Protein Kinase Inhibitors: Inventing New Patent Strategies

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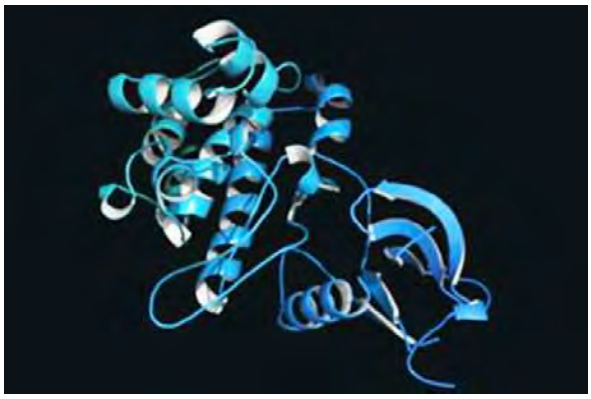

Illustration of Protein kinase inhibitor

Protein kinase inhibitors are the second most targeted group of drug targets, after G-protein coupled receptors, as the human body encodes over 500 protein kinases. Protein kinase inhibitors work by blocking the action of one or more protein kinases. Protein kinases are enzymes that add a PO4 phosphate group to an amino acid, generally serine, threonine, or tyrosine. Protein kinase inhibitors were first developed to treat cancer, which causes hyperactive protein kinases. By inhibiting overactive protein kinases, kinase inhibitors can regulate cell signaling pathways and stop uncontrolled cell growth and oncogenesis.

There are several different types of protein kinase inhibitors, classified based on the structure of the enzyme bound antagonist complex. The majority of inhibitors target the APT-site of the kinase in its active state. Type II inhibitors induce a distinguishable complex, as they occupy an additional hydrophobic pocket. Recently, naturally occurring kinase inhibitors have been discovered as a new class of kinase inhibitors, which can bind directly to tyrosine kinases to alter phosphorylation. Many of these naturally occurring kinase inhibitors have antioxidant properties and are sold on pharmacy shelves including resveratrol, quercetin, curcumin, and chrysin.

Protein kinase inhibitors were first discovered for the treatment of cancer in the late 1970's and early 1980's, when the first oncogene was found to be a protein kinase.

Following this discovery, the first protein kinase inhibitors, known as naphthalene sulphonamides were synthesized. This led to further research and development until the first protein kinase inhibitor was approved by the Food and Drug Administration (FDA) in 2001, known as imatinib or Gleevec. This medication is used to treat a number of cancers, for example, chronic myeloid leukemia, gastrointestinal stromal tumors, acute lymphoblastic leukemia, as well as several others. Protein kinase inhibitors are ideal treatment options for patients diagnosed with cancer as they provide targeted therapy and limited toxicity, as compared to chemotherapy which can have a very narrow therapeutic index.

Currently, 37 kinase inhibitors have received FDA approval for different oncology-based indications, and over 150 kinase inhibitors are currently in clinical trials. Roughly 25% of all drug development is currently directed towards kinase inhibitors. Kinase inhibitors are being studied for many uses beyond oncology, including diseases such as liver ischemia, Crohn's disease, osteoarthritis, and ischemia reperfusion. At the present moment, 2 kinase inhibitors have been approved for non-oncology-based treatments. These include Xeljanz approved for arthritis and Ofef approved for pulmonary fibrosis.

As kinase inhibitors have exhibited potentials far beyond oncology uses, the question remains, does a drug found to treat a new indication need a new patent? This is a complex problem, that can be traced back to aspirin.

Aspirin, also known as acetylsalicylic acid, was synthetized in 1899, and a patent was granted to Frederick Bayer & Company on March 6, 1899 for acetylsalicylic acid. Under the Patent Act of 1836, a patent filed in 1899 would have been valid for 14 years with an extension of up to an additional 7 years. However, patents for aspirin continued to be filed today. This is done through a process known as drug repositioning; whereby, approved drugs and compounds are found to treat a different disease state. For example, Viagra was originally discovered to treat pulmonary hypertension, and only later on was it discovered to also be able to treat erectile dysfunction. Furthermore, the well-known antibiotic erythromycin, used to treat bacterial infections of the skin and respiratory tract, was repositioned to treat a condition of delayed gastric emptying known as gastroparesis.

Through the process of drug repositioning, new methods of treatments are discovered and utilized. When a drug is first discovered for its initial use, a patent is generally obtained to cover the chemical compound, as well as patents that may cover methods of treating a disease state with the compound. After patents for the original compound have expired, new filings can be obtained by others pertaining to new methods of treatment or use that were not covered originally. For example, a search of recent aspirin filings shows patents

obtained in the past five years showing unique methods for preparing aspirin, combining aspirin together in dosage forms with other medications, as well as stable aspirin preparations. These filings come almost 120 years after the original patent for acetylsalicylic acid was first obtained.

A review of patent filings at the United States Patent and Trademark Office (USPTO) indicates that the number of kinase inhibitor filings is on the rise. Since 2001, there have been 23,198 patents applications relating to kinase inhibitors filed at the USPTO. Over the past five years the number of patent applications filed relating to kinase inhibitors has continued to rise, with the exception of 2015. Furthermore, the number of patent applications filed relating to kinase inhibitors over the past 5 years accounts for 40% of all filings of patent applications relating to kinase inhibitors since 2001. As of early December 2018, there have been 1,915 patent applications relating to kinase inhibitors filed.

Year	# of Patent Applications
2014	1,847
2015	1,796
2016	1,960
2017	2,024
2018	1,915

Number of patent applications filed relating to Kinase Inhibitors

As scientists continue to discover and explore drug discovery in this area, we can expect to see an increase in patent filings over the next few years. This may include new drugs that have been discovered, as well as old drugs that have been shown to do a new trick. Either way, as 2018 has drawn to a close, we can expect 2019 to be a year filled with exciting medical breakthroughs and innovation.