**Lung Cancer: affected Gene/Genome, Current Treatment Profile, and Prospective of Targeted Drug Delivery System**

Kangkan Sarma1\*, Dr (Mohd) Habban Akhter1, Dr Swati Arya2, Preety Gautam3, Monika Dhaka4, Vaishnavi Shinde5

1 School of Pharmaceutical and Population Health Informatics (SoPPHI), DIT University, Dehradun 248009, India, habban.akhter@dituniversity.edu.in; habban2007@gmail.com (M.H.A); sarma\_kangkan@outlook.com (K. S);

2 G. D. Goenka University, Sohna, Gurugram, Haryana 122103, India; aryaswati2020@gmail.com (S. A)

3 Hygia Institute of Pharmacy (HIOP), Faizullahganj, Prabandh Nagar, Ghaila road, Lucknow-226020, India; preetypreety411@gmail.com (P.G)

4 Sanskar College of Pharmacy and Research, NH-24, Jindal Nagar, Ghaziabad, Uttar Pradesh-201302, India; monikadhaka93@gmail.com (M. D)

5NET Pharmacy College, Mantralayam road, Raichur-584103, Karnataka, India; shindevaishu22@gmail.com (V.S)

\*Correspondence author: sarma\_kangkan@outlook.com (K.S.); habban.akhter@dituniversity.edu.in

**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.

1. **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 withnitrogen 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.

1. **Etiological factors pathophysiology to affect genetic make ups:**
2. **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 1015 – 1017/ puff) increases the release of oxidants, damage the oxidative barriers and airway repair capability [56, 57]. Direct-acting carcinogens orreactive 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].

1. **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 H2O2, 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].**

1. **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].**

1. **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].**

1. **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].**

1. **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].**

1. **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].**

1. **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-

* + 1. **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].

* + 1. **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].

* + 1. **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].

* + 1. **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, ErlotinibshRNA survivin | Drug efficacy increases in EGFR drug resistance cases  | Anti-EGFR aptamers | Active | 149 |
| 11 | Liposome | Osimertinib  | Drug efficacy enhances in EGFR resistant NSCLC  | - | Passive | 150 |

* 1. **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-

* + 1. **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].

* + 1. **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].

* + 1. **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].

* + - 1. **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].

* + - 1. **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].

* + - 1. **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].

* + - 1. **MEK Inhibition:**

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

* + - 1. **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].

* + - 1. **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].

* + - 1. **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].

* + - 1. **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.

* + 1. **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].

Table2**: 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, lower visibility, and Kras silencing | Apolipoprotein E3 | Active | 181 |
| 4 | ultra-pH sensitive micelles | Triptolide | Cellular uptake & therapeutic effect enhanced through lysosomal pH buffering and rapid drug release | - | Passive | 182 |
| 5 | Quantum dots | Desmethyl Erlotinib | Cytotoxic enhancement | - | Passive | 183 |

* 1. **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].

* + 1. **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.
		2. **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].
		3. **Pathway blocking therapies**
			1. **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].

* + - 1. **LKB1 and metabolism of glucose and lipid**
				1. **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].

* + - * 1. **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].

* + - * 1. **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.

* + - 1. **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].

* + - 1. **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].

* + - 1. **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].

* + - 1. **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.

* + - 1. **SIKs and AMPK dependent transcriptional control of metabolism**
				1. **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].**

* + - * 1. **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 differentiation174. 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].

* + - * 1. **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].

* + - * 1. **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.

* + - * 1. **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].

* + - * 1. **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].

* + - * 1. **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.

* + - * 1. **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].

* 1. **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].

* + 1. **Therapies for BRAF mutation:**
			1. **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].

* + - 1. **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.

## 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.

## ****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].

## ****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].

1. 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].

1. **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].



**Fig 1: TME modulation**

1. **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].



**Fig 2.** Solid Lipid Nanoparticle

* 1. **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].



**Fig 3.** Liposome.

 **6.3 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].



**Fig 4.** Polymeric Nanoparticle**.**

**6.5 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].

****

**Fig5:** Gold nanoparticle

**6.6** **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].

**6.7.** **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].

1. 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.

1. 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.

**Author Contributions:** Conceptualization, M.H.A; K.S.; and S.A.; methodology, K.S.; S.A.; M.H.A.; software, V.S.; validation, M.H.A.; K.S; and P.G; formal analysis, K.S and P.G; S; investigation, M.H.A and P.G.; resources, V.S.; M.D.; data curation, K.S.; M.H.A; S.A.; writing—original draft preparation, M.H.A and K.S.; writing—review and editing, K.S.; P.G.; M.D.; V.S.; visualization, M.H.A and S.A.; K.S.; supervision, M.H.A.; project administration, M.H.A.; funding acquisition, S.A.; M.D;. All authors have read and agreed to the published version of the manuscript.

**Funding:** NA.

**Institutional Review Board Statement:** NA.

**Informed Consent Statement:** NA.

**Data Availability Statement:** NA.

**Acknowledgments:**

**Conflicts of Interest:** Declare none.

**References**

1. WHO. *WHO Global Report on Trends in Prevalence of Tobacco Smoking 2000–2025*, 2nd ed. Available online: <https://apps.who.int/iris/handle/10665/272694> (accessed on 2 December 2020).
2. Allemani, C.; Matsuda, T.; Di Carlo, V.; Harewood, R.; Matz, M.; Nikšić, M.; Bonaventure, A.; Valkov, M.; Johnson, C.J.; Estève, J.; et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* **2018,** *391*, 1023–1075*.* http://doi.org/10.1016/S0140-6736(17)33326-3.
3. Goss, P.E.; Strasser-Weippl, K.; Lee-Bychkovsky, B.L.; Fan, L.L.J.; Chavarri-Guerra, Y.; Liedke, P.E.R.; Pramesh, C.S.; Badovinac-Crnjevic, T.; Sheikine, Y.; Chen, Z.; et al. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol.* **2014**, *15*, 489–538*.* https://doi.org/10.1016/S1470-2045(14)70029-4.
4. Van der Heyden, J.H.A.; Schaap, M.M.; Kunst, A.E.; Esnaola, S.; Borrell, C.; Cox, B.; Leinsalu, M.; Stirbu, I.; Kalediene, R.; Deboosere, P.; et al. Socioeconomic inequalities in lung cancer mortality in 16 European populations. *Lung Cancer* **2009**, *63*, 322–330*.* https://doi.org/10.1016/j.lungcan.2008.06.006.
5. Walters, S.; Maringe, C.; Coleman, M.P.; Peake, M.D.; Butler, J.; Young, N.; Bergström, S.; Hanna, L.; Jakobsen, E.; Kölbeck, K.; et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: A population-based study 2004–2007. *Thorax***2013**, *68*, 551–564. <https://doi.org/10.1136/thoraxjnl-2012-202297>.
6. Zhang, J.; Fujimoto, J.; Zhang, J.; Wedge, D.C.; Song, X.; Zhang, J.; Seth, S.; Chow, C.W.; Cao, Y.; Gumbs, C.; et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* **2014**, *346*, 256–259. <https://doi.org/10.1126/science.1256930>.
7. Alberg, A.J.; Brock, M.V.; Ford, J.G.; Samet, J.M.; Spivack, S.D. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest***2013**, *143* (Suppl. S5), e1S–e29S. <https://doi.org/10.1378/chest.12-2345>.
8. Devesa, S.S.; Bray, F.; Vizcaino, A.P.; Parkin, D.M. International lung cancer trends by histologic type: Male: Female differences diminishing and adenocarcinoma rates rising. *Int. J. Cancer***2005**, *117*, 294–299. <https://doi.org/10.1002/ijc.21183>.
9. Hasin, D.S. US Epidemiology of Cannabis Use and Associated Problems. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2018**, *43*, 195–212. <https://doi.org/10.1038/npp.2017.198>.
10. Krewski, D.; Lubin, J.H.; Zielinski, J.M.; Alavanja, M.; Catalan, V.S.; Field, R.W.; Klotz, J.B.; Létourneau, E.G.; Lynch, C.F.; Lyon, J.L.; et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J. Toxicol. Environ. Health Part A***2006**, *69*, 533–597. <https://doi.org/10.1080/15287390500260945>.
11. Bade, B.C.; Dela Cruz, C.S. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clin. Chest Med.* **2020**, *41*, 1–24. <https://doi.org/10.1016/j.ccm.2019.10.001>.
12. Liu, P.; He, K.; Li, Y.; Wu, Q.; Yang, P.; Wang, D. Exposure to mercury causes formation of male-specific structural deficits by inducing oxidative damage in nematodes. *Ecotoxicol. Environ. Saf.* **2012**, *79*, 90–100. <https://doi.org/10.1016/j.ecoenv.2011.12.007>.
13. Brenner, D.R.; McLaughlin, J.R.; Hung, R.J. Previous lung diseases and lung cancer risk: A systematic review and meta-analysis. *PLoS ONE***2011**, *6*, e17479. <https://doi.org/10.1371/journal.pone.0017479>.
14. Caramori, G.; Adcock, I.M.; Casolari, P.; Ito, K.; Jazrawi, E.; Tsaprouni, L.; Villetti, G.; Civelli, M.; Carnini, C.; Chung, K.F.; et al. Unbalanced oxidant-induced DNA damage and repair in COPD: A link towards lung cancer. *Thorax***2011**, *66*, 521–527. <https://doi.org/10.1136/thx.2010.156448>.
15. Matakidou, A.; Eisen, T.; Houlston, R.S. Systematic review of the relationship between family history and lung cancer risk. *Br. J. Cancer* **2005**, *93*, 825–833. <https://doi.org/10.1038/sj.bjc.6602769>.
16. Caliri, A.W.; Tommasi, S.; Besaratinia, A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutat. Research. Rev. Mutat. Res.* **2021**, *787*, 108365. https://doi.org/10.1016/j.mrrev.2021.108365.
17. Yamaoka, K.; Kataoka, T. Confirmation of efficacy, elucidation of mechanism, and new search for indications of radon therapy. *J. Clin. Biochem. Nutr.* **2022**, *70*, 87–92. <https://doi.org/10.3164/jcbn.21-85>.
18. Valavanidis, A; Vlachogianni, T.; Fiotakis, Tobacco smoke: Involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int. J. Environ. Res. Public Health* **2009**, *6*, 445–462. https://doi.org/10.3390/ijerph6020445.
19. Coluzzi, E.; Leone, S.; Sgura, A. Oxidative Stress Induces Telomere Dysfunction and Senescence by Replication Fork Arrest. *Cells* **2019**, *8*, 19. <https://doi.org/10.3390/cells8010019>.
20. Liu, G.; Cheresh, P.; Kamp, D.W. Molecular basis of asbestos-induced lung disease. *Annu. Rev. Pathol.* **2013**, *8*, 161–187. <https://doi.org/10.1146/annurev-pathol-020712-163942>.
21. Gout, T. Role of ATP binding and hydrolysis in the gating of the cystic fibrosis transmembrane conductance regulator. Ann. Thorac. Med. **2012**, *7*, 115–121. <https://doi//10.4103/1817-1737.98842>.
22. Yang, H.; Rivera, Z.; Jube, S.; Nasu, M.; Bertino, P.; Goparaju, C.; Franzoso, G.; Lotze, M.T.; Krausz, T.; Pass, H.I.; et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 12611–12616. <https://doi.org/10.1073/pnas.1006542107>.
23. Klebe, S.; Leigh, J.; Henderson, D.W.; Nurminen, M. Asbestos, Smoking and Lung Cancer: An Update. *Int. J. Environ. Res. Public Health* **2019**, *17*, 258. <https://doi.org/10.3390/ijerph17010258>.
24. Kou, F.; Wu, L.; Ren, X.; Yang, L. Chromosome Abnormalities: New Insights into Their Clinical Significance in Cancer. *Mol. Ther. Oncolytics***2020**, *17*, 562–570. <https://doi.org/10.1016/j.omto.2020.05.010>.
25. Weir, B.A.; Woo, M.S.; Getz, G.; Perner, S.; Ding, L.; Beroukhim, R.; Lin, W.M.; Province, M.A.; Kraja, A.; Johnson, L.A.; et al. Characterizing the cancer genome in lung adenocarcinoma. *Nature* **2007**, *450*, 893–898.
26. Davies, H.; Bignell, G.R.; Cox, C.; Stephens, P.; Edkins, S.; Clegg, S.; Teague, J.; Woffendin, H.; Garnett, M.J.; Bottomley, W.; et al. Mutations of the BRAF gene in human cancer. *Nature***2002**, *417*, 949–954. <https://doi.org/10.1038/nature00766>.
27. Ni, X.; Zhuo, M.; Su, Z.; Duan, J.; Gao, Y.; Wang, Z.; Zong, C.; Bai, H.; Chapman, A.R.; Zhao, J.; et al. Reproducible copy number variation patterns among single circulating tumor cells of lung cancer patients. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 21083–21088. <https://doi.org/10.1073/pnas.1320659110>.
28. Cristofanilli, M.; Budd, G.T.; Ellis, M.J.; Stopeck, A.; Matera, J.; Miller, M.C.; Reuben, J.M.; Doyle, G.V.; Allard, W.J.; Terstappen, L.W.; et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N. Engl. J. Med.* **2004**, *351*, 781–791. <https://doi.org/10.1056/NEJMoa040766>.
29. Wang, C.; Yin, R.; Dai, J.; Gu, Y.; Cui, S.; Ma, H.; et al. Whole-genome sequencing reveals genomic signatures associated with the inflammatory microenvironments in Chinese NSCLC patients. *Nature communications*, **2018**,  *9*(1), 2054. <https://doi.org/10.1038/s41467-018-04492-2>.
30. Krebs, M.G.; Sloane, R.; Priest, L.; Lancashire, L.; Hou, J.M.; Greystoke, A.; Ward, T.H.; Ferraldeschi, R.; Hughes, A.; Clack, G.; et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2011**, *29*, 1556–1563. <https://doi.org/10.1200/JCO.2010.28.7045>.
31. Magbanua, M.J.; Sosa, E.V.; Scott, J.H.; Simko, J.; Collins, C.; Pinkel, D.; Ryan, C.J.; Park, J.W. Isolation and genomic analysis of circulating tumor cells from castration resistant metastatic prostate cancer. *BMC Cancer***2012**, *12*, 78. <https://doi.org/10.1186/1471-2407-12-78>.
32. Seto, M.; Honma, K.; Nakagawa, M. Diversity of genome profiles in malignant lymphoma. *Cancer Sci.* **2010**, *101*, 573–578. <https://doi.org/10.1111/j.1349-7006.2009.01452.x>.
33. Dalmay, T.; Edwards, D.R. MicroRNAs and the hallmarks of cancer. *Oncogene***2006**, *25*, 6170–6175. <https://doi.org/10.1038/sj.onc.1209911>.
34. Hassanpour, S.H.; Dehghani, M.A. Review of cancer from perspective of molecular. *J.* Cancer Res. Pract. **2017**, 4, 127–129. <https://doi.org/10.1016/j.jcrpr.2017.07.001>.
35. Lazebnik, Y. What are the hallmarks of cancer? *Nat. Rev. Cancer***2010**, *10*, 232–233. <https://doi.org/10.1038/nrc2827>.
36. Macé, A.; Kutalik, Z.; Valsesia, A. Copy Number Variation. *Methods Mol. Biol.* **2018**, *1793*, 231–258. <https://doi.org/10.1007/978-1-4939-7868-7_14>.
37. Landesman-Milo, D.; Ramishetti, S.; Peer, D. Nanomedicine as an emerging platform for metastatic lung cancer therapy. *Cancer Metastasis Rev.* **2015**, *34*, 291–301*.* https://doi.org/10.1007/s10555-015-9554-4.
38. Zappa, C.; Mousa, S.A. Non-small cell lung cancer: Current treatment and future advances. *Transl. Lung Cancer Res.* **2016**, *5*, 288–300. <https://doi.org/10.21037/tlcr.2016.06.07>.
39. Travis, W.D.; Brambilla, E.; Nicholson, A.G.; Yatabe, Y.; Austin, J.H.M.; Beasley, M.B.; Chirieac, L.R.; Dacic, S.; Duhig, E.; Flieder, D.B.; et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer***2015**, *10*, 1243–1260. <https://doi.org/10.1097/JTO.0000000000000630>.
40. Bychkov, A. WHO Classification. Available online: https://www.pathologyoutlines.com/topic/lungtumorWHO.html (accessed on 3 April 2023).
41. Kim, E.S. Chemotherapy Resistance in Lung Cancer. *Adv. Exp. Med. Biol.* **2016**, *893*, 189–209. <https://doi.org/10.1007/978-3-319-24223-1_10>.
42. Manser, R.; Wright, G.; Hart, D.; Byrnes, G.; Campbell, D.A. Surgery for early stage non-small cell lung cancer. *Cochrane Database Syst. Rev.* **2005,** 20*05*, CD004699. <https://doi.org/10.1002/14651858.CD004699.pub2>.
43. Neubert, R.H.H. Potentials of new nanocarriers for dermal and transdermal drug delivery*. Eur. J. Pharm. Biopharm.* **2011**, *77*, 1–2*.* https://doi.org/10.1016/j.ejpb.2010.11.003.
44. Schiller, J.H.; Harrington, D.; Belani, C.P.; Langer, C.; Sandler, A.; Krook, J.; Zhu, J.; Johnson, D.H.; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N. Engl. J. Med.* **2002**, *346*, 92–98. <https://doi.org/10.1056/NEJMoa011954>.
45. Sebastian, N.T.; Xu-Welliver, M.; Williams, T.M. Stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC): Contemporary insights and advances. *J. Thorac. Dis.* **2018**, *10* (Suppl. S21), S2451–S2464. <https://doi.org/10.21037/jtd.2018.04.52>.
46. Decuzzi, P.; Lee, S.; Bhushan, B.; Ferrari, M. A theoretical model for the margination of particles within blood vessels. *Ann. Biomed. Eng.* **2005**, *33*, 179–190. <https://doi.org/10.1007/s10439-005-8976-5>.
47. Tan, J.; Shah, S.; Thomas, A.; Ou-Yang, H.D.; Liu, Y. The influence of size, shape and vessel geometry on nanoparticle distribution. *Microfluid. Nanofluidics***2013**, *14*, 77–87. <https://doi.org/10.1007/s10404-012-1024-5>.
48. Singh, A.P.; Biswas, A.; Shukla, A.; Maiti, P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. *Sig. Transduct. Target. Ther.***2019**, *4*, 33. <https://doi.org/10.1038/s41392-019-0068-3>.
49. Steven, A.; Fisher, S.A.; Robinson, B.W. Immunotherapy for lung cancer. *Respirology* **2016**, *21*, 821–833. <https://doi.org/10.1111/resp.12789>.
50. Vaughan, H.J.; Green, J.J.; Tzeng, S.Y. Cancer-Targeting Nanoparticles for Combinatorial Nucleic Acid Delivery. *Adv. Mater.* **2020**, *32*, e1901081. https://doi.org/10.1002/adma.201901081.
51. Valavanidis, A; Vlachogianni, T; Fiotakis, K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int J Environ Res Public Health*. **2009**;6(2):445-462. doi:10.3390/ijerph6020445
52. U.S. Department of Health and Human Services. [The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014](http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
53. U.S. Department of Health and Human Services. [The Health Consequences of Smoking: A Report of the Surgeon General](http://www.ncbi.nlm.nih.gov/books/NBK44695/pdf/TOC.pdf). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
54. U.S. Department of Health and Human Services. [The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General](http://www.surgeongeneral.gov/library/reports/secondhandsmoke/fullreport.pdf). Rockville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
55. National Toxicology Program. [Tobacco-Related Exposures](https://ntp.niehs.nih.gov/ntp/roc/content/profiles/tobaccorelatedexposures.pdf). In: Report on Carcinogens. Fourteenth Edition. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2016
56. Eiserich, J; van der Vilet, A; Handelman, G; Halliwell, B; Cross, C. Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction. Am J Clin Nutr 1995. 62:1490S–1500S
57. Mazzone P, Tierney W, Hossain M, Puvenna V, Janigro D, Cucullo L. 2010. Pathophysiological impact of cigarette smoke exposure on the cerebrovascular system with a focus on the blood-brain barrier: expanding the awareness of smoking toxicity in an underappreciated area. Int J Environ Res Public Health. 7:4111–4126
58. Coluzzi E, Leone S, Sgura A. Oxidative Stress Induces Telomere Dysfunction and Senescence by Replication Fork Arrest. *Cells*. 2019;8(1):19. Published 2019 Jan 3. doi:10.3390/cells8010019
59. Lodish H, Berk A, Zipursky SL, et al. Molecular Cell Biology. 4th edition. New York: W. H. Freeman; 2000. Section 12.4, DNA Damage and Repair and Their Role in Carcinogenesis. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK21554/>
60. Furrukh M. Tobacco Smoking and Lung Cancer: Perception-changing facts. Sultan Qaboos Univ Med J. 2013;13(3):345-358. doi:10.12816/0003255
61. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst. 1999;91:1194–1210.
62. Loft S, Svoboda P, Kasai H, Tjønneland A, Møller P, Sørensen M, Overvad K, Autrup H, Raaschou-Nielsen O. Prospective study of urinary excretion of 7-methylguanine and the risk of lung cancer: Effect modification by mu class glutathione-S-transferases. Int J Cancer. 2007 Oct 1;121(7):1579-84. doi: 10.1002/ijc.22863. PMID: 17565746.
63. Zisman DA, Keane MP, Belperio JA, Strieter RM, Lynch JP 3rd. Pulmonary fibrosis. Methods Mol Med. 2005;117:3-44. doi:10.1385/1-59259-940-0:003
64. Saito, A., Hakamata, Y., Yamada, Y. et al. Pleural thickening on screening chest X-rays: a single institutional study. Respir Res **20,**138 (2019). https://doi.org/10.1186/s12931-019-1116-9
65. Liu G, Cheresh P, Kamp DW. Molecular basis of asbestos-induced lung disease. Annu Rev Pathol. 2013;8:161-187. doi:10.1146/annurev-pathol-020712-163942
66. Gout T. Role of ATP binding and hydrolysis in the gating of the cystic fibrosis transmembrane conductance regulator. Ann Thorac Med. 2012;7(3):115-121. doi:10.4103/1817-1737.98842
67. Yang H, Rivera Z, Jube S, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. Proc Natl Acad Sci U S A. 2010;107(28):12611-12616. doi:10.1073/pnas.1006542107
68. Klebe S, Leigh J, Henderson DW, Nurminen M. Asbestos, Smoking and Lung Cancer: An Update. Int J Environ Res Public Health. 2019;17(1):258. Published 2019 Dec 30. doi:10.3390/ijerph17010258
69. Nymark P, Lindholm PM, Korpela MV, et al. Gene expression profiles in asbestos-exposed epithelial and mesothelial lung cell lines. *BMC Genomics*. 2007;8:62. Published 2007 Mar 1. doi:10.1186/1471-2164-8-62
70. Garkavtsev I, Kley N, Grigorian I. *et al.* The Bloom syndrome protein interacts and cooperates with p53 in regulation of transcription and cell growth control. *Oncogene* **20,**8276–8280 (2001). <https://doi.org/10.1038/sj.onc.1205120>
71. Dolzan V and Franko A (July 20th 2019). Asbestos-Related Pleural Diseases: The Role of Gene-Environment Interactions, Diseases of Pleura, Jelena Stojšić, IntechOpen, DOI: 10.5772/intechopen.88193.
72. Bononi A, Goto K, Guntulu Ak, Yoshikawa Y, Mitsuru E, et all: Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma, PNAS December 2020, 117 (52) 33466-33473
73. Darby S, Hill D, Doll R. Radon: a likely carcinogen at all exposures. Annals of Oncology 2001; 12(10):1341–1351.
74. Lorenzo-González, M., Torres-Durán, M., Barbosa-Lorenzo, R., Provencio-Pulla, M., Barros-Dios, J. M., & Ruano-Ravina, A. (2019). Radon exposure: a major cause of lung cancer. Expert Review of Respiratory Medicine, 2019 Sep;13(9):839-850
75. Grzywa-Celi´nska A, Krusi´nski A, Mazur J, Szewczyk K, and Kozak K. Radon—The Element of Risk. The Impact of Radon Exposure on Human Health, Toxics **2020**, 8(4), 120
76. Alavanja M, Biologic damage resulting from exposure to tobacco smoke and from radon: implication for preventive interventions, Oncogene (2002) 21, 7365 – 7375.
77. Sethi TK, El-Ghamry MN, Kloecker GH. Radon and lung cancer. Clin Adv Hematol Oncol. 2012 Mar;10(3):157-64. PMID: 22402423.
78. Taylor JA, Watson MA, Devereux TR, Michels RY, Saccomanno G, Anderson M. p53 mutation hotspot in radon-associated lung cancer. Lancet. 1994;343:86-87.
79. Ruano-Ravina A, Faraldo-Valles MJ, Barros-Dios JM. Is there a specific mutation of p53 gene due to radon exposure? A systematic review. Int J Radiat Biol. 2009;85:614-621.
80. Ruano-Ravina A, Perez-Becerra R, Fraga M, Kelsey KT, Barros-Dios JM. Analysis of the relationship between p53 immunohistochemical expression and risk factors for lung cancer, with special emphasis on residential radon exposure. Ann Oncol. 2008;19:109-114.
81. Bastide K, Guilly MN, Bernaudin JF, et al. Molecular analysis of the Ink4a/ Rb1-Arf/Tp53 pathways in radon-induced rat lung tumors. Lung Cancer. 2009;63:348-353.
82. Xu NY, Zhang SP, Nie JH, Li JX, Tong J. Radon-induced proteomic profile of lung tissue in rats. J Toxicol Environ Health A. 2008;71:361-366.
83. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: a case-control study. Eur Respir J. 2008;31(2):280-286. doi:10.1183/09031936.00065707
84. UNODC. *World Drug Report.*2012
85. Tashkin D, Gliederer F, Rose J, et al. Tar, CO and THC delivery from the 1st and 2nd halves of a marijuana cigarette. Pharmacol Biochem Behav. 1991;40:657–61.
86. Wu T, Tashkin D, Djahed B, Rose J. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med. 1988;318:347–51.
87. Ateş A, Arikan M, Özgök A. An Unusual Cause of Carbon Monoxide Poisoning: Narghile Smoking. Am J Case Rep. 2016;17:660-662. Published 2016 Sep 13. doi:10.12659/ajcr.899590
88. Weawer LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med. 2009;360:1217–25
89. Kim HR, Jung MH, Lee SY, Oh SM, Chung KH. Marijuana smoke condensate induces p53-mediated apoptosis in human lung epithelial cells. J Toxicol Sci. 2013;38(3):337-47. doi: 10.2131/jts.38.337. PMID: 23665932.
90. Olcina M, Lecane PS, Hammond EM. Targeting hypoxic cells through the DNA damage response. Clin Cancer Res. 2010;16(23):5624-5629. doi:10.1158/1078-0432.CCR-10-0286
91. US Environmental Protection Agency Greenhouse Gas Emissions. [(accessed on 12 October 2017)]; Available online: <https://www3.epa.gov/climatechange/ghgemissions/>
92. Falcon-Rodriguez CI, Osornio-Vargas AR, Sada-Ovalle I, Segura-Medina P. Aeroparticles, composition, and lung diseases. Front Immunol. 2016;7:3. doi: 10.3389/fimmu.2016.00003.
93. Li R, Zhou R, Zhang J. Function of PM2.5 in the pathogenesis of lung cancer and chronic airway inflammatory diseases. Oncol Lett. 2018;15(5):7506-7514. doi:10.3892/ol.2018.8355
94. Jeong SC, Cho Y, Song MK, Lee E, Ryu JC. Epidermal growth factor receptor (EGFR)-MAPK-nuclear factor(NF)-κB-IL8: A possible mechanism of particulate matter(PM) 2.5-induced lung toxicity. Environ Toxicol. 2017;32:1628–1636. doi: 10.1002/tox.22390.
95. Pope CA, III, Bhatnagar A, Mccracken JP, Abplanalp W, Conklin DJ, O'Toole T. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res. 2016;119:1204. doi:10.1161/CIRCRESAHA.116.309279.
96. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, Hoffmann B, Fischer P, Nieuwenhuijsen MJ, Brunekreef B, et al. Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE) Lancet Oncol. 2013;14:813–822. doi: 10.1016/S1470-2045(13)70279-1.
97. Wei S, Zhang H, Tao S. A review of arsenic exposure and lung cancer. Toxicol Res (Camb). 2019;8(3):319-327. Published 2019 Jan 23. doi:10.1039/c8tx00298c
98. Rothkamm K., Barnard S., Moquet J., Ellender M., Rana Z., Burdak-Rothkamm S. Environ. Mol. Mutagen. 2015;56:491–504.
99. Aardema M. J. Environ. Mol. Mutagen. 2013;54:617–620.
100. Sage A. P., Minatel B. C., Ng K. W., Stewart G. L., Dummer T. J. B., Lam W.W. L.L., Martinez V. D. Oncotarget. 2017;8:25736–25755.
101. Henikoff S., Smith M. M. Cold Spring Harbor Perspect. Biol. 2015;7:a019364.
102. Lichtenstein P, Holm NV, Verksalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer-analyses of cohort of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343:78–85. doi: 10.1056/NEJM200007133430201.
103. Kanwal M, Ding XJ, Cao Y. Familial risk for lung cancer. Oncol Lett. 2017;13(2):535-542. doi:10.3892/ol.2016.5518
104. Ahlbom A, Lichtenstein P, Malmström H, Feychting M, Hemminki K, Pedersen NL. Cancer in twins: Genetic and non-genetic familial risk factor. J Nat Canc Isnt. 1997;89:287–293. doi: 10.1093/jnci/89.4.287.
105. Siddiqui F, Siddiqui AH. Lung Cancer. [Updated 2020 Nov 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482357/>
106. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med*. 2012;18:382-4
107. Birchmeier C, Sharma S, Wigler M. Expression and rearrangement of the ROS1 gene in human glioblastoma cells. *Proc Natl Acad Sci U S A*. 1987;84:9270-4
108. Kuwako, K., & Okano, H. (2018). Versatile Roles of LKB1 Kinase Signaling in Neural Development and Homeostasis. Frontiers in Molecular Neuroscience, 11.354
109. Chitsazzadeh V, Coarfa C, Drummond JA, et al. Cross-species identification of genomic drivers of squamous cell carcinoma development across preneoplastic intermediates. Nat Commun. 2016;7:12601. Published 2016 Aug 30. doi:10.1038/ncomms12601
110. Li YY, Hanna GJ, Laga AC, Haddad RI, Lorch JH, Hammerman PS. Genomic analysis of metastatic cutaneous squamous cell carcinoma. Clin Cancer Res. 2015;21(6):1447-1456. doi:10.1158/1078-0432.CCR-14-1773
111. Sarin, K.Y., Lin, Y., Daneshjou, R. *et al.* Genome-wide meta-analysis identifies eight new susceptibility loci for cutaneous squamous cell carcinoma. *Nat Commun* **11,**820 (2020). <https://doi.org/10.1038/s41467-020-14594-5>
112. Karlsson A, Brunnström H, Lindquist KE, et al. Mutational and gene fusion analyses of primary large cell and large cell neuroendocrine lung cancer. *Oncotarget*. 2015;6(26):22028-22037. doi:10.18632/oncotarget.4314
113. Kim, KB., Dunn, C.T. & Park, KS. Recent progress in mapping the emerging landscape of the small-cell lung cancer genome. *Exp Mol Med* **51,**1–13 (2019). <https://doi.org/10.1038/s12276-019-0349-5>
114. Gaur P, Bhattacharya S, Kant S, Kushwaha RAS, Singh G, Pandey S. *EGFR* Mutation Detection and Its Association With Clinicopathological Characters of Lung Cancer Patients. *World J Oncol*. 2018;9(5-6):151-155
115. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C, Tang JL. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016 Nov 29;7(48):78985-78993. doi: 10.18632/oncotarget.12587. PMID: 27738317; PMCID: PMC5346692.
116. Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. *J Thorac Dis*. 2010;2(1):48-51.
117. National Center for Biotechnology Information (2021). PubChem Gene Summary for NCBI Gene 1956, EGFR - epidermal growth factor receptor (human). Retrieved July 29, 2021 from <https://pubchem.ncbi.nlm.nih.gov/gene/EGFR/human>.
118. de Mello RA, Neves NM, Tadokoro H, Amaral GA, Castelo-Branco P, Zia VAA. New Target Therapies in Advanced Non-Small Cell Lung Cancer: A Review of the Literature and Future Perspectives. *J Clin Med*. 2020;9(11):3543. Published 2020 Nov 3. doi:10.3390/jcm9113543
119. Gupta, R., Dastane, A., Forozan, F. *et al.* Evaluation of EGFR abnormalities in patients with pulmonary adenocarcinoma: the need to test neoplasms with more than one method. *Mod Pathol* **22,**128–133 (2009). <https://doi.org/10.1038/modpathol.2008.182>
120. Hong W, Wu Q, Zhang J, Zhou Y. Prognostic value of EGFR 19-del and 21-L858R mutations in patients with non-small cell lung cancer. Oncol Lett. 2019;18(4):3887-3895. doi:10.3892/ol.2019.10715
121. Douillard JY, Ostoros G, Cobo M et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, singlearm study. Br J Cancer 2014; 110(1): 55–62.
122. Rosell R, Moran T, Queralt C et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009; 361(10): 958–967.
123. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361(10): 947–957
124. Assoun S., Brosseau S., Steinmetz C., Gounant V., Zalcman G. Bevacizumab in advanced lung cancer: State of the art. *Future Oncol.*2017;13:2515–2535. doi: 10.2217/fon-2017-0302.
125. Garon, E.B.; Ciuleanu, T.-E.; Arrieta, O.; Prabhash, K.; Syrigos, K.N.; Goksel, T.; Park, K.; Gorbunova, V.; Kowalyszyn, R.D.; Pikiel, J.; et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. Lancet 2014, 384, 665–673.
126. Socinski, M.A.; Bondarenko, I.; Karaseva, N.A.; Makhson, A.M.; Vynnychenko, I.; Okamoto, I.; Hon, J.K.; Hirsh, V.; Bhar, P.; Zhang, H.; et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial. J. Clin. Oncol. 2012, 30, 2055–2062.
127. Nan X, Xie C, Yu X, Liu J. EGFR TKI as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer. *Oncotarget*. 2017;8(43):75712-75726. Published 2017 Aug 9. doi:10.18632/oncotarget.20095
128. Paez J.G., Jänne P.A., Lee J.C., Tracy S., Greulich H., Gabriel S., Herman P., Kaye F.J., Lindeman N., Boggon T.J., et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science.*2004;304:1497–1500. doi: 10.1126/science.1099314.
129. Wang, S., Cang, S. & Liu, D. Third-generation inhibitors targeting *EGFR* T790M mutation in advanced non-small cell lung cancer. *J Hematol Oncol* **9,**34 (2016). <https://doi.org/10.1186/s13045-016-0268-z>
130. Lin L., Bivona T.G. Mechanisms of Resistance to Epidermal Growth Factor Receptor Inhibitors and Novel Therapeutic Strategies to Overcome Resistance in NSCLC Patients. *Chemother. Res. Pract.*2012;2012:817297. doi: 10.1155/2012/817297. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437267/)] [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/22970367)] [[CrossRef](https://dx.doi.org/10.1155/2012/817297)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Chemother.+Res.+Pract.&title=Mechanisms+of+Resistance+to+Epidermal+Growth+Factor+Receptor+Inhibitors+and+Novel+Therapeutic+Strategies+to+Overcome+Resistance+in+NSCLC+Patients&author=L.+Lin&author=T.G.+Bivona&volume=2012&publication_year=2012&pages=817297&pmid=22970367&doi=10.1155/2012/817297&)]
131. Caldemeyer, L., Dugan, M., Edwards, J. *et al.* Long-Term Side Effects of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. *Curr Hematol Malig Rep* **11,**71–79 (2016). <https://doi.org/10.1007/s11899-016-0309-2>
132. Bronte G, Silvestris N, Castiglia M, et al. New findings on primary and acquired resistance to anti-EGFR therapy in metastatic colorectal cancer: do all roads lead to RAS?. *Oncotarget*. 2015;6(28):24780-24796. doi:10.18632/oncotarget.4959
133. Engelman, J. A. et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **316**, 1039–1043 (2007).
134. Sergina, N. V. et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature* **445**, 437–441 (2007).
135. Shen, H. et al. Alteration in Mir-21/PTEN expression modulates gefitinib resistance in non-small cell lung cancer. *PloS ONE* **9**, e103305 (2014).
136. Ono, N. et al. Enhanced antitumor activity of erlotinib in combination with the Hsp90 inhibitor CH5164840 against non-small-cell lung cancer. *Cancer Sci.* **104**, 1346–1352 (2013).
137. Karyagina TS, Ulasov AV, Slastnikova TA, Rosenkranz AA, Lupanova TN, Khramtsov YV, Georgiev GP and Sobolev AS (2020) Targeted Delivery of 111In Into the Nuclei of EGFR Overexpressing Cells *via* Modular Nanotransporters With Anti-EGFR Affibody. *Front. Pharmacol.* 11:176. doi: 10.3389/fphar.2020.00176
138. Scott, A. M., Wolchok, J. D., & Old, L. J. (2012). *Antibody therapy of cancer. Nature Reviews Cancer, 12(4), 278–287.* doi:10.1038/nrc3236
139. Gazdar, A. F. (2009). Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene* 28 Suppl 1, S24–S31. doi: 10.1038/onc.2009.198
140. Cryer, A. M., Chan, C., Eftychidou, A., Maksoudian, C., Mahesh, M., Tetley, T. D., Spivey, A. C., & Thorley, A. J. (2019). Tyrosine Kinase Inhibitor Gold Nanoconjugates for the Treatment of Non-Small Cell Lung Cancer. *ACS applied materials & interfaces*, *11*(18), 16336–16346. <https://doi.org/10.1021/acsami.9b02986>
141. Lu, X., Liu, S., Han, M., Yang, X., Sun, K., Wang, H., Mu, H., Du, Y., Wang, A., Ni, L., & Zhang, C. (2019). Afatinib-loaded immunoliposomes functionalized with cetuximab: A novel strategy targeting the epidermal growth factor receptor for treatment of non-small-cell lung cancer. *International journal of pharmaceutics*, *560*, 126–135. https://doi.org/10.1016/j.ijpharm.2019.02.001
142. Song, Z., Lin, Y., Zhang, X., Feng, C., Lu, Y., Gao, Y., & Dong, C. (2017). Cyclic RGD peptide-modified liposomal drug delivery system for targeted oral apatinib administration: enhanced cellular uptake and improved therapeutic effects. *International journal of nanomedicine*, *12*, 1941–1958. <https://doi.org/10.2147/IJN.S125573>
143. Coelho, S. C., Almeida, G. M., Pereira, M. C., Santos-Silva, F., & Coelho, M. A. (2016). Functionalized gold nanoparticles improve afatinib delivery into cancer cells. *Expert opinion on drug delivery*, *13*(1), 133–141. <https://doi.org/10.1517/17425247.2015.1083973>
144. Kulkarni, N. S., Parvathaneni, V., Shukla, S. K., Barasa, L., Perron, J. C., Yoganathan, S., Muth, A., & Gupta, V. (2019). Tyrosine kinase inhibitor conjugated quantum dots for non-small cell lung cancer (NSCLC) treatment. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, *133*, 145–159. <https://doi.org/10.1016/j.ejps.2019.03.026>
145. Kim, D. H., Choi, Y. J., Sung, K. J., Yoo, S. A., Sung, Y. H., Kim, J. K., Choi, C. M., Yun, M., Lee, E. Y., Jin, Y. S., Cook, S., Rho, J. K., & Lee, J. C. (2018). Efficacy of nano-particulated, water-soluble erlotinib against intracranial metastases of EGFR-mutant lung cancer. *Molecular oncology*, *12*(12), 2182–2190. <https://doi.org/10.1002/1878-0261.12394>
146. Hsu, F. T., Liu, H. S., Ali, A. A. A., Tsai, P. H., Kao, Y. C., Lu, C. F., Huang, H. S., & Chen, C. Y. (2018). Assessing the selective therapeutic efficacy of superparamagnetic erlotinib nanoparticles in lung cancer by using quantitative magnetic resonance imaging and a nuclear factor kappa-B reporter gene system. *Nanomedicine : nanotechnology, biology, and medicine*, *14*(3), 1019–1031. <https://doi.org/10.1016/j.nano.2018.01.010>
147. Bakhtiary, Z., Barar, J., Aghanejad, A., Saei, A. A., Nemati, E., Ezzati Nazhad Dolatabadi, J., & Omidi, Y. (2017). Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer. *Drug development and industrial pharmacy*, *43*(8), 1244–1253. <https://doi.org/10.1080/03639045.2017.1310223>
148. Dora, C. P., Trotta, F., Kushwah, V., Devasari, N., Singh, C., Suresh, S., & Jain, S. (2016). Potential of erlotinib cyclodextrin nanosponge complex to enhance solubility, dissolution rate, in vitro cytotoxicity and oral bioavailability. *Carbohydrate polymers*, *137*, 339–349. <https://doi.org/10.1016/j.carbpol.2015.10.080>
149. Lv, T., Li, Z., Xu, L., Zhang, Y., Chen, H., & Gao, Y. (2018). Chloroquine in combination with aptamer-modified nanocomplexes for tumor vessel normalization and efficient erlotinib/Survivin shRNA co-delivery to overcome drug resistance in EGFR-mutated non-small cell lung cancer. *Acta biomaterialia*, *76*, 257–274. <https://doi.org/10.1016/j.actbio.2018.06.034>
150. Von Hoff D.D., Mita M.M., Ramanathan R.K., Weiss G.J., Mita A.C., Lorusso P.M., Burris H.A., 3rd, Hart L.L., Low S.C., Parsons D.M., et al. Phase I Study of PSMA-Targeted Docetaxel-Containing Nanoparticle BIND-014 in Patients with Advanced Solid Tumors. *Clin. Cancer Res.*2016;22:3157–3163. doi: 10.1158/1078-0432.CCR-15-2548. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/26847057)] [[CrossRef](https://doi.org/10.1158/1078-0432.CCR-15-2548)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Clin.+Cancer+Res.&title=Phase+I+Study+of+PSMA-Targeted+Docetaxel-Containing+Nanoparticle+BIND-014+in+Patients+with+Advanced+Solid+Tumors&author=D.D.+Von+Hoff&author=M.M.+Mita&author=R.K.+Ramanathan&author=G.J.+Weiss&author=A.C.+Mita&volume=22&publication_year=2016&pages=3157-3163&pmid=26847057&doi=10.1158/1078-0432.CCR-15-2548&)]
151. M. Malumbres, M. Barbacid, RAS oncogenes: the first 30 years, Nat. Rev. Cancer 3 (2003) 459–465.
152. A.E. Karnoub, R.A. Weinberg, Ras oncogenes: split personalities, Nat. Rev. Mol. Cell Biol. 9 (2008) 517–531.
153. Ferrer I, Zugazagoitia J, Herbertz S, John W, Paz-Ares L, Schmid-Bindert G. KRAS-Mutant non-small cell lung cancer: From biology to therapy. Lung Cancer. 2018;124:53-64. doi:10.1016/j.lungcan.2018.07.013
154. Downward J. Targeting RAS signalling pathways in cancer therapy. *Nat Rev Cancer.*2003;3(1):11–22. [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/12509763)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Nat+Rev+Cancer&title=Targeting+RAS+signalling+pathways+in+cancer+therapy&author=J.+Downward&volume=3&issue=1&publication_year=2003&pages=11-22&pmid=12509763&)]
155. K. Scheffzek, M.R. Ahmadian, W. Kabsch, et al., The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants, Science 277 (1997) 333–338
156. Sedighi A, Li PC. Kras gene codon 12 mutation detection enabled by gold nanoparticles conducted in a nanobioarray chip. *Anal Biochem*. 2014;448:58-64. doi:10.1016/j.ab.2013.11.
157. Kwak MS, Cha JM, Yoon JY, et al. Prognostic value of KRAS codon 13 gene mutation for overall survival in colorectal cancer: Direct and indirect comparison meta-analysis. *Medicine (Baltimore)*. 2017;96(35):e7882. doi:10.1097/MD.0000000000007882
158. Skoulidis F., Byers L.A., Diao L., Papadimitrakopoulou V.A., Tong P., Izzo J. Co-occurring genomic alterations define major subsets of KRAS- mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov.*2015;5(8):860–877.
159. Adderley H, Blackhall FH, Lindsay CR. KRAS-mutant non-small cell lung cancer: Converging small molecules and immune checkpoint inhibition. *EBioMedicine*. 2019;41:711-716. doi:10.1016/j.ebiom.2019.02.049
160. Ghimessy A, Radeczky P, Laszlo V, et al. Current therapy of KRAS-mutant lung cancer. *Cancer Metastasis Rev*. 2020;39(4):1159-1177. doi:10.1007/s10555-020-09903-9
161. Liu C, Zheng S, Jin R, Wang X, Wang F, Zang R, et al. The Superior Efficacy of anti-PD-1/PD-L1 Immunotherapy in KRAS-mutant non-Small Cell Lung Cancer That Correlates With an Inflammatory Phenotype and Increased Immunogenicity. Cancer Lett (2020) 470:95–105. doi: 10.1016/j.canlet.2019.10.027
162. Mingying, X. Xiaoling, X, Yun, F. KRAS-Mutant Non-Small Cell Lung Cancer: An Emerging Promisingly Treatable Subgroup, Frontiers in Oncology, 11, 2021 https://doi.org/10.3389/fonc.2021.672612.
163. Ferrer I, Zugazagoitia J, Herbertz S, John W, Paz-Ares L, Schmid-Bindert G. KRAS-Mutant non-small cell lung cancer: From biology to therapy. Lung Cancer. 2018;124:53-64. doi:10.1016/j.lungcan.2018.07.013
164. Naidoo, J., & Drilon, A. (2015). KRAS-Mutant Lung Cancers in the Era of Targeted Therapy. Advances in Experimental Medicine and Biology, 155–178.
165. Schiller JH, Adak S, Feins RH, Keller SM, Fry WA, Livingston RB, Hammond MEM, Wolf B, Sabatini L, Jett J, Kohman L, Johnson DH. Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: a laboratory ancillary study on an Eastern Cooperative Oncology Group prospective randomized trial of postoperative adjuvant therapy. *Journal of Clinical Oncology.*2001;19(2):448–457. doi: 10.1200/jco.2001.19.2.448
166. Janes MR, Zhang J, Li LS, Hansen R, Peters U, Guo X, et al. Targeting KRAS Mutant Cancers With a Covalent G12c-Specific Inhibitor. *Cell* (2018) 172(3):578–89.e17. doi: 10.1016/j.cell.2018.01.006
167. Lito P, Solomon M, Li LS, Hansen R, Rosen N. Allele-Specific Inhibitors Inactivate Mutant KRAS G12C by a Trapping Mechanism. *Science* (2016) 351(6273):604–8. doi: 10.1126/science.aad6204
168. Li B, Skoulidis F, Falchook G, Sacher A, Velcheti V, Dy G, et al. CodeBreaK 100: Registrational Phase 2 Trail of Sotorasib in KRAS P.G12C Mutated non-Small Cell Lung Cancer. Abstract No. Ps01.07. In: 2020 World Conference on Lung Cancer Singapore, Worldwide Virtual Event (2021).
169. Turke AB, Song Y, Costa C, et al. MEK inhibition leads to PI3K/AKT activation by relieving a negative feedback on ERBB receptors. *Cancer Res*. 2012;72(13):3228-3237. doi:10.1158/0008-5472.CAN-11-3747
170. Takezawa K, Okamoto I, Yonesaka K, Hatashita E, Yamada Y, Fukuoka M, Nakagawa K (2009) Sorafenib inhibits non-small cell lung cancer cell growth by targeting B-RAF in KRAS wild-type cells and C-RAF in KRAS mutant cells. Cancer Res 69(16):6515–6521. doi:10.1158/0008-5472.CAN-09-1076 50. Dingemans AM, Mellema WW, Groen H
171. Davies BR, Logie A, McKay JS, Martin P, Steele S, Jenkins R, Cockerill M, Cartlidge S, Smith PD (2007) AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/ extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. Mol Cancer Ther 6(8):2209–2219. doi:10.1158/1535-7163.mct-07-0231
172. Yang L, Zhou Y, Li Y, et al. Mutations of p53 and KRAS activate NF-κB to promote chemoresistance and tumorigenesis via dysregulation of cell cycle and suppression of apoptosis in lung cancer cells. *Cancer Lett*. 2015;357(2):520-526. doi:10.1016/j.canlet.2014.12.003
173. Wang, Q., Yang, S., Wang, K. *et al.* MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. *J Hematol Oncol* **12,**63 (2019). <https://doi.org/10.1186/s13045-019-0759-9>
174. Konstantinidou G, Ramadori G, Torti F, et al. RHOA-FAK is a required signaling axis for the maintenance of KRAS-driven lung adenocarcinomas. *Cancer Discov*. 2013;3(4):444-457. doi:10.1158/2159-8290.CD-12-0388
175. Sato H, Yamamoto H, Sakaguchi M, et al. Combined inhibition of MEK and PI3K pathways overcomes acquired resistance to EGFR-TKIs in non-small cell lung cancer. *Cancer Sci*. 2018;109(10):3183-3196. doi:10.1111/cas.13763
176. O'Sullivan, É., Keogh, A., Henderson, B., Finn, S. P., Gray, S. G., & Gately, K. (2023). Treatment Strategies for KRAS-Mutated Non-Small-Cell Lung Cancer. *Cancers*, *15*(6), 1635. <https://doi.org/10.3390/cancers15061635>
177. Huang, L., Guo, Z., Wang, F. *et al.* KRAS mutation: from undruggable to druggable in cancer. *Sig Transduct Target Ther* **6**, 386 (2021). <https://doi.org/10.1038/s41392-021-00780-4>
178. Bäumer, N., Tiemann, J., Scheller, A. *et al.* Targeted siRNA nanocarrier: a platform technology for cancer treatment. *Oncogene* **41**, 2210–2224 (2022). <https://doi.org/10.1038/s41388-022-02241-w>
179. Skupin-Mrugalska, P., & Minko, T. (2020). Development of Liposomal Vesicles for Osimertinib Delivery to EGFR Mutation-Positive Lung Cancer Cells. *Pharmaceutics*, *12*(10), 939. <https://doi.org/10.3390/pharmaceutics12100939>
180. Li, Y. X., & Pang, H. B. (2021). Macropinocytosis as a cell entry route for peptide-functionalized and bystander nanoparticles. *Journal of controlled release : official journal of the Controlled Release Society*, *329*, 1222–1230. https://doi.org/10.1016/j.jconrel.2020.10.049
181. Wang, F., Zhang, Z. RETRACTED ARTICLE: Nanoformulation of Apolipoprotein E3-Tagged Liposomal Nanoparticles for the co-Delivery of KRAS-siRNA and Gemcitabine for Pancreatic Cancer Treatment. *Pharm Res* **37**, 247 (2020). <https://doi.org/10.1007/s11095-020-02949-y>
182. Kong, C; Li, Y; Liu, Z; Ye, Junxiao; W, Zhaohui; Z, Ling; Kong, W; Liu, H; Liu, C; Pang, H; Hu, Z; Gao, J; Qian, F (2019). *Targeting the Oncogene KRAS Mutant Pancreatic Cancer by Synergistic Blocking of Lysosomal Acidification and Rapid Drug Release. ACS Nano, (), acsnano.8b08246–.*https://doi.org/10.1021/acsnano.8b08246
183. Kulkarni, N. S., Parvathaneni, V., Shukla, S. K., Barasa, L., Perron, J. C., Yoganathan, S., Muth, A., & Gupta, V. (2019). Tyrosine kinase inhibitor conjugated quantum dots for non-small cell lung cancer (NSCLC) treatment. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, *133*, 145–159. <https://doi.org/10.1016/j.ejps.2019.03.026>
184. Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, et al. (January 1998). "Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase". Nature Genetics. **18** (1): 38–43
185. Shackelford DB, Shaw RJ. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. Nat Rev Cancer. 2009;9:563–575. doi:10.1038/nrc2676
186. Veleva-Rotse, B.O., Smart, J.L., Baas, A.F. et al. STRAD pseudokinases regulate axogenesis and LKB1 stability. Neural Dev **9,**5 (2014).
187. Marcus AI, Zhou W. LKB1 regulated pathways in lung cancer invasion and metastasis. J Thorac Oncol. 2010;5(12):1883-1886.
188. Nakada D, Saunders TL, Morrison SJ. Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. Nature. 2010;468(7324):653-658.
189. Sun Z, Jiang Q, Li J, Guo J. The potent roles of salt-inducible kinases (SIKs) in metabolic homeostasis and tumorigenesis. Signal Transduct Target Ther. 2020 Aug 12;5(1):150. doi: 10.1038/s41392-020-00265-w. PMID: 32788639; PMCID: PMC7423983.
190. Shire NJ, Klein AB, Golozar A, Collins JM, Fraeman KH, et al. (2020) *STK11* (*LKB1*) mutations in metastatic NSCLC: Prognostic value in the real world. PLOS ONE 15(9): e0238358
191. Vernieri, C., Ganzinelli, M., Rulli, E., Farina, G., Bettini, A. C., Bareggi, C., Rosso, L., Signorelli, D., Galli, G., Lo Russo, G., Proto, C., Moro, M., Indraccolo, S., Busico, A., Sozzi, G., Torri, V., Marabese, M., Massimo, B., & Garassino, M. C. (2020). *LKB1* mutations are not associated with the efficacy of first-line and second-line chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC): a post hoc analysis of the TAILOR trial. *ESMO open*, *5*(3), e000748. <https://doi.org/10.1136/esmoopen-2020-000748>
192. Sitthideatphaiboon, P., Galan-Cobo, A., Negrao, M. V., Qu, X., Poteete, A., Zhang, F., Liu, D. D., Lewis, W. E., Kemp, H. N., Lewis, J., Rinsurongkawong, W., Giri, U., Lee, J. J., Zhang, J., Roth, J. A., Swisher, S., & Heymach, J. V. (2021). *STK11*/LKB1 Mutations in NSCLC Are Associated with KEAP1/NRF2-Dependent Radiotherapy Resistance Targetable by Glutaminase Inhibition. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *27*(6), 1720–1733. <https://doi.org/10.1158/1078-0432.CCR-20-2859>
193. Sumbly, V., & Landry, I. (2022). Unraveling the Role of STK11/LKB1 in Non-small Cell Lung Cancer. *Cureus*, *14*(1), e21078. <https://doi.org/10.7759/cureus.21078>
194. Pópulo H, Lopes JM, Soares P. The mTOR signalling pathway in human cancer. Int J Mol Sci. 2012;13(2):1886-1918. doi:10.3390/ijms13021886
195. Zhou W, Marcus AI, Vertino PM. Dysregulation of mTOR activity through LKB1 inactivation. Chin J Cancer. 2013;32(8):427-433. doi:10.5732/cjc.013.10086
196. Mehvish Showkat, Mushtaq A. Beigh, Khurshid I. Andrabi, "mTOR Signaling in Protein Translation Regulation: Implications in Cancer Genesis and Therapeutic Interventions", Molecular Biology International, vol. 2014, Article ID 686984, 14 pages, 2014. https://doi.org/10.1155/2014/686984
197. Zhang Y, Meng Q, Sun Q, Xu Z-X, Zhou H, Wang Y, LKB1 deficiency-induced metabolic reprogramming in tumorigenesis and non-neoplastic diseases, Molecular Metabolism, https:// doi.org/10.1016/j.molmet.2020.101131.
198. Ciccarese F, Zulato E, Indraccolo S. LKB1/AMPK Pathway and Drug Response in Cancer: A Therapeutic Perspective. *Oxid Med Cell Longev*. 2019;2019:8730816. Published 2019 Oct 31. doi:10.1155/2019/8730816
199. Mo H, Jeter R, Bachmann A, Yount ST, Shen CL, Yeganehjoo H. The Potential of Isoprenoids in Adjuvant Cancer Therapy to Reduce Adverse Effects of Statins. *Front Pharmacol*. 2019;9:1515. Published 2019 Jan 4. doi:10.3389/fphar.2018.01515
200. Amin F, Fathi F, Reiner Ž, Banach M, Sahebkar A. The role of statins in lung cancer. Archives of Medical Science. 2021;17(6). doi:10.5114/aoms/123225.
201. Holstein, S. A. (2011). *The Isoprenoid Biosynthetic Pathway and Statins. The Enzymes, 279–299.* doi:10.1016/b978-0-12-415922-8.00012-4
202. Flavin R, Peluso S, Nguyen PL, Loda M. Fatty acid synthase as a potential therapeutic target in cancer. Future Oncol. 2010;6(4):551-562. doi:10.2217/fon.10.11
203. Lupu, R., & Menendez, J. (2006). Pharmacological Inhibitors of Fatty Acid Synthase (FASN)-Catalyzed Endogenous Fatty Acid Biogenesis: A New Family of Anti-Cancer Agents? Current Pharmaceutical Biotechnology, 7(6), 483–494. doi:10.2174/138920106779116928
204. Sadowski, M. C., Pouwer, R. H., Gunter, J. H., Lubik, A. A., Quinn, R. J., & Nelson, C. C. (2014). The fatty acid synthase inhibitor triclosan: repurposing an anti-microbial agent for targeting prostate cancer. Oncotarget, 5(19). doi:10.18632/oncotarget.2433
205. Ross, F. A., MacKintosh, C., & Hardie, D. G. (2016). AMP-activated protein kinase: a cellular energy sensor that comes in 12 flavours. The FEBS Journal, 283(16), 2987–3001. doi:10.1111/febs.13698
206. Zhang Y, Meng Q, Sun Q, Xu Z-X, Zhou H, Wang Y, LKB1 deficiency-induced metabolic reprogramming in tumorigenesis and non-neoplastic diseases, Molecular Metabolism, https:// doi.org/10.1016/j.molmet.2020.101131
207. Ro S-H, Fay J, Cyuzuzo CI, Jang Y, Lee N, Song H-S and Harris EN (2020) SESTRINs: Emerging Dynamic Stress-Sensors in Metabolic and Environmental Health. Front. Cell Dev. Biol. 8:603421. doi: 10.3389/fcell.2020.603421
208. Tiainen M, Vaahtomeri K, Ylikorkala A, Mäkelä TP. Growth arrest by the LKB1 tumor suppressor: induction of p21(WAF1/CIP1). *Hum Mol Genet*. 2002;11(13):1497-1504. doi:10.1093/hmg/11.13.1497
209. Karuman P, Gozani O, Odze RD, et al. The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. *Mol Cell*. 2001;7(6):1307-1319. doi:10.1016/s1097-2765(01)00258-1
210. Feng Z, Hu W, de Stanchina E, et al. The regulation of AMPK beta1, TSC2, and PTEN expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res. 2007;67(7):3043-3053. doi:10.1158/0008-5472.CAN-06-4149
211. Lützner N, Kalbacher H, Krones-Herzig A, Rösl F (2012) FOXO3 Is a Glucocorticoid Receptor Target and Regulates LKB1 and Its Own Expression Based on Cellular AMP Levels via a Positive Autoregulatory Loop. PLoS ONE 7(7): e42166. <https://doi.org/10.1371/journal.pone.0042166>
212. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res*. 2011;21(3):381-395. doi:10.1038/cr.2011.22
213. Clocchiatti, A., Florean, C., & Brancolini, C. (2011). *Class IIa HDACs: from important roles in differentiation to possible implications in tumourigenesis. Journal of Cellular and Molecular Medicine, 15(9), 1833–1846.* doi:10.1111/j.1582-4934.2011.01321.x
214. Walkinshaw DR, Weist R, Kim GW, et al. The tumor suppressor kinase LKB1 activates the downstream kinases SIK2 and SIK3 to stimulate nuclear export of class IIa histone deacetylases. *J Biol Chem*. 2013;288(13):9345-9362. doi:10.1074/jbc.M113.456996
215. El-Tanani M, Dakir el-H, Raynor B, Morgan R. Mechanisms of Nuclear Export in Cancer and Resistance to Chemotherapy. *Cancers (Basel)*. 2016;8(3):35. Published 2016 Mar 14. doi:10.3390/cancers8030035
216. Zhu, Hx., Shi, L., Zhang, Y. *et al.* Myocyte enhancer factor 2D provides a cross-talk between chronic inflammation and lung cancer. *J Transl Med* **15,**65 (2017). https://doi.org/10.1186/s12967-017-1168-x
217. Zheng H, Zhao W, Yan C, et al. HDAC Inhibitors Enhance T-Cell Chemokine Expression and Augment Response to PD-1 Immunotherapy in Lung Adenocarcinoma. *Clin Cancer Res*. 2016;22(16):4119-4132. doi:10.1158/1078-0432.CCR-15-2584
218. Sun, Z., Jiang, Q., Li, J. *et al.* The potent roles of salt-inducible kinases (SIKs) in metabolic homeostasis and tumorigenesis. *Sig Transduct Target Ther* **5,**150 (2020). <https://doi.org/10.1038/s41392-020-00265-w>
219. Rodón, L., Svensson, R. U., Wiater, E., Chun, M. G. H., Tsai, W.-W., Eichner, L. J., … Montminy, M. (2019). *The CREB coactivator CRTC2 promotes oncogenesis in LKB1-mutant non–small cell lung cancer. Science Advances, 5(7), eaaw6455.* doi:10.1126/sciadv.aaw6455
220. Zhou X, W. Li J, Chen Z, Ni W, Li X, Yang R, Shen H, Liu J, DeMayo FJ, Lu J, Kaye FJ, Wu L. Dependency of LKB1-inactivated lung cancer on aberrant CRTC-CREB activation eLife 2021;10:e66095 DOI: 10.7554/elife.66095
221. Yang R, Li SW, Chen Z, et al. Role of INSL4 Signaling in Sustaining the Growth and Viability of LKB1-Inactivated Lung Cancer. *J Natl Cancer Inst*. 2019;111(7):664-674. doi:10.1093/jnci/djy166
222. Oh, T.-I.; Lee, M.; Lee, Y.-M.; Kim, G.-H.; Lee, D.; You, J.S.; Kim, S.H.; Choi, M.; Jang, H.; Park, Y.-M.; et al. PGC1α Loss Promotes Lung Cancer Metastasis through Epithelial-Mesenchymal Transition. Cancers 2021, 13, 1772. https:// doi.org/10.3390/cancers13081772
223. Tan, Z., Luo, X., Xiao, L., Tang, M., Bode, A. M., Dong, Z., & Cao, Y. (2016). *The Role of PGC1  in Cancer Metabolism and its Therapeutic Implications. Molecular Cancer Therapeutics, 15(5), 774–782.* doi:10.1158/1535-7163.mct-15-0621
224. Li W, Wong CC, Zhang X, et al. CAB39L elicited an anti-Warburg effect via a LKB1-AMPK-PGC1α axis to inhibit gastric tumorigenesis. *Oncogene*. 2018;37(50):6383-6398. doi:10.1038/s41388-018-0402-1
225. Flavin R, Peluso S, Nguyen PL, Loda M. Fatty acid synthase as a potential therapeutic target in cancer. Future Oncol. 2010;6(4):551-562. doi:10.2217/fon.10.11
226. Lupu, R., & Menendez, J. (2006). Pharmacological Inhibitors of Fatty Acid Synthase (FASN)-Catalyzed Endogenous Fatty Acid Biogenesis: A New Family of Anti-Cancer Agents? Current Pharmaceutical Biotechnology, 7(6), 483–494. doi:10.2174/138920106779116928
227. Jung EJ, Kwon SW, Jung BH, Oh SH, Lee BH. Role of the AMPK/SREBP-1 pathway in the development of orotic acid-induced fatty liver. *J Lipid Res*. 2011;52(9):1617-1625. doi:10.1194/jlr.M015263
228. Li J, Yan H, Zhao L, et al. Inhibition of SREBP increases gefitinib sensitivity in non-small cell lung cancer cells. *Oncotarget*. 2016;7(32):52392-52403. doi:10.18632/oncotarget.10721
229. Shirai, T., Inoue, E., Ishimi, Y., & Yamauchi, J. (2011). *AICAR response element binding protein (AREBP), a key modulator of hepatic glucose production regulated by AMPK in vivo. Biochemical and Biophysical Research Communications, 414(2), 287–291.* doi:10.1016/j.bbrc.2011.08.120
230. E. Inoue, J. Yamauchi, AMP-activated protein kinase regulates PEPCK gene expression by direct phosphorylation of a novel zinc finger transcription factor, Biochem. Biophys. Res. Commun. 351 (2006) 793–799.
231. A.E. Gadalla, T. Pearson, A.J. Currie, N. Dale, S.A. Hawley, A. Randall, D.G. Hardie, B.G. Frenguelli, AICA riboside both activates AMP-activated protein kinase and competes with adenosine for the nucleoside transporter in the CA1 region of the rat hippocampus, J. Neurochem. 88 (2004) 1272–1282
232. Jin R, Zhou W. TIF-IA: An oncogenic target of pre-ribosomal RNA synthesis. *Biochim Biophys Acta*. 2016;1866(2):189-196. doi:10.1016/j.bbcan.2016.09.003
233. Hoppe, S., Bierhoff, H., Cado, I., Weber, A., Tiebe, M., Grummt, I., & Voit, R. (2009). *AMP-activated protein kinase adapts rRNA synthesis to cellular energy supply. Proceedings of the National Academy of Sciences, 106(42), 17781–17786.* doi:10.1073/pnas.0909873106
234. Wang J, Zhang J, Xu L, Zheng Y, Ling D, Yang Z. Expression of HNF4G and its potential functions in lung cancer. Oncotarget. 2017;9(26):18018-18028. Published 2017 Dec 4. doi:10.18632/oncotarget.22933
235. Wang C, Zhang T, Liao Q, et al. Metformin inhibits pancreatic cancer metastasis caused by SMAD4 deficiency and consequent HNF4G upregulation. Protein Cell. 2021;12(2):128-144. doi:10.1007/s13238-020-00760-4
236. Chavez, J. A., Roach, W. G., Keller, S. R., Lane, W. S., & Lienhard, G. E. (2008). *Inhibition of GLUT4 Translocation by Tbc1d1, a Rab GTPase-activating Protein Abundant in Skeletal Muscle, Is Partially Relieved by AMP-activated Protein Kinase Activation. Journal of Biological Chemistry, 283(14), 9187–9195.* doi:10.1074/jbc.m708934200
237. Granot Z, Swisa A, Magenheim J, et al. LKB1 regulates pancreatic beta cell size, polarity, and function. *Cell Metab*. 2009;10(4):296-308. doi:10.1016/j.cmet.2009.08.010
238. Hargett SR, Walker NN, Keller SR. Rab GAPs AS160 and Tbc1d1 play nonredundant roles in the regulation of glucose and energy homeostasis in mice. *Am J Physiol Endocrinol Metab*. 2016;310(4):E276-E288. doi:10.1152/ajpendo.00342.2015
239. Mafakheri S, Flörke RR, Kanngießer S, et al. AKT and AMP-activated protein kinase regulate TBC1D1 through phosphorylation and its interaction with the cytosolic tail of insulin-regulated aminopeptidase IRAP. *J Biol Chem*. 2018;293(46):17853-17862. doi:10.1074/jbc.RA118.005040
240. Chen, L., Chen, Q., Xie, B., Quan, C., Sheng, Y., Zhu, S., … Chen, S. (2016). *Disruption of the AMPK–TBC1D1 nexus increases lipogenic gene expression and causes obesity in mice via promoting IGF1 secretion. Proceedings of the National Academy of Sciences, 113(26), 7219–7224.* doi:10.1073/pnas.1600581113
241. Parida S, Siddharth S, Sharma D. Role of Omentin in Obesity Paradox in Lung Cancer. *Cancers (Basel)*. 2021;13(2):275. Published 2021 Jan 13. doi:10.3390/cancers13020275
242. Joshi, M., Rice, S. J., Liu, X., Miller, B., & Belani, C. P. (2015). *Trametinib with or without Vemurafenib in BRAF Mutated Non-Small Cell Lung Cancer. PLOS ONE, 10(2), e0118210.* doi:10.1371/journal.pone.0118210
243. Mu Y, Yang K, Hao X, Wang Y, Wang L, Liu Y, Lin L, Li J and Xing P (2020) Clinical Characteristics and Treatment Outcomes of 65 Patients With BRAF-Mutated Non-small Cell Lung Cancer. *Front. Oncol.* 10:603. doi: 10.3389/fonc.2020.00603
244. Gautschi O, Milia J, Cabarrou B, et al. Targeted Therapy for Patients with BRAF-Mutant Lung Cancer: Results from the European EURAF Cohort. *J Thorac Oncol*. 2015;10(10):1451-1457. doi:10.1097/JTO.0000000000000625
245. Proietti I, Skroza N, Michelini S, et al. BRAF Inhibitors: Molecular Targeting and Immunomodulatory Actions. *Cancers (Basel)*. 2020;12(7):1823. Published 2020 Jul 7. doi:10.3390/cancers12071823
246. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol*. 2015;7(2):122-136. doi:10.1177/1758834014566428
247. Thorpe, L. M., Spangle, J. M., Ohlson, C. E., Cheng, H., Roberts, T. M., Cantley, L. C., & Zhao, J. J. (2017). *PI3K-p110α mediates the oncogenic activity induced by loss of the novel tumor suppressor PI3K-p85α. Proceedings of the National Academy of Sciences, 114(27), 7095–7100.* doi:10.1073/pnas.1704706114
248. Scheffler M, Bos M, Gardizi M, et al. PIK3CA mutations in non-small cell lung cancer (NSCLC): genetic heterogeneity, prognostic impact and incidence of prior malignancies. *Oncotarget*. 2015;6(2):1315-1326. doi:10.18632/oncotarget.2834
249. Yamamoto, H., Shigematsu, H., Nomura, M., Lockwood, W. W, Sato, M., Okumura, N., … Gazdar, A. F. (2008). *PIK3CA Mutations and Copy Number Gains in Human Lung Cancers. Cancer Research, 68(17), 6913–6921.* doi:10.1158/0008-5472.can-07-5084
250. Zhang, M., Jang, H., & Nussinov, R. (2020). *PI3K inhibitors: review and new strategies. Chemical Science.* doi:10.1039/d0sc01676d
251. Xu, F., Na, L., Li, Y. *et al.* RETRACTED ARTICLE: Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. *Cell Biosci* **10,**54 (2020). <https://doi.org/10.1186/s13578-020-00416-0>
252. Tan AC. Targeting the PI3K/Akt/mTOR pathway in non-small cell lung cancer (NSCLC). Thorac Cancer. 2020;11(3):511-518. doi:10.1111/1759-7714.13328
253. Le T, Gerber DE. ALK alterations and inhibition in lung cancer. *Semin Cancer Biol*. 2017;42:81-88. doi:10.1016/j.semcancer.2016.08.007
254. Sahu A, Prabhash K, Noronha V, Joshi A, Desai S. Crizotinib: A comprehensive review. *South Asian J Cancer*. 2013;2(2):91-97. doi:10.4103/2278-330X.110506
255. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. *J Biomed Biotechnol*. 2011;2011:583929. doi:10.1155/2011/583929
256. Din, F.U.; Aman, W.; Ullah, I.; Qureshi, O.S.; Mustapha, O.; Shafique, S.; Zeb, A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int. J. Nanomed.* **2017**, *12*, 7291–7309. <https://doi.org/10.2147/IJN.S146315>.
257. Madni, A.; Tahir, N.; Rehman, M.; Raza, A.; Mahmood, M.A.; Khan, M.I.; Kashif, P.M. Hybrid Nano-carriers for potential drug delivery. *Adv. Technol. Deliv. Ther.* **2017**, 54–87.<https://doi.org/10.5772/66466>
258. Dhaliwal, A.; Zheng, G. Improving accessibility of EPR-insensitive tumor phenotypes using EPR-adaptive strategies: Designing a new perspective in nanomedicine delivery. *Theranostics***2019**, *9*, 8091–8108. <https://doi.org/10.7150/thno.37204>.
259. Blanco, E.; Shen, H.; Ferrari, M. Principles of design for overcoming biological barriers to drug delivery. *Nat. Biotechnol.* **2015**, *33*, 941–951. <https://doi.org/10.1038/nbt.3330>.
260. Kay, M.A.; Glorioso, J.C.; Naldini, L. Viral vectors for gene therapy: The art of turning infectious agents into vehicles of therapeutics. *Nat. Med.* **2001**, *7*, 33–40. <https://doi.org/10.1038/83324>.
261. Peer, D.; Karp, J.M.; Hong, S.; Farokhzad, O.C.; Margalit, R.; Langer, R. Nanocarriers as an emerging platform for cancer therapy. *Nat. Nanotechnol.* **2007**, *2*, 751–760. <https://doi.org/10.1038/nnano.2007.387>.
262. Rawal, S.; Patel, M. Bio-Nanocarriers for Lung Cancer Management: Befriending the Barriers. *Nano-Micro Lett.* **2021**, *13*, 142. <https://doi.org/10.1007/s40820-021-00630-6>.
263. Newman, S.P. Drug delivery to the lungs: Challenges and opportunities. *Ther. Deliv*. **2017**, *8*, 647–661. <https://doi.org/10.4155/tde-2017-0037>.
264. Plaunt, A.J.; Nguyen, T.L.; Corboz, M.R.; Malinin, V.S.; Cipolla, D.C. Strategies to Overcome Biological Barriers Associated with Pulmonary Drug Delivery. *Pharmaceutics***2022**, *14*, 302. <https://doi.org/10.3390/pharmaceutics14020302>
265. Guo, Y.; Cao, X.; Zheng, X.; Abbas, S.K.J.; Li, J.; Tan, W. Construction of nanocarriers based on nucleic acids and their applications in nanobiology delivery systems. *Natl. Sci. Rev.* **2022**, *9*, nwac006. <https://doi.org/10.1093/nsr/nwac006>.
266. Vaughan, H.J.; Green, J.J.; Tzeng, S.Y. Cancer-Targeting Nanoparticles for Combinatorial Nucleic Acid Delivery. *Adv. Mater.* **2020**, *32*, e1901081. https://doi.org/10.1002/adma.201901081.
267. Mendes, B.B.; Conniot, J.; Avital, A.; Yao, D.; Jiang, X.; Zhou, X.; Sharf-Pauker, N.; Xiao, Y.; Adir, O.; Liang, H.; et al. Nanodelivery of nucleic acids. *Nat. Rev. Methods Prim.* **2022**, *2*, 24. <https://doi.org/10.1038/s43586-022-00104-y>.
268. Song, W.; Tang, Z.; Zhang, D.; Yu, H.; Chen, X. Coadministration of Vascular Disrupting Agents and Nanomedicines to Eradicate Tumors from Peripheral and Central Regions. *Small* **2015**, *11*, 3755–3761. <https://doi.org/10.1002/smll.201500324>
269. Hu, C.; Cun, X.; Ruan, S.; Liu, R.; Xiao, W.; Yang, X.; Yang, Y.; Yang, C.; Gao, H. Enzyme-triggered size shrink and laser-enhanced NO release nanoparticles for deep tumor penetration and combination therapy. *Biomaterials***2018**, *168*, 64–75. <https://doi.org/10.1016/j.biomaterials.2018.03.046>.
270. Chen, J.; Ding, J.; Wang, Y.; Cheng, J.; Ji, S.; Zhuang, X.; Chen, X. Sequentially Responsive Shell-Stacked Nanoparticles for Deep Penetration into Solid Tumors. *Adv. Mater.* **2017**, *29*, 1701170. <https://doi.org/10.1002/adma.201701170>.
271. Kumari, R.; Sunil, D.; Ningthoujam, R.S. Hypoxia-responsive nanoparticle based drug delivery systems in cancer therapy: An up-to-date review. *J. Control. Release Off. J. Control. Release Soc.* **2020**, *319*, 135–156. <https://doi.org/10.1016/j.jconrel.2019.12.041>.
272. Niu, Y.; Zhu, J.; Li, Y.; Shi, H.; Gong, Y.; Li, R.; Huo, Q.; Ma, T.; Liu, Y. Size shrinkable drug delivery nanosystems and priming the tumor microenvironment for deep intratumoral penetration of nanoparticles. *J. Control. Release Off. J. Control. Release Soc.* **2018**, *277*, 35–47. <https://doi.org/10.1016/j.jconrel.2018.03.012>.
273. Zhang, X.; An, L.; Tian, Q.; Lin, J.; Yang, S. Tumor-microenvironment activated second near-infrared agents for tumor imaging and therapy. *J. Mater. Chem. B* **2020***,***8**, 4738-4747 https://doi.org/10.1039/d0tb00030b.
274. Han, H.; Valdepérez, D.; Jin, Q.; Yang, B.; Li, Z.; Wu, Y.; Pelaz, B.; Parak, W.J.; Ji, J. Dual Enzymatic Reaction-Assisted Gemcitabine Delivery Systems for Programmed Pancreatic Cancer Therapy. *ACS Nano***2017**, *11*, 1281–1291. <https://doi.org/10.1021/acsnano.6b05541>.
275. Plaunt, A.J.; Nguyen, T.L.; Corboz, M.R.; Malinin, V.S.; Cipolla, D.C. Strategies to Overcome Biological Barriers Associated with Pulmonary Drug Delivery. *Pharmaceutics***2022**, *14*, 302. https://doi.org/10.3390/pharmaceutics14020302.
276. Kim, S.M.; Faix, P.H.; Schnitzer, J.E. Overcoming key biological barriers to cancer drug delivery and efficacy. *J. Control. Release Off. J. Control. Release Soc.* **2017**, *267*, 15–30. <https://doi.org/10.1016/j.jconrel.2017.09.016>.
277. Kay, M.A.; Glorioso, J.C.; Naldini, L. Viral vectors for gene therapy: The art of turning infectious agents into vehicles of therapeutics. *Nat. Med.* **2001**, *7*, 33–40. <https://doi.org/10.1038/83324>.
278. Yokoi, K.; Kojic, M.; Milosevic, M.; Tanei, T.; Ferrari, M.; Ziemys, A. Capillary-wall collagen as a biophysical marker of nanotherapeutic permeability into the tumor microenvironment. *Cancer Res.* **2014**, *74*, 4239–4246. <https://doi.org/10.1158/0008-5472.CAN-13-3494>.
279. Beg, S.; Almalki, W.H.; Khatoon, F.; Alharbi, K.S.; Alghamdi, S.; Akhter, M.H.; Khalilullah, H.; Baothman, A.A.; Hafeez, A.; Rahman, M.; et al. Lipid/polymer-based nanocomplexes in nucleic acid delivery as cancer vaccines. *Drug Discov. Today* **2021**, *26*, 1891–1903. <https://doi.org/10.1016/j.drudis.2021.02.013>.
280. Tenzer, S.; Docter, D.; Kuharev, J.; Musyanovych, A.; Fetz, V.; Hecht, R.; Schlenk, F.; Fischer, D.; Kiouptsi, K.; Reinhardt, C.; et al. Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology. *Nat. Nanotechnol.* **2013**, *8*, 772–781. <https://doi.org/10.1038/nnano.2013.181>.
281. Nel, A.E.; Mädler, L.; Velegol, D.; Xia, T.; Hoek, E.M.; Somasundaran, P.; Klaessig, F.; Castranova, V.; Thompson, M. Understanding biophysicochemical interactions at the nano-bio interface. *Nat. Mater.* **2009**, *8*, 543–557. <https://doi.org/10.1038/nmat2442>.
282. Sahay, G.; Alakhova, D.Y.; Kabanov, A.V. Endocytosis of nanomedicines. *J. Control. Release Off. J. Control. Release Soc.* **2010**, *145*, 182–195. <https://doi.org/10.1016/j.jconrel.2010.01.036>.
283. Cheng, M.; Liang, X.; Shi, L.; Zhang, Q.; Zhang, L.; Gong, Z.; Luo, S.; Wang, X.; Zhang, X. Folic acid deficiency exacerbates the inflammatory response of astrocytes after ischemia-reperfusion by enhancing the interaction between IL-6 and JAK-1/pSTAT3. *CNS Neurosci. Ther.* **2023**, *29*, 1537–1546. <https://doi.org/10.1111/cns.14116>.
284. Hoffmann, M.; Gerlach, S.; Hoffmann, C.; Richter, N.; Hersch, N.; Csiszár, A.; Merkel, R.; Hoffmann, B. PEGylation and folic-acid functionalization of cationic lipoplexes-Improved nucleic acid transfer into cancer cells. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1066887. <https://doi.org/10.3389/fbioe.2022.1066887>.
285. Rodriguez, P.L.; Harada, T.; Christian, D.A.; Pantano, D.A.; Tsai, R.K.; Discher, D.E. Minimal “Self” peptides that inhibit phagocytic clearance and enhance delivery of nanoparticles. *Science* **2013**, *339*, 971–975. <https://doi.org/10.1126/science.1229568>.
286. Parodi, A.; Quattrocchi, N.; van de Ven, A.L.; Chiappini, C.; Evangelopoulos, M.; Martinez, J.O.; Brown, B.S.; Khaled, S.Z.; Yazdi, I.K.; Enzo, M.V.; et al. Synthetic nanoparticleNPs functionalized with biomimetic leukocyte membranes possess cell-like functions. *Nat. Nanotechnol.* **2013**, *8*, 61–68. <https://doi.org/10.1038/nnano.2012.212>.
287. Prapainop, K.; Witter, D.P.; Wentworth, P., Jr. A chemical approach for cell-specific targeting of nanomaterials: Small-molecule-initiated misfolding of nanoparticle corona proteins*. J. Am. Chem. Soc.* **2012**, *134*, 4100–4103. <https://doi.org/10.1021/ja300537u>.
288. Overchuk, M.; Zheng, G. Overcoming obstacles in the tumor microenvironment: Recent advancements in nanoparticle delivery for cancer theranostics. *Biomaterials***2018**, *156*, 217–237. https://doi.org/10.1016/j.biomaterials.2017.10.024.
289. Zhou, Y.; Chen, X.; Cao, J.; Gao, H. Overcoming the biological barriers in the tumor microenvironment for improving drug delivery and efficacy. *J. Mater. Chem. B***2020**, *8*, 6765-6781. <https://doi.org/10.1039/d0tb00649a>.
290. Junttila, M.R.; de Sauvage, F.J. Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature***2013**, *501*, 346–354. <https://doi.org/10.1038/nature12626>.
291. Azzi, S.; Hebda, J.K.; Gavard, J. Vascular permeability and drug delivery in cancers. *Front. Oncol.* **2013**, *3*, 211. <https://doi.org/10.3389/fonc.2013.00211>.
292. Fang, J.; Nakamura, H.; Maeda, H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv. Drug Deliv. Rev.* **2011**, *63*, 136–151. <https://doi.org/10.1016/j.addr.2010.04.009>.
293. Roma-Rodrigues, C.; Mendes, R.; Baptista, P.V.; Fernandes, A.R. Targeting Tumor Microenvironment for Cancer Therapy. *Int. J. Mol. Sci.* **2019,** 20, 840. <https://doi.org/10.3390/ijms20040840>
294. Li, S.; Xu, Z.; Alrobaian, M.; Afzal, O.; Kazmi, I.; Almalki, W.H.; Altamimi, A.S.A.; Al-Abbasi, F.A.; Alharbi, K.S.; Altowayan, W.M.; et al. EGF-functionalized lipid-polymer hybrid nanoparticles of 5-fluorouracil and sulforaphane with enhanced bioavailability and anticancer activity against colon carcinoma. *Biotechnol. Appl. Biochem.* **2022**, *69*, 2205–2221. <https://doi.org/10.1002/bab.2279>.
295. Ahmad, J.; Ameeduzzafar, Ahmad, M.Z.; Akhter, H.M. Surface-Engineered Cancer Nanomedicine: Rational Design and Recent Progress. *Curr. Pharm. Des.* **2020**, *26*, 1181–1190. <https://doi.org/10.2174/1381612826666200214110645>.
296. Akhter, M.H.; Rizwanullah, M.; Ahmad, J.; Ahsan, M.J.; Mujtaba, M.A.; Amin, S. Nanocarriers in advanced drug targeting: Setting novel paradigm in cancer therapeutics. *Artif. Cells Nanomed. Biotechnol.* **2018**, *46*, 873–884. <https://doi.org/10.1080/21691401.2017.1366333>.
297. Sever, R.; Brugge, J.S. Signal transduction in cancer. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a006098. <https://doi.org/10.1101/cshperspect.a006098>
298. Hossen, S.; Hossain, M.K.; Basher, M.K.; Mia, M.N.H.; Rahman, M.T.; Uddin, M.J. Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. *J. Adv. Res.* **2018**, *15*, 1–18. <https://doi.org/10.1016/j.jare.2018.06.005>.
299. Ding, C.; Tong, L.; Feng, J.; Fu, J. Recent Advances in Stimuli-Responsive Release Function Drug Delivery Systems for Tumor Treatment. *Molecules* **2016**, *21*, 1715. <https://doi.org/10.3390/molecules21121715>.
300. Alves, A.C.S.; Bruinsmann, F.A.; Guterres, S.S.; Pohlmann, A.R. Organic Nanocarriers for Bevacizumab Delivery: An Overview of Development, Characterization and Applications. *Molecules* **2021**, *26*, 4127. <https://doi.org/10.3390/molecules26144127>.
301. Peng, Y.; Bariwal, J.; Kumar, V.; Tan, C.; Mahato, R.I. Organic nanocarriers for delivery and targeting of therapeutic agents for cancer treatment. *Adv. Ther.* **2020**, *3*, 1900136. <http://doi.org/10.1002/adtp.201900136>.
302. Abdelaziz, H.M.; Freag, M.S.; Elzoghby, A.O. Solid lipid nanoparticle-based drug delivery for lung cancer. In *Nanotechnology-Based Targeted Drug Delivery Systems for Lung Cancer*; Academic Press: Cambridge, MA, USA2019; pp. 95–121. https://doi.org/10.1016/B978-0-12-815720-6.00005-8.
303. Dhiman, N.; Awasthi, R.; Sharma, B.; Kharkwal, H.; Kulkarni, G.T. Lipid Nanoparticles as Carriers for Bioactive Delivery. *Front. Chem.* **2021**, *9*, 580118. <https://doi.org/10.3389/fchem.2021.580118>
304. Kutlu, M.; Kus, G.; Ulukaya, E. Lipid Nanoparticles Loaded with Ceranib-2 as Anticancer Agents. WO Patent 2020018049A3, 27 February 2020.
305. Naseri, N.; Valizadeh, H.; Zakeri-Milani, P. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. *Adv. Pharm. Bull.* **2015**, *5*, 305–313. <https://doi.org/10.15171/apb.2015.043>
306. Choi, S.H.; Jin, S.E.; Lee, M.K.; Lim, S.J.; Park, J.S.; Kim, B.G.; Ahn, W.S.;Kim, C.K. Novel cationic solid lipid nanoparticles enhanced p53 gene transfer to lung cancer cells. *Eur. J. Pharm. Biopharm. Off. J. Arb. Fur Pharm. V***2008**, *68*, 545–554. <https://doi.org/10.1016/j.ejpb.2007.07.011>.
307. Naguib, Y.W.; Rodriguez, B.L.; Li, X.; Hursting, S.D.; Williams, R.O.; Cui, Z., 3rd. Solid lipid nanoparticle formulations of docetaxel prepared with high melting point triglycerides: In vitro and in vivo evaluation*. Mol. Pharm.* **2014**, *11*, 1239–1249. <https://doi.org/10.1021/mp4006968>
308. Yan, Z. Preparation Method of Folic Acid Targeted Silymarin Solid Lipid Nanoparticles. China Patent 111195239A, 26 May 2020**.**
309. Chamundeeswari, M.; Jeslin, J.; Verma, M.L. Nanocarriers for drug delivery applications. *Environ. Chem. Lett.* **2019**, *17*, 849–865. https://doi.org/10.1007/s10311-018-00841-1.
310. Weber, S.; Zimmer, A.; Pardeike, J. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for pulmonary application: A review of the state of the art. *Eur. J. Pharm. Biopharm. Off. J. Arb. Fur Pharm. V***2014**, *86*, 7–22. <https://doi.org/10.1016/j.ejpb.2013.08.013>.
311. Hu, L.; Jia, Y. Preparation and characterization of solid lipid nanoparticles loaded with epirubicin for pulmonary delivery. *Die Pharm. Int. J. Pharm. Sci.* **2010**, *65*, 585-587.
312. da Rocha, M.C.O.; da Silva, P.B.; Radicchi, M.A.; Andrade, B.Y.G.; de Oliveira, J.V.; Venus, T.; Merker, C.; Estrela-Lopis, I.; Longo, J.P.F.; Báo, S.N. Docetaxel-loaded solid lipid nanoparticles prevent tumor growth and lung metastasis of 4T1 murine mammary carcinoma cells. *J. Nanobiotechnol.* **2020**, *18*, 43. <https://doi.org/10.1186/s12951-020-00604-7>.
313. Pi, C.; Zhao, W.; Zeng, M.; Yuan, J.; Shen, H.; Li, K.; Su, Z.; Liu, Z.; Wen, J.; Song, X.; et al. Anti-lung cancer effect of paclitaxel solid lipid nanoparticles delivery system with curcumin as co-loading partner in vitro and in vivo. *Drug Deliv.* **2022**, *29*, 1878–1891. <https://doi.org/10.1080/10717544.2022.2086938>.
314. Mouzouvi, C.R.A.; Umerska, A.; Bigot, A.K.; Saulnier, P. Surface active properties of lipid nanocapsules. *PLoS ONE***2017**, *12*, e0179211. <https://doi.org/10.1371/journal.pone.0179211>.
315. Kim, J.; Ramasamy, T.; Choi, J.Y.; Kim, S.T.; Youn, Y.S.; Choi, H.G.; Yong, C.S.; Kim, J.O. PEGylated polypeptide lipid nanocapsules to enhance the anticancer efficacy of erlotinib in non-small cell lung cancer. *Colloids Surf. B Biointerfaces***2017**, *150*, 393–401. <https://doi.org/10.1016/j.colsurfb.2016.11.002>.
316. Schultze, E.; Ourique, A.; Yurgel, V.C.; Begnini, K.R.; Thurow, H.; de Leon, P.M.M.; Campos, V.F.; Dellagostin, O.A.; Guterres, S.R. Encapsulation in lipid-core nanocapsules overcomes lung cancer cell resistance to tretinoin. *Eur. J. Pharm. Biopharm.* **2014**, *87*, 55–63. <https://doi.org/10.1016/j.ejpb.2014.02.003>.
317. AkhoondZardini, A.; Mohebbi, M.; Farhoosh, R.; Bolurian, S. Production and characterization of nanostructured lipid carriers and solid lipid nanoparticles containing lycopene for food fortification. *J. Food Sci. Technol.* **2018**, *55*, 287–298. <https://doi.org/10.1007/s13197-017-2937-5>.
318. Beloqui, A.; Solinís, M.Á.; Rodríguez-Gascón, A.; Almeida, A.J.; Préat, V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. *Nanomed. Nanotechnol. Biol. Med.* **2016**, *12*, 143–161. <https://doi.org/10.1016/j.nano.2015.09.004>..
319. Chauhan, I.; Yasir, M.; Verma, M.; Singh, A.P. Nanostructured Lipid Carriers: A Groundbreaking Approach for Transdermal Drug Delivery. *Adv. Pharm. Bull.* **2020**, *10*, 150–165. <https://doi.org/10.34172/apb.2020.021>.
320. Han, Y.; Li, Y.; Zhang, P.; Sun, J.; Li, X.; Sun, X.; Kong, F. Nanostructured lipid carriers as novel drug delivery system for lung cancer gene therapy. *Pharm. Dev. Technol.* **2016**, *21*, 277–281. <https://doi.org/10.3109/10837450.2014.996900>.
321. Lin, G.; Mi, P.; Chu, C.; Zhang, J.; Liu, G. Inorganic Nanocarriers Overcoming Multidrug Resistance for Cancer Theranostics. *Adv. Sci.* **2016**, *3*, 1600134. <https://doi.org/10.1002/advs.201600134>.
322. Ghosn, Y.; Kamareddine, M.H.; Tawk, A.; Elia, C.; El Mahmoud, A.; Terro, K.; El Harake, N.; El-Baba, B.; Makdessi, J.; Farhat, S. Inorganic Nanoparticles as Drug Delivery Systems and Their Potential Role in the Treatment of Chronic Myelogenous Leukaemia. *Technol. Cancer Res. Treat.* **2019**, *18*, 1533033819853241. <https://doi.org/10.1177/1533033819853241>.
323. Chen, S.; Hao, X.; Liang, X.; Zhang, Q.; Zhang, C.; Zhou, G.; Shen, S.; Jia, G.; Zhang, J. Inorganic Nanomaterials as Carriers for Drug Delivery. *J. Biomed. Nanotechnol.* **2016**, *12*, 1–27. <https://doi.org/10.1166/jbn.2016.2122>.
324. Desai, N.; Momin, M.; Khan, T.; Gharat, S.; Ningthoujam, R.S.; Omri, A. Metallic nanoparticles as drug delivery system for the treatment of cancer. *Expert Opin. Drug Deliv.* **2021**, *18*, 1261–1290. <https://doi.org/10.1080/17425247.2021.1912008>.
325. Chandrakala, V.; Aruna, V.; Angajala, G. Review on metal nanoparticles as nanocarriers: Current challenges and perspectives in drug delivery systems. *Emergent Mater.* **2022**, *5*, 1593–1615. <https://doi.org/10.1007/s42247-021-00335-x>.
326. Amrita, V.V.P.U.Nanoparticles Comprising Sorafenib. World Patent 2014087413A1, 12 October 2014.
327. Minji, S.; Chenggen, Q.; Xue, Y. Cisplatin Prodrug-Manganese Dioxide Nano Drug-Loading System and Preparation Method and Application Thereof. Chinese Patent 111214488A, 2 June 2020.
328. Jun, G.; Yuan, L.; Licheng, W.; Han, H. Double-Effect Treatment Targeted Drug Delivery System and preparation Method and Application Thereof. Chinese Patent 110652497A, 7 January 2020.
329. Tadic, M.; Kralj, S.; Jagodic, M.; Hanzel, D.; Makovec, D. Magnetic properties of novel superparamagnetic iron oxide nanoclusters and their peculiarity under annealing treatment. *Appl. Surf. Sci.* **2014***, 322*,255–264.<https://doi.org/10.1016/j.apsusc.2014.09.181>.
330. Kralj, S.; Makovec, D. Magnetic Assembly of Superparamagnetic Iron Oxide Nanoparticle Clusters into Nanochains and Nanobundles. *ACS Nano***2015**, *9*, 9700–9707. <https://doi.org/10.1021/acsnano.5b02328>.
331. Akbarzadeh, A.; Samiei, M.; Joo, S.W.; Anzaby, M.; Hanifehpour, Y.; Nasrabadi, H.T.; Davaran, S. Synthesis, characterization and in vitro studies of doxorubicin-loaded magnetic nanoparticles grafted to smart copolymers on A549 lung cancer cell line. *J. Nanobiotechnology* **2012**, *10*, 46. https://doi.org/10.1186/1477-3155-10-46
332. Carvalho, A.; Fernandes, A.R.; Baptista, P.V. Nanoparticles as delivery systems in cancer therapy. *Appl. Target. Nano Drugs Deliv. Syst.* **2019**,257–295*.* https.//doi.org/10.1016/b978-0-12-814029-1.00010-7.
333. Baeza, A. Ceramic Nanoparticles for Cancer Treatment. *Bio-Ceram. Clin. Appl.* **2014**, 421–455. https://doi.org/10.1002/9781118406748.ch14.
334. Tiwari, A.; Rohiwal, S. Synthesis and Bioconjugation of Hybrid Nanostructures for Biomedical Applications. In Hybrid Nanostructures for Cancer Theranostics; Elsevier: Amsterdam, The Netherlands **2019** https://doi.org/[10.1016/b978-0-12-813906-6.00002-0](https://dx.doi.org/10.1016/b978-0-12-813906-6.00002-0).
335. Singh, D.; Singh, S.; Sahu, J.; Srivastava, S.; Singh, M.R. Ceramic nanoparticles: Recompense, cellular uptake and toxicity concerns. *Artif. Cells Nanomed. Biotechnol.* **2016**, *44*, 401–409. <https://doi.org/10.3109/21691401.2014.955106>.
336. Pednekar, P.P.; Godiyal, S.C.; Jadhav, K.R.; Kadam, V.J. Mesoporous silica nanoparticles: A promising multifunctional drug delivery system. In *Nanostructures for Cancer Therapy*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 593–621. <https://doi.org/10.1016/B978-0-323-46144-3.00023-4>.
337. Rajani, C.; Borisa, P.; Karanwad, T.; Borade, Y.; Patel, V.; Rajpoot, K.; Tekade, R.K. Cancer-targeted chemotherapy: Emerging role of the folate anchored dendrimer as drug delivery nanocarrier. In *Pharmaceutical Applications of Dendrimers*; Elsevier: Amsterdam, The Netherland, 2020; pp. 151–198. https://doi.org/[10.1016/B978-0-12-814527-2.00007-X](http://dx.doi.org/10.1016/B978-0-12-814527-2.00007-X).
338. Bharti, C.; Nagaich, U.; Pal, A.K.; Gulati, N. Mesoporous silica nanoparticles in target drug delivery system: A review. *Int. J. Pharm. Investig.* **2015,***5*, 124–133. <https://doi.org/10.4103/2230-973X.160844>.
339. Sun, M.; Gu, P.; Yang, Y.; Yu, L.; Jiang, Z.; Li, J.; Le, Y.; Chen, Y.; Ba, Q.; Wang, H. Mesoporous silica nanoparticles inflame tumors to overcome anti-PD-1 resistance through TLR4-NFκB axis. *J. Immunother. Cancer* **2021**, *9*, e002508. <https://doi.org/10.1136/jitc-2021-002508>.