with survival after EGFR TKI therapy, as does occur by Akt activation [66, 67]. Both erlotinib and gefitinib have been tested in randomized studies combined with cytotoxic chemotherapy as first-line treatment for metastatic NSCLC. These studies revealed no overall survival benefit by adding  the either drug to chemotherapy, though a retrospective subset analysis infers that non-smoker patients may  benefit from these combinations [68, 69].Cetuximab (a humanized monoclonal antibody) binds to the extracellular domain of EGFR and  has been studied in NSCLC. Also, cetuximab is being studied in combination with chemoradiation commonly for stage III NSCLC [70] and with chemotherapy in the neoadjuvant setting for resectable stage IB–IIIA NSCLC [71]. Apart from these, other agents targeting the EGFR pathway in the clinical study include lapatinib (targeting EGFR and HER2), panitumumab (targeting EGFR), and HK-272 (targeting EGFR and HER2)[72].

**Angiogenesis inhibitors**

Angiogenesis (the growth of new blood vessels from pre-existing vasculature) is essentially required for tumor development to supply adequate oxygenation and nutrients to the tissues for proliferation, thus presenting angiogenesis as a rational target for cancer therapy [73, 74].VEGF (Vascular endothelial growth factor) is chiefly the growth factor monitoring angiogenesis in normal and tumor cells [75]. The VEGF family comprises of about six growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E and placental growth factor [PlGF]) and the three receptors (VEGFR-1 [Flt-1], VEGFR-2 [KDR/Flk-1], and VEGFR-3 [Flt-4])[72]. The VEGF/VEGFR pathway is frequently found to be upregulated in lung cancer [76], and VEGF overexpression is linked with tumor development and poor prognosis in NSCLC [77–79]. Several agents are designed to target the VEGF/VEGFR signalling pathway and are currently under investigation. The monoclonal antibodies targeting VEGF and the VEGFR TKIs are amongst the best studied [72].

Bevacizumab (Avastin), a monoclonal antibody [80, 81] generally binds to all the isoforms of VEGF-A and has been investigated  inclinical trials. A recent randomized study revealed that addingbevacizumab to paclitaxel and carboplatin for the first-line treatment of advanced non-squamous NSCLC patients provides a vital survival benefit[81], and thus, recently,bevacizumab has been approved for use in NSCLC. VEGFR TKIs are the small molecules that preferentially binds to the ATP pocket of tyrosine kinase (TK)  residues of the intracellular domain of VEGFR, thereby inhibiting downstream pathways. These compounds often target other receptor TKs, like EGFR and c-KIT. One of the developed inhibitor, ZD6474 (Zactima) an oral, dual kinase inhibitor  responsible for targeting the VEGFR-2 and, to a reduced extent, EGFR. Combining ZD6474 with docetaxel as second-line therapy for advanced NSCLC patients [82] enhanced progression-free survival as compared to docetaxel alone in a randomized phase II clinical study[83], and a Phase III trial has been initiated for confirmation purposes [72].

**PI3K/Akt/PTEN pathway inhibitors**

PI3Ks are the key regulators of various cellular processes, including cell growth, cell proliferation, apoptosis, and cytoskeletal rearrangement. The PI3K  signalling pathway is frequently seen to be activated in many human cancers via  a sequence of events encompassing activation of upstream receptor TKs (including PDGFR and EGFR) or mutations occurring in PIK3CA,  which encodes the catalytic subunit of PI3K [84]. Akt is the essential downstream effector of PI3Ks and is constitutively stimulated in NSCLCs [85]. While PIK3CA mutations are observed to occur in about 4% of NSCLC tumors [86, 87], the expression of PTEN protein, which tends to inhibit the PI3K/Akt pathway, is often reduced or lost in lung cancers, signifying an alternate mechanism of activating this pathway. Preclinical trials of LY294002 (PI3K inhibitor) have shown that the agent augments the sensitivity of NSCLC cells to radiation and chemotherapy and phase I study of this agent is underway [85]. Various inhibitors of mammalian target of rapamycin (mTOR), a downstream target for PI3K signalling, have been developed. These may include rapamycin and its analogs temsirolimus (CCI-779), AP23573, and everolimus (RAD001)[88].  These agents have shown promising anti-tumour activity in early clinical studies [72].

**RAS/RAF/MEK/ERK pathway inhibitors**

The RAS family of proto-oncogenes, HRAS, KRAS, and NRAS are the plasma membrane–related G proteins that the chief regulators of signalling pathways involved in normal cell differentiation and survival and proliferation [89]. RAS/RAF/MEK pathway becomes activated in lung cancer by activating KRAS mutations (probably in codon 12), which happen in ~20% of lung cancers, predominantly adenocarcinomas [90]. Although the distinctive functionsof HRAS, NRAS, and KRAS have yet to be established,  KRAS mutations are accountable for around 90% of RAS mutations in lung cancer. KRAS mutations are seen in lung cancers that arise in smokers and are linked with poor survival [91]. Additionally, KRAS and EGFR mutations appear to be mutually exclusive in lung cancers[92], and KRAS mutations are related to primary resistance to EGFR TKI therapy [93]. Many agents targeting diverse components involving in the RAS pathway have been developed [93] and are currently under clinical investigation [89]. One among them is farnesyl transferase inhibitors (FTIs), one of the most studied, and tipifarnib and lonafarnib, are the two orally bioavailable FTIs being investigated in combination  with cytotoxic therapy in a clinical study in lung cancer [94].

**Tumor suppressor gene therapy**

The p53 tumor suppressor is a chief cellular gatekeeper that becomes activated by multiple stress signals particularly oncogenes, DNA damage, and hypoxia, resulting in the expression of downstream genes that participate in cell-cycle arrest, aiding in DNA repair mechanism or initiation of apoptosis. p53 is commonly inactivated through mutation in lung cancer of around 50% of NSCLCs  and 90% of SCLCs [95, 96]. Renewal of p53 function in the cells of lung cancer with either mutant or deleted p53 result in apoptosis of tumour cells[97], and therefore these findings have led to the improvement of pharmacological methods of reactivating p53, particularly by gene replacement therapy. The clinical study  on p53 gene therapy employed with a retroviral p53 expression vector in NSCLC patients has revealed that gene therapy is preferentially safe and feasible, with little evidence of antitumor activity [98]. FUS1 is a newly discovered tumour suppressor gene found on chromosome number 3p21.3, a region that is usually deleted in lung cancer. It was reported in the literature that frequent loss of FUS1 protein expression or absence of posttranslational modification of the FUS1 protein had been observed in the majority of SCLCs and NSCLCs and exogenous overexpression of FUS1 protein in 3p21.3-deficient lung cancer cells resulted in inhibiting tumor cell proliferation and apoptosis [99, 100]. Furthermore, trials are awaited to govern  these gene therapies' clinical benefits in lung cancer [72].

**Histone Deacetylase Inhibition**

Hypermethylation of promoter regions of tumor suppressor genes denotes epigenetic events of gene silencing that play a vital role in the tumor initiation and progression [101]  and hence represents an attractive target for therapeutic approaches. Histone deacetylases (HDACs) aids in the reversible modification of histones and suppress transcription of genes engaged in cell proliferation by restricting transcription factor access to DNA. HDAC inhibitors also can reverse gene silencing and exerts  anti-proliferative effects by upregulation of tumor suppressor gene expression. Several HDAC inhibitors include  suberoylanilide hydroxamic acid (SAHA), depsipeptide, and valproic acid, are either in or be studied for clinical trials in lung cancer [72].

**Proteasome inhibitors**

The ubiquitin-proteasome system plays a fundamental role in protein homeostasis by regulating the degradation of proteins that participate in the cell cycle, DNA transcription and repair, angiogenesis, apoptosis, and cell growth [72]. A proteasome inhibitor, Bortezomib (Velcade), has illustrated cytotoxic activity either as a single agent or in combination with chemotherapy in preclinical studies of lung cancer cell lines [102]. Furthermore, a randomized phase II trial proceeded on the bortezomib alone versus bortezomib along with docetaxel validated modest activity of both the therapies  similar to that of second-line treatments for NSCLC [103]. Further studies of bortezomibin lung cancer, used in combination with chemotherapy are estimated [72]**.**

**Insulin Growth Factor Pathway Inhibition**

The insulin growth factor (IGF) pathway aids in the bone and skeletal muscle's growth and differentiation. It generally consists of two receptors (insulin receptor (IR) and insulin-like growth factor 1 receptor (IGF-1R)) and principally three ligands (IGF-1, IGF-2, and insulin) [104]. Insulin-like growth factor 1 receptor, basically a receptor tyrosine kinase that essentially forms homodimers and heterodimers with HER2 and IR. Like HER2, IGF-1R does not appear to be present in a mutated form in cancers. Activation on ligand binding leads to the upregulation of several signalling pathways that includethe RAS/RAK/MEK and PI3K/AKT/mTOR pathways. Dysregulationin the IGF signalling in lung cancer is proved by frequent (up to 70%) over-expression of IGF-1R in NSCLC [105, 106], where an increase in signalling results in drug resistance and ultimately tumor growth [107]. Also, the upregulation of IGF-1 is mainly linked to an increased risk of lung cancer [108][109]. Phase III study (ADVIGO 1016) exploiting the efficacy of combining carboplatin, figitumumab, and paclitaxel as the first-line therapy in advanced NSCLC patients was also terminated the lack of effectiveness and adverse effects [110].

**Enhancing apoptosis**

Cancer cells have a characteristic feature for the ability to evade apoptosis. Bcl-2, an anti-apoptotic protein whose overexpression was observed in 75%-95% of SCLCs and 10%–35% of NSCLCs [90] and the pre-clinical data have revealed that oblimersen sodium (Genasense) which is an antisense oligonucleotide that targets Bcl-2 and confers resistance to traditional cytotoxic chemotherapy, radiotherapy, and monoclonal antibodies. Randomized phase II trials done on oblimersen combined with chemotherapy are underway in NSCLC and SCLC [111]. A potential small-molecule inhibitor of the anti-apoptotic proteins, Bcl-XL, Bcl-2,and Bcl-w, has been further developed (ABT-737) and exhibits single-agent preclinical activity against both the SCLC and NSCLC [112].

**Heat Shock Protein Inhibition**

Heat shock proteins are molecular chaperones primarily involved in stability, post-translational folding, activation, and maturation of various other proteins required for signal transduction and cell cycle progression. Moreover, they are oncogenic chaperone proteins, and the inhibition of HSP90 (the well- known HSP proteins) leads to the degradation of oncogenes such as BCR-ABL, HER2, and BRAF, resulting in inhibiting the multiple oncogenic transduction pathways [113]. Geldanamycin, a natural compound HSP90 inhibitor from which various other 17–amino acid derivatives have been developed, such as 17-AAG, SNX-5422, ganetespib, and retaspimycin [114].

**Telomerase inhibitor**

Many pieces of the literature revealed that the  enzyme  telomerase  is  up-regulated in the cancer stem cells , and also, the telomerase inhibitors can  potentially target both the cancer stem cells and more mature cancer  cells. Telomeres are repetitive sequences located at the end of mammalian chromosomes that help protect from degradation and loss of many essential genes [115]. With each cell division, telomeres shorten progressively, which restricts the life span of somatic cells. The shortening of telomere and consequent cell death can be overcome by telomerase enzyme, which aids in stabilization of telomere length by adding DNA sequence repeats taking place at the telomeric ends of chromosomes. Human telomerase comprises two essential components, a functional telomerase RNA (hTR, also known as TERC) component and a telomerase reverse transcriptase (hTERT) catalytic subunit. Activation of telomerase is supposed to a vital role in the immortalization of cells, which is  an early step in tumorigenesis.

Telomerase is universally expressed in human tumors, while telomerase activity is either reduced or absent in normal tissue. Though silenced in normal cells, telomerase is activated in approximately more significant than 80% of NSCLCs and around 100% in SCLCs.183-1. Thus, telomerase represents an attractive therapeutic approach for lung cancer, and many agents targeting telomerase have been developed. GRN163L is a novel telomerase antagonist that targets the RNA template region of Htr. Preclinical data have demonstrated that GRN163L hinders in vivo xenograft tumor growth of lung cancer cells and anchorage-independent growth [116], and phase I studies with this agent is in process. Recently treatments targeting telomerase are in development, which includes gene therapy (telomerase oncolytic virus therapy), reverse transcriptase inhibitors, and immunotherapy (vaccines) [115].

**Other cancer stem cell-targeted approaches**

In addition to targeting essential survival and self-renewal pathways, recent indications in glioblastomas suggested that the cancer stem cell population is resistant to the conventional radiation therapy like the cells are more efficient in inducing repair of the damaged DNA when equated with the bulk of the tumor cells. A strategical approach to circumvent cancer stem cell resistance to the cytotoxic therapy would pharmacologically inhibit checkpoint kinases that help control the cell cycle to allow  DNA repair (e.g., Chk1, Chk2)[117]. Other studies have revealed the probability of inducing stem cell differentiation with soluble factors like bone morphogenetic proteins as a potential therapeutic target [118]. Approaches required to treat the CSC population specifically include selective targeting by using CSC detection molecules, sensitization of CSCs to the conventional mode of therapies and differentiation therapies, inhibiting signaling pathways essential for CSCs such as Wnt, Hh, and Notch signalling pathways; and telomerase inhibition. Inhibition of the Hh pathway has been evaluated with cyclopamine (a naturally occurring inhibitor of SMO), resulting in the development of synthetic oral inhibitors withclinical activity in basal cell carcinoma [119]. Inhibition in the Notch signalling pathway was potentially demonstrated with γ-secretase inhibitors [59].

**CONCLUSION**

Despite the advanced technology, cancer mortality incidence including that of lung cancer has not yet declined. Enormous resources have been employed globally for developing a preventive, diagnostic, and therapeutic approach for lung cancer. Relapse and metastasis of malignant cells in patients are the demerits that occur after traditional cancer therapies, such as surgery, radiation, or chemotherapy. Drug development with robust and viable lead candidates remains challenging for scientists, which involves an array of transition from screening trials to a drug candidate, which entails expertise and experience. Natural products and their derivatives have been well recognized for many years as a source of promising therapeutic agents and structural diversity. Heterocyclic compounds are the privileged scaffolds that have emerged as a promising agent for designing and developing drugs. They can serve as useful tools to alter the polarity, lipophilicity, and hydrogen-bonding capacity of molecules, resulting in improved pharmacological, physicochemical, pharmacokinetic, and toxicological properties of drug candidates for lung cancer. The synthetic cyclic compounds employed as anticancer drugs imitate natural ligands and substrates to disturb the obscure balance in cells. Molecular hybridization is an innovative and attractive approach that provides a platform for the designing and developing novel drug prototypes with improved pharmacokinetics and pharmacodynamics activity. Currently used anticancer drugs targeting DNA or RNA activity mostly rely on their inhibition against synthesis, transcription factors, and enzymes. The majority of these anticancer drugs display a lack of selectivity and participate in drug resistance, limiting the efficacy of anticancer drugs. However, novel therapeutic strategies are being developed to overcome these complications, which may discover novel anticancer drugs with low toxicity and resistance.

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