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REVIEWARTICLE

CHARACTERIZATION AND DEVELOPMENT OF CHEMICAL COMPOUNDS TARGETING LUNG, PANCREATIC, AND COLORECTAL CANCERS: A COMPREHENSIVE REVIEW

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Abstract

Due to high incidence, aggressive progression, and limited therapeutic efficacy, lung, pancreatic, and colorectal cancer represent a significant share of cancer-related deaths. Cancer remains a major cause of global morbidity and mortality. Despite considerable progress in traditional treatments such as surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, challenges like drug resistance, systemic toxicity, tumor heterogeneity, and recurrence continue to hinder long-term success. Therefore, the identification, study, and creation of new chemical compounds have become a promising approach to improving cancer treatment outcomes. By integrating current knowledge on chemical compound development and mechanistic insights across these three major cancer types, this review identifies existing research gaps, summarizes recent therapeutic advances, and outlines future directions for the rational design of safer and more effective anticancer agents. The findings presented herein are expected to support researchers and clinicians in advancing precision oncology and developing next-generation therapeutics for improved patient outcomes. With cancer being the rising cause of morbidity and mortality in the world today challenges the global health systems. Cancer is often diagnosed at advanced stages and possesses poor prognosis due to cancer having high metastatic potential and limited response to treatment therapies. The process of oncology despite extensive advancement such as chemotherapy regimens faces issues of drug resistance, systemic toxicity and lack of ability to detect tumor specificity. This review provides a comprehensive overview of recent advances in the development of chemical compounds targeting lung, pancreatic, and colorectal cancers. It discusses the structural diversity, biological activities, and molecular mechanisms of natural products, synthetic molecules, and semi synthetic derivatives with demonstrated anticancer potential. Particular emphasis is placed on their interactions with key signaling pathways involved in tumor initiation and progression.

Keywords: Cancer, drug development, molecular targets, natural products, synthetic compounds, targeted therapy.

INTRODUCTION

Cancer is referred to as a group of diseases characterised by abnormal development of cells that divides uncontrollably and can infiltrate and destroy normal cells, thus this research will specifically focus on lung, pancreatic and colon cancer. It often has the ability to spread throughout the body ranking it the 2nd leading cause of death worldwide (Mayo Clinic , 2022). There are many other type of cancers including breast cancers that are common in females and prostate cancer in males followed by lung and skin cancer affecting the population as a whole. It is necessary that

cancers are detected early in order to treat the cancer effectively and minimize damage to normal cells however due to late detections there is increased morbidity and mortality(World Health Organization, 2025).

To initiate with, lung cancer is caused by harmful cell growth in lungs. Lung cancer starts usually in the lung airways(bronchi or bronchioles) or small air sacs (alveoli) then it moves to the lungs referred to as metastatic lung cancer. There are two types of lung cancer: non-small cell lung cancer and small cell lung cancer. A person with lung cancer will experience cough, bone pain, jaundice, shortness of breath and

wheezing(Mayo Clinic, 2024a). However there are other types of lung cancers which are lymphomas, sarcomas and pleural mesothelioma. Lung cancers have various stages that tend to worsen with time(Clinic, 2022). As of 2020 there were 2.21 million new cases of lung cancers followed by 1.8 million deaths recorded globally (World Health Organization, 2025) making lung cancer the leading cause of death worldwide.

Moreover, pancreatic cancer is a type of cancer that begins growth as a growth of cells in the pancreas which lies behind the lower part of the stomach. The most common type of cancer affecting pancreas is pancreatic ductal adenocarcinoma which is rarely detectable at early stage making it life threatening. A person with pancreatic cancer will lose appetite, have dark -colored urine, itching, and belly pain radiating to sides and back(Mayo Clinic, 2024). Pancreatic cancer as of 2023 has showcased a rise in young females than men due to poor lifestyle and addiction to alcohol use and chronic smokers(Cedars Sinai, 2023) which hikes the death toll as of 2020 to 466,000 deaths worldwide(Sung *et al.*, 2021).

Furthermore, descending the human body the common type of cancer affecting the population is colon cancer. Colon is the last part of the digestive tract and it is the first and longest part of the large intestine. The cancer cells initiate from the lining of the intestine growing into small clumps as polyps and enlarged into cancerous cells. Colon cancer is not easily detected at early stage however a person with blood in stool(hematochezia), is a sign of having colon cancer(Mayo Clinic, 2023). Colon cancer is followed by lung cancer having a peak death toll of 935,000 deaths since 2020(Sung *et al.*, 2021).

Subsequently, with growing cases of cancers in Fiji as of 2025 according to The Fiji Times published on 2nd february, there has been a constant rise in the cases of cancer reaching its peak at 1731 cancer patients from 2021-2024(Wise and Wise, 2025). The most common cancer affecting males in Fiji are, Liver, Prostate, Lung, Stomach and Colon cancer where by common cancers causing mortality in women are, Cervix, Breast, Uterus, Ovary, and Liver. Lung cancer however peaks in male population due to smoking habits while stomach cancer that metastasizes into the pancreases overtime also peaked scenarios common in males followed by colon cancer(MHMS FIJI, 2014).

Consequently, colon or colorectal cancer is ranked 4th most common cancer causing mortality worldwide whereas lung cancer ranked 9th followed by pancreatic cancer ranked 12th as of 2022 according to Global Cancer Observatory that is a under World Health Organization for International Agency For Research on Cancer. Despite technological advancement, treatment options including surgery, chemotherapy,radiotherapy, and biological therapies have unmet significant clinical needs when it comes to detecting and treating cancers. Poor effectiveness of treatment occurs due to resistance, poor drug penetration and limiting success in tests that detect pancreatic, lung and colon cancer before metastasis takes place thus invasion of tumor cells to other vital organs and worsening causes of death(Sung *et al.*, 2021).

However, with advancing scientific knowledge with the help of small molecule chemical compounds there has been introduction of alternative chemicals to treat cancers. These compounds having characteristics of favorable pharmacokinetics, oral bioavailability, and ability to penetrate solid tumors makes it suitable for targeting and overcoming intracellular pathways and resistance, thus it allows not only extracellular targets but also intracellular where chemical compounds can control the influence of oncogenic drivers(Open Access Government, n.d.).

Conclusively, this research project will target to characterise biological and medical chemistry and pharmacological profiling of small molecular chemical compounds that are used as alternatives for treatment over chemotherapy and surgery as small molecular compounds have high specificity of penetration in cells that targets lung, pancreatic,and colon cancer.

Cancer

Cancer is a disease where there is abnormal and uncontrolled growth of cells. It initiates with small growth that starts to spread called metastatic cancer. The abnormal cells start to divide rapidly and invade nearby tissues and if in case infects blood then multiple organs are under stress. There are two main categories of cancer: hematologic(blood cancers) and solid tumors. Common cancers are lung, breast, colorectal and prostate cancers that affect the global population making them the primary cause of deaths.

Lung cancer

Lung cancer, also called lung carcinoma, is a malignant tumor originating in the lungs. It occurs due to genetic damage to the DNA in airway cells, often caused by cigarette smoking or exposure to harmful chemicals. These damaged cells multiply uncontrollably, leading to tumor formation. If untreated, the tumors spread throughout the lung, impairing its function. Eventually, lung tumors metastasize, spreading to other parts of the body.(Mayo Clinic, 2024a).

Lung cancer is the most common cancer worldwide, representing 12.3% of all cases, with an estimated 2.2 million new cases and 1.8 million deaths projected in 2025. Tobacco smoking is the primary cause, responsible for 80%–90% of lung cancers in smokers. Incidence varies significantly by geography, race, and gender, with some studies indicating that women may be more susceptible to lung cancer from tobacco carcinogens. A lifetime smoker has a 20- to 30-fold higher risk of developing lung cancer compared to a nonsmoker. In 2000, lung cancer caused approximately 1.1 million deaths worldwide, accounting for 17.8% of all cancer deaths. However, only 11% of heavy smokers develop lung cancer, suggesting a potential role of genetic factors in susceptibility. Nicotine addiction is the powerful engine that prevents smokers from quitting. The many lung cancer-specific carcinogens (including polycyclic aromatic hydrocarbons and nitrosamines) in the particulate matter of tobacco smoke have to be metabolized before they are either secreted or can bind to DNA with the formation of adducts. DNA adducts may be repaired or lead to apoptosis. If they persist, miscoding mutations in key genes such as P53 or RAS

may cause genetic instability, leading to further mutational damage and eventually to cancer. (John D Minna *et al*).

Classification

Lung cancer is primarily classified into two main types based on the size and appearance of malignant cells as observed by a histopathologist under a microscope:

1. **Small cell lung cancer** (SCLC; 15% of cases) - located near the centre of the lungs (major airways), these cells are small with indistinct boundaries and lack visible nucleoli.
2. **Non-small-cell lung cancer** (NSCLC; 85% of cases) - This group includes three types of cancer: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. Adenocarcinomas account for nearly 40% of lung cancers. The cells grow in three-dimensional clusters and produce mucin as shown in Fig. 2. Squamous-cell carcinomas make up about 30% of lung cancer cases (in large airways with tumor bearing sheath of cells and keratin).

Symptoms

- nonspecific respiratory problems – coughing, shortness of breath, or chest pain .
- dull, persistent chest pain (25%-50%)
- Fever
- Night sweats
- Horner's syndrome- Tumors in the thorax
- Pancoast tumor (shoulder pain)

(Mayo Clinic, 2024a).

Staging:

Non-small Cell Lung Cancer Stages

- **Stage 0** (carcinoma/tumor in-situ) : early stage, not spreading
- **Stage I:** 2 substages, 1A and 1B, based on the size of the tumor (cancer not spreading)
- **Stage II** is divided into stage IIA and IIB, with each stage then broken into additional sections, depending on These tumors may have spread to lymph node but not to other organs.
- **Stage III** is divided into IIIA, IIIB or IIIC,: Most commonly, the cancer has spread to the lymph nodes in the mediastinum (the area in the chest between the lungs).
- **Stage IV** is the most advanced form of NSCLC. In this stage, the cancer has metastasized, or spread, to the lining of the lung or other areas of the body.

Small Cell Lung Cancer Stages

- **Limited stage** is only in one lung with spread to lymph nodes only.
- **Extensive stage** has spread to tissue outside the originally affected lung like the opposite lung or distant organs.

(American Lung Association, 2025).

Diagnosis and tests

- Blood test
- Chest X-ray
- CT-scan
- PET-CT scan
- Bronchoscopy and biopsy
- Thoracoscopy
- Mediastinoscopy

- Percutaneous needle biopsy
(National Health Service, 2022)

Treatment

- i. Surgery- Wedge resection
 - a. Segmental resection
 - b. Lobectomy
 - c. Pneumonectomy
- ii. Radiation therapy
- iii. Chemotherapy
- iv. Stereotactic body radiotherapy
- v. Targeted therapy
- vi. Immunotherapy
- vii. Palliative care (Mayo Clinic, 2024a).

II: Pancreatic cancer

Pancreas is a vital organ that is located in the abdomen region which is on the left side behind the stomach. It plays a crucial role in the digestion process by producing digestive juices that aids in digestion of food and it releases hormones such as insulin to break down glucose regulating sugar levels.

A cancer in pancreas is when pancreatic cells mutate(change) and uncontrollably divide forming a tumor. Pancreatic cancer is not detectable at early stage until it metastases which makes it resistant to common cancer drugs(Cleveland clinic, 2023). Initiation of the growth of tumor cells in pancreas grows in the ducts of pancreas known as adenocarcinoma tumors that surround the pancreatic duct. Growth of tumor cells leads to variation and mutation in DNA which results in abnormal cell growth and multiplication.

The global standing of pancreatic cancer as of 2022 under World Cancer Research Fund is 12th most common cancer with 510,992 cases worldwide(World Cancer Research Fund, 2024). Mainly pancreas cancer is most common in individuals with smoking habits, type 2 diabetes, chronic inflammation of pancreas, family history, obese people and those with chronic alcohol consumption(Mayo Clinic, 2024b).

Symptoms of pancreatic cancer

- Abdominal pain and back pain
dull and persistent pain, radiating sometimes
- Unexplained weight loss
- Loss of appetite
- Jaundice, eye, skin, and urine tend to appear yellow in color
- Fatigue- weakness
- Chances of developing diabetes
- Digestive problems
- bloating and greasy stool(Mayo Clinic, 2024b).
- Fluid buildup and swelling in abdomen(ascites)

Stages :

- **Stage 0:** carcinoma in situ-abnormal cells in the pancreatic ducts
- **Stage I:** localized tumor less than 4 cm
- **Stage II:** tumor may be more than 4 cm and may invade nearby lymph nodes
- **Stage III:** tumor targets major blood vessels
- **Stage IV:** cancer cells have metastasized to other nearby organs like the liver, lungs and

peritoneum(American Cancer Society, 2024b).

Diagnosis and tests:

- Imaging test
 - CT scan
 - MRI scan
 - PET
 - Endoscopic Ultrasound
- Blood test
 - High levels of carbohydrates antigen(CA) 19-9 a type of protein which is present in blood in pancreatic cancer
- Staging laparoscopy
 - Determine extent of tumor
 - Incision and insert tube with camera in abdomen to see abnormalities
- Genetic testing(Cleveland clinic, 2023).

Treatment:

- Surgery
 - Whipple procedure
 - pancreaticoduodenectomy(if cancer in head of pancreas-remove head of pancreas)
 - Distal pancreatectomy
 - Cancer in tail of pancreas(remove tail of pancreas)
 - Total pancreatectomy
 - Removal of entire cancer pancreas,gallbladder, spleen, and part of your stomach and small intestine.
- chemotherapy
 - Use drug to kill cancer cells
- Radiation therapy
 - Using x-ray with high energy to kill cancer cells.
- Targeted therapy
 - Using drugs that specifically targets certain proteins(these proteins control growth of cancer cells and spread). Common drugs: Erlotinib, Olaparib, Larotrectinib, Entrectinib(Cleveland clinic, 2023).

III: Colon cancer

Colon is the first and longest part of the large intestine which is part of the digestive system as it is a long tube that helps carry digested food to your rectum and out of your body. It is an important part of the digestive system that breaks down food for body use.

A cancer cell starts to develop in the colon lining is known as colon cancer or colorectal cancer. Just like other cells in the human body cells in the colon undergo continuous growing, dividing and dying in healthy individuals, however in colon cancer the cells present in the lining of the colon and rectum area continuously grow without dying out even though they are supposed to die out to allow new cell growth. This continuous cell growth without cell death leads to uncontrolled cell growth that eventually grows into small polyps. Once there is growth of polyps it is not yet a cancerous cell but with time as it grows large in size it becomes cancerous tumors. An individual with colorectal cancer at first doesn't have symptoms thus making it hard to detect at an early stage. Colorectal cancer is often diagnosed at advanced stages where

treatment options are limited and chances of survival are diminished.

According to the World Health Organization it is noted that colorectal cancer is the 3rd most common cancer worldwide that accounts for 10% of all cancer cases and the 2nd leading cause of death worldwide. It was also noted that colon cancer mainly affects older individuals with many cases with people aged 50 years and above. People with a history of inflammatory bowel disease, family history of colon cancers,diabetic, obese, smokers, alcohol intakers, and any previous radiation therapy of cancers and older age individuals are most susceptible to colon cancer.

Symptoms of colon cancer:

- Experiencing abdominal pain, aches and cramps
 - Belly pain
- Changes in bowel movements(changes in how one poops)
 - Diarrhea
 - constipation
- Blood in stool
- Bloated stomach
- Unexplained weight loss
- Vomiting
- Anemia

Stages :

- Stage 0- precancerous cell in the mucosa(innermost lining of the colon wall)
- Stage I- cancer has grown in wall of intestine not yet spreading
- Stage II- spreading of cancer further in the intestine, hasn't spread to lymph nodes
- Stage IIA- cancer spread in most of the colon
- Stage IIB- cancer in outer layer of the colon wall
- Stage IIC- cancer has spread to nearby organs
- Stage III- cancer in lymph nodes
 - Stage IIIA- cancer in wall of colon and in 1 of 4 lymph nodes
 - Stage IIIB- spreads to all four lymph nodes
 - Stage IIIC- spreading to nearby organs and there lymph nodes
- Stage IV- cancer has metastasized to other areas of your body affecting liver, lungs and ovaries in females.

Diagnosis and Tests:

- Complete blood count
- Comprehensive metabolic panel
- Carcinoembryonic antigen(CEA) assay: cancer cells and normal cells release CEA into the blood thus a high level of CEA may give a sign of cancer
- X -ray
- CT scan
- MRI scan
- PET scan
- Colonoscopy
- Sigmoidoscopy

Treatment:

- Polypectomy
- laparoscopy
- Partial colectomy
- Surgical resection with colostomy

- Radiofrequency ablation
- Chemotherapy
- Targeted therapy
- Immunotherapy

(American Cancer Society, 2024), (Cleveland Clinic, 2022a), (Mayo Clinic, 2023b), (CDC, 2024)

Small Chemical compounds Targeting Cancer

With growing drawbacks from current treatment options such as immunotherapy and chemotherapy there is a drastic need for new treatments for colon cancer that targets the oncogenic drivers of colon cancers. Studies show that by targeting site Cdc42 with small molecular drug like AZA197, helps suppress primary colon cancer initiation and ensures survival of individuals by regulation of PAK1 in preclinical xenograft(graft tissue taken from one species and grafted into another species).

A small signalling protein, the Rho GTPases plays a crucial role in regulating cellular processes that includes, cytoskeleton organization, cell polarity, transcriptional dynamics cell cycle, cell motility, vesicle trafficking and regulation of tumor progression(promotes cancer cell proliferation, migration and invasion). It is a protein that inhibits or acts as a molecule switch, where it switches active GTP-bound state into inactive GDP-bound state(Liu *et al.*, 2024).

A: TARGETING Cdc42 cells

Cancer poses a threat to health and longevity of life as cancer has characteristics such as sustaining proliferative signals, evading growth suppressors, and resisting cell death. Thus, Rho GTPases expression levels in cancer are altered(Liu *et al.*, 2024). Rho GTPases control numerous signalling pathways that help regulate gene expressions, cell migration, cell proliferation and cell survival that are all part of all stages of cancer progression.

Therefore, AZA197 inhibits selectively Cdc42 that is used for treatment of colon cancer which was designed from information obtained from drugs that inhibit Rho GTPases activity that leads to inhibition of cell growth, motility, and survival pathways making therapeutic agents for cancer cells. This was investigated using the mouse xenograft method that resembled human colon cancer cells, thus tumors were removed after the above treatment(Zins *et al.*, 2013). AZA197 selectively inhibits Cdc42 which is a member of Rho GTPase; it does not inhibit Rac1 or RhoA (indicates high target specificity).

AZA197 helps:

- Decreased proliferation of colon cancer cells
- Reduced cell migration and invasion(prevents metastasising)
- Increased apoptosis(programs cell death)
- Downregulation of PAK1 and ERK signaling pathways

Methods of targeting Cdc42:

- Cell lines and molecular profiling
- Compound generation- designed by National Cancer Institute chemical database, targeted against Rho GTPases
- Cytotoxicity assay- to assess AZA197 -induced cytotoxicity by measuring lactate

dehydrogenase(LDH) release which indicates cell membrane damage.

- Rho GTPase activation assays- measures activation levels of Rac1, Cdc42 and RhoA after treatment with AZA197 where colon cancer cells were seeded in 6 well plates and treated with AZA197 where it was most effective on Cdc42.
- Guanine nucleotide-exchange assays in vitro-evaluates whether AZA197 inhibits GEF-mediated nucleotide exchange on Cdc42.
- Cell proliferation assay
- FACS analysis
- Migration assay
- Invasion assay- colon cancer cells are added on top of Biocoat matrigel invasion chamber.
- Visualization of the actin cytoskeleton and fluorescence microscopy

AZA197 impairs Cdc42-mediated cell motility and invasion in colon cancer cells by disrupting actin cytoskeleton reorganization and filopodia formation, confirming its anti-metastatic potential(Zins *et al.*, 2013). JAK2 and STAT3 signaling pathways are activated by interleukin-6, which regulates cell growth, differentiation, immune response and it is abnormally activated in individuals with cancers. It is a viable target for colon cancer therapy, Ergotamine is an FDA-approved drug that demonstrates significant anti-cancer potential and could be repurposed for colon cancer treatment(Chandrasekhar *et al.*, 2024).

JAK2 pathway inhibition induces cell cycle arrest and apoptosis in colon cancer. Some JAK2 inhibitors include ruxolitinib, baricitinib and fedratinib that target JAK1 AND JAK2(Chandrasekhar *et al.*, 2024).

C: Enhancing chemoresistance with combined kras and TP53

Individuals with colon cancer often have resistance to chemotherapy due to genomic variation where APC, TP53, KRAS, and PIK3CA are the genes that are mutated in advanced colon cancer patients. With the help of CT scan and carcinoembryonic antigen levels the mutated genes in colon cancer and its sensitivity to chemotherapy drugs were assessed.

Chemotherapy is used for patients with stage III or stage IV cancer where often the anticancer drugs in patients with metastatic cancer finally succumb to chemoresistance as the tumors become drug resistant and makes it the reason behind treatment failures and deaths in colon cancer patients(Marbun, Erlina and Lalisang, 2022).

Having identified the mutation of genes allows understanding the treatment option better.

Genes:

- **APC**- initiates early adenoma formation, leads to uncontrolled WNT (a ligand that is overexpressed in tumors) signaling and crypt hyperplasia. Leads to therapy resistance.
- **KRAS**- mutation occurs early and drives proliferation via MAPK signaling. Intermediate adenoma.
- **TP53**- mutations occur late, this allows cells with DNA damage to evade apoptosis. Late adenoma(loss of cell cycle control).

- **PIK3CA**- mutation enhances survival and resistance to apoptosis(invasion and metastasis), the tumor starts to further grow.
- **MLH1**- inactivation causes microsatellite instability, this leads to hypermutated tumors.(Zhuang *et al.*, 2021).

D: Targeting SMAD4

SMAD4 is a crucial mediator in the Transforming Growth Factor Beta (TGF- β) signaling pathway, governing essential cellular processes like cell growth, differentiation, apoptosis and migration. In this pathway, TGF- β binding to cell surface receptors triggers the activation of SMAD proteins, forming a complex with SMAD4.

Induces cell cycle arrest controls cell proliferation and eliminating damaged cells, helps in wound healing and control metastasis **E. TARGETING MET**

MET has been considered as a promising drug target for the treatment of MET-dependent diseases, particularly non-small cell lung cancer (NSCLC). Small molecule MET inhibitors with mainly three types of binding modes (Ia/Ib, II, and III) have been developed (Chaofan Wang, Xiaoyun Lu, 2023)

I: KRAS G12C inhibitor :

- **Drugs used:** Sotorasib and Adagrasib
- **Mechanism:** covalently binds to cysteine residue in the KRAS G12C mutant, locks the bond in an inactive GDP-bound state. Also used to treat small cell lung cancer.

II: PIK3CA inhibitor:

- **Drug used:** Alpelisib
- **Mechanism:** it selectively targets the PI3K α isoform that is encoded by PIK3CA which reduces signaling and tumor cell survival(ecancer, 2025).

III: TP53 Reactivator:

- **Drug used:** APR-246(Eprexetapopt)
- **Mechanism:** reactivates apoptosis and cell cycle arrest pathways(Hu *et al.*, 2021).

IV: WNT Pathway Inhibitor:

- **Drugs used:** LGK974 and PRI-724
- **Mechanism:** inhibits porcupine, an enzyme essential for WNT ligand secretion, blocks transcription of WNT genes, also treats pancreatic cancer(Nives Pećina-Šlaus *et al.*, 2023).

V: MSI-H Immunotherapy:

- **Drugs used:** pembrolizumab and Nivolumab
- **Mechanism:** blocks PD-1, unleashing T cell-mediated attack on tumors with high mutational burden(Petrelli *et al.*, 2020).

F: Targeting ALK (Anaplastic lymphoma kinase)

Rearrangements of the anaplastic lymphoma kinase (ALK) gene have been recognized as powerful oncogenic drivers in various cancers, including non-small cell lung cancer (NSCLC). The development of ALK inhibitors, specifically tyrosine kinase inhibitors (TKIs), has significantly enhanced the prognosis for patients with ALK-mutated NSCLC. Nevertheless, both intrinsic and acquired resistance to ALK TKIs eventually develop over time.

Structurally, ALK is made up of:

- An extracellular domain,
- a single-pass transmembrane helix,

- and an intracellular tyrosine kinase domain.

ALK activation:

- endogenous ALKAL1 and ALKAL2 ligands bind to the extracellular domains,
- dimerization,
- autophosphorylation,
- activation of downstream signaling pathways critical for cellular proliferation, survival, and differentiation.

There are currently five ALK TKI approved by the US FDA for the treatment of NSCLC :

- crizotinib (first-generation),
- ceritinib, alectinib, brigatinib (second-generation),
- and lorlatinib (third-generation).

molecular mechanism of resistance:

- intrinsic- a de novo lack of response to treatment and is considered within 3 months of therapy. And has been observed in 4%-10% of patients with ALK-positive NSCLC
 - acquired- disease progression after a period of initial clinical benefit.
1. ALK-dependent (“on-target”) - retain their dependence on ALK
 2. ALK-independent (“off-target”)- utilize alternative ALK-independent pathways to support proliferation.

Alternative strategies to overcome ALK inhibitor resistance

Immunotherapy

- effective in treating NSCLC without actionable mutations, but underwhelming in ALK-positive patients.
- lower response rate and shorter PFS in ALK positive than ALK wild-type patients.
- A combination of ALK TKI and immunotherapy is being tested.

4th-generation ALK TKI

- activity against single and some mutations associated with lorlatinib resistance
- TPX-0131(compact macrolytic molecule) bind to ATP binding boundaries to overcome AKL resistance mutations (solvent front, gatekeeper,compounds).

Combination therapies

- MET amplification is one of the pathways of off-target resistance
- Combination therapies (lorlatinib + crizotinib and alectinib + capmatinib) have shown some modest benefits.
- the use of MEK inhibitors with ALK TKI study involving brigatinib + binimetinib and alectinib + cobimetinib was closed due to slow accrual.

Antibody-drug conjugates

- monoclonal antibody attached to a cytotoxic drug via a chemical linker
- binds to cancer antigen and is internalized by endocytosis
- ADC fuse with lysosomes and release cytotoxic drug (payload) which kill cancer
- no direct targets for ALK yet but pathways involve ALK-independent patterns.

Proteolysis-targeting chimeras

- two ligands connected by a link that binds to the protein of interest and an E3 ubiquitin ligase
- ALK can be targeted via protein degradation despite the presence of on-target resistance mutations.
- first ALK-targeted PROTAC showed degradation but non-specifically degraded other kinases.

Targeting drug-tolerant persister cells

- Cancer cells in persister state remain in cell cycle arrest and evade cell cancer death.
- survive exposure to TKI which lead to acquired genetic alterations and relapse
- further research is currently evaluating different methods to target persister cells.

Vaccine therapy

- immune response is triggered by targeting ALK
- It was effective first in preclinical mouse model
- 17% of patients had natural anti-ALK antibodies
- prophylactically and therapeutically impaired the growth of ALK+ NSCLC tumors
- has the potential to generate anti-tumor response and stimulate a tumor response

(Darin Poei *et al*,2024).

Small chemical compounds for targeting lung cancer

Lung cancer is traditionally classified into non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and carcinoid. NSCLC accounts for approximately 80% of all lung cancers and is further sub typed into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma . In addition to EGFR, ALK, KRAS, MET, AND TP53, there are several other molecular abnormalities that could potentially be treated with drugs already approved for other malignancies or with investigational agents (Sacha I Rothschild, 2015).

For targeting EGFR

Epidermal growth factor receptors (EGFRs), also known as ErbB1 and HER1, are part of the receptor tyrosine kinase family. Inhibiting EGFR's tyrosine kinase activity is a promising approach for cancer therapy. Various small-molecule EGFR tyrosine kinase inhibitors (EGFR-TKIs), from medicinally privileged compounds to commercial drugs, have been reviewed with emphasis on their molecular structure and mechanisms of action.

Because the EGFR signaling pathway regulates cell proliferation, growth, survival, and differentiation, and mutated EGFR genes cause overproduction of EGFR protein leading to several cancers, understanding the molecular interactions between EGFR and its inhibitors is crucial. This will enable the development of more effective and selective EGFR-TKIs, improving cancer treatment and saving more lives.

- is part of receptor family together with HER2, HER3, HER4
- involved in cancers such as lung, breast, colon and pancreatic cancers
- Two classes of anti-EGFR drugs: small-molecule tyrosine kinase inhibitors (TKIs) which targets

intracellular site, and monoclonal antibodies (mAbs) which block extracellular domain

- EGFR-TKIs which are FDA approved include; gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib.
- Erlotinib, lapatinib, and icotinib bind to the EGFR in a reversible manner and have been approved as first-line therapies for advanced NSCLC and pancreatic cancer.

Members of the EGFR family regulate the production, survival, movement, and structure of various embryonic and adult cell types. Signaling from EGFR, ErbB3, and ErbB4 is controlled by ligand-dependent oligomerization, while ErbB2 is regulated through oligomerization with ligated forms of other family members. EGFR, ErbB2, and ErbB4 signal via active tyrosine kinase scaffolds, whereas ErbB3 signals through ligand-induced oligomerization and activation of the other family members.

- tyrosine trans-phosphorylation is inhibited by TKIs blocking EGFR activation
- there are reversible and irreversible EGFR-TKIs
- non-covalent interactions are used to bind reversible inhibitors to the ATP site
- under development of most EGFR inhibitors are highly selective and reversible
- recently, few irreversible TKIs have also emerged

The approved EGFR-TKIs are also divided into 3 categories based on their target kinases :

1. Selective EGFR inhibitors such as gefitinib, targets EGFR with high selectivity.
2. Dual EGFR inhibitors such as lapatinib, which target EGFR and ErbB2.
3. The third is multi-kinase inhibitors such as brigatinib, pyrotinib, and vandetanib

Classification into First-, Second-, Third-, and Fourth-Generation TKIs:

1. First-Generation EGFR-TKIs -Gefitinib, Erlotinib, Icotinib, Lapatinib, Vandetanib
2. second generation- Afatinib, dacomitinib, neratinib, canertinib, pelitinib, brigatinib.
3. The first third-generation EGFR-TKIs Osimertinib, olmutinib, rociletinib, naquotinib, avitinib, nazartinib.

Fourth-Generation EGFR-TKIs: EAI001, EAI045, DDC4002, DDC-01-163- Small molecule chemical compounds are more effective means of treating cancers as small molecules are easily able to enter cells and reach both the extracellular and intracellular genes. It helps to easily modulate specific proteins that help cancer cells to grow and survive.

Most importantly it helps bypass resistance mechanisms that reduce systemic toxicity as the small molecules are target specific with high precision and availability of the inhibitor drugs in pills that improves patient compliance. These chemicals can also be used with chemotherapy, radiation and immunotherapy as it helps improve immune response and reduces metastasis. Zaidi *et al.* (2011) demonstrated the synthesis, surface functionalization, and bioconjugation of ligand-passivated quantum dots for sensitive biological detection, highlighting their potential as

versatile nanoplateforms for biomarker detection and targeted cancer diagnostics.

CONCLUSION

Continuous advancements in chemical biology have led to the discovery and development of novel anticancer compounds with enhanced specificity and efficacy. The combination of chemical synthesis, computational drug design, and biological evaluation is vital for identifying innovative therapeutic approaches against cancer. Interdisciplinary collaborations have played a significant role in this rapidly advancing field, resulting in groundbreaking discoveries in targeted therapies, small-molecule inhibitors, and promising compounds with unique mechanisms of action (Dr. Mateusz Kciuk and Dr. Beata Marciniak, 2025). This research project focused more on the small molecule inhibitors and targeted therapies. Colorectal cancer cells grow and divide without dying leading to development of tumor. According to the World Health Organization it is noted that colorectal cancer is the 3rd most common cancer worldwide. APC, KRAS, TP53, PIK3CA, and MSI are the most commonly mutated genes in colon cancer. Several small molecule inhibitors are discussed above for targeting these mutated genes. A cancer in pancreas is when pancreatic cells mutate (change) and uncontrollably divide forming a tumor. The global standing of pancreatic cancer as of 2022 under World Cancer Research Fund is 12th most common cancer with 510,992 cases worldwide. Along with surgery there are several therapies used to treat pancreatic cancer such as ; radiotherapy and chemotherapy. KRAS, p16/CDKN2A, TP53 and SMAD4/DPC4 are the commonly mutated genes in pancreatic cancer. Several methods of inhibition for the mutated genes are discussed above. Lastly, lung carcinoma is a malignant tumor that starts in the lungs and eventually metastasizes to other parts if not treated. The most common cause of lung cancer is cigarette smoking. Lung cancer is the most common form of cancer in the world (12.3% of all cancers), with an estimated 1.2 million new cases in 2000. EGFR, ALK, KRAS, MET, and TP53 are the commonly mutated genes in lung cancer.

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AUTHOR'S CONTRIBUTIONS

Zaidi NH: conceptualization, literature survey, writing original draft. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The associated author can provide the empirical data used to support the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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