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Research Progress of Small-Molecule Targeted Anti-Tumor Drugs

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Abstract. At present, malignant tumor is still the second most fatal disease in the world. Different from conventional treatment methods of malignant tumor such as surgery, chemotherapy and radiotherapy, molecular targeted therapy, as a new method of tumor treatment, is becoming a hot spot in tumor treatment research with its advantages of high efficacy, low toxic side effects and high specificity. With the continuous development of molecular biological mechanisms and the continuous promotion and support of the biotechnology industry, the exploration of tumors has also further deepened. More and more tumor specific molecular targets have been recognized by people, followed by the development of anti-tumor small molecule targeted drugs. The thesis aims to summarize and review the tumor targets and the corresponding small molecule targeted drugs according to the different molecular biological characteristics of tumors. In the March 2011 issue of Cell, professor Douglas Hanahan and professor Robert A. Weinberg published a review: Hallmarks of Cancer: The Next Generation, which summarized the hot spots and advances in oncology in the last decade, and expanded the six features of tumor cells to ten. These ten characteristics are as follows: Self-sufficient Growth Signals, Insensitivity to Antigrowth Signals, Resisting the Cell Death, Limitless Replicative Potential, Sustained Angiogenesis, Tissue Invasion and Metastasis, Avoiding Immune Destruction, Tumor Promotion Inflammation, Deregulating Cellular Energetics, and Genome Instability and Mutation. In this thesis, we elaborate the current research progress of small molecule targeted anti-tumor drugs from the classification of ten characteristics of tumors.

Key words: Anti-tumor Drugs, Chemosynthetic Small Molecule Drugs, Molecular Targeted Therapy, Target.

SELF-SUFFICIENCY IN GROWTH SIGNALS

Normal tissue cells can accurately regulate the production and release of growth-related signals and factors, which enables cells to enter the normal growth and differentiation cycle, maintaining normal tissue structure and function. Tumor cells gradually attribute to self-sufficiency in growth signals by disrupting the regulation of signaling pathways. Most signaling pathways that maintain tumor cell growth rely on cell surface receptors, particularly molecules that contain the tyrosine kinase domain. This study mainly introduces mitogen activated protein kinase (MAPK) signaling pathway and epidermal growth factor receptor (EGFR) signaling pathway.

MAPK Signaling Pathway

The MAPK signaling pathway can regulate cell proliferation, survival and differentiation. This pathway transmits signals from the extracellular to the cell nucleus via specific cascade phosphorylation of RAS, RAF, MEK and ERK. The RAF family consists of the serine-serine kinases ARAF, BRAF and CRAF. The phosphorylase RAF protein further activates MEK1 and MEK2, which in turn phosphorylates ERK1 and ERK2, activates transcription factors, regulates cell proliferation, survival and differentiation. Therefore, in recent years, small molecule inhibitors targeting MEK1 and MEK2 have been gradually recognized and presented with promising clinical effects. In 2015, Cobimetinib fumarate (Figure 1), developed by Exelixis and Genentech Inc, came into the market for the treatment of advanced melanoma and melanoma, which can be used in combination with Vemurafenib for the treatment of advanced

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inoperable Metastatic melanoma orifice. However, most patients who take these drugs can get resistance and cause tumor recurrence. In 2013, Trametinib bimethyl sulfoxide (Figure 2), developed by Glaxo SmithKline, appeared on the market for the treatment of non-small cell lung cancer, metastatic melanoma, BRAF mutated melanoma, and Melanoma.

Binimetinib (Figure 3) developed by Array BioPharma, Novartis and Pierre Fabre Medicament for the treatment of carcinoma of fallopian tube, colorectal cancer, peritoneal cancer, ovarian cancer, and melanoma has already been in the NDA stage. Developed by Array BioPharma and AstraZeneca, Serumetinib Sulfate (Figure 4) for the treatment of differentiated thyroid carcinoma, non-small cell lung cancer and uveal melanoma has already been in Phase III clinical.

High-frequency BRAF mutations are common in melanoma, thyroid cancer, colorectal cancer, etc. Therefore, in recent years, small molecule inhibitors targeting BRAF have been gradually recognized and presented with promising clinical effects. In 2011, the small molecule inhibitor Vemurafenib (Figure 5) approved by FDA significantly inhibited BRAF (V600E), CRAF, and wild-type BRAF for the treatment of advanced or unresectable melanoma. Dabrafenib, approved in 2013, is a reversible inhibitor of ATP competition that selectively inhibits BRAF (V600E) for the treatment of advanced metastatic metastases or unresectable melanoma.

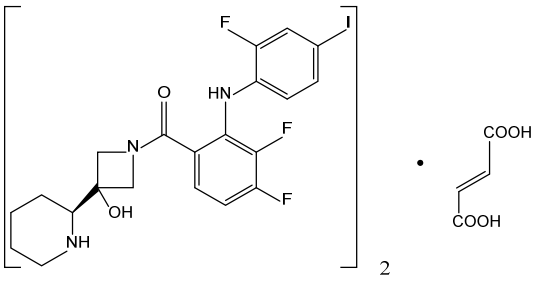

FIGURE 1. Cobimetinib fumarate

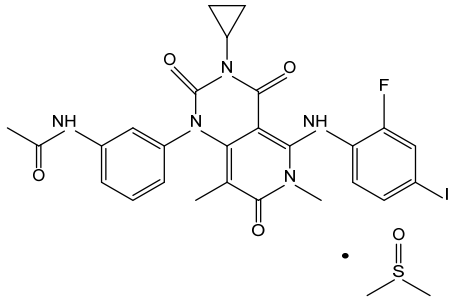

FIGURE 2. Trametinib bimethyl sulfoxide

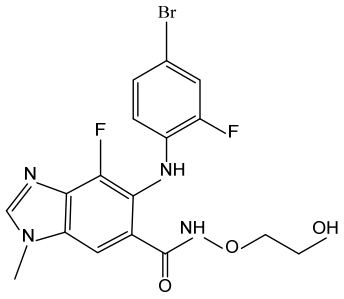

FIGURE 3. Binimetinib

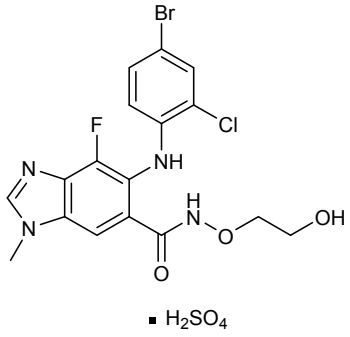

FIGURE 4. Selumetinib Sulfate

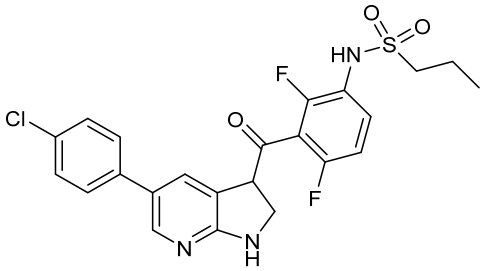

FIGURE 5. Vemuraafenib

EGFR Signaling Pathway

EGFR is an epidermal growth factor receptor on the surface of cell membranes. It has tyrosine kinase (TK) activity. It is encoded by the proto-oncogene c-erbB-1 with a molecular weight of 170 kDa. EGFR contains three regions, an extracellular region, a transmembrane region, and an intracellular region with TK activity. When EGFR unites with its ligand, its conformation changes, forming homodimerization or allodimerization, which in turn activates the tyrosine kinase, phosphorylating receptors' own tyrosine residue. Phosphorylated tyrosine kinases recruit SH2-domain-containing signal transduction proteins and activate various downstream signaling pathways such as MAPK, P13K/Akt, and STAT, etc. Abnormal signals ultimately lead to malignant phenotype such as uncontrolled cell proliferation and inhibition of apoptosis.

EGFR is highly expressed in epithelial-derived tumors, and its targeted drugs also have achieved remarkable efficacy in tumor therapy. The mechanism of small molecule inhibitors of EGFR tyrosine kinase is mainly to block the activation of tyrosine kinase through the competitive binding of ATP and ligand binding sites, thereby inhibiting the activation of EGFR, thus further inhibiting the growth of tumor cells and promoting apoptosis.

Currently, available drugs targeting the EGRFR signaling pathway include Neratinib maleate (Figure 6) developed by Pfizer and Puma Biotechnology in 2017 for the treatment of HER2 positive metastatic breast cancer. In 2017, Baricitinb (Figure 7), developed by Ariad, was used for the treatment of anaplastic lymphoma kinase positive non-small cell lung cancer and metastatic small cell lung cancer. In 2016, Ollinginib (Figure 8) developed by Hanmi, Boehringer Ingelheim and ZAI Lab, was used to treat non-small cell lung cancer. In 2015, Osimertinib Mesylaye (Figure 9), developed by AstraZeneca, was used to cure non-small cell lung cancer. In 2013, Afatinib dimaleate (Figure 10), developed by Boehringer Ingelheim, was used to treat metastatic squamous cell non-small cell lung cancer and non-small cell lung cancer. In 2011, Icotinib Hydrochloride (Figure 11) developed by Beta Pharmaceuticals was used for the treatment of non-small cell lung cancer. In 2007, Lapatinib ditosylate Hydrate (Figure 12), developed by Glaxo SmithKline, was used to treat ER-positive metastatic breast cancer, HR-negative-HER2-positive metastatic breast cancer, breast cancer, HER2-positive metastatic breast cancer and HER2-positive advanced breast cancer. In 2004, Erlotinib Hydrochloride (Figure 12), developed by Genentech and Astellas, was used to treat non-small cell lung cancer, metastatic non-small cell lung cancer and pancreatic cancer. In 2002, Gefitinib (Figure 13), developed by AstraZeneca, was used as therapy for non-small cell lung cancer and metastatic non-small cell lung cancer.

The drugs currently in the NDA stage are: Pyrotinib Maleate (Figure 14), developed by Jiangsu Hengrui Pharma, for the treatment of HER2-positive metastatic breast cancer. Developed by Celgene and Clovis Oncology, Rociletinib Hydrobromide (Figure 15) will be used for the treatment of non-small cell lung cancer.

The drugs in clinical phase III are as follows: Naquotinib, developed by Astellas, for the treatment of non-small cell lung cancer and solid tumors (Figure 16). Varlitinib Ditosylate (Figure 17) developed by Array BioPharma for the treatment of gastric cancer, breast cancer, solid tumor and pancreatic cancer. And Tesevatinib (Figure 18), developed by Exelixis and Kadmon, for the treatment of non-small cell lung cancer and autosomal dominant polycystic kidney disease.

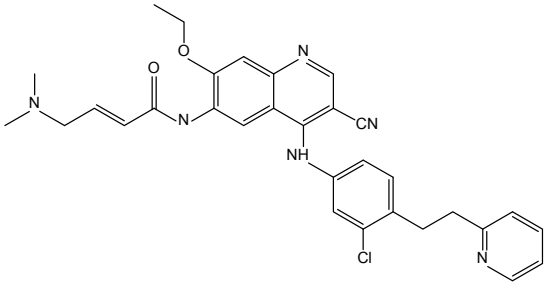

FIGURE 6. Neratinib maleate

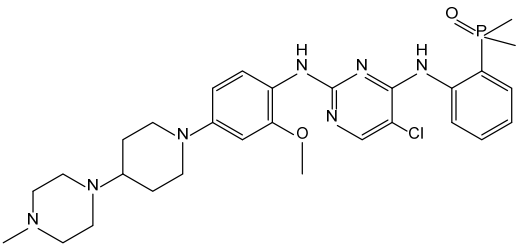

FIGURE 7. Baricitinb

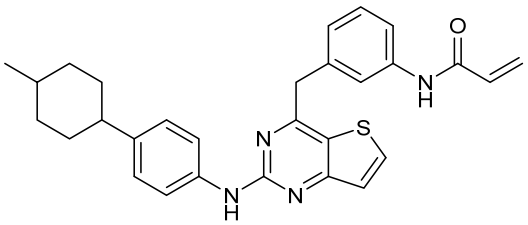

FIGURE 8. Olmutinib

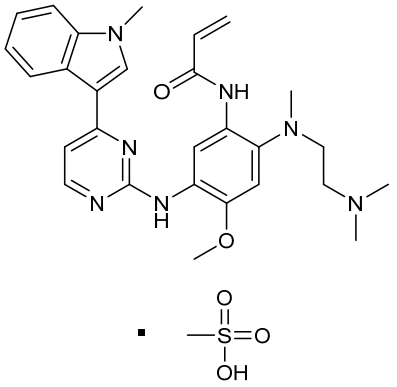

FIGURE 9. Osimertinib Mesylaye

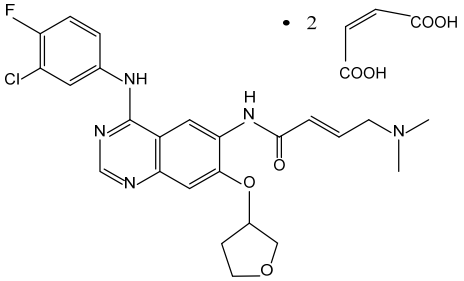

FIGURE 10. Afatinib dimaleate

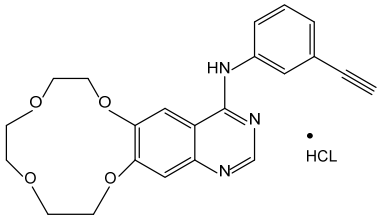

FIGURE 11. Icotinib Hydrochloride

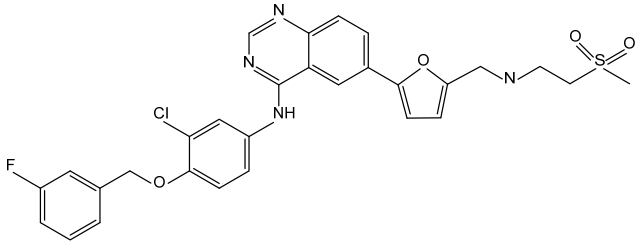

FIGURE 12. Erlotinib Hydrochloride

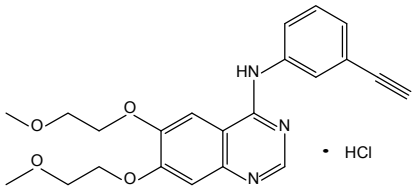

FIGURE 13. Gefitinib

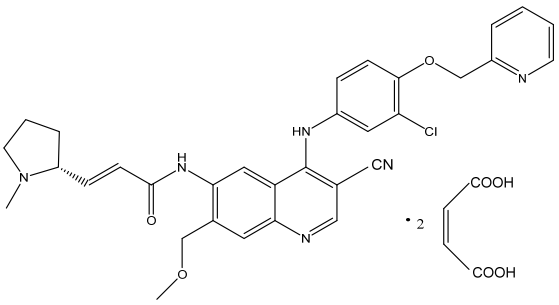

FIGURE 14. Pyrotinib Maleate

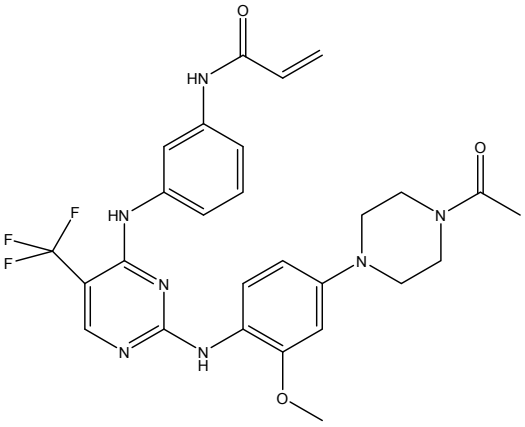

FIGURE 15. Rociletinib Hydrobromide

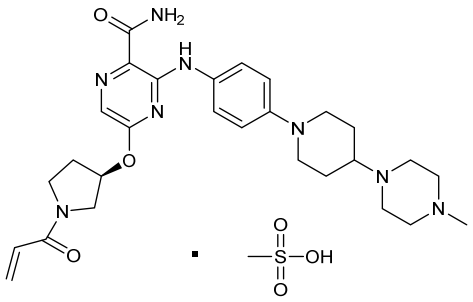

FIGURE 16. Naquotinib

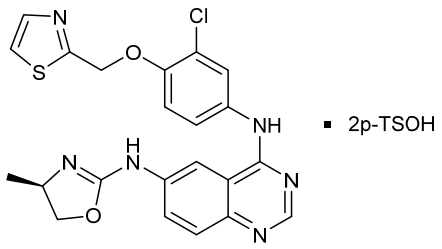

FIGURE 17. Varlitinib Ditosylate

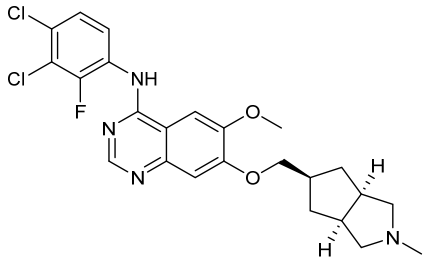

FIGURE 18. Tesevatinib

INSENSITIVITY TO ANTIGROWTH SIGNALS

In addition to maintaining self-sufficient growth signals, tumor cells must also avoid strong negative regulatory growth signals, the most common of which depends on tumor suppressor genes. Among many tumor suppressor genes, p53 is the most famous. In all malignant tumors, mutations in the gene appear in more than 50% of cases. As a transcription factor, p53 controls the initiation of the cell cycle. Meanwhile, p53 can promote the expression of ubiquitin-protein ligase MDM2 and MDM4. MDM2 can negatively feedback and regulate p53 for degradation via ubiquitination, and finally p53 and MDM2/MDM4 are in an equilibrium state.

Based on this biological mechanism, Roche conducted a study of the small molecule inhibitor RG7112 (Figure 19) in 2010. Experiments indicated that RG7112 can induce the up-regulation of p53 and MDM2 expression, which is of certain clinical benefits for cancer patients. Relevant research has entered the clinical trial stage. RG7388 (Figure 20) is the second generation MDM2 small molecule inhibitor reported by Roche. The Phase I clinical trials initiated in 2011, which were used to evaluate treating advanced malignant tumors and the efficacy and safety in the treatment of acute myeloid leukemia, alone or in combination with cytarabine, and drug interactions in the treatment of solid tumors joint with posaconazole. APG-115, a MDM2-p53 inhibitor developed by Jiangsu Yasheng, was clinically approved by the FDA in 2016 and CFDA in 2017. This is the first domestic anti-tumor drug MDM2-p53 inhibitors that came into the clinical. It can form high-efficiency inhibition on sarcoma, primary liver cancer, primary gastric cancer and other tumors.

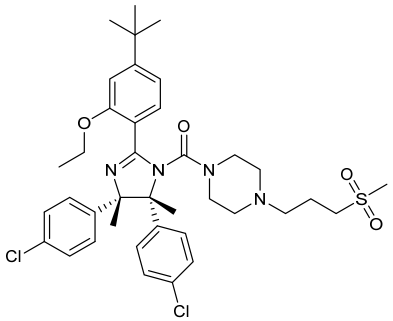

FIGURE 19. RG7112

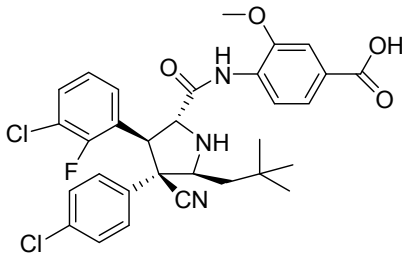

FIGURE 20. RG7388

RESISTING CELL DEATH OF TUMOR CELLS

Cell death, especially apoptosis resistance, plays an important role in the tumorigenesis and progression of malignant tumors. Apoptosis not only plays an important role in tumorigenesis and progression of tumors, but also chemotherapy, radiotherapy and biotherapy are mainly used to treat tumors by inducing apoptosis. The Bcl-2 protein family is an important kind of apoptosis regulators, which are divided into three types, inhibiting apoptotic proteins (Bcl-w, Bcl-2, McL-1, Bcl-xl, etc.), promoting apoptotic proteins (Bak, BaX, Bok, etc.) and pro-apoptotic proteins (Bim, Bid, Puma, etc.) that only contain BH3 domain. Bcl-2 regulates apoptosis by forming a dimer with Bax and its own dimerization. The balance between Bcl-2 and Bax protein in cell death signal checkpoints determines cell survival or apoptosis. Due to its high expression in cancer cells, Bcl-2 family protein inhibitors can selectively play an anti-tumor role in tumor cells. At present, Bcl-2 family protein has become one of important targets for anticancer drug development. A large number of bcl-2 family protein small molecule inhibitors are in different development stages.

However, the Bcl-2 target is difficult to formulate drugs, mainly for several reasons: 1. The action mechanism of Bcl-2 stationing is PPI (protein-protein interaction), and the binding interface of the target is relatively large. 2. Among many targets of similar mechanisms of action, the Bcl-2 target binding pocket is relatively large, with approximately 13 to 15 amino acids. 3. The Bcl-2 target is located on the mitochondrial membrane. Since the mitochondrial cells have a double membrane, the drug needs to enter the cell through the cell membrane and then act on the mitochondrial membrane. In 2016, Venetoclax (Figure 21), developed by Abbott, was launched for the treatment of chronic lymphocytic leukemia. This is the world's first commercially available Bcl-2 inhibitor.

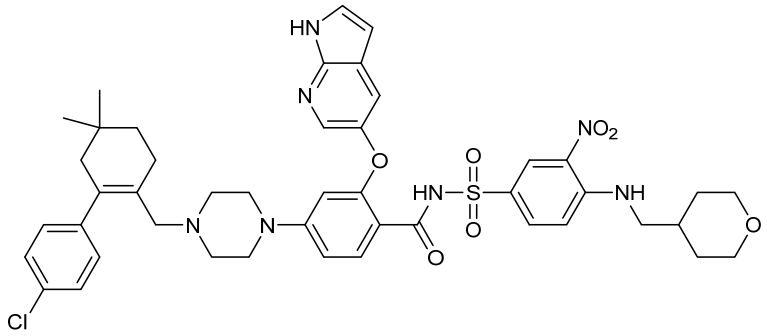

FIGURE 21. Venetoclax

GENOME INSTABILITY AND MUTATION

DNA damage is always accompanied by mammalian cells. Failure to repair it timely and accurately will further lead to genomic instability, which is an important prerequisite and feature of cancer. DNA damage repair mechanisms play a significant role in maintaining genomic stability. Tumor cells can activate the damage repair mechanism of their own DNA, leading to drug resistance of radiotherapy and chemotherapy. Therefore, blocking DNA repair pathways is an important approach to tumor therapy. Poly (ADP-ri-bose) polymerase [PARP] is a single-stranded DNA repair enzyme that conducts excision repair of single-stranded damage during DNA replication through a base excision repair pathway, participating in DNA replication and transcription and maintaining the stability of the genome. Therefore, PARP is considered to be the sensory receptor of DNA damages. PARP inhibitors were initially developed to enhance the efficacy of chemotherapy drugs, and were later mainly targeted at DNA repair- defective cancers.

In 2014, Lyparza (Olaparib) developed by AstraZeneca (Figure 22) was approved to be marketed for the treatment of advanced ovarian cancer with BRCA gene deletion in female patients with targeted inhibition of PARP. In 2016, Rucaparib (Figure 23), developed by Pfizer and Clovis Oncology, was marketed for the treatment of ovarian cancer and advanced ovarian cancer with BRCA mutations. In 2017, Niraparib (Figure 24), developed by Merck, Tesaro, ZAI pharmaceutical and Janssen, came into the market for the treatment of recurrent epithelial ovarian cancer, carcinoma of fallopian tube and primary peritoneal cancer.

Currently, RARP inhibitors in phase III clinical trials include: Veliparib (Figure 25) developed by AbbVie for the treatment of HER2-negative metastatic breast cancer, ovarian cancer, metastatic non-small cell lung cancer, BRCA-positive breast cancer and breast cancer; Talazoparib (Figure 26) developed by Medivation for the treatment of metastatic breast cancer and solid tumors.

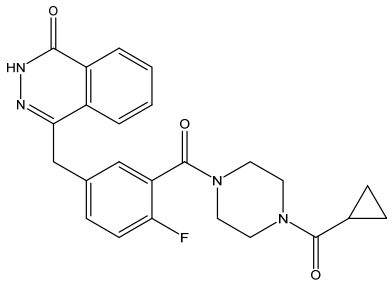

FIGURE 22. Olaparib

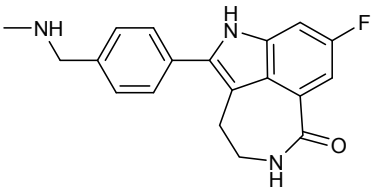

FIGURE 23. Rucaparib

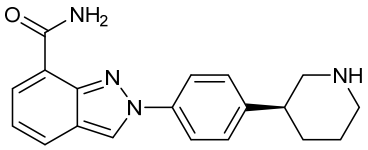

FIGURE 24. Niraparib

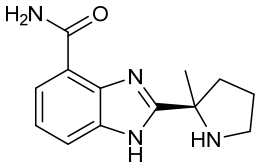

FIGURE 25. Veliparib

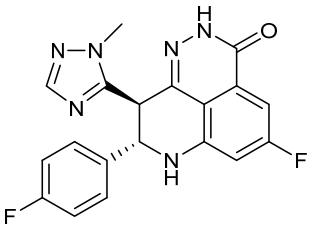

FIGURE 26. Talazoparib

SUSTAINED ANGIOGENESIS OF TUMOR

The formation of neovascularization plays an important role in the occurrence, development and metastasis of tumors. Tumor angiogenesis is a common feature of all solid tumors. Data demonstrated that the growth and metastasis of malignant tumors must rely on abundant nutrient supply. Without angiogenesis, the growth volume of tumor tissue cultured in vitro should not exceed 4 mm3, and the tumor in vivo should not exceed 1-2 mm3. Vascular endothelial growth factor (VEGF) and its receptor VEGFR can specifically promote the division, proliferation and migration of endothelial cells, and play an important role in the process of tumor neovascularization. Therefore, VEGF and VEGFR have become the most widely used targets for cancer treatment. Monoclonal antibody therapeutics targeting VEGF have been widely used in the clinical treatment of a variety of solid tumors, such as FDA-approved Bevacizumab against VEGF/VEGFRs, mainly for the treatment of metastatic colorectal cancer, non-small cell lung cancer, metastatic breast cancer, metastatic renal cell carcinoma, and glioma.

Small molecule drugs targeting VEGF are still in clinical trials. Small molecule drugs for VEGFRs are now available on the market. In 2018, Anlotinib Dihydrochloride (targeting VEGRF3/2) (Figure 27), developed by Chia Tai-Tianqing, came into the market for the treatment of non-small cell carcinoma. Since 2015, Lenvatinib Mesylate (for VEGFR3/2/1) (Figure 28), developed by Eisai has been marketed for the treatment of differentiated thyroid cancer, renal cell carcinoma, and advanced renal cell carcinoma, thyroid cancer and hepatocellular carcinoma. In 2014, Apatinib Mesylate apatinib (for VEGRF2) (Figure 29), developed by Jiangsu Hengrui Co., was launched for the treatment of metastatic gastric cancer. In 2012, Apatinib Mesylate (for VEGRF2) (Figure 30), developed by Pfizer, appeared on the market for the treatment of renal cell carcinoma. In 2012, Cabozantinib S-malate (for VEDFR3/2/1) (Figure 31), developed by Exelixis, was available for the treatment of renal cell carcinoma, advanced renal cell carcinoma and medullary thyroid carcinoma. In 2006, Sunitinib Malate (for VEGFR3/2/1) (Figure 32), developed by Pfizer, was marketed for the treatment of renal cell carcinoma, gastrointestinal stromal cancer, advanced renal cell carcinoma, pancreatic neuroendocrine tumor and gastric cancer.

The following drugs are in the DNA stage: Fruquintinib (for VEGFR3/2/1) developed by Hutchison Whampoa and Eli Lilly (Figure 33) for the treatment of gastric cancer, non-small cell lung cancer and colorectal cancer.

The drugs in Phase III clinical trials include: Orantinib (for VEGFR2) developed by Pfizer and Taiho Pharma (Figure 34) for the treatment of solid tumors and hepatocellular carcinoma; Sulfatinib developed by Hutchison MediPharma (for VEGFR2) (Figure 35) for the treatment of neuroendocrine tumors, thyroid cancer and biliary tract cancer; Tesevatinib (Figure 18) developed by Exelixis and Kadmon can also target VEGFRs; Dovitinib Lactate (for VEGFR2) developed by Novartis (Figure 35) for the treatment of cell carcinoma and solid tumors; Famitinib Malate (VEGFR3/2/1) developed by Jiangsu Hengrui Co., Ltd. (Figure 36) for the treatment of gastrointestinal stromal tumors, Lung cancer and liver cancer.

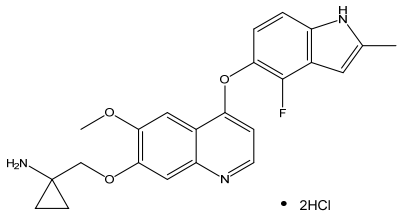

FIGURE 27. Anloinib Dihedrochloride

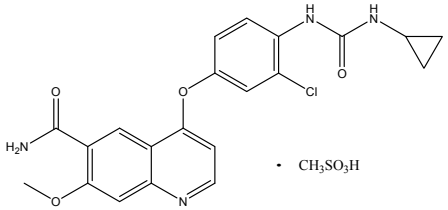

FIGURE 28. Lenvatinib Mesylate

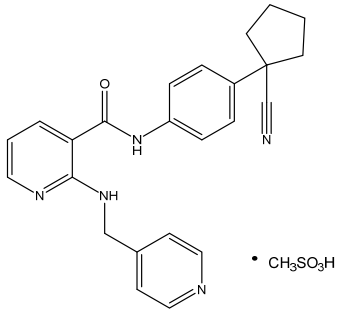

FIGURE 29. Apatinib Mesylate

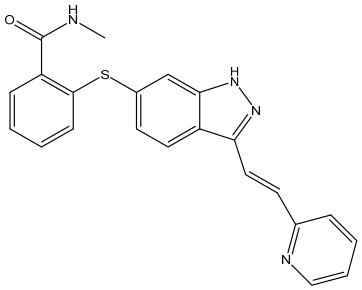

FIGURE 30. Axitinib

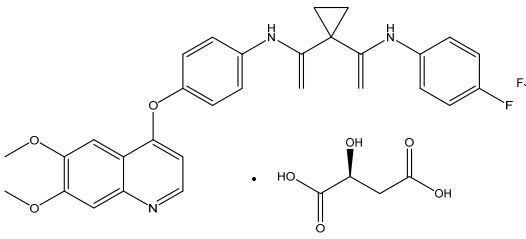

FIGURE 31. Cabozantinib S-malate

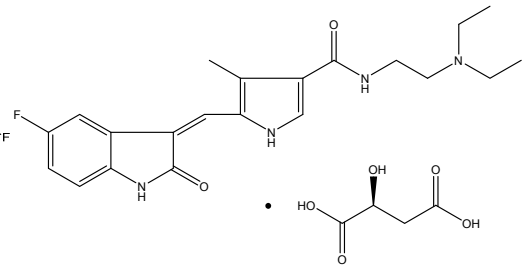

FIGURE 32. Sunitinib Malate

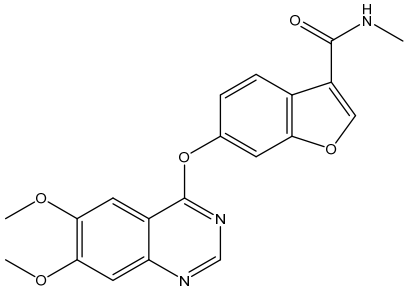

FIGURE 33. Fruquintinib

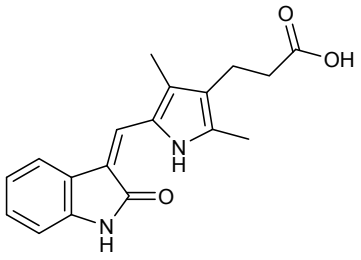

FIGURE 34. Orantinib

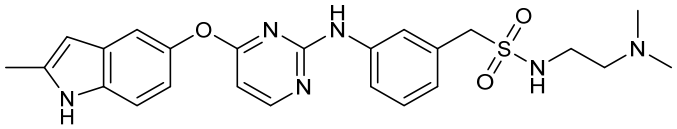

FIGURE 35. Sulfatinib

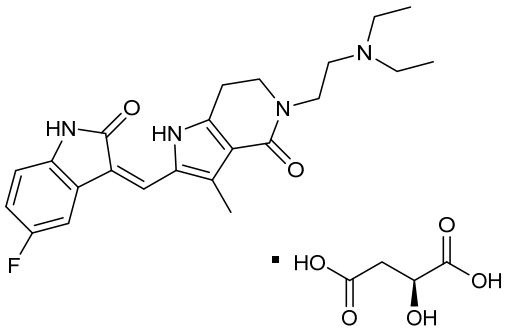

FIGURE 36. Famitinib Malate

TISSUE INVASION AND METASTASIS

Metastasis is another important biological feature of malignant tumors and a major bottleneck of clinical cancer treatment. Therefore, the study of targeted tumor metastasis is the key to treating tumors and improving the survival rate of cancer patients. In recent years, a more representative target is hepato-cyte growth factor (HGF). HGF is a polypeptide growth factor involved in the proliferation and migration of various cells, which has a significant inducing effect on tumor invasion and metastasis. The receptor for HGF is the Met transmembrane protein encoded by the proto-oncogene c-met. Many tumor cells overexpress Met. At present, many small molecule inhibitors targeted HGF/c-met have arrived at clinical research level.

The c-Met inhibitors that have been marketed include: Crizotinib (Figure 37), developed by Pfizer in 2011, for the treatment of non-small cell carcinoma, mesenchymal lymphoma, kinase-positive non-small cell carcinoma, and ROS1-positive non-small cell carcinoma; Cabozantinib S-malate (Figure 38), developed by Exelixis in 2012. However, these two inhibitors are not single target drugs. Besides c-Met, they also inhibite other targets, belonging to multi-target inhibitors.

The drugs in phase III clinical trials are as follows: Tivantinib (Figure 38) developed by first and third republic Hyoma Hakko Kirin Pharmaceutical for the treatment of hepatocellular carcinoma; Volitinib (Savolitinib) developed by Hutchison Whampoa and AstraZeneca (Figure 39) is used to treat gastric cancer, non-small cell carcinoma and renal cell carcinoma.

In addition to HGF, CDl47 molecules have aroused more and more attention in recent years. CDl47 molecules, also known as matrix metalloproteinase (MMPs) inducers, are widely highly-expressed in tumor cells and promote tumor invasion and metastasis by inducing the secretion of MMPs. At present, the monoclonal antibody agent Licartin targeting CDl47 has been used in the clinical treatment of hepatocellular carcinoma, and small molecule inhibitors against CDl47 have also entered the preclinical research stage (data unpublished).

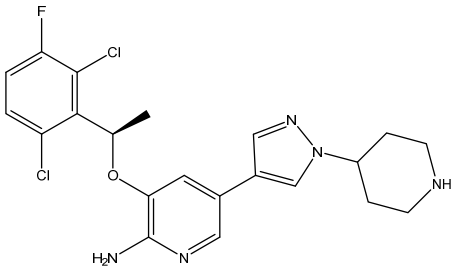

FIGURE 37. Crizotinib

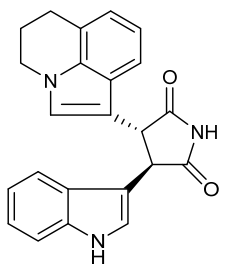

FIGURE 38. Tivantinib

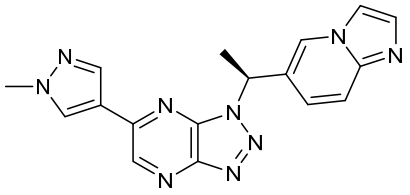

FIGURE 39. Volitinib

DEREGULATING CELLULAR ENERGETICS

The significant increase of tumor cell glycolysis is one of the basic features of tumor energy metabolism abnormalities. Rapidly, proliferating tumor cells take up a large amount of glucose through aerobic glycolysis for anabolic metabolism and energy production, namely the "Warburg effect". Key regulatory enzymes for glucose metabolism and lipid metabolism have attracted much attention. For instance, hexokinase II (HKII), lactate dehydrogenase A (LDHA), and fatty acid synthase involved in lipid metabolism are reported to participate in the metabolism of tumor cells and promote the proliferation of tumor cells. The inhibitors that block them also present the effects of significantly destroying tumor metabolism and inhibiting tumors. The glycolytic enzyme inhibitors studied at present include a 1 hexose kinase inhibitor such as 3-BrPA, a chloridamine 2 lactic dehydrogenase inhibitor such as inosine hypoxanthine nucleoside, gossypol 3 pyruvate kinase and enolization enzyme inhibitors such as inosine chitosan, L-cysteine and 6-phosphofrutokinase inhibitors and glyceraldehyde-3-phosphate dehydrogenase inhibitors, etc.

Studies have shown that 3-BrPA3- Bromopyruvic acid (Figure 40) has a significant inhibitory effect on the hepatoma cell line AS-30D that expresses a high glycolytic phenotype, although its research is in an early stage and the anti-cancer effect has not been reported. However, with the deepening of the research, glycolytic enzyme represented by 3-BrPA is expected to be a promising anti-cancer drug. [2]

The glutamine metabolism in amino acid metabolism has attracted much attention in recent years. The changes of glutamine metabolism in cancer cells play a essential role in the macromolecular biosynthesis of tumor cells, the regulation of signaling pathways and the maintenance of redox homeostasis. Therefore, intervention of this important metabolic process can be used as one of the strategies for cancer therapy. The current anti-cancer strategy of blocking glutamine metabolism is mainly via the key molecules targeting involved in the metabolism of glutamine.

For example, SLClA5(ASCT2) is a sodium dependent amino acid transporter that is mainly responsible for the transport of small molecule neutral amino acids, including glutamine. All the tumors dependent on glutamine highly express SLClA5, such as lung cancer, colon cancer, liver cancer, etc. GPNA small molecule inhibitors can suppress the glutamine uptake and induce ROS enrichment by combining ASCT2, thus inhibiting lung cancer cell growth. SLC7A5 (LATl) is a bi-directional translocator regulating outflows of cell glutamine and the inflow of leucine at the same time, which is up-regulated by HIF - 2 alpha and MYC stimulation, and highly expressed in the kidney cells and prostate cancer cells. The small molecule inhibitor Benzylserine (Figure 41) can inhibit the transport of glutamine by targeting type I amino acid transporters 1 (LATl) and SLC7A5, and further inhibit the proliferation of melanoma cells by inhibiting the mTOR signaling pathway.

Glutaminase (GLS) is an enzyme that catalyzes the deamination of glutamine to glutamate. The GLS gene encodes two enzymes, GLS1 and GLs2, which play different roles in cell energy metabolism and oxidative defense. GLs1 is mainly expressed in the kidney, while GLS2 is mainly expressed in the liver. Related reports have indicated that both small molecule inhibitors BPTES (Figure 42) and CB-839 (Figure 43) can specifically inhibit glutaminase, showing good tumor inhibition properties in a variety of preclinical animal models.

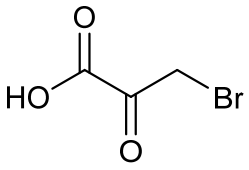

FIGURE 40. BrPA

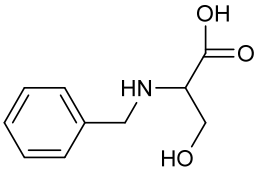

FIGURE 41. Benzylserine

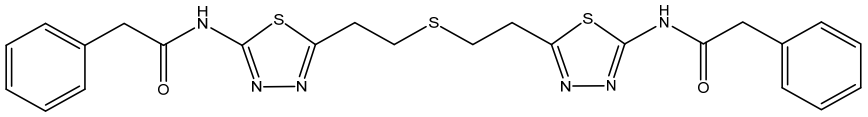

FIGURE 42. BPTES

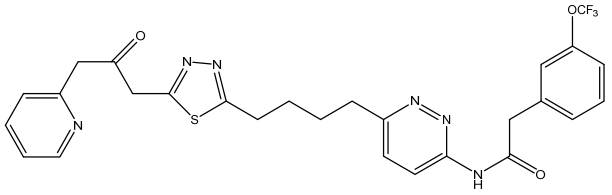

FIGURE 43. CB-839

AVOIDING IMMUNE DESTRUCTION

Compared with normal cells, tumor cells have a large number of antigen molecules on their surface due to the epigenetic alterations and gene mutations, etc., which can be recognized and eliminated by the immune system. T cells are the core performers of anti-tumor immunity, and their activation requires not only the stimulation of the first signal provided by the antigen presenting cells, but also the stimulation of the second signal provided by the costimulatory molecules. We refer to these immunosuppressive signals as immune checkpoints. In the process of tumor occurrence and development, tumor cells can pass the immune checkpoint to inhibit T cell activation, thereby avoiding immune destruction. The use of immune checkpoint inhibitors can relieve the immunosuppression of tumor patients and exert the anti-tumor effects of T cells to achieve the purpose of treating tumors. So far, more than 10 kinds of ligands or receptors that mediate the second signal have been identified, while cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and ligands PD-L1 are relatively well-developed immunological checkpoint molecules. The FDA has approved the monoclonal antibody Ipilimumab targeting CTLA-4 for the treatment of melanomas, and the PD-1 being target for the treatment of melanoma and non-small cell lung cancer monoclonal drug Pembmlizumab. There are no small molecule inhibitors on the market for this type of target, but there have been numerous researches.

LIMITLESS REPLICATIVE POTENTIAL

Telomere and telomerase play an important role in the infinite replication of tumor cells. Telomere is the ribonucleoprotein complex of guanine-rich repetitive DNA sequence and telomere-binding proteins, at the 3'-end of eukaryotic chromosomes. They maintain the integrity and stability of chromosomes mainly by preventing degradation of chromosome DNA, terminal fusion, deletion and abnormal recombination. Telomerase is a special DNA polymerase with reverse transcriptase assay that can compensate for the shortening of the ends of chromosomes during cell division, causing tumor cells to avoid normal cell replication-decay mechanism. Studies have found out that telomerase activity is enhanced in tumor cells. Therefore, intervention in the development of tumors by effectively inhibiting the activity of telomerase has become another new strategy for tumor therapy. The relevant representative drug is the antisense nucleotide inhibitor GRNl63L against template sequence. Antisense oligonucleotides can complement the specificity of target RNA or DNA, reducing the telomerase activity in malignant tumor cells, leading to a decline in proliferation and inducing apoptosis. The latest clinical trial data suggest that the combination of GRNl63L and paclitaxel/no combination of bevacizumab in the treatment of locally recurrent or metastatic breast cancer has passed the phase I clinical trial successfully. The application of GRNl63L in the treatment of non-small cell lung cancer after initial induction chemotherapy has achieved remarkable curative effect, and the phase ii clinical trial has been finished. A phase I clinical trial of GRNl63L combined with bortezomib and dexamethasone for the treatment of recurrent or refractory multiple myeloma was completed. At the same time, some heated studies include telomerase inhibitor g-tetramer, novel heterocyclic azole derivatives, and telomerase inhibitor AZT, etc. However, small molecule inhibitors targeting telomerase have not yet been put into clinical application. [3]

TUMOR PROMOTION INFLAMMATION

In recent years, there have been numerous studies on the "inflammation-cancer chain". In some cases, inflammation can serve as a significant marker of early tumor development and further promote tumor development. Studies have shown that some anti-inflammatory drugs can also be used in cancer intervention strategies. These drugs include non-steroidal anti-inflammatory drugs (NSAIDs), selective cox-2 inhibitors and natural compounds with anti-inflammatory properties. It is generally believed that the anti-cancer mechanism of NSAIDs can be divided into two categories, one of which is the COXs dependent pathway, that is, working out by inhibiting the cyclooxygenase. Cyclooxygenase is the key enzyme for prostaglandin synthesis, and there are two isomers in the body, namely cox-1 and cox-2. At present, the research on cox-2 is rather in-depth. Cox-2 can be involved in the occurrence and development of tumors by abnormal expression leading to the increase of PG, promoting tumor cell proliferation and inhibiting tumor cell apoptosis, indirectly activating oncogenes or inducing tumor suppressor gene mutation such as p53, promoting angiogenesis, endothelial cell migration and blood spread. NSAIDs exert antitumor activity by inhibiting cyclooxygenase. The other kind is the non-dependent pathway of cyclooxygenase, such as inhibiting nuclear factor Nf-KB and promoting the effect of reactive oxygen species (ROS) on the intervention of the occurrence and development of tumor. However, the exact anti-cancer mechanism and anti-cancer effect need to be further explored.

CONCLUSIONS

To sum up, molecular targeted therapy has become an important strategy for tumor treatment at present, and more and smaller molecule targeted drugs have been applied in clinical practice and achieved certain curative effects. However, the problems of clinical application of small molecule targeted drugs such as acquired drug resistance as well as toxic and side effects have gradually emerged. We ought to have a deeper understanding of the pathogenesis of tumors and the molecular mechanism of the target, so as to truly realize the "Acts appropriately to the situation". Meanwhile, targeted therapy should be combined with "individualized treatment" and "precision medical treatment" to "act according to actual circumstances" for different patients, so as to minimize the toxic and side effects of drugs and improve curative effects. Considering the complexity of tumors, we are supposed to try multi-target and multi-drug combination therapy as much as possible to minimize the risks of drug resistance. It is expected that the small molecule targeted therapy strategy of tumors will reach a higher level in the future and become an important means to cure malignant tumors.

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