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The Application of Small Molecule Drugs: Cancer Therapy

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ABSTRACT

According to the World Health Organization, Cancer is one of the world's deadliest diseases and is the second leading cause of death in the United States. Cancer has been responsible for almost 10 million deaths worldwide in 2020, with the most common forms of cancer being breast, lung, and colon & rectum cancer. To put into scale just how deadly the disease is, the rate of cancer deaths per year is about 158 per 100,000 men and women. Current traditional cancer therapies include chemotherapy, radiation therapy, and surgery. Although these traditional cancer therapy methods have been somewhat effective over the past decades, they come with serious adverse health effects and have been related to very serious long-term side effects. As a result, over the recent years, targeted cancer therapy using small molecule drugs has become a focus in the medical field of cancer treatment. Small molecule drugs have a very advanced and tunable targeting ability which is effective in passing through cell membranes and reaching their designed intracellular targets. Most of these drugs can be administered orally, and due to their very small size, they are able to pass through a variety of obstacles in order to inhibit certain cancer-related biomolecules. In this review, I provide a summary of several different SMIs (small molecule inhibitors) that can be used in cancer therapy and explain recent advances as well as future outlooks in the field of SMIs for cancer treatment.

The Application of Small Molecule Drugs: Cancer Therapy

Currently, the three forms of therapy for Cancer include surgery, chemotherapy, and radiation therapy. Surgery is fairly straightforward and is used to remove the tumor and nearby tissue during an operation. There are several adverse side effects to cancer surgery which include numbness, lymphedema, appetite loss, swelling, and organ dysfunction (V. Lavanya, M. Adil, N. Ahmed, A. Rishi, S. Jamal, 2014). As for Chemotherapy, drugs are used in order to target and kill the rapidly dividing cancer cells. However, many of these drugs are unable to distinguish the difference between normal cells and cancer cells, which can cause them to target normal cells as well - causing damage to bone marrow, hair follicles, and digestive tracks. This causes the patient, being treated by chemotherapy, to experience adverse effects including diarrhea, fatigue, anemia, alopecia, and nausea, just to list a few. When it comes to radiation therapy, high-energy waves (in the form of radiation) are used to destroy cancer cells. However, similar to the effects of chemotherapy, radiation therapy can cause swelling in tissues, pose harm to epithelial surfaces, and can incur patients to intestinal damage. Many popular, current cancer therapy systems being used in the industry combine the methodologies of chemotherapy and radiation therapy. Because of the many adverse effects posed by current forms of therapy, Cancer Research has been shifted towards the fields of targeted cancer therapy - using the approach of searching for specific molecular targets, which can help slow down or diminish the effects of cancer on the body and nearby cells. Using targeted cancer therapy methods, research is able to differentiate healthy cells and cancer cells- avoiding any healthy cells being destroyed, and side effects occurring.

When it comes to targeted drug delivery and therapy, there are two types of compounds that can be used: Small Molecule Drugs and Macromolecule drugs (G. Wilkes, 2018). The main difference between the

two are size; Macromolecule are about 150,000 Da, while small molecule drugs are less than 500 Da. Due to the small size of these small molecule drugs, they are able to easily and effortlessly traverse through cell membranes, bind to cell receptors or targets, and do the task they were designed to do. When it comes to cancer therapy and targeted drug delivery using these molecules, the two main options used in clinical practice include small molecule agents and monoclonal antibodies (macromolecule).

Scientific Review

Small Molecule Kinase Inhibitors

Protein kinase is a type of enzyme which is responsible for catalyzing the transfer of a phosphate group, from ATP to protein residues. Phosphates, in contrast, have the exact opposite function of protein kinase, where they are responsible for removing a phosphate group from a protein. The counter mechanisms between the protein kinase and phosphates are what cause the regulation of protein activity in the body and improve the plasticity of the epigenome. However, when the protein kinase is overexpressed, it messes up this balance- and in turn causes promotion in cell proliferation, survival, and growth. The biochemical reaction that protein kinase is responsible for catalyzing is: MgATP1−+protein−O:H→protein−O:PO32−+MgADP+H+

The protein kinase enzyme supports and carries out many things which have an important role in cell growth, proliferation, and differentiation. Protein Kinase inhibitors have the job of regulating these protein kinases, preventing, and proving therapy for the various disease protein kinases are linked to- including cancer. The Protein Kinase inhibitors are classified into six different types, all of which have separate binding locations and functions (See Figure 1).

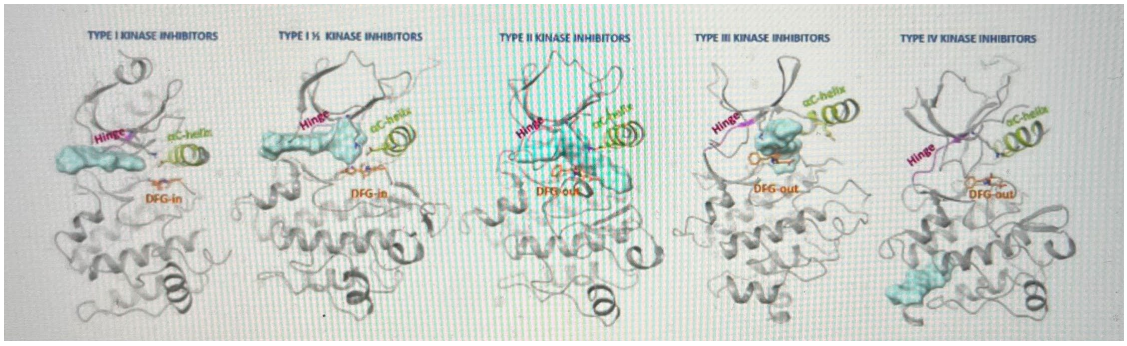


Figure 1. The structures of the 6 types of kinase inhibitors. The indicator of weather the kinase is active or inactive, is the position of the C-helix together with the DFG motif. The ATP binding gatekeeper and cleft are shown in the structure as well. From Gluza, K., & Dobrzańska, M. (2016, June 16). New horizons in next-generation small molecule kinase inhibitors. Drug Target Review. https://www.drugtargetreview.com/article/12269/new-horizons-next-generation-small-molecule-kinase-inhibitors/

RTKs, receptor tyrosine kinases, is one of the most common targets for anti-cancer drugs. Activation of these targets have been linked to the downstream signaling involving pivotal cytoplasmic kinases being activated. In turn, this causes increased cell growth and survival, especially in cancer cells, and is found to contribute to the progression and spreading of cancer. In many cancers, the activation and overexpression of these RTKs leads to promotion in cancer cell growth and survival, contributing to cancer-associated angiogenesis. So, by preventing and regulating these RTKs, we are able to control and manage cancer cell growth. To go more in detail, scientists and researchers have observed that the activation of tyrosine kinase leads to a

downstream signaling cascade- which sends a signal through a certain pathway affecting various different growth factor receptors. These growth factor receptors, when activated, can have a big effect on the development and progression of neoplastic diseases, like cancer.

There have been many FDA-approved kinase inhibitors that have made it past clinical trials and into general use for cancer patients, one of which includes Crizotinib. This drug, manufactured by Xalkori, is a small molecule inhibitor drug used to treat NSCLC (non-small cell lung cancer) and ALCL (anaplastic large cell lymphoma). It can be administered orally through a capsule and works by blocking the action of a natural substance, Tyrosine, which is needed to help cancer cells multiply and grow.

Small Molecule MMPs, HSPs Inhibitors

MMPs, Matrix metalloproteinases, are a group of endopeptidases like the protein kinase. However, the difference between them is their functions- MMPs are involved in the degradation of extracellular matrices (See Figure 2), which is known for promoting cell invasion and migration. There are over 20 MMPs that are naturally in humans, and they are generally regulated by the TIMPs (tissue inducers of metalloproteinases). When a patient has cancer, certain gelatinases like MMP-2 and MMP-9 turn to target signaling pathways and aggravate cancer cell migration and invasion. This causes the promotion of cancer-related tumor growth and metastasis spreading. However, these MMPs did not find great success at clinical trials and came with certain side effects making it less desirable than Kinase inhibitors, for example. The main reason why they were not able to pass the clinical trials was because of the fact that the MMP inhibitors would non-specifically bind to a variety of different MMPs in the body- including a few that were not identified as having cancer-promotion functions. This means that certain normal, healthy MMPs are harmed which can lead to various adverse side effects in the body.

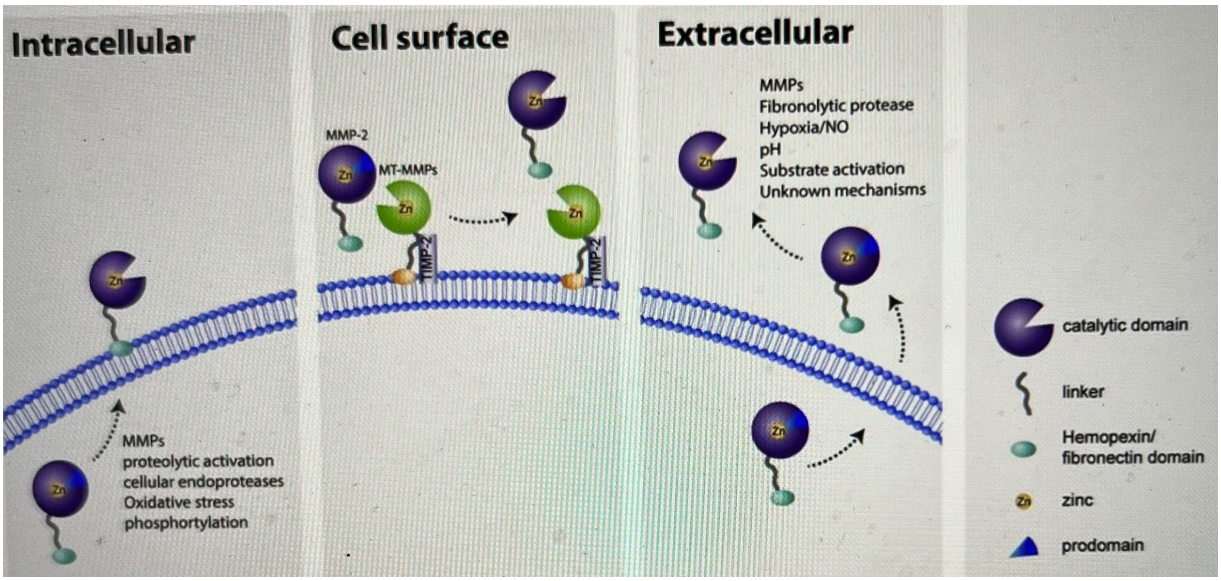


Figure 2. Schematic representing different types of MMP activation. These different types of activation of MMPs are what case the degradation of extracellular matrices, resulting in promotion of cancer cell invasion and migration. From Gaffney, J., Solomonov, I., Zehorai, E., & Sagi, I. (2015, May 1). Multilevel regulation of matrix metalloproteinases in tissue homeostasis indicates their molecular specificity in vivo. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0945053X15000268

HSPs, Heat shock proteins, are chaperons that are responsible for folding and transporting proteins across the cellular membrane. This is related to cancer progression and aggression because it is also responsible for the folding and transport of oncoproteins. These oncoproteins play an important role in many signaling pathways and are found to support and promote cancer. Through extended and deep research, scientists have observed that the expression levels of HSPs are particularly high when a patient has cancer, when compared to a normal person. These high expression levels of HSPs have been linked to resistance to chemotherapy and inhibition of apoptosis (C. Soti, P. Csermely). So, through the use of HSP inhibitors, scientists were able to regulate the expression levels of HSPs, which in turn resulted in a patient being less resistant to chemotherapy and more open to cancer-cell apoptosis inside their body. This allowed a slower progress in cancer cell growth and allowed room for cancer-management- hence why it is used as a target for targeted cancer inhibitors.

Small Molecule Proteasome Inhibitors

Proteosomes are large enzymes in the body that are expressed in the nucleus and cytoplasm of all eukaryotic cells. They are mainly responsible for protein degradation and play roles in maintaining cellular protein homeostasis. They are responsible for various tasks regarding cell survival, proliferation of malignant cells, and DNA repair (A. Nunes, C. Annunziata, 2019). The small molecule proteosome inhibitors work on a specific pathway known as the UPP, ubiquitin proteasome pathway. This pathway is known to help maintain homeostasis at a cellular level, and also favors cancer cell survival by promoting cell proliferation and inhibiting apoptosis of tumors. The UPP is involved in degradation of cell cycle regulators and proteolysis of various cyclin kinases, both of which contribute to transition (from one phase to another) of the cell cycle. The UPP plays a major role in tumor cell survival and progression due to the resistance to cancer cell aptosis. Through the use of proteosome inhibitors, scientists were able to prevent the degradation of the cell cycle and aptotic regulators. This lowered the efficacy and survival rate of cancer cells, allowing for ease of cancer management and therapy.

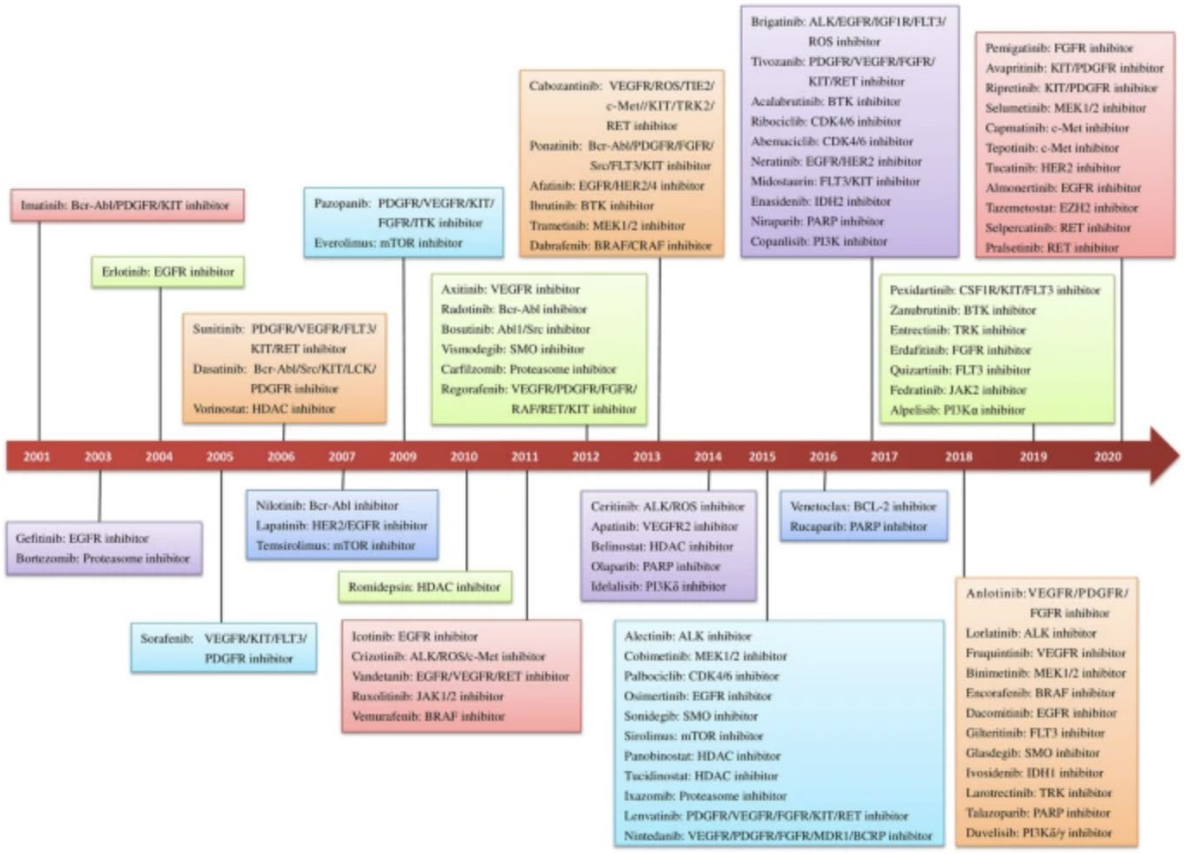
One example of a small molecule proteasome inhibitor is bortezomib, manufactured by Velcade. It is mainly used to treat various special cancers, including renal carcinoma, mantle cell lymphoma, and multiple myeloma. Bortezomib was shown to promote apoptosis, or cell death, of cancer cells and had tumor suppressing abilities. It was able to successfully suppress the p53 gene, which led to promotion in cancer cell aptosis. The main disadvantage of Bortezomib comparing to other competing drugs (like oprozomib, ixazomib, and marizomib) is that Bortezomib must be administered through injection, whereas these other inhibitors are able to be orally administered. However, the use of UPP-targeting drugs during clinical trials were linked with some adverse effects like thrombocytopenia and peripheral neuropathy. Additionally, when the patients were taking bortezomib- the researchers noticed that the cancer in their bodies eventually started developing resistance to the drug.

Concluding Statements - Future Outlooks and Limitations

Currently, there are exactly 89 small-molecule drugs designed to treat cancers which have been approved by the FDA and/or NMPA. Although molecular biology and use of targeted drugs have been a relatively long researched area, it has only gained attention of the general public over the last decade. Consequently, the development and application of small molecule drugs – which can use the knowledge of molecular structure in order to effectively target intracellular and extracellular cell – have entered at a rapid development stage. As a result, over the last decade or so, the success of small molecule targeted cancer drugs has been of higher success than conventional chemotherapy, and other types of traditional cancer therapy.

However, the rate at which new drugs are researched and developed are very slow- with many of them failing at clinical phases (See Figure 3). This is mainly due to the various limitations that small molecule drugs

bring, as well as the limited experience we have in the field. One of these limitations include the body developing drug resistance- after a period of clinical use. The drug-resistance that is developed by the body after period of use of anti-cancer drugs have mainly been caused by gene mutations, amplifications, apoptosis.



neline for the approval of small-molecule targeted anti-cancer drugs

Figure 3. A timeline showing the approval, targets, and name of small-molecule inhibitors for cancer treatment. From Zhong, L., Li, Y., Xiong, L., Wang, W., Wu, M., Yuan, T., Yang, W., Tian, C., Miao, Z., Wang, T., & Yang, S. (2021, May 31). Small molecules in targeted cancer therapy. Signal Transduction and Targeted Therapy.https://www.nature.com/articles/s41392-021-00572-w?error=cookies_not_supported&code=79503ca7-6a44-488f-9834-8fe078a1b219#Fig1

The leading reason that contributes to cancer drug resistance is gene mutations. There are two main types of gene mutations: gene mutations induced by the drugs, and drug-resistant mutations that have already existed by chance. When the treatment has just started, the cancer cell with no mutations dominates and decrease the number.

However, when a period of time has passed and the drug is fully introduced to the cells, the cancer cells with no mutations will be killed allowing the cells with resistant mutations to become mainstream and split across the population.

Another common reason contributing to cancer drug resistance is amplification. When certain genes, like MET, CSC, and efflux transporters, are amplified, they tend to resist the inhibitor by hindering it from doing its job. For instance, the CSC theory says that different cells withing a tumor, all originate from the same

single subpopulation of cells with self-renewable and differentiation capabilities. Due to this theory connecting the methodologies of tumor cells and stem cells, we can conclude that amplifying CSC gene, which causes drug resistance and recurrency to increase, at the original subpopulation level can cause the rest of the tumor cell population to change- allowing for resistance to drugs across all tumor cells.

Aside from gene mutations and amplifications, another major challenge for anti-cancer drugs at a clinical trial phase is the low efficacy. The lower efficacy of targeted anti-cancer drugs, when compared to the traditional means of cancer treatment, is why it has not been adopted as the main form of cancer treatment yet. Currently, the reason why many patients go through chemotherapy, radiation, and surgery for cancer treatment is that anti-cancer drugs are not very versatile, as of now, and have only worked in limited number of patients. Due to the pre-existing mutations explained earlier, less than 20% of patients with NSCLC are sensitive to EGFR inhibitors (type of small molecule inhibitor). This means that these EGFR inhibitors have less than 20% chance of efficacy in treating a patient with NSCLC.

In conclusion, the current state of small molecule drugs, although seemingly promising, is not very ready for providing efficient and effective treatment for cancer at a public level. Due to the various benefits that small molecule drugs bring (like low cost), it can be used in the near future to treat cancer in patients around the world (no matter where they life, whether it be a low- or middle-income country). Along with continuing to explore current cancer targets and increasing the efficiency of current drugs on the market, researchers should also explore new types of cancer treatments and other pathways that play a significant role in cancer and tumor cells. Additionally, it is important to note that the power of small molecule drugs have been researched to work well when combined with other means of cancer treatment like tumor immunotherapy. So, although scientists have implemented this and gotten it over clinical trials yet, it is hopeful to believe that in the next decade, small molecule drugs like ADC and PROTAC will gain significant development and improvement. Soon, there definitely be new small molecule drugs on the public market with increased efficacy- and further & continued research in this field may result in a revolutionary medicine being discovered. There is no doubt that small-molecule targeted drugs will continue to be in the mainstream research area for cancer treatment, given their unique advantages over macromolecule drugs.

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