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Editorial
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Small Molecule Inhibitors: Suitable Drugs for Targeted-Based Cancer Therapy

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Editorial

Cancer has appeared as the main disease and leading cause of death after cardiovascular disorders and has been described as a complicated disease of uncontrolled cell proliferation [1]. Over the past century, there has been a dramatic increase in the frequency of cancer [2-4].

Chemotherapy, radiotherapy and surgery, as well as combination of these methods have been the main options for cancer treatment for several years. Among these methods, chemotherapy and cytotoxic agents have been widely used for cancer treatment. However, cytotoxic effects on healthy cells have hampered the effectiveness of these drugs [5]. Therefore, developing more specific/selective and effective drugs as well as proper strategies with minimal side-effects are necessary [6,7].

Targeted-based cancer therapy (TBCT) (personalized medicine) drugs and methods have recently been demonstrated as proper and the most acceptable options for treatment [6]. Monoclonal antibodies (mAbs) [8] and small molecule inhibitors (SMIs) [5,7] are efficient and the most specific reagents for targeting tumor cells. During the recent years, several SMIs (Table 1) and mAbs have been approved by authorities for cancer treatment [8]. In this regard, SMIs have been noted to be more efficient but less specific than mAbs for targeting tumor cells [9].

SMIs are small reagents (around 500 Da) that block the activity of key molecules inside the cells and suppress the biological functions of tumor cells such as proliferation and differentiation. These agents bind to intracellular targets with distinct structures [5-7,9-14]. Various molecules, including receptor tyrosine kinases and intracellular molecules involved in cell signaling have been described as proper targets. However, several other molecules remain to be investigated for targeting by SMIs such as ROR1 and ROR2 tyrosine kinases [8,9,15,16].

Recently, there has been an increasing interest in developing new SMIs. However, due to non-specific effects or failure to pass various stages of clinical trials, only a few molecules have been approved by FDA for cancer treatment (Table 1). Recently, new classes of SMIs with high specificity and selectivity for tumor cells have been produced and most of them are in various stages of clinical trials [7-9].

Small molecule inhibitors, particularly tyrosine kinase inhibitors (TKIs) are categorized into five types [11,17-19].

Type 1 inhibitors are the most frequent type that binds to the ATP-binding site of the kinase and prevents tyrosine phosphorylation. This group of SMIs is named ATP competitors and mimics the role of ATP [17]. Type II binds to inactive structure of kinase enzymes and occupies an extra hydrophobic pocket formed by a conserved amino acid sequence (DFG sequence). These inhibitors are more specific and selective than the first type with slower off-rate [18,19]. The 3rd type binds to the allosteric part of the enzyme substrate close to the ATP-binding site. These inhibitors are very selective and specific. Type IV inhibitors form an irreversible bond to a cysteine residue within the active site of the target. Therefore, a cysteine residue within the active site of the target is essential for designing these types of inhibitors, which are very specific for the target. HKI-272 as an inhibitor of epidermal growth factor receptor (EGFR) and Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib) are type IV inhibitors [19]. The last type is classified as a new group, and a few TKIs are categorized in this group. Type V inhibitors are bivalent compounds that bind to different regions of the target.

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Table 1: US FDA approved small molecule inhibitors for targeted cancer therapy.

Name	Trade name	Mol. mass (g/mol)	Target	IC_{50} (nM) (cell-free assays)	Malignancy
Afatinib	Gilotrif	485.94	HER2, EGFR	15	NSCLC, squamous cell carcinoma of the head and neck, breast cancer
Alectinib*	Alecensa	482.62	ALK	1.9	NSCLC
Axitinib	Inlyta	386.47	VEGFR1, VEGFR2, VEGFR3, PDGFR, KIT	0.1, 0.2, 0.1-0.3, 1.6, 1.7	RCC
Belinostat	Beleodaq	318.35	HDAC	27	peripheral T-cell lymphoma
Brigatinib*	Alunbrig	528.22	ALK, ROS	0.6, 0.9	NSCLC
Cabozantinib (XL184)	Cometriq	501.51	VEGFR2, c-MET, KIT, AXL, FLT3	0.035, 1.3, 4.6, 7, 11.3	Medullary thyroid cancer, progressive metastatic medullary thyroid cancer
Ceritinib	Zykadia	558.14	ALK	0.2	NSCLC
Cobimetinib	Cotellic	531.3	MEK1	4.2	Advanced melanoma
Crizotinib	Xalkori	450.34	MET, ALK, MTH1	11, 24, 72	NSCLC
Dasatinib	Sprycel	488.01	ABL, SRC. c-KIT	<1, 0.8, 79	CML, ALL
Deforolimus	-	990.2	mTOR	0.2	Advanced soft tissue, bone sarcoma
Erlotinib	Tarceva	393.44	EGFR	2	NSCLC, pancreatic cancer
Everolimus	Zortress	958.23	mTOR	1.6-2.4	Advanced kidney cancer, subependymal giant cell astrocytoma, MBC, pancreatic neuroendocrine tumors, RCC
Gefitinib	Iressa	446.9	EGFR	37	NSCLC
Ibrutinib	Imbruvica	440.5	BTK, ITK, EGFR, HER2	0.5	CLL
Icotinib	Conmana	391.15	EGFR	5	NSCLC (approved in China)
Idelalisib	Zydelig	415.42	PI3K (p110δ)	2.5	CLL, follicular B-cell non-Hodgkin lymphoma, relapsed small lymphocytic lymphoma
Imatinib	Gleevec	589.7	ABL, KIT, PDGFR	600, 100, 100	Gastrointestinal stromal tumor, leukemias
Ixazomib	Ninlaro	361.03	20S proteasome	3.4	Multiple myeloma
Lapatinib	Tykerb	581.06	EGFR, HER-2	10.8, 9.2	Breast cancer
Lenvatinib	Lenvima	426.85	VEGFR2/3	4, 5.2	Thyroid carcinoma
Midostaurin*	Rydapt	570.64	PKCα/β/γ, SYK, FLK-1, AKT, PKA, KIT, FGR, SRC, FLT3, PDGFRβ and VEGFR1/2	80-500	AML
Nilotinib	Tasigna	529.52	BCR-ABL	<30	CML
Niraparib*	Zejula	320.39	PARP1, PARP2	3.8, 2.1	Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers
Olaparib	Lynparza	435.08	PARP1, 2	5, 1	Advanced ovarian cancer
Osimertinib	Tagrisso	499.62	EGFR (3rd generation)	12.92-494	NSCLC
Palbociclib	Ibrance	447.53	CDK4, 6	11, 16	Breast cancer
Panobinostat	Farydak	349.43	HDAC	5	Multiple myeloma
Pazopanib	Votrient	437.52	VEGFR1, 2, 3, PDGFR, FGFR, c-KIT, c-FMS	10, 30, 47, 84,74,140, 146	RCC, advanced soft tissue sarcoma
Ponatinib	Iclusig	532.56	BCR-ABL, PDGFRα, VEGFR2, FGFR1, SRC	0.37, 1.1, 1.5, 2.2, 5.4	CML, Philadelphia chromosome positive ALL
Regorafenib	Stivarga	482.82	VEGFR1, 2, 3, PDGFRβ, KIT, RET, RAF-1	13, 4.2, 46, 22, 7, 1.5, 2.5	Metastatic colon cancer
Ribociclib*	Kisqali	434.55	CDK4, 6	10, 39	Breast cancer
Rucaparib**	Rubraca	323.37	PARP1	1.4	Advanced ovarian cancer
Sirolimus	Rapamune	914.17	mTOR	0.1	HCC
Sonidegib	Odomzo	485.5	Hedgehog signaling pathway	2.5	Advanced basal cell carcinoma
Sorafenib	Nexavar	464.83	RAF-1, B-RAF, VEGFR-2	6, 22, 90	RCC, hepatocellular carcinoma
Sunitinib	Sutent	532.56	VEGFR2, PDGFRβ	80, 2	RCC, gastrointestinal stromal tumor,
Temsirolimus	Torisel	1030.28	mTOR	1760	RCC
Vandetanib	Caprelsa	475.35	VEGFR2, 3, RET	40, 110, 500	Metastatic medullary thyroid cancer
Venetoclax**	Venclexta	868.44	BCL-2	<0.01	CLL

*US FDA approved in 2017, ** 2016, HER2: human epidermal growth factor receptor 2, EGFR: epidermal growth factor receptor, NSCLC: non-small cells lung carcinoma, ALK: anaplastic lymphoma receptor tyrosine kinase, VEGFR: vascular endothelial growth factor receptor, PDGFR: platelet-derived growth factor receptor, RCC: renal cell carcinoma, HDAC: histone deacetylase, FLT3: Fms-like tyrosine kinase 3, CML: chronic myeloid leukemia, ALL: acute lymphoblastic leukemia, mTOR: mammalian target of rapamycin, MBC: metastatic breast cancer, BTK, Bruton's tyrosine kinase, ITK: interleukin-2-inducible T-cell kinase, CLL: chronic lymphocytic leukemia, PI3K: phosphatidylinositide 3-kinase, PKC: protein kinase C, SYK: spleen tyrosine kinase, AML: acute myeloid leukemia, PARP: poly ADP ribose polymerase, CDK: cyclin-dependent kinase, FGFR: fibroblast growth factor receptor.

This dual binding can extensively increase affinity and improve the selectivity of inhibitor for the target. These new inhibitors may represent the most valuable drugs for targeted cancer therapy and exploring signal transduction pathways inside tumor cells.

Finally, resistance to the most or all SMIs and other drugs (e.g., mAbs) is a major obstacle in front of patients and researchers. Therefore, better strategies are necessary to prevent drug resistance by tumor cells. On the other hand, a deeper understanding of resistance mechanisms in tumor cells, specific targeting of cancer stem cells as well as combination and sequential drug treatments may be necessary to prevent tumor cell resistance.

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