LUNG CANCER: AFFECTED GENE/GENOME, CURRENT TREATMENT PROFILE, AND PROSPECTIVE OF TARGETED DRUG DELIVERY SYSTEM

Abstract

Lung cancer is the second highest occurrence and lowest survival rate cancer. It is due to its late-stage diagnosis, poor prognosis, and intra-tumoral heterogeneity nature. Further, the drug delivery to the lung is challenging and it affects the treatment effectiveness. They release chemokines and cytokines from the tumor microenvironment (TME). To improve the effectiveness of treatment, researchers emphasize personalized genomic targeting adjuvant therapies along with conventional ones. This study explored the different genomic changes occur due to the prime etiological factors, their reported treatment profile, and nanocarrier roles and strategies to improve the treatment profile's effectiveness by striving for TME. A biofunctionalized nanocarrier stimulates biosystem interaction, cellular uptake, immune system escape, and vascular changes for penetration into the TME. Inorganic metal compounds scavenge reactive oxygen species (ROS) through their photothermal effect. Stroma, hypoxia, pH, and immunity-modulating agents conjugated or modified nanocarriers co-administered with condition-modulating agents can regulate extracellular matrix (ECM), Cancer-associated fibroblasts (CAF),Tyro3, Axl, and Mertk receptors (TAM) regulation, regulatory T-cell (Treg) inhibition, and myeloid-derived suppressor cells (MDSC) inhibition. Again, biomimetic conjugation or the surface modification of nanocarriers using ligands can enhance active targeting to the genome by bypassing the TME. A carrier system with biofunctionalized inorganic metal compounds and organic compound complex-loaded drugs is convenient for lung-targeted therapy.

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I. INTRODUCTION

According to the World Health Organization (WHO), lung cancer is the second-highest diagnosis (11.4%), and the leading cause of death (18%) among all forms of cancer in 2020 [1]. The 5-year survival rate of lung cancer patients worldwide was 19% during 2010–2014. A few countries, like Japan (33%), Israel (27%), and the Republic of Korea (25%), had a higher survival rate [2]. The prime reasons for the low survival rate are late-stage diagnosis, lack of awareness, socioeconomic conditions, environmental contamination, and the metastatic and intra-tumoral heterogeneity nature of the tumor [3–6].

The common etiological factors for lung cancer development are tobacco smoking (causes 80% of cases in the United States and other countries), occupational asbestos exposure (5–10% globally), cannabis or marijuana smoking (4% in the USA in 2002–2014), radon exposure (10% in the Western World), air pollution, group 1 carcinogen arsenic exposure, inflammation and cellular damage during respiratory infection, chronic obstructive pulmonary disease-related inflammation and scarring, and family history of lung cancer [7–15]. Other associated increased risk factors for lung cancer are systemic sclerosis patients, smoker breast cancer survivor, HIV infected patients with idiopathic pulmonary fibrosis, certain fibrotic pneumoconioses patients, and lung cancer survivor.

These etiological agents have different free radicals, reactive oxygen species, gaseous free radicals, and reactive electrophiles that depending upon the dose, dimension, bio durability, and surface reactivity**,** react with nitrogen and oxygen atoms lesions in DNA, modify a few nucleotide to distort the basic pattern of base pairing leads to incorrect nucleotides incorporation during replication [16-22]. Cell repair mechanism can repair the abduct DNA damage, but the escape portions change the coding of the DNA. Repeated exposure to etiological factors instruments to a series of genomic changes like copy number variations (CNVs), single-nucleotide variations (SNVs), and insertions/deletions (INDELs) of exomes in the autosomal chromosome lead to permanent change in the sequence and that start to from the primary tumor followed by metastasis via circulating tumor cells [23-25]. Genetic mutations affect protein synthesis and disrupt the cell cycle progression and promote carcinogenesis. The study of circulatory tumor cells for metastatic cancer & genomics of the tumor cells for the non-invasive types helps in diagnosis & prognosis purposes. Circulating tumor cell analysis is helpful for the prediction of disease progression, survivability of patients, and personalized therapy as cell-free DNA fragments found in peripheral blood [23-28]. With the advancement of technology, single-cell whole-genome amplification (WGA) and whole exomes sequencing (WES) methods are helpful to detect genomic changes [27, 29].

In concise, lung cancer occurs through either one or combination of the factors like mutation of protoncogene, tumor suppressor genes, DNA repair gene dysfunction, erosion of apoptotic mechanism, limitless telomere replication, sustained angiogenesis, increment of invasion & metastasis, and escape from immunity [29-37].

Histologically, lung cancer is classified into non-small cell lung cancer (NSCLC, 85%), and small cell lung cancer (SCLC, 13%) [38]. Further, NSCLC subdivides into lung adenocarcinoma (40%), squamous cell carcinoma (25–30%), and large cell carcinoma (5–

10%) [36–38]. In 2015, WHO modified the classification of lung cancer based on immunohistochemistry, genetic studies for the personalized treatment strategies, and small biopsy and cytologic samples [39–41]. This new classification objective is to overcome drug resistance, intracellular accumulation, metastasis, invasion, side effects, toxicity, and develop a more personalized novel treatment regime [42]. The current treatment regime depends upon the stage of cancer progression, health of the patients, and affordability at the time of diagnosis. The different treatment methods are surgery (wedge resection, segmental resection, lobectomy, and pneumonectomy), radiation therapy, chemotherapy, stereotactic body radiotherapy, targeted drug therapy, immunotherapy, and palliative care.

Though the advancement of the treatment regime impacted the treatment profile, late-stage diagnosis (metastasis stage) creates a burden [3, 4, 5]. So, the emphasis has increased on chemotherapy and pathway-blocking agents through targeted drug delivery systems for advanced-stage patients [43].

Chemotherapy is a prominent therapy to control the growth of cancer cells. It can be used before and after surgery in NSCLC patients and with targeted or radiation therapy in the late stage of cancer. Excessive toxicity makes it controversial regarding the effective use of chemotherapeutic agents in lung cancer treatment. Chemotherapeutic agents can damage the DNA or RNA of cancer cells to inhibit their reproduction. The common adverse effects of chemotherapy are nausea, vomiting, sore mouth, weight change, and hair loss [44, 45].

Targeting therapy is designed to alter the specific abnormalities in the cancer cells and their microenvironment. This therapy acts as adjuvant in early as well as late stage of the disease progression. It involves targeting specific genes or proteins using a drug-loaded carrier system to deliver into a projected site. A modification of the carrier system enhances the efficacy of the drug at the targeted site. The limitations of conventional therapy can be overcome by using targeted drug delivery systems. It may causes site-specific nano-toxicity and minimal toxicity to surrounding cells. Optimization of targeted drug delivery is one of the biggest challenges [42, 46–49].

As the cancer is an acquired disease of genetic alteration, nucleic acids have a promising treatment profile for the same. This genetic alteration can be improved using the delivery of DNA and other nucleic acids to control the genetic expression profile of target cells. The delivery of nucleic acid to the targeted cell is challenging due to its instability, off-target effects, and traversal of biological barriers [50]. The delivery of nucleic acids to the targeted site can be achieved using nucleic acid cargo or nanocarrier as the nucleic acid vehicle.

II. ETIOLOGICAL FACTORS PATHOPHYSIOLOGY TO AFFECT GENETIC MAKE UPS:

1. **Smoking:** Smoke is a mixture of numerous chemicals with carcinogenic, toxic potential, stable free radicals, reactive oxygen species (ROS), and gaseous free radical species [51]. Tobacco smoke contains at least 69 cancer-causing agents like Beryllium, Cadmium, Nickel, Polonium-210, tobacco-specific nitrosamine out of 250 harmful chemicals amongst the 7000 chemicals [51, 55]. The free radicals of the smoke (up to 10^{15} – 10^{17}/

puff) increases the release of oxidants, damage the oxidative barriers and airway repair capability [56, 57]. Direct-acting carcinogens or reactive electrophiles react with nitrogen and oxygen atoms lesions in DNA, modify certain nucleotides to distort the basic pattern of base pairing. It leads to incorrect nucleotides incorporation during replication [58, 59]. The liver enzymes activate indirect-acting carcinogens by introducing electrophilic centers to the inactive form of carcinogen. Though, liver enzyme takes part to detoxify obnoxious chemicals, it also activates indirect-acting carcinogens. Detoxification begins with a series of oxidation reactions catalyzed by cytochrome P-450 [59]. Cytochrome P-450 enzymes- lipoxygenase, cyclo-oxygenase, myeloperoxidases, and monoamine oxidases infrequently metabolized these carcinogens to intermediate metabolites. Glutathiones, sulfatases, or uridine-5′-diphosphate-glucuronosyltransferases (U5′DPGT) detoxify the intermediate metabolites. But a small amount of metabolite secreted reacts covalently at guanine & adenine of DNA to produce metabolic activation [60, 61]. Carcinogens like polycyclic aromatic hydrocarbons (PAHs), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) need metabolic activation for their carcinogenic functions. Metabolic DNA methyl abducts, produce from the metabolic activation react with alpha-hydroxylase, and produces 7-methylguanine or O6 methyl-guanine, which are the precursor or risk factors of lung cancer [60-62]. Cell repair mechanism can repair the abduct DNA damage, but few portions escape and change the coding of the DNA. Cell apoptosis can remove the miscoding gene, but permanent mutation on the oncogene or tumor suppressor gene can lead to lung cancer. The commonly mutated proto-oncogene & tumor suppressor genes are- KRAS (~30%), EGFR (4%), EML4 ALK (2%), P53 (>50%), P16(>70%), STK11 (11%) fragile histidine triad protein (F-HIT), T790M [60-62].

2. **Asbestos Exposure:** Asbestos exposure increases the risks for developing mesothelioma, bronchogenic carcinoma, and lung cancer. It causes pulmonary fibrosis, pleural abnormalities, alveolar epithelial cell apoptosis by ATP-dependent process characterized as membrane blebbing, cell shrinkage, nuclear chromatin condensation, and DNA fragmentation [63-66]. The fiber of asbestos cause's toxicity & carcinogenesis depends upon the dose, dimension, bio durability, surface reactivity, and the genetic background of the host exposed. High asbestos doses over short periods promote acute neutrophil-predominant inflammation, whereas low doses over prolonged exposure periods accumulate in the body. These accumulated asbestos fibers are cyto-toxic to human mesothelial cells (HM). Asbestos-exposed HM activates poly (ADP-ribose) polymerase, secrete H_2O_2, deplete ATP, and translocate high-mobility group box1 protein (HMGB1) from the nucleus to cytoplasm and the extracellular space. HMGB1 promotes alveolar macrophage (AM) -predominant chronic inflammation. Chronic inflammation leads to cytokines (TNF-α) release and mutagenic reactive oxygen species from the inflammatory cells [65, 67, 68]. Mutation on the BLM gene affects the helicase activity negatively and the permeability of the mitochondrial membrane [69]. But, BLM protein causes an anti-proliferative effect in the presence of P53. Mutated BLM gene affects p53 mediated growth inhibition [70]. Other genes that are affected by asbestos exposures are- BIRC4, BMP2, CD44, CSNK2A1, CSTB, BTG2, CALU, BIRC5, ADD3, CASP8, KRAS, MARK1, NFKB2, pRB, YAP, JUN, MYC, BAP1, GSTM1, etc [69, 71, 72].

3. **Radon Exposure:** Radon is a chemically inert radioactive natural gas. It seeps out from closed spaces like underground mines and rocks [73]. Radioactive compounds convert to electrically charged radon progeny like lead isotope, alpha, and beta radioactive isotope [74]. They can bind with the tiny dust and aerosol particle of air and can ingest into the lung [75]. The adherence of the fusion dust particle to the epithelial cells of lung linings can change or damage the DNA either by radiation interaction or by free radicals [76]. It is a linear energy transfer with low penetration capability. Alpha radioactive particles can transfer more energy to root a sizeable number of ionizing events [77]. Recently many pathways have suggested radon exposure carcinoma. Various studies have reported the role of mutations of the p53 and p16 tumor suppressor loci, but no particular locus has proven to be predominant. But, RAGE and S100A6 proteins have a role in radon-induced inflammation, fibrosis, and carcinogenesis [78-82].

4. **Cannabis Smoking:** The concentration of carcinogenic poly-aromatic hydrocarbons in cannabis smoke is up to twice the concentration of tobacco smoke [83]. The forms of cannabis products are flower or herb (marijuana), resin (hashish), and oil (hashish oil) [84]. Due to smaller butt size and deep holding after smoking leads to deposition & accumulation of carcinogenic products at the lower respiratory tract [83, 85, 86]. These enhance the absorption of carbon monoxide from cannabis joints [86]. The absorbed carbon monoxide in the lungs competes & displaces oxygen to bind with hemoglobin and forms carboxy-hemoglobin. It may result in hypoxia and cause the production of free oxygen radicals and lipid per oxidation. Hypoxia may be followed by re-oxygenation and reperfusion injury [87, 88]. Even exposure to hypoxia may lead to replication arrest during both the initiation- elongation phases and decreased levels of nucleotides. DNA damage response of hypoxia can induce p53 dependent apoptosis [89]. Cells experiencing hypoxia/re-oxygenation are sensitive to lose the DNA damage response like Chk1, ATM, ATR, and PARP [90]. Again, marijuana smoke condenses have more than 150 PAHs, which can damage the coding of DNA. Repeated exposure can damage the tumor suppressor gene and proto-oncogene [89].

5. **Air Pollution:** The incomplete combustion of fossil fuel, biofuel, farming fuel, cooking fuel, industrial dust, desert dust, transports lead to an increase in the release of particulate matter (PM). Particulate matter like PM2.5 and PM10 are common in the air [91, 92]. Other common forms of outdoor air pollution include- nitrogen dioxide, sulfur dioxide, ozone gas, carbon monoxide, polycyclic aromatic hydrocarbons. These particles can increase pulmonary disease incidences. Already researcher has reported that PM2.5 can trigger asthma, COPD, lung cancer through activating different pathways [93]. It can activate AMP-activated protein kinase (AMPK) catalytic subunit α1, signal transducer and activator of transcription (STAT)-1, vascular endothelial growth factor receptor (VEGF), Mitogen-activated protein kinase (MAPK), nuclear factor κB (NF-κB), and interleukin (IL)-8 signaling [92, 94]. These results in systemic inflammation, endothelial cell apoptosis, and an increased risk of lung cancer [95, 96].

6. **Arsenic Exposure:** Arsenic exposure changes the cellular mechanism. Arsenic exposure exhibit genotoxicity and break the DNA double-strand, chromosomal damage in the primary epithelial lung cells. It increases the ROS level, which leads to the angiogenesis process [97, 98, 99]. Arsenic impairs the DNA repair process by binding to DNA repair proteins and enhances genetic instability. Again, it can alter the microRNA expression,

epigenetic change, and histone structure changes [100, 101]. It leads to the promotion of cell proliferation & carcinogenic properties [97].

7. **Heritable Factors:** According to the study on 44788 twin, researchers found that the risk of development of lung cancer is 7.7 and 6.7 fold more on monozygotic and dizygotic twins, respectively (concordance rate in twins 0.10-0.11) [102, 103]. Again, another study reveals that shared environments and lifestyles affect the onset of lung cancer, not the genetic factors [103, 104].

III. LUNG CANCER: GENES AND GENOME

According to the hypothesis, repeated exposure to etiological factors leads to lung epithelium dysplasia, and over a period genetic mutations occur. Genetic mutations affect protein synthesis and disrupt the cell cycle progression and promote carcinogenesis. Different etiological factor affects the copy number, single-nucleotide, and insertions/deletions (INDELs) of exomes in the autosomal chromosome to start from the primary tumor to metastasis via circulating tumor cells. In non-invasive types of cancer, genomics studies help to prognosis & diagnosis of cancer through the circulatory system as cell-free DNA fragments found in peripheral blood [23-29]. Circulating tumor cell analysis is helpful for the prediction of disease progression, survivability of patients, and personalized therapy. With the advancement of technology, single-cell whole-genome amplification (WGA) and whole exomes sequencing (WES) methods are helpful to detect genomic changes [23, 29]

In small-cell lung cancer (SCLC), MYC, BCL2, and p53 mutations contribute to the development of the disease, while in non-small-cell lung cancer (NSCLC), EGFR, KRAS, and p16 mutations contribute to its development. [105]. Key molecular targets that exhibit molecular genetic variation include lung adenocarcinoma patients with RET proto-oncogene mutations account for approximately 01-02% of all cases [106]. There is a ROS1 fusion proto-oncogene gene in 2% of NSCLCs [107]. Significantly mutated genes found through standard, gene-specific, and category-based tests in percentage-wise descending order for lung adenocarcinoma in 188 genes analysis are –p53, ALK1, STK11, EGFR, LRP1B, NF1, ATM, APC, EPHA3, PTPRD, CDKN2A, ERBB4, KDR, FGER4, NTRK1, RB1, NTRK3, EPHA5, PDGFRA, GNAS, LTK, INHBA, PAK3, ZMYND10, NRAS, SLC38A3 [108]. In squamous cell carcinoma, mutated genes are- TP53, CDKN2A, NOTCH1/2, PIK3CA, FGFR3, BRAF, RAS, BRCA2, and EGFR [109, 110, 111]. Large cell carcinomas with commonly mutated genes are TP53 (83%), KRAS (22%), and MET (12%). Mutated genes found in large cell carcinoma with neuroendocrine features are- TP53 (88%), STK11 (16%), and PTEN (13%) [112]. The commonly deleted gene in small cell carcinoma is- RB1, TP53, CDKN2A, FHIT, RASSF1A, and PTEN, and amplified genes are- MYC, MYCL, MYCN, CCNE1, MET, FGER1, SOX2, SOX4, IRS2, NFIB [113].

1. **EGFR Mutation:** According to a study, the prevalence of EGFR mutations in NSCLC was 32.3%- 35% [114,115]. The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase1 glycoprotein encoded with the EGFR gene at the cell surface. As per the instruction of the EGFR gene, the extracellular epidermal growth factor receptor domain binds to its ligand for autophosphorylation through intrinsic

tyrosine kinase to trigger signal transduction to control cellular proliferation [116, 117]. It blocks apoptosis, stimulates cell survival, proliferation, and migration through activating different pathways like MAPK (Mitogen-activated protein kinase), PI3K (Phosphatidylinositol 3-kinase), STAT3 (signal transducers and activators of transcription3), and STAT5 (signal transducers and activators of transcription5) [118]. Sustained activation, over-expression, and mutation of the tyrosine kinase domain of EGFR receptor lead to activation of the RAS-anti-apoptotic cascade in 43-89% aggressive types of EGFR mutated NSCLC [116, 119].Out of the 28 exons of EGFR, exon 19 deletion (19-Del) and exon 21(21-L858R) point mutation accounts for almost 85% of EGFR mutation in non-small cell lung cancer [120]. 40%–60% of South-East Asian patients or 10%–20% of Caucasian patients suffer lung adenocarcinoma due to the mutation of EGFR [121-123].

The treatment Profile for EGFR Mutation are

- **Chemotherapy:** Chemotherapy alone and with combination therapy is a commonly used treatment regime in EGFR mutated NSCLC. The combination increases the overall survival of the patients with adverse effects. Examples are Bevacizumab paclitaxel/carboplatin combination increases the survival rate with decrease tumor growth from 25 to 95% but causes life-threatening bleeding [118, 124]. Ramucirumab Docetaxel combination increases the survival rate by 10.5% but causes neutropenia, leucopenia, fatigue, and hypertension [118, 125]. Albumin-bound paclitaxel has a higher response rate but has adverse effects like thrombocytopenia and anemia [118, 126].

- **Anti EGFR Pathway Blocking Therapy:** Tyrosine kinase inhibitors (TKIs) are the anti-EGFR target drugs. 1st generation USFDA approved TKIs like Gefitinib and Erlotinib reversibly compete with ATP to bind to the intracellular kinase domain of EGFR to block phosphorylation through binding to the ATP-binding site to control the downstream signal of EGFR [127, 128]. 2nd generation Afatinib, Dacomitinib irreversibly binds to the kinase domain to block the phosphorylation. Third-generation TKIs Osimertinib inhibits EGFR resistance mutations by binding covalently to EGFR and targeting T790M (TK domain mutation) mutation [129]. 70% of EGFR-mutated tumors respond clinically to TKIs, whereas others don't respond due to EGFR exon 20 duplications or PTEN or PIK3CA mutation [130]. The side effects of TKIs are stomatitis, diarrhea, skin rash, paronychia, bleeding, arrhythmia, pancreatitis, hepatotoxicity [131].

- **Other Therapies:** TKIs resistance leads to PIK3CA, KRAS, BRAF mutation, and MET amplification [132]. So, the combination of the targeted drugs with TKIs can tackle the problem. Like crizotinib or SGX532, MET inhibitor combination with TKIs can enhance the sensitivity [133]. KRAS inhibitors have efficacy in vitro to treat EGFR mutation [134]. Knockdown of miR-21 increased the sensitivity to Gefitinib in vitro and in vivo by inhibiting the PTEN/PI3K/AKT pathways [135]. A combination of-TKIs and JAK/STAT pathways inhibitors can decrease drug resistance in NSCLC [136].

- **Nanocarrier Based Targeted Therapies:** EGFR-targeted antibodies or tyrosine kinase inhibitors or fusion drugs can target the extracellular EGFR domain to prevent ligand binding and interrupt signal cascades to cancer cells [137, 138, 139]. Recently researcher has found that Afatinib loaded gold nanoparticle enhances the loaded drug efficacy.

Table1: Reported nanocarriers based targeted drug delivery system for EGFR mutation

Sl No	Nanocarrier	Drugs	Effects	Targeting Ligand	Target	Ref
1	Gold Nanoparticle	Afatinib	Drug efficacy, compatibility enhances	-	Passive	140
2	Liposome	Afatinib	Improves tumor cells selectivity, internalization of the drug to the site	Anti EGFR monoclonal antibody	Active	141
3	RGD and PEG modified Liposome	Apatinib	Improves cellular uptake & therapeutic effects	Cyclic RGD	Active	142
4	PEGylated gold nanoparticles	Afatinib	Cellular uptake & therapeutic effect enhanced	PEG	Active	143
5	Quantum dots	Desmethyl Erlotinib	Cytotoxic enhancement	-	Passive	144
6	Nanoparticle platform utilizing fat and supercritical fluid	Erlotinib	Improve solubility	-	Passive	145
7	Iron oxide nanoparticle	Erlotinib	Improves therapeutic efficacy along with extrinsic & intrinsic apoptotic pathway	-	Passive	146
8	Solid Lipid nanoparticle	Erlotinib	Shows improve therapeutic efficacy of the drug	-	Passive	147
9	Cyclodextrin nanosponges	Erlotinib	Increases solubility, dissolution, cellular uptake and cytotoxicity.	-	Passive	148
10	Dendrimers	Chloroquine, Erlotinib shRNA	Drug efficacy increases in EGFR drug resistance cases	Anti-EGFR aptamers	Active	149

		survivin				
11	Liposome	Osimertinib	Drug efficacy enhances in EGFR resistant NSCLC	-	Passive	150

2. **KRAS Oncogene Mutation:** Kirsten rat sarcoma viral oncogene homolog (KRAS) is a family member of the human rat sarcoma virus (RAS) gene, encodes with GTPase membrane-bound protein. It regulates different signaling pathways of cell processes through activating GDP–GTP exchange (guanine nucleotide exchange factors) [151, 152, 153]. RAS links with upstream cell surface receptors- EGFR, FGFR, and ERBB2–4 to downstream proliferation. It also links with survival pathways such as RAF-MEK-ERK, PI3K-AKT-mTOR, and RALGDS-RA [154]. When RAS oncoproteins mutated, it prevents the increment of the catalytic rate of intrinsic GTPase by GTPase-activating proteins (GAP). It leads RAS to activate GTP- binding site to activate oncogenic and cellular signal transduction pathways [153, 155]. Commonly mutated genes in RAS mutant cancer cells are KRAS (86%), NRAS (11%), and HRAS (3%). KRAS oncogene mutations occur in almost 20–40% of lung adenocarcinomas depending upon different factors like smoker or non-smoker, race [153]. In NSCLC, Codons 12 (G12C, G12V, and G12D), 13, and 61 are the most mutated codon of the KRAS oncogene [156, 157]. KRAS-mutant NSCLC associate with genetic co-mutations of STK11 (32%), TP53 (40%) CDKN2A/ B (19.8%) inactivation coupled with low thyroid transcription factor-1 (TTF-1) expression [158, 159].

Drugs used for KRAS mutated NSCLC

- **Chemotherapy:** Cytotoxic chemotherapy is the standard of care for patients with advanced KRAS -mutant NSCLC. It is also used after surgery and with combination therapy with different targeted drugs [160].

- **Immunotherapy:** There is a positive correlation between PD-L1 expression, tumor mutation burden, and T-cell infiltration in NSCLC with KRAS mutations. So, immunotherapy can use for the high T-cell infiltrate KRAS-mutant NSCLC. Different researchers have reported contra indicatory remarks on immunotherapy because this therapy can modulate the tumor microenvironment, co-mutation of other prime genes, and variance in PD-1 expression [161, 162].

- **Pathway Blocking Therapies:** The areas of KRAS therapy are to develop GTPase-activating proteins for hydrolyzing GTP to GDP for terminating the signal to the inactive form to bind KRAS for integrating external signals from extracellular ligands. Further, targeted KRAS therapy can inhibit mutant KRAS to activate downstream signaling of downstream pathways (RAF-MEK- ERK and NF-kB) for cell proliferation. It also inhibits the mutant KRAS to activate MET or the PI3K-AKT-mTOR and RHO-FAK pathways for mutant cell survival [160, 163- 165].

- **KRAS Inhibition:** The mutant cysteine locates the P2 pocket in the switch II region. It exists in the inactive GDP-binding conformation of KRAS. This GDP-binding confirmation can use to make irretrievable inhibitors of the KRAS G12C gene. Inhibitors of the KRAS allele that target the G12C can trap oncoproteins in an inactive state by inhibiting the reactivation of exchanged nucleotides, preventing tumor cell proliferation [166, 167]. Sotorasib (AMG510), a selective and irreversible KRAS G12C targeted agent, was recently approved by the FDA based on positive results from preliminary clinical trials [168].

- **EGFR Therapy:** Due to the position of EGFR in the signaling cascade, mutant KRAS persistently activates EGFR signaling [153]. It is also closely linked with RAF-MEK-ERK for survival through the negative feedback mechanism [169]. TKIs can use for the treatment of KRAS mutation [164].

- **RAF Inhibition:** Rapidly Accelerated Fibrosarcoma (RAF) is downstream of mutant KRAS. Many RAF inhibitors are multi tyrosine kinase inhibitors that lack specificity for RAF alone [170].

- **MEK Inhibition:** Mitogen-activated protein kinase (MEK) inhibitors-selumetinib, allosterically inhibit MEK protein through non-ATP-competitive binding [171].

- **NF-kB Inhibition:** Loss of p53 function and continuous active KRAS (G12D) collaboratively activate nuclear factor-kappa B transcription factor (NF-κB) in human lung cancer tissues and cell lines. Using NFkB inhibitors, the researcher has found the reduction of IκBαM cells. It results in suppression of anti-apoptosis and increment of chemo-sensitivity in lung cancer cells [172].

- **MET Inhibitors:** MET (c-MET) inhibitors are a class of molecules to inhibit the enzymatic activity of the MET tyrosine kinase resistance that occurs through MET-gene amplification [173].

- **FAK Inhibitors:** Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase. Mutant KRAS associate with epigenetic silencing CDKN2A locus mutation deregulates FAK for downstream signaling pathways. There are no pharmacological drugs available to inhibit FAK, but the researcher has found that silencing of FAK causes significant loss of cell viability, apoptosis in mutant KRAS, p53 deficient cells [174].

- **PI3K Pathway Inhibition:** In KRAS mutated TKI resistance cell, phosphoinositide-3 kinase (PI3K) gets activated through the compensatory feedback mechanism for cell survival, differentiation, motility, and proliferation [175]. PI3K inhibitors block these activities.

- **Nanocarrier Based Targeted Therapy:** A few strategies to overcome the complication of KRAS mutation are passive targeting, expression reduction, interrupting membranal location, and signal transmission inhibition of KRAS mutation using chemoradiotherapeutic agents or a combination of the above. But due

to the lack of precision and satisfied clinical results of the mentioned treatment profiles due to heterogenicity & metastasis nature, the focus on targeted drug delivery regimes is increasing with newer nanocarrier-based approaches [176, 177].

There are two types of targeted gene delivery systems- viral & non-viral based. For targeted drug delivery using nanocarrier, interest has shifted towards nucleic acid-based viral transfer using lentiviruses or adenoviruses to the cells of interest. So, the small interfering RNA (siRNA) based or conjugated nanocarrier is a choice to use RNA interference as a molecular therapeutic modality [178]. Recently researchers found that the siRNA-loaded BSA nanoparticles inhibit the growth of lung cancer cells by evading endosomal entrapment and mediating sequence-specific KRAS knockdown (Table 2) [179]. Another approach is macropinocytosis of nanocarrier-loaded active pharmaceutical ingredients. But due to macropinocytosis's universal cellular nature, the modification of nanocarrier is essential [180]. In a recent study researchers had found that an apolipoprotein E3-tagged liposomal nanocarrier for co-delivering gemcitabine and KRAS-siRNA induces cell apoptosis and lowers cell viability compared with single-drug therapy (Table 2). It also shows the siRNA-mediated silencing of KRAS mutations [181]. In another study, researchers found that in pancreatic KRAS mutant cancer, ultra pH-sensitive micelle loaded with triptolide shows better therapeutic efficacy through the simultaneous lysosomal pH buffering and rapid drug release capacity of the nanocarrier [182].

Table 2: Reported nanocarriers based targeted drug delivery system for KRAS mutation

Sl no.	Nanocarrier	Drugs	Effects	Targeting Ligand	Target	Ref
1	BSA Nanoparticle	siRNA	Evades endosomal entrapment & mediates sequence specific KRAS knockdown to inhibit the NSCLC growth.	-	Passive	179
2	Poly(lactide) surrounded by poly(ethylene glycol) nanoparticle	Docetaxel	Shows improved tolerability, manageable toxicity, tumor shrinkage in lesser dose of Docetaxel in clinical trial	PSMA	Active	178
3	Apolipoprotein E3 Liposome	Gemcitabine, siRNA	Improves cellular uptake, cytotoxicity,	Apolipoprotein E3	Active	181

			lower visibility, and Kras silencing			
4	ultra-pH sensitive micelles	Triptolide	Cellular uptake & therapeutic effect enhanced through lysosomal pH buffering and rapid drug release	-	Pas sive	182
5	Quantum dots	Desmethyl Erlotinib	Cytotoxic enhancement	-	Pas sive	183

3. **LKB-1 Tumor Suppression Mutation:** Liver Kinase B1 (LKB1) is a Serine/ Threonine kinase 11(STK11) enzyme encoded with the STK11 gene for tumor suppression. LKB1 synonyms are Serine/threonine kinase 11 (STK11) or renal carcinoma antigen NY-REN-19 [184]. LKB1 takes part in DNA Damage Response (DDR) caused by different etiological factors for regulating 14 AMP Kinases (AMPK) to control the cellular functions like cellular growth, metabolism, autophagy, energy homeostasis, polarity, and suppress inflammation in cells. When energy stress engenders, LKB1 triggers catabolic processes & block anabolic processes. STRAD subunits synchronize the LKB1 mitochondrial trigger catabolic processes. Again, the LKB1 balances MO25 without a phosphorylation mechanism [185, 186, 187]. Even hematopoietic stem cell division, depletion, and pancytopenia are crop up by LKB1 loss or mutation [188]. LKB1 mutations decrease the phosphorylation process for AMPKs and affect cellular functions [189]. Approximately 5–30% of NSCLC cases occur due to LKB1 mutation [190].

- **Chemotherapy:** Chemotherapy remains the top treatment profile for LKB1 mutant lung cancer. According to a recent randomized trial, LKB1 mutations are unrelated to the efficacy of first- and second-line chemotherapy in non-small-cell lung cancer patients [191]. But chemotherapeutic agents that target mTOR, glutaminase, and PD-L1 increase the overall survival in NSCLC patients.

- **Radiotherapy:** This therapy can combine with other therapies for better therapeutic outcomes in LKB1 mutant lung cancer patients. But, single therapy using radioisotopes can cause LKB1 mutations by associating KEAP1/NRF2-dependent radiotherapy resistance targetable by glutaminase inhibition [192]. Compared to radiotherapy with/ without chemotherapy, recent clinical trials show the effects of glutaminase inhibitors, mTOR inhibitors, and anti-PD-L1 therapy in lung cancer patients have yielded promising results [193].

- **Pathway Blocking Therapies:**

➢ **Inhibition of mTOR:** mTOR (the mammalian target of rapamycin) is a serine/ threonine kinase signaling pathway that belongs to the PI3K-related protein kinase (PIKKs) family with the C-terminus homology to the catalytic domain of P13K is responsible for the growth factors, nutrients, and energy requires for cell survival,

growth, proliferation, and motility. It has two distinct protein complexes- mTOR complex1 (mTORC1) and mTOR complex2 (mTORC2). mTORC1, sensitive to rapamycin, regulates mRNA translation through activation of S6K1 and 4EBP1 in response to diverse stimuli. Whereas, mTORC2 resistant to rapamycin, activates PKC-α, AKT, and regulates the actin cytoskeleton. Actin cytoskeleton controls the cell structural support, axonal growth, cell migration, organelle transport, and phagocytosis. Mutation of LKB1 leads to the deregulation of the PI3K pathway, AKT pathway, S6K1, 4EBP1, eIF4E and activates the hamartin (TSC1)/tuberin (TSC2) complex. S6 kinase (S6K) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) are the downstream regulators of mTOR. Deregulation and activation of the above mention pathways lead to uncontrolled cell proliferation. Therefore, mTOR inhibitors are the therapeutic target to control the LKB1 mutation NSCLC. Rapamycin analogs-deforolimus, everolimus, and temsirolimus are few mTOR inhibitors used to treat multiple cancers in single-drug therapy or in combination with inhibitors of other pathways [194, 195, 196].

- **LKB1 and Metabolism of Glucose and Lipid**

Inhibition of ACC Activity: De novo fatty acid (FA) synthesis, storage, and lipolysis help sustain rapid cancer growth & signaling. Reprogramming of lipid metabolism is one of the hallmarks of cancer cells. So, targeting altered lipid metabolic pathways is a promising anticancer strategy. In the LKB1 mutated cancer cells, excessive lipids and cholesterol are present as lipid droplets (LDs) due to the acetyl-coenzymeA carboxylase (ACC) catalyzation. Since LKB1 deficiency removes the inhibition of ACC, targeting ACC in LKB1-proficient cancer cells may possess beneficial clinical outcomes [197, 198].

HMG-CoA Reductase Inhibitors: HMG-CoA reductase inhibitors are the structural analog of HMG-CoA that competitively inhibits the enzyme HMG-CoA reductase to catalyze the conversion of HMG-CoA to mevalonate and cholesterol. This mechanism leads to lower the production of cholesterol and enhances the expression of LDL receptors by clearing & lowering LDL cholesterol from plasma. Mevalonate and cholesterol are precursors for farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Tumor cell needs non-sterol isoprenoid for the prenylation of proteins for excessive growth and proliferation. An example is GGPP non-sterol isoprenoid molecules over express in lung adenocarcinoma. Statins inhibit iso-prenylation of Rho, Ras, Rac1 GTP binding protein. It also reduces angiogenesis through down-regulating pro-angiogenic factors [199-201].

FASN Inhibition: Fatty acid synthase (FASN) involves the lipogenesis process of reductive de novo long-chain fatty acids from acetyl-CoA, malonyl-CoA, and NADPH. The FASN phenomenon is significantly up-regulated in cancerous cells, whereas the same is low in non-cancerous cells. As per the different studies, siRNA knockdown and pharmacological inhibition of FASN leads to apoptosis of cancerous cells [203, 204]. So, the targeted FASN inhibitor with the dietary modification can be an area for NSCLC.

- **LKB1- AMPK Control Subsidiary Growth Regulation through Transcription Control:** LKB1 is a metabolic regulator with tumor suppressor function. LKB1 mutation fails to activate AMPKs and inhibits the induction of excess glycolysis produced by suppressing hexokinase-II (HK-II). AMPKs block cell growth through inhibition of lipid, glycogen, rRNA biosynthesis, blocking key signaling pathways, and G1 cell cycle arrest [205]. Inactive AMPK alpha leads to cancer cell proliferation by shifting the metabolic oxidative phosphorylation to aerobic glycolysis. Besides, the energy for cancer cells proliferation requires precursors for the biosynthesis of cellular components. Aerobic glycolysis diverts multiple biological macromolecules into other metabolic pathways for the cellular components. Targeted therapies that mediate the effect of LKB1 in aerobic oxidation could be beneficial for cancer treatment like mitochondrial metabolism inhibitors; activation of the LKB1 signals [206].

- **SESTRINs Expression Promoting Agent:** SESTRINs (SESN1, SESN2, and SESN3) are stress-inducible proteins for metabolic regulation. Oxidative and irradiation stress activate Sesn1 in p53 dependent manner. DNA damaging oxidative stress and over nutrition stress in the lung, liver, adipose, kidney, and pancreas activate Sesn2. Sestrins activate AMPKs and have antioxidant functions for suppressing ROS. Sestrins are p53 target genes for tumor suppression and act through mTOR inhibition. Again p53 is physically associates with LKB1 for tumor suppression. Reactivation of AMPKs & blocking of mTOR can control cancer cell growth [185, 207-209].

- **PRKAB1 Gene Regulation:** The heterotrimeric complexes of AMPKs have alpha, beta, and gamma subunits, encoded with the different genes in the vertebrate. Protein Kinase AMP-Activated Catalytic Subunit Alpha 1 (PRKAA1) and Protein Kinase AMP-Activated Non-Catalytic Subunit Beta 1 (PRKAB1) gene frequently amplified in tumor cells and Protein Kinase AMP-Activated Catalytic Subunit Alpha 2 (PRKAA2) gene in some cases [205]. Out of these, PRKAB1 is a p53 responsive gene that can inhibit mTOR. So, regulating the PRKAB1 gene may be a strategy to control the LKB1 mutation [210].

- **FOXO3 Transcription Regulation Enhancement:** AMPKs, the metabolic stress sensor activates by LKB1 to control the cell cycle, cell proliferation & sustain the energy homeostasis through balancing the ATP producing and ATP consuming pathways. This balancing occurs through the metabolic target enzyme's rapid phosphorylation and transcriptional regulation modulation. AMPKs phosphorylation of FOXO3, a glucocorticoid receptor target, activates the transcriptional activity to mimic the metabolic stress. Thus, deprivation of energy conditions activates FOXO3 for transcriptional and post-translational activity [185, 211]. Targeted drugs for FOXO transcription regulation and enhancement through activating AMPKs in LKB1 mutant cancer or without can be a possible therapy.

- **SIKs and AMPK Dependent Transcriptional Control of Metabolism**

  Histone Deacetylation Inhibition: Histone, the protein for structural support of chromosome, helps the DNA molecules through its octamer to fit into the cell

nucleus. Post-translational modification histone acetylation changes chromatin structure through epigenetic modification and regulates gene expression. The acetylation of ϵ-amino groups of conserved lysine residue influences histone transcription. Lysine acetylation control through two enzymes named histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylation of the lysine group using cofactor acetyl CoA by HAT neutralizes the positive charge of lysine. It weakens the histone-DNA interaction, augments chromatin accessibility, and results in the recruitment of transcription factors in genes [212, 213]. Whereas the HDAC catalytically removes the acetyl group to promotes chromatin condensation to repress gene transcriptions. Out of all 18 HDACs, the restriction of repression activity of class IIa HDACs (HDAC4, 5, 7, and 9) can fulfill through monitoring sub cellular localization. Class IIa HDACs control the enzyme distribution in the cytoplasm and nucleus through nuclear localization signal (NLS) and nuclear export signal (NES). Class IIa HDAC's interaction with 14-3-3 proteins can mask the NLS sequence to prevent the interaction with importin-alpha. Even it can change the confirmation to favor nuclear exports. A specific extracellular signal like the calcium/calmodulin-dependent protein kinase family (CaMK) promote the nuclear export of class IIa HDACs and stimulates the expression of MEF2 target genes by dissociating class II histone deacetylase (HDACs) from the DNA-binding domain[212]. LKB1 activates microtubule affinity-regulating kinases (MARK2 and -3), AMPKs, and SIK. These kinases regulate class IIa HDAC for nuclear export for resistance to therapy [214, 215]. Again in NSCLC, chronic inflammation is a prominent factor where MEF2 expression increases [216]. So, using class IIa HDAC inhibitor, the transcription can regulate. According to the reports, HDAC inhibitors increased chemokine expression, enhanced T cell infiltration, and T cell-dependent tumor regression in lung adenocarcinoma [217]**.**

CREB Inhibition: c-AMP response element-binding protein is a phosphorylation-dependent leucine zipper transcription factor of DNA binding proteins that actively regulate cellular responses like proliferation, survival, and differentiation[174]. LKB1 activates the AMPKs and SIK through phosphorylation to obtain metabolic homeostasis during stress conditions. Activated SIKs phosphorylate CREB-regulated transcription co-activators (CRTC) block its binding with 14-3-3 for nuclear transport. SIK phosphorylation also takes part in CRTC1 ubiquitination and degradation. Again, CRTC (1, 2, 3) is the co-activator of CREB drove gene transcription through histone acetyltransferase. In LKB1 mutant or null cell, phosphorylation hampered the SIKs activation, leads to increased CRTC dephosphorylation activation for CREB transcription through the cAMP-responsive element (CRE)-containing promoters. The activation of the SIK-CRTC-CREB signaling axis may be a potential targeted therapy for aggressive LKB1-inactivated NSCLC [218-221].

PGC1 Regulation: Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), a protein encodes with the PPARGC1A gene. PGC-1α is a transcriptional co-activator to regulate the genes expression involved in energy metabolism. Recently, researchers have found that a decreased PGC1α correlates with the epithelial-mesenchymal transition (EMT) and lung cancer distant metastasis [222]. PGC1α acts as a stress sensor transcriptional activator. In energy deprivation conditions, AMPK dependent phosphorylation and SIRT1 mediates deacetylation

activates PGC1α. Therefore promoting the LKB1-AMPK-PGC1α axis may be a potential target to control LKB1, LKB1-KRAS mutant NSCLC [223, 224].

SREBP1 Inhibition: Sterol regulatory element-binding proteins (SREBPs) are leucine zipper transcription factors for sterol regulation to uptake and biosynthesis of fatty acids, cholesterol that encodes with SREBF 1 and 2 genes. In the LKB1 mutant cell, cancer proliferation needs fatty acids and cholesterol [225, 226]. When LKB1 cells functionalized normally, it releases AMPKs, and lipid biosynthesis pathways are in control [226, 227]. Again, SREBP inhibition increases TKI sensitivity in non-small cell lung cancer cells [228]. So, the inhibition of SREBP1 may be a potential target therapy for the NSCLC.

AREBP Regulation: Heterodimer metabolic sensor serine/threonine-protein kinase complex AMPK controls the AMP/ATP ratio through LKB1. In LKB1 null/ mutated cell, un-control proliferation, metastasis occurs due to lack of AMPK & SIK inactivation. Nucleotide 5-aminoimidasole-4-carboxamide-1-b-D-ribofuranoside (AICAR) treatment is an artificial way to AMPK phosphorylation activation. AICAR transports into the cell through an adenosine transporter. AICAR phosphorylate AICAR ribonucleoside through adenosine kinase phosphorylation. It mimics the effect of AMP in the AMPK system. The activation of AMPK inhibits fatty acid, cholesterol, glycogen, protein synthesis. It represses the PEPCK gene expression through the transcription factor named AICAR response element-binding protein (AREBP). PERCK controls gluconeogenesis. So, AREBP-AICAR-AMPK may be a potential target to control LKB1 mutant NSCLC [229-231].

RNA Polymerase-I Regulation: In stress and low energy state conditions, cells down-regulate energy-consuming processes like the transcription of rRNA. LKB1 through AMPK and SIK tries to control the homeostasis of cells. Activation of AMPK triggers phosphorylation inactivation of TIF-IA at serine residue 635. TIF-IA is a transcription factor. It connects RNA polymerase I with the UBF/SL-1 complex for initiating the transcription of pre-ribosomal RNA. Inactivation of TIF-IA disrupts the transcription and inhibits rRNA synthesis through abrogating interaction between promoter-bound SL1 and TIF-IA. So, RNA polymerase I may be a targeted point for LKB1 null NSCLC [232, 233].

HNF4G Down-Regulation: Hepatocyte nuclear factor-4 gamma (HNF4G) is a nuclear receptor encodes with the HNF4G gene whose expression elevates in lung cancer tissues through the potential upstream mediator AKT signaling pathway [234]. Again in pancreatic ductal adenocarcinoma cell with SMAD4 deficiency, metformin act through AMPK mediated phosphorylation and suppress HNF4G [235]. So, there may be a relation between LKB1 deficiencies with HNF4G up-regulation and may be a target for LKB1 mutated NSCLC.

GLUT4 Enhancer Factor (GEF) Regulation:In LKB1-deficient pancreatic β cells, the secretion of insulin increases as the conserved kinase can't control cell polarity and energy metabolism and enhance GLUT4 translocation [236, 237]. Rab GTPase-activating proteins (Rab GAPs) AS160 and Tbc1d1 regulate the glucose uptake, glucose homeostasis through GLUT4 [236-238]. In response to insulin, AKT and

AMPK phosphorylation in Rab GAP-TBC1DI protein did not alter the intrinsic Rab GAP activity but disrupt interaction with insulin-regulated aminopeptidase [239]. So, targeted delivery to control the GLUT4 through Rab GAP may be a potential therapy for LKB1 mutated NSCLC. AMPK–TBC1D1 disruption increases lipogenic gene expression leads to obesity [240]. Obese patients have higher survival through unique cytokines or adipokines like omentin [241].

4. **BRAF Mutation:** V-RAF murine sarcoma viral oncogene homolog B1 (BRAF) is a serine/threonine kinase protein encoded with the BRAF gene to regulate cell growth. Auto-phosphorylate of the kinase activation loop of BRAF enhance phosphorylation of the downstream effectors MEK and ERK to promote cell proliferation and survival through an allosteric mechanism. BRAF proto-oncogene mutations count from 01% to 05% in NSCLC. 50% of BRAF mutations are of V600E point mutation on exon 15, and the remaining 50% are non-V600E BRAF mutations [242, 243, 244].

   Therapies for BRAF mutation:

   - **BRAF Inhibition:** BRAF inhibitors selectively interfere mitogen-activated protein kinase pathway through the BRAF kinase, regulate proliferation and T-cell receptor signaling. Resistance to BRAF inhibition occurs through MAPK/ ERK reactivation or P13K/AKT activation [245].

   - **MEK Inhibition:** MEK is a downstream protein kinase that prevents the reactivation of the MAPK pathway in the presence of BRAF or RAS mutations. MEK inhibitors bind to a unique site near the ATP binding pocket of the protein kinase and induce conformational changes to restrict the activation loop movement for reducing the rate of Raf-mediated MEK phosphorylation to arrest the signaling pathway. Again, BRAF inhibitor's resistance occurs through the MAPK pathway, so the combination therapy of BRAF inhibitors with MAPK inhibitors is a solution [245, 246]. Targeted delivery with this combination may be a solution for the BRAF mutant NSCLC.

5. **PIK3CA mutation in NSCLC**: Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases involve in the serine-threonine kinase, AKT pathway to regulate cell proliferation, survival, and motility. Heterodimeric enzymes PI3Ks have the PIK3CA gene with a catalytic subunit p110 alpha protein, and in NSCLC, p110 mutation is common. Loss of the p85 alpha regulatory subunit of P13K increases the oncogenic activity of P13K-p110 alpha [247]. The effects of PIK3CA mutation occur in exon 9 of the helical binding domain and 20 of the catalytic domain. PIK3CA mutation commonly co-occurs with KRAS, EGFR, BRAF, and ALK mutation[248]. Again, chromosomal copy number amplification activates oncogene and increased mRNA expression. PIK3CA locate at chromosome 3q26, which amplifies commonly in lung cancers. PIK3CA proto-oncogene mutation occurs in 02% to 07% of all NSCLCs [249]. The common strategy to control the PI3KCA ontogenesis is inhibition of PI3K/AKT/mTOR pathway.

Therapies for PIK3CA mutation

- **PI3K Inhibition:** It is the direct approach to block PIK3CA mutation, but the effectivity of the P13 inhibitors is not satisfactory. Recently researcher has proposed two theories to treat the PIK3CA mutation. They are- by combining allosteric, orthosteric drugs and rescue mutations to guide drug discovery [250].

- **AKT Inhibition:** Protein kinase B or AKT is a serine-threonine kinase over expressed in lung, breast, ovarian, gastric, and pancreatic carcinomas. It commonly activates in BRAFv600E and PI3KH1047 mutation cell lines. Mutation of PI3KCA up regulates the AKT to activate PI3K/AKT/mTOR pathway and oncogenesis [212, 213]. AKT inhibitor inhibits phosphorylation and breaks DNA double-strand to delay tumor growth. AKT inhibition targeted therapy using AKT target proteins are FoxO1, Glycogen synthase kinase-3 (GSK-3), mTOR, and PTEN are helpful to control the PI3KCA mutation [251].

- **mTOR Inhibition:** mTOR is another therapeutic target for PIK3CA mutation, and details are in the above mTOR section**.**

6. **ALK Mutation:** Anaplastic Lymphoma Kinase (ALK) gene encodes with a transmembrane tyrosine kinase on chromosome2. It activates by extracellular ligand-induced dimerization molecular alterations. The mutation of the ALK gene occurs through the fusion with the echinoderm microtubule-associated protein-like 4 (EML4) gene [252, 253]. EML4-ALK fusion oncoprotein is approximately available in 03-07% of NSCLC. TKI crizotinib is a MET, ROS1 inhibitor that inhibits ALK and c-Met phosphorylation in a concentration-dependent manner to control EML4-ALK fusion proteins expression along with ALK's signal transduction to arrest the cell cycle and apoptosis [254]. Resistance of crizotinib occurs due to the ALK kinase domain mutation, copy number gain (CNG) of the EML4-ALK fusion gene. Second-generation ALK inhibitors, ceritinib, and alectinib ATP competitive TKI and inhibits ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1on the surface of the cell against wild-type ALK and crizotinib resistance secondary mutations of ALK [253].

7. **TP53 Mutation:** The TP53 gene is a tumor suppressor gene located at the short arm of chromosome 17 (17p13) to activate the transcription of downstream genes (p21, to maintain DNA repair, cell-cycle arrest, apoptosis, autophagy, metabolism, and aging. Inactivation of TP53 increases malignancy, drug resistance and decreases survivability and drug resistance. TP53 gene mutation occurs in almost 50% of NSCLC patients. TP53 protein has four domains in the structure named as- N-terminal trans-activation domain, DNA-binding domain, oligomerization domain, and the C-terminus negative regulatory domain. Inactivation of TP53 increases malignancy and decreases survivability and drug resistance [255].

IV. NOVEL NANOCARRIERS BASED TREATMENT APPROACH

Nanocarriers, a colloidal preparation with a higher number of pores, can be used for the diagnosis and delivery of targeted drugs, nucleic acids, proteins, and diagnostic agents at the desired rate and time to the targeted site through passive, active targeting, pH, and temperature specificity to block pathways and reduce systemic drug toxicity [256–258]. As a result of NPs' small size, tailored surfaces, improved solubility, and multifunctionality, NPs provide superior stability, solubility, and bioavailability. It delivers the magnetic, thermal, electrical, and optical forms of active pharmaceutical ingredients used as targeted radiational, chemotherapeutic, gene therapeutic, immunotherapeutic, and combinational agents to treatment sites through the EPR effects. Depending upon the types, nature, and intention of the use of drugs, they are encapsulated or entrapped or dissolved, or absorbed in nanocarriers. Nanocarriers, a circulating cargo, can enhance the circulation lifetime, permeability, and retention of active pharmaceutical ingredients [259, 260]. Viral vector nanocarriers can deliver nucleic acid therapies [261]. In concise, a nanocarrier is a system that can control, manipulate, and fabricate micron-sized structures and devices. Optimization of the physical properties of NPs facilitates the delivery of drug at a specific rate and time to the desired sites. In addition to protecting the active medicament from premature degradation, nanocarriers control and improve drug distribution with intracellular accumulation, penetration, and shelf-life [262, 263]. Nanobiocarriers are the bioactive or targeting vector or ligand to deliver active pharmaceutical moiety to mimic and control the unnecessary cellular extravasations, growth, and cellular events. Additionally, nanobiocarriers enable the delivery of drugs with optimal bio-compatibility, biointeraction, safety, and efficacy [264].

A nanocarrier charge can deliver DNA or mRNA to overexpress a gene, small interfering RNAs or microRNAs to knock down a gene, or nucleic acids to trigger pattern-recognition receptors to stimulate the immune system [265]. A plasmid containing both a promoter and the gene of interest is used to treat DNA overexpression by bypassing the plasma membrane and nuclear envelope. After reaching the nucleus, it export and transcribes into mRNA and translates into the desired protein in the cytoplasm. Single-stranded mRNA also can use for the same purpose, but it is less stable and has a lesser chance of undesired insertion into the genome, like plasmid DNA, to cause mutagenesis [265-267]. But, RNAi can interrupt mRNA translation to decrease the target gene expression, and this problem can solve using short-length dsRNA like siRNA. Although the sequence of nucleic acids can have functional impacts on biological targets, many physical and chemical considerations are not heavily dependent on nucleic acid sequence encapsulated in nanocarrier for delivery. So, the chemical and physical properties of the nucleic acid should consider [265-267].

Co-delivery of multiple nucleic acids of the same type but with different sequences in a single delivery vehicle follows the same design principles to necessitate changes to nanocarrier design to deliver distinct cellular and subcellular locations. Again, the tumor heterogeneity and MDR cause multiple therapeutic agents to target different cellular pathways. But, the multitargeted nucleic acid cargo can cause intrinsic toxicity and virus immunogenicity to prevent repetitive administration [265, 266]. The challenges of nucleic acid cargo are- the physical and chemical properties' similarity and extracellular and intracellular trafficking routes overlaps. As nucleic acids possess a negative charge in their structure, generally positively charged polymers can use to prepare NPs. Cationic polymers like poly(l-lysine), polyethyleneimine, polyamidoamine, poly(beta-amino ester), and cationic

lipids are used [266]. Again, the size and physical properties of the nucleic acid impact its loading to nanocarriers. Further, surface modification of the nucleic acid NP improves its cellular uptake in the targeted site. Nanocarriers can classify as organic, inorganic, or hybrid based on the components used in their development. Commonly used nanocarriers for nucleic acid delivery are liposomes, solid lipid, polymeric, gold, mesoporous silica, and iron oxide NPs [268].

Cancerous cell proliferation and migration profiles are different from those of normal cells. A therapeutic dosage form should enter the TME to control cancerous cell proliferation and migration. The penetration of conventional dosage forms to the TME is less due to its heterogeneity and the above-mentioned other factors. In addition, traditional drug delivery systems are less specific for cancer cells. Due to the lack of specificity and less penetration to the TME, the required concentration of the drug doesn't reach to eliminate the cancer cells. Non-eliminated cancer cells alter metabolic signaling pathways and drug metabolism, inactivate drugs, suppress apoptosis, alter epigenetic, change drug targets, enhance DNA repair, alter epithelial-mesenchymal transition, and enhance gene amplification. As a result, cancer cells cause multiple drug resistance and survive, rocket, and migrate [269-273].

As the nanocarriers have a diverse range (from 01-1000nanometer) and can tune according to the requirement of the (<200 nm) targeted site, the study and use of nano carrier-based targeted drug delivery have increased. Again, the nanoparticulate nanocarriers can incorporate multiple targeting agents to enhance the bioavailability, drug delivery, absorption, targeting precision, and stimulus technique. Understanding and identifying cancer cells' physiochemical behavior can help optimize nanocarriers. In addition, the releasing pattern of drugs from nanocarriers determines the effectiveness of nanocarrier-based drug delivery systems [269, 274].

V. STRATEGIES TO OVERCOME TUMOR MICROENVIRONMENT:

The self-defense mechanism of the respiratory tract impacts drug delivery and absorption in the lung surface through mechanical, chemical, and immunological barriers. Behavioral barriers also added instruments to it. Targeted therapy is the formulation approach to overcome the lung surface barriers to the targeted site by bypasses the gastrointestinal tract and has a better pharmacokinetic profile [275]. The relation of the active drugs' physicochemical properties with the biological functions affects the development of targeted therapy & treatment profiles [276].

The mononuclear phagocytes of the immune system reduce the reach of nanotherapeutics through opsonization and sequestration processes. It occurs in a protein corona around nanoparticles using the opsonization and sequestration processes. The formation of protein corona depends upon the size and surface chemistry of the nanoparticles. After protein corona formation, it absorbs the nanoparticles, internalizes them, fuses them to the lysosomes, and reduces their specificity [277–282].

Cancer cells chisel their TME using different factors, like the release of chemokines and cytokines. These secretions reprogrammed the environment for further tumor growth and disease progression. Nanoparticles can passively and limitedly reach the TME using the EPR effect. The tumor heterogeneity acts as a barrier for drug delivery to the TME through

uncontrolled vascular events, resistance produced by the stroma, hypoxia, pH, and immune reshaping. For stable drug delivery to the targeted TME, there is a need for favorable vascular network events, regulation of stromal activities, or manipulation of hypoxia, pH, and immunity. In a heterogenic TME, the incremental demand for nutrients increases growth factors and forms leaky vessels. It increases the angiogenesis of tumor cells. It also enhances the interstitial fluid pressure through the leaky vessels and decreases blood flow to the site. So, the drug-loaded nanoparticles can't reach and accumulate in the targeted space [283–293]. Again, in lung cancer treatment, multiple drug resistances decrease the effectiveness of the treatment profile. A combination of medications for respiratory tract diseases changes the compliance rate of the drugs. The modulation of the TME using a single drug therapy with multiple targeting strategies can overcome these issues [284, 294-296]. A few strategies to optimize drug delivery to the TME are active targeting, TME modulation, and TME responsive targeted drug delivery [283, 293, 294].

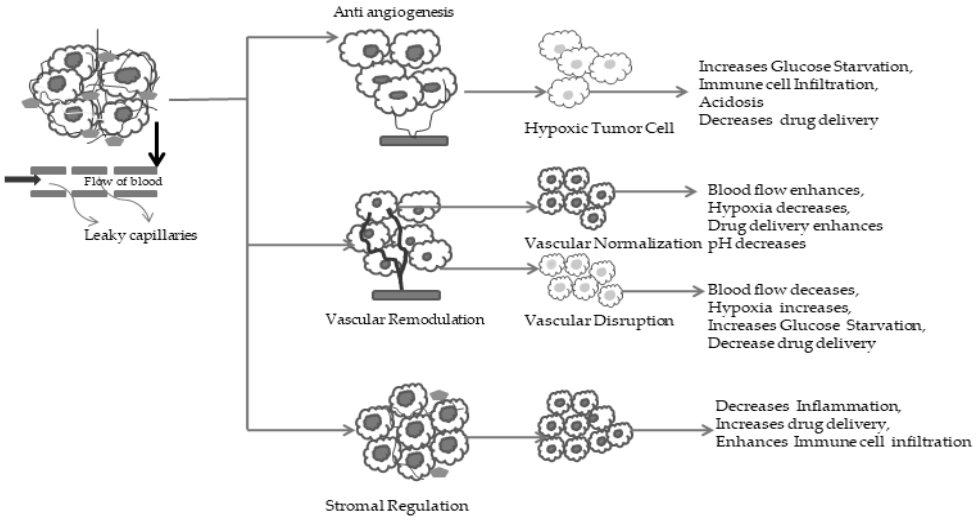

Figure 1: TME modulation

VI. REPORTED NANOCARRIER FOR THE TREATMENT OF GENE MUTANT LUNG CANCER OVERCOMING TME

1. **Solid Lipid Nanoparticle:** Solid lipid nanoparticles (SLN) are a surrogate of the colloidal drug delivery system, which can carry lipophilic, hydrophilic drugs, nucleic acids, and proteins to the targeted site. The size range of SLNs is 40–1000 nm [297]. It is a versatile, biocompatible, stable nanocarrier system with less toxicity. It is suitable for both active and passive targeting. Solid lipid nanoparticles are prepared by dispersing the melted solid lipid in water, followed by the addition of emulsifying agents through different homogenization techniques or micro-emulsification. Supercritical fluid, solvent emulsification/evaporation, double emulsion, and spray drying methods can be used to prepare SLNs [298]. Primary solid lipids used in the SLN preparation are fatty acids, mono-, di-, triglycerides, or waxes. These biodegradable lipids of SLN can offer sustained release of drugs deep into the lungs and are for the pulmonary drug delivery system. Solid lipid nanoparticles have a larger surface area and can load higher doses of active medicament. As per the requirement, in SLN, the drug can be incorporated into the matrix, shell, or core. SLN can be used in the preparation of oral dosage forms. Recently, studies have shown the higher transfection efficacy of cationic SLNs for the p53 gene

targeting lung cancer [299]. A high melting point triglyceride in the SLN formulation is more efficient in the tumor cell environment [300]. Clinical updates indicate that folic acid-modified silymarin SLN enhances internalization through folate receptors in TME [301], as shown in Table 3. The main disadvantages of SLNs are their lower drug-loading efficacy and drug expulsion during storage. It can be rectified by mixing lipids with oil in a 70:30 to 99.9:0.01 ratio. SLNs can be optimized further by using appropriate ligands to overcome the TME, other than passive targeting [298, 302, 303].

In a study, researchers found that inhalable epirubicin-loaded SLN caused more cytotoxicity than epirubicin solution in the A549 cell line [304]. SLN loaded with docetaxel also prevented tumor growth and lung metastasis in 4T1 murine mammary carcinoma cells [305]. In a study, researchers found that the dual drug curcumin and paclitaxel-loaded SLN showed the highest tumor inhibitory action (78.42%) in the A549 cell line compared to other cell lines rather than the drugs separately administered. As well as enhancing P-glycoprotein efflux, this formulation reverses the MDR pathway and down-regulates NF-kB [306]. Enhanced green fluorescence protein plasmids and doxorubicin-loaded transferrin-conjugated SLN show improved anticancer activity [307].

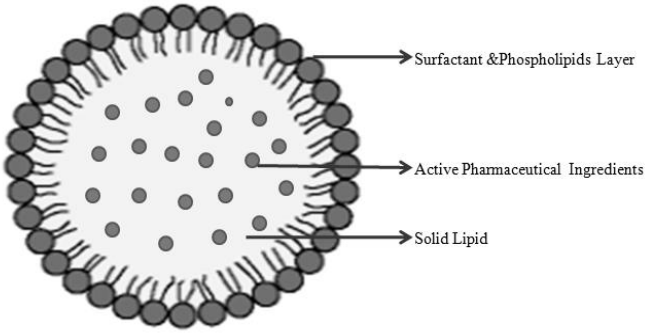

Figure 2: Solid Lipid Nanoparticle

2. **Liposomes:** Liposomes are spherical vesicles with an aqueous core surrounded by natural phospholipids or synthetic amphiphiles and sterols in one or more bilayers with particle sizes ranging from 25 to 2500nm [308]. This lipid-based drug delivery carrier is suitable for hydrophilic and lipophilic drugs as it has aqueous and lipidic layers. It can deliver macromolecules like DNA, proteins, imaging, and active chemotherapeutic agents. It is a non-toxic, stable, high vascular density, and adjustable surface nanocarrier with a higher retention time in the targeted site. The half-life of this bilayer formulation is short in the systemic circulation. The preparation of liposomes generally begins with drying lipids from organic solvents, dispersing them in aqueous media, followed by purification and analysis. The composition of a bilayer determines the rigidity or fluidity and charge of the layer. Long-chain acyl-functional phospholipids form the rigid, impermeable bilayer structure of the liposome. Unsaturated phosphatidylcholine shapes a flexible, permeable liposome. The commonly used phospholipids in liposome preparation are phosphatidylethanolamine and phosphatidylcholine. Microfluidizers, membrane extrusion, sonication, and homogenization techniques can control liposome size and size distribution. This nanocarrier nanoparticle can use for active, passive, pH, magnetic, stimuli-responsive, and thermo-responsive targeting. Liposomes can enhance the loaded drug's efficacy at the targeted site, therapeutic index, and stability. It also reduces the

loaded drug's toxicity and exposure to sensitive tissue [309, 310]. Biofunctionalization liposomes enhance loaded drug efficacy in resisting lung cancer therapy through active targeting [311]. Again, in another clinical update, researchers found that irinotecan and veliparib-loaded nono-liposomal intravenous formulations show combinational synergy for PARP and topoisomerase-1 inhibition along with better efficacy [312]. The disadvantages of liposomes are lower solubility, a shorter half-life, leakage of encapsulated drugs, oxidation, hydrolysis, and a higher production cost. Limitations and benefits of liposome drug carriers depend on liposome interaction with cells and their fate in vivo after administration. The interactions of liposomes with the cell surfaces take place either through adsorption or endocytosis. A liposome can categorize according to its functional modification: conventional, PEGylated, ligand-targeted, and theranostic [309, 310]. These differently modulated liposomes can overcome the bio-physiochemical difficulties of the active medicaments to reach the targeted sites. As well as liposome-loaded drugs suppressing the TME, soluble mediators in liposomal drug delivery systems inhibit TME immunity [313].

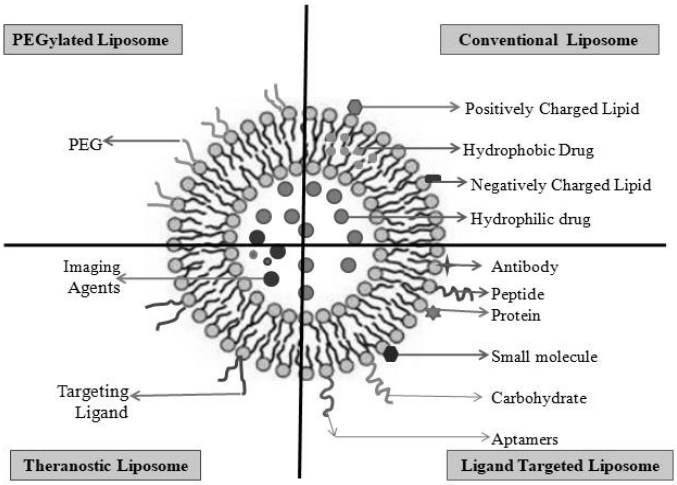

Figure 3: Liposome.

3. **Polymeric Nanocarriers:** Polymeric nanoparticle carriers are small (1-1000nm), adjustable, rapid absorbable versatile colloidal carrier systems to control the release of the entrapped active drug within the polymeric shell. The polymeric nanoparticles can classify into- Polymeric nanocapsule (Reservoir system) and Nanosphere (Matrix system). Preparation methods for polymeric nanoparticles include solvent evaporation and diffusion, nano-precipitation, and reverse salting. Generally, nanoprecipitation method is used to prepare polymeric nanocapsules. The stability of this nanocarrier depends upon the adsorption of the active medicament into the nanoparticle surface and surfactant presence. Microbial contamination is one of the challenges of this type of formulation. This problem can resolve by adding preservative spray drying or lyophilization. The drug delivery system is suitable for cancerous cell treatment using drug-nucleic acid combinations. These nanoparticles can induce anti-tumor immunity CD8+ T-cells by regulating the lymphatic system and activating dendritic cells in TME [315-317]. The advantages of polymeric nanoparticles include- multiple therapeutic targeting and independent control of drug release. The main disadvantages of polymeric

nanoparticles are the synchronization of pharmacokinetic & biodistribution of loaded compounds [315, 316]. *Novoselova M.V. et al.* (2020) have found that the internalization of polymeric multilayer capsules in lung cancer cells is 75% higher than in healthy lungs. Embedding gemcitabine and clodronate in polymeric multilayer capsules inhibited macrophage-induced tumor growth [318]. In another study, silibinin, a low-water-soluble drug encapsulated in polycaprolactone/Pluronic F68 nanoparticles, showed sustained release in the systemic circulation for up to 48 hours, inhibited tumor growth, and improved the loaded drug efficacy [319]. In a clinical update, the researchers found that polymeric nanoparticles loaded with Docetaxel can overcome drug resistance to refractory cancer [320]. Another clinical update, polymeric micelles loaded with anticancer drugs are capable of releasing drugs whose AUC, Cmax, and Volume of distribution are unstable [321]. As reported, polymeric nanoparticles entrapped with hypoxia-responsive photosensitizer and chemotherapeutic drugs produce reactive oxygen species that enhance efficacy and the photodynamic response of cancer treatments [322].

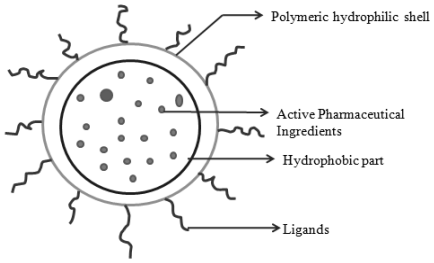

Figure 4: Polymeric Nanoparticle**.**

4. **Gold Nanoparticle:** Gold nanoparticles (GNPs) are 5 to 400nm in size and vary in shape; they are optoelectric, mildly antibacterial, and targeted drug delivery carriers. Their antibacterial activity depends on the intensification of ROS generation in the microbial cells. Other biomedical applications of GNPs are photodynamic immunotherapy for cancer treatment, diagnostic agents, etc. The photothermal activity of GNP is due to the excitement of electrons when irradiated with laser light. GNPs can synthesize using the bottom-up reduction method of chloroauric acid (HAuCl4). Commonly used reducing agents are sodium citrate, borohydride, polyalcohol, amines, etc. The reported absorption of GNP in oral administration is low. IV administration of GNP accumulates in the spleen, liver, and lung, and elimination is less. GNP increases glucose and catalytic enzymes (alanine aminotransferase and aspartate transaminase). It affects liver function [322-325]. In a study, researchers found that methotrexate conjugated GNP in a lower dose inhibits tumor growth compared to methotrexate (without loading or conjugated) in Lewis lung carcinoma [325]. In another study, researchers reported significant cytotoxicity and apoptosis in lung cancer stem cells when aluminum (III) phthalocyanine chloride tetra sulfonic acid and anti-CD133 antibody bioconjugate GNP were administered [326]. On the A549 cell line, researchers found that silibinin-conjugated gold nanoparticles released pH-responsively enhanced silibinin efficacy up to 4-5 times [327]. In a recent clinical update, researchers have found that T-cell, microRNA, or peptide-conjugated or entrapped gold nanoparticles enhance the EPR effect and its photothermal nature to inhibit cancer cell growth [328].

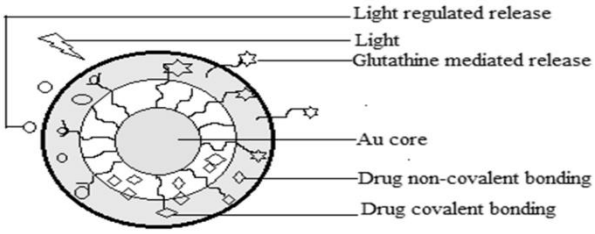

Figure 5: Gold nanoparticle

5. **Mesoporous Silica Nanocarrier:** Mesoporous silica nanoparticles are solid, tunable, and porous nanocarriers with high encapsulation capacity through endocytosis. These nanoparticles have uniform pore size ranges of 2-6 nm. There are three types of MSNs - ordered MSNs, hollow MSNs, and core/shell MSNs. A hollow MSN can load more drugs than the others. Surface functionalization can enhance nanoparticles' physicochemical properties. A few techniques for preparing MSNs are growth quench, confinement techniques, separation of confinement, and growth techniques. Functionalization can be done with co-condensation, multifunctionalization, and grafting methods. The surface modification allows this nanoparticle to target actively and passively [329-332]. Human cells are more likely to internalize 50 nm MSNs, although smaller particles exhibit longer circulation times. As particle size influences cytotoxicity, micrometric particles of 1 mm are less toxic than nanometric particles of 200 nm. Again, cationic nanoparticles are more immunogenic and cytotoxic than neutral or anionic ones. In melanoma treatment, FDA has approved multimodal silica nanoparticles [329]. Conjugating ligands folic acid, DNA aptamers, transferrin, and antibodies with MSN can enhance the efficacy of photodynamic targeted therapy for cancer. Researchers have found that MSN injection before anti-PD-1 resensitizes to overcome tumor resistance improves anti-PD-1 activity, and protects immunity [333, 334]. Researchers also found that siRNA co-delivered with chemotherapeutic drugs loaded in MSN synergistically enhanced their efficacy and survivin protein inhibition [334, 335]. In another study, folic acid-modified MSN loaded with multidrug-resistant protein-1 siRNA and myricetin reduces cell viability, suppress tumor, and up-regulates the expression levels of cleaved Caspase-3 and PARP in cancer cell line A549 and NCI-H1299 [336]. In a clinical update, researchers have found that an antitumor drug loaded in pH-responsive mesoporous silica-coated gold nanoparticles can cause a photothermal effect in addition to the loaded drug mechanism to produce anticancer activity specifically in the tumor cells [337].

6. **Hybrid Nanocarrier:** The advantages and disadvantages of a variety of drug nanocarriers are discussed above. Recently, adding a combinational approach can mimic the disadvantages of nanocarriers and increase their efficacy. So, the concept of hybrid nanocarriers has arrived. These hybrid systems combine the benefits of different structural components to synergize the outcome of the therapy. Erosion and degradation are the processes by which the hybrid nanoparticles release the entrapped active medicaments from the core. Multiple layers of lipids, polymers, and organic-inorganic compounds may protect the core materials, along with the solubility and permeability modifications of the entrapped active ingredients [338]. Recently, curcumin and survivin shRNA loaded in polymeric hybrid nanoparticles with PLGA conjugated triblock

polymers (W5R4K-PEG2K-PHIS) showed better penetration into the TME and synergistic tumor suppression action [339].

VII. CONCLUSION

Lung cancer has a lower survival rate due to the complexity of delivering the active drugs to the targeted sites. Biological barriers, behavioral nature, and tumor heterogeneity impact the delivery of drugs to the lung cancer ailment. There have been many attempts to overcome the barriers through different therapeutic approaches like chemotherapy, immunity modulation therapy, radiation therapy, chemotherapy, stereotactic body radiotherapy, etc. Recently, other than the above therapeutic options, interest in targeted drug delivery systems is increasing as adjuvant therapy in both early and late stages of disease progression. The reason is that most of the above-mentioned conventional therapies got resistant after a certain period and the therapeutics accumulation in the intracellular region is minimal to cause toxicity in the tumor microenvironment. In addition to that, conventional therapies are unlikely to enter the tumor microenvironment.

Targeting gene or genome using targeting therapy can improve the treatment profile in many ways. It blocks the genetic expression or decrease the mutation. Further, we have found that nanocarrier-based targeting drug delivery can overcome the TME barriers and enhance the targeting efficacy of the loaded drug. The selection of the nanocarrier for depends upon different factors- 1. Physiochemical nature of the loaded drug- solubility, permeability, molecular weight, and stability. 2. Nanocarrier specificity and size. 3. The biocompatibility and toxicity of the nanocarrier. Biodegradable nanocarriers are often preferred as they can be metabolized and eliminated from the body, reducing the risk of long-term toxicity. 4. Drug-release kinetics. 5. Preclinical data. 6. Scalability for manufacturing. 7. Regulatory consideration. Therefore, selecting a nanocarrier for treating a particular targeted area based on individual requirements can be challenging.

Though there is no direct access method to evaluate the performance and comparison of nanocarriers, quantitative metrics can solve this issue. The quantitative metrics are- 1. Particle size distribution using dynamic light scattering (DLS), transmission electron microscopy (TEM), or scanning electron microscopy (SEM). 2. Encapsulation efficiency. 3. Drug loading capacity. 4. Release kinetics. 5. Stability. 6. Cellular uptake and intracellular localization using flow cytometry, confocal microscopy, or electron microscopy. 7. Cytotoxicity using MTT and lactate dehydrogenase assay.

Nanocarriers also have potential risks and downsides. Common risks and possible side effects include- immunogenicity, off-target effect, toxicity, premature drug release, drug resistance, and tumor heterogeneity. Nanocarriers may exhibit inherent toxicity if not adequately eliminated from the body. Rigorous toxicity evaluations and optimization of nanocarrier properties, such as size, surface charge, and composition, can help mitigate this risk. Nanocarriers also can experience drug leakage or premature release of the therapeutic payload before reaching the target site. It can result in suboptimal drug concentrations at the intended site and can reduce its efficacy. Strategies such as improved encapsulation techniques, surface modifications, or utilizing stimuli-responsive nanocarriers can help minimize premature drug release. Targeted therapy using nanocarriers can be affected by drug resistance mechanisms and the heterogeneity of lung cancer tumors. Combining

nanocarrier-based therapy with other treatment modalities or developing strategies to address drug resistance can help overcome this limitation.

In this study, we have found multiple nanocarriers with different possibilities. Depending upon the requirements and targeting strategy, nanocarriers can modify to optimize the required outcome.

Future Prospective:

In light of advances in nanotechnology, various research studies are underway to find more convenient cancer treatments. NSCLC remains a substantial clinical challenge though chemotherapy and surgery are the few standards of care. Drug delivery to the targeted site remains challenging despite newer drugs for different histological subtypes and driver mutations. So, the emphasis on the nanocarrier based genome targeting drug delivery system as an add-on therapy to the current regime will lead to more effectiveness. Here, according to different studies, we found that biofunctionalized inorganic metal compounds with organic compound complex-loaded drugs may be a carrier system for the NSCLC targeted therapy. Especially, with active targeting through surface modifications of receptors overexpressed in lung cancer cells (folic acid, peptide, somatostatin). The biofunctionalization of the nanocarrier enhances the biosystem interaction, cellular uptake, immune system abscond, and vascular alteration to penetrate the tumor microenvironment. Again, inorganic metal compounds have the photothermal effect that scavenges the reactive oxygen species. Further, the loaded pathway-blocking agents can inhibit rapid cancer cell growth**.**

In this study, we have discussed the different possibilities of pathway blocking agents role in controlling the genomic expression and different possible nanocarrier systems and their reported efficacy. This study will help to develop new targeted therapeutics using a modified bioconjugate hybrid nanocarrier that can act through active targeting by bypassing TME and target the genome of cancerous cells. Further, this study will give an idea about different nanocarrier's efficacy in a concise form, along with their mechanism. It will help to compare nanocarriers in diverse conditions for developing personalized therapy.

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