Review: Novel Target for Cancer Therapy


Department of Medicinal and Pharmaceutical Chemistry, L. M. College of Pharmacy, Ahmedabad

ABSTRACT
Cancer is an important area of interest in the life sciences because it has been a major killer disease throughout human history. Heterocyclic molecules are well known to play a critical role in health care and pharmaceutical drug design. Currently a number of heterocyclic compounds are available commercially as anticancer drugs and great efforts have been put to the identification of novel anticancer targets for novel anticancer drug discovery.

INTRODUCTION
Cancer is not one disease, but a large group of diseases characterized by uncontrolled growth and spread of abnormal cells. Cancer is becoming a very serious public health problem in the USA and other developed countries. The American Cancer Society estimates every year the number of new cancer cases and deaths expected in the USA and compiles the most recent cancer incidence data from the National Cancer Institute and mortality data from National Cancer for Health Statistics. A total number of 1,372,910 new cancer cases and 5,70,280 deaths were expected in the USA in 2005. Currently, about 25% of deaths in the USA are due only to cancer [1].

Anticancer activity of heterocyclic compounds

Acridine
DACA, \{N-[2-(dimethylamino)-ethyl]acridine-4-carboxamide; NSC 601316\} 1 is a DNA-intercalating agent and dual topoisomerase (topo) I/II inhibitor currently in clinical trial as an anticancer drug [2]. Substitutions in the acridine ring of DACA have significant effects on biological activity; most 7-substituted DACA analogues had cytotoxicities similar to DACA, whereas most 5-substituted derivatives were more cytotoxic but relatively less effective against JLA and JLD cell lines than the wild type JLC. Cell line studies showed that the 5,7-disubstituted...
analogs of DACA retained both the broad-spectrum effectiveness of the 7-substituted derivatives and the higher cytotoxic potency of the 5-substituted derivatives.
Benzimidazole
A number of 5-substituted terbenzimidazoles synthesized and evaluated as mammalian topoisomerase-I poisons and for cytotoxicity against a human lymphoblastoma cell line, RPMI-8402 in which 5-chloro derivative 2 exhibited excellent activity [3].
Benzothiazole
Chung et al. evaluated the cytotoxic activities of 2-[(substituted-1,3-benzothiazole-2-yl)aminomethyl]-5,8-dimethoxy-1,4-naphthoquinones 3 against SNU-1 cells. Study shows that the compounds with highly hydrophobic 6-substituents will be more active [4].

Camptothecin
In 1985, it was reported by Hsiang et al. [5] that the cytotoxic activity of camptothecin (CPT) was attributed to a novel mechanism of action involving the nuclear enzyme topoisomerase-I, and this discovery of unique mechanism of action revived the interest in CPT and its analogues as anticancer agents. Kim D. K et al.[6] synthesized camptothecin derivative 4 which is active against SKOV-3 human ovarian cancer cells.

Indole
Due to interesting biological activities, unique chemical structures, and low availabilities of marine indole alkaloids, indoles have been considered an attractive field in medicinal chemistry for the discovery of new anticancer drugs. Jiang et al. [7] synthesized a number of indolylpyrimidine 5 and indolylpyrazine 6 and evaluated their cytotoxicities against a panel of 60 human tumor cell lines. QSAR results suggest that the most important determinant for the cytotoxic activities of these compounds against different cancer cell lines is the hydrophobic parameters of the whole molecules. The linear Clog P models suggest that the highly hydrophobic molecules will be more active.

Isatin
Isatin (1H-indole-2,3-dione) is an endogenous compound identified in humans. This class of compounds possesses a wide range of biological activities [8] that include antiallergic, anticancer, anticonvulsant, antidiuretic, antithrombotic, antitubercular, antiviral, anxiogenic, immunosuppressant, muscle relaxant, and sedative activities. Vine et al. [9] synthesized a variety of isatins in which derivative 7 give good cytotoxic activities against the human monocyte like histiocytic lymphoma (U937) cell line in vitro.

Isoquinoline
Sami et al. [10] and Cho et al. [11] synthesized a series of (4, 8, 9, 10, or 11)-substituted-2-[2, (dimethylamino)ethyl]-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-diones 8 and 3-arylisooquinoline 9 respectively exhibited excellent cytotoxic activities against a SK-MEL-2 melanoma cancer cell lines.

Paclitaxel derivative
Paclitaxel is a well-known anticancer drug for the treatment of different kinds of metastatic tumors. Despite its success in the chemotherapy, there are demands to improve its efficacy as well as lower its toxicity. The QSAR of paclitaxel derivatives suggest that the key modification at certain positions may result in the significant improvement of its activity. Baloglu et al. [12] synthesized paclitaxel derivative 10 and he found excellent cytotoxic activities against prostate cancer (PC3).
Phenanthredine
A series of esters and amides of 2,3-dimethoxy-8,9-methylenedioxy-benzo[i] phenanthridine-12-carboxylic acid \( \text{1} \) was synthesized by Zhu et al. [13] as potent cytotoxic and DNA topoisomerase-I targeting agents.

Pyrrolo[2,3-d]Pyrimidines
Stanley D. et al. [14, 15] synthesized a series of 4,6-bis-anilino-1\( H \)-pyrrolo[2,3-d]pyrimidines and screened for inhibition of IGF-1R which is an attractive target for oncology. In summary, a key developability issue was observed for potent IGF-1R inhibitor \( \text{2} \) with \( IC_{50} = 2.0 \text{ Nm} \) wherein an acid mediated cyclization of the pyrimidine moiety onto the pendant carboxamide led to facile hydrolysis in vitro and in vivo. Remarkable improvements in both inhibitor stability and potency were realized via substitution at C(4) with carboxamide containing 5-membered heteroaryl amines \( \text{3} \) with \( IC_{50} = 1.6 \text{ Nm} \), a constrained lactam \( \text{4} \) with \( IC_{50} = 0.8 \text{ Nm} \), or indolines \( \text{5} \) with \( IC_{50} = 0.5 \text{ Nm} \). Further biological characterization and in vivo pharmacokinetics of this subclass of exceptionally potent and acid-stable inhibitors of IGF-1R will be reported in due course.

Pyrrrole
Pyrrrole based chemotherapeutic agents have a long drug history, which includes antiinflammatory, antihelminthic, antimycotic, and antibiotic drugs. Furthermore, the pyrrrole moiety has been incorporated in several nonnucleoside reverse transcriptase inhibitors and antiproliferative agents, as well as the DNA minor groove binders Distamycin - A and Tallimustine. In recent years, the in vitro anticancer activity of diazopyrroles and triazenopyrroles has been reported. A number of agents of this class are under intensive development by research groups throughout the world. Cocco et al. [16] synthesized \( N \)-phenyl-3-pyrrolecarbothioamide \( \text{6} \) which exhibited good cytotoxic activities against melanoma cell lines.

Novel Anticancer Targets
Tumor Angiogenesis Inhibitors
The growth and metastasis of cancer cells are dependent on angiogenesis. Angiogenesis has been functionally defined as the sprouting of new vessels from preexisting blood vessels and is an essential process in wound healing; What’s more, angiogenesis is a critical process in tumor cells invasion [17]. It is deemed that only those cells, which have completed neovascularization, are capable of growing violently in size and volume, especially when the tumor size is beyond 2-3 mm. The process of angiogenesis induced by tumor cells consists of several distinct stages including slow growth of tumor cells without blood vessels, and after that releasing specific angiogenic growth factors [18]; the changes of endothelial cell configuration and the degradation of basement membrane and extracellular matrix (ECM) and proliferation, migration, invasion and differentiation into capillaries endothelial cell and eventual maturation into blood vessels. This process is initiated and mediated in part by the interaction of specific angiogenic growth factors with their receptors and the subsequent triggering of signaling pathways and gene expression programs essential for angiogenic progression [18]. As a result, disrupting the production and expression of these factors derived from tumor tissues will be of great value for the inhibition of tumor cells invasion, growth, and metastasis. Keeping the number of links associated with angiogenesis, this review will solely focus on several of them in detail, especially Intergins and Matrix Metalloproteinase (MMPs).
The Drug Discovery Based on Integrins as Target

Integrins are a family of transmembrane heterodimeric glycoprotein receptors composed of α and β subunits, mediating the adhesion of cells with the ECM, invasion, migration and neovascularization of tumor cells [19-21]. Recent studies have indicated that integrins form cytoplasmic complexes with many factors including Src family kinase and NF-kB, etc. The complexes formed play a unique role in cell signal transduction pathway, mediating a number of cell physiological function and pathological changes, including the cells differentiation, proliferation, migration and invasion and metastasis of tumor cells. The three most important routes mediated by integrins are as follows: FAK-Ras- MAPK, PAK-PI-3K, and FAK-STAT1. Although the relationship between integrins and the ECM is complicated, growing evidence shows that avb3 integrin receptors are closely associated with adhesion and antiapoptosis of tumor cells. The role of avb3 integrin in angiogenesis is also supported by the fact that blockade of avb3 receptors decreases angiogenesis and regresses tumors and triggers endothelial apoptosis. Currently, a series of small molecular peptidomimetics inhibitors for integrins has been designed according to the structure of avb3 integrin receptors and conformation of RGD (Arg-Gly-ASP) [22,23]. The notable one is Thalidomide, a derivative of glutamic acid. Several phase trials have been published as a single agent for malignant glioma [24]. Furthermore, it is indicated that Thalidomide inhibits the metastasis by interrupting the expression of integrin receptors and inhibiting the angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in a phase - I trial with Thalidomide plus Temozolomide for the treatment of brain melanoma metastasis. The therapeutic drugs applied for the treatment of tumor include monocloned antibodies (mABs) (Vitaxin) of integrin avb3 receptors and small molecular antagonist EMD121974, cyclic Arg-Gly-Asp-D-Phe (N-methyl) Val). A phase I clinical trial showed that there was no immune response to Vitaxin in any patient [25], and the in vitro experiment conducted by Taga and coworkers indicates that EMD121974 suppresses brain tumor growth through induction of apoptosis both in brain capillary and brain tumor cells by preventing their interaction with the matrix proteins, vitronectin and tenascin. The dual action of this peptide explains its potent growth suppression of orthotopically transplanted brain tumors [26].

The Drug Discovery Based on Matrix Metalloproteinases (MMPs) as Target

Matrix Metalloproteinases (MMPs) are a family of calcium and zinc dependent endopeptidases, which play a critical role in the degradation of ECM and tissue remodeling and wound healing [27-30]. The activity of MMPs is regulated by endogenous Tissue Inhibitors of Matrix Metalloproteinases (TIMPs). In the presence of specific stimuli exemplified by cytokines and growth factors, MMPs are up regulated destroying the balance between MMPs and TIMPs, resulting in the chronic activation of MMPs and an excessive degradation of ECM components, which are believed to contribute to numerous pathological conditions: i.e. cancer, osteoarthritis, rheumatoid arthritis, angiogenesis, periodontal disease, pulmonary emphysema, skin ulceration, atherosclerosis, and central nervous system diseases. Up to now, it has been reported that the mammal MMPs gene family consists of at least 26 structurally related members, among which MMP-2 and 9 are proved to be highly correlated with cancer. They also regulate host defense mechanisms and normal cell function. However, blocking all MMPs may not lead to a positive therapeutic outcome. At present, numerous MMPs inhibitors are in various developmental stages for different symptoms, mostly in cancer and arthritis. Compounds currently under clinical trials as Matrix metalloproteinase inhibitors (MMPIs) include marimastat 17, tanomastat (Bay-
All these compounds are applied to treat different types of cancer, such as ovarian cancer, breast cancer, malignant glioma, pancreatic cancer, NSCLC, advanced bladder carcinoma, etc [31,32]. However, most of these clinical trials of MMPIs have yielded disappointing results, perhaps due to the inappropriate study design or tumor staging, or lack of selectivity. Positive results have been seen in gastric cancer with marimastat (17). Hydroxyproline is known as one of specific amino acid of collagens, which are the substrates of MMPs. So it is assumed that the derivatives of hydroxyproline may specifically interact with MMPs in a competitive manner. The caffeic acid or gallic acid have proved to inhibit MMP-2 and MMP-9 respectively, so they are linked with hydroxyproline to find potent compounds with inhibiting activity against MMP-2 and MMP-9. The structures of pyrrolidine peptidomimetic inhibitors synthesized in our lab among which 21 and 22 have shown high inhibitory activity against MMP-2 and MMP-9 with IC\textsubscript{50} of 11.5 nM and 7.7 nM respectively [33]. In vivo, all these derivatives display favorable inhibitory potency to metastasis of tumor cells with the metastasis inhibition rate of H22 mouse liver carcinoma model higher than 92%, which indicates that the strategy to design MMPIs of praline analogs is a remarkable success.

B. Cell Signal Transduction Pathway Inhibitors or Manipulators

Cell Signal Transduction is a necessary process in which cells respond to the stimulation outside [34]. During growth and metastasis of tumor cells, the growth factor and its receptors respond abnormally, resulting in the out of control malignant proliferation of tumor cells. Taken together, the selective blockade of the autocrine and paracrine cell signal transduction, destroying the mechanism of auto control growth regulation, is potential for the NDD of anticancer agents.

The Drug Discovery Based on Tyrosine Kinase (TK) as Target

TK are a family of mono-transmembrane α-helix proteins including membrane receptor tyrosine kinase and cytoplasm non-receptor tyrosine kinase. The membrane receptor TK related to tumorigenesis includes epidermal cell growth factor receptor (EGFR) tyrosine kinase, and vascular endothelial growth factor receptor (VEGFR) tyrosine kinase [24,34], while the non-receptor tyrosine kinases include Src kinase and Bcr-abl kinase, etc. Upon ligand binding, the receptors dimerize or couple with the cytoplasm kinase, and TK is activated and the tyrosine kinase domains phosphorylate the C terminal tyrosine residues, named as autophosphorylation, after that a subsequent phosphorylating activation process occurs called a kinases cascade, which results in the amplification of the signal. During the process, a number of proteins are phosphorylated, which lead to a subsequent cellular event such as proliferation, division, adhesion, morphogenesis, angiogenesis, metastasis and antiapoptosis of cells. TK plays a crucial role in the action of EGFR; the mutation of the ATP-binding site of EGFR is closely associated with TK activity, disrupting the formation of tumorigenic signals [35]. Taken together, the inhibition of TK will result in the suppression of cell activity related to EGFR, providing a new strategy for the treatment of cancer. The enzyme inhibitors 23, 24 which is in clinical trial to TK.
The Drug Discovery Based on Farnesyltransferase (FTase) as Target

Ras protein, a low-molecular-weight GDP/GTP-binding guanine triphosphatase encoded by Ras gene, plays a critical role in signal transduction of cell growth and differentiation [24,36]. In normal process of signal transduction, Ras performs its function in a GTP-binding form. However, Ras itself has no ability to bind to the membrane due to its low hydrophobicity. It must be modified by enzymes, with a lipid modification called farnesylation, which enhances its hydrophobicity, binding to the cell inner membrane. After performing its function, Ras protein was hydrolyzed into the GDP binding form. In malignant transformation, invasion and spread of
cancer, Ras mutations or constitutive activation have been described. The continuous cell growth signals are out of control causing cell differentiation and proliferation excessively resulting in tumorigenesis. As described in recent reports, there is a phenomenon of overexpression of Ras gene in 30%-40% of thyroid carcinoma, over 50% of colon carcinoma and 90% of pancreatic carcinoma, which suggests the principal role of Ras in cell signal transduction and tumorigenesis. Apparently, inhibiting the activity of Ras protein can prevent the cell signal transduction, which is one of the most important targets for anticancer drugs design [37]. There is a specific carboxyl terminal sequence in all members of Ras family, known as CAAX, where C is cysteine, AA is aliphatic amino acids, and X is any amino acid, preferably methionine or serine. Farnesylation is catalyzed by Farnesyltransferase (FTase), with a farnesyl in farnesylpyrophosphate (FPP) bound with the thiol group of Cys, anchoring Ras to the cell membrane, which is a required step of the cancer-causing activity of Ras. SCH66336 25, also known as lonafarnib or Sarasar is an 11-pyperidinyl tri-halogenated analog with better pharmacokinetics and potency. A phase II clinical trial is conducted by the M. D. Anderson Cancer Center evaluating the efficiency of SCH66336 25 with a combination of Temozolomide for recurrent glioblastoma multiform (GBM) [38]. Two of the three human GBM xenografts demonstrated substantial growth inhibition in response to SCH66336 25, with up to 69% growth inhibition after 21 days of treatment. Zarnestra 26, also known as tipifarnib or R115777, is a nonpeptidomimetic methyl quinolone derivative that can inhibit Ras FTase selectively. Recently, two clinical trials are underway: one is under phase II for breast cancer [39] and renal carcinoma, and the other is under phase II/III for pancreatic carcinoma [24,40]. The main dose limiting toxicities that have been reported are myelosuppression, fatigue and neurotoxicity with R115777 26. Two other Phase III trials of R115777 in colorectal (versus placebo) and pancreatic (with gemcitabine versus placebo) cancers have failed to show a survival benefit. It is likely that the future clinical direction of FTase will be as combination therapy, especially with the taxanes, where synergy has been seen in a variety of preclinical studies [41].

C. The Drug Discovery Based on Aminopeptidase N (APN) as Target

Aminopeptidase N (APN), which is identical to Myeloid Plasma Membrane Glycoprotein CD13 (gp150) [42], is a type-II, membrane bound, zinc-dependent metalloectopeptidase widely expressed on the surface of renal and intestinal brush border cells, placenta and central neural system [43]. APN is overexpressed on tumor cells playing a crucial role in tumor invasion and
angiogenesis [44]. APN can not only hydrolyze the amino acids of C-terminal, the neural amino acids fragment in particular [45,46], but also degrade the primary components of ECM [47,48], facilitating the invasion, growth and metastasis of cancer cells. Furthermore, APN is also involved in the down regulation of signal peptides, such as enkephalines and can cleave bioactive proteins on the cell surface, including several cytokines and antigen delivering cells, degrading lots of immunoactive substances, weakening the immunopotency of the body, depressing the recognition of macrophage and NK cells to surface antigen on tumor cells and the ability to kill these cells directly. Consequently, the inhibition of APN activity will result in the enhancement of granulocytes chemotaxis improving the immunopotency of the body. In a present study [49], it has been discovered that in monocytes APN is linked to the phosphorylation of mitogen-activated protein kinases (MAPK) and to an increase in the concentration of \( \text{Ca}^{2+} \) evoked by mAbs to APN, which induces the intracellular signal cascade reaction of these cells with the phosphatidylinositol-3-kinase (PI-3K) involved. APN was also shown to be the major receptor for the transmissible gastroenteritis virus (TGEV) [50], which causes a severe gastroenteritis in newborn pigs, and for the human coronavirus 229E (HCV229E) [51], which causes upper respiratory infections. Unlike MMPs, APN functions as an exopeptidase, that is, it displays its activity extracellularly, just like neural endopeptidase (NEP, CD10), dipepidylpeptidase IV (DPPIV, CD26), APA, and serum \( \text{g-glutamyl transpeptidase (} \text{g-GT, CD224}) \). APN plays a critical role in tumorigenesis through the possible mechanisms listed below: a) Degrading ECM, promoting the growth and metastasis of primary tumor. b) Participating in the Angiogenesis of tumor tissues. c) Degrading bioactive peptides, interleukin, cytokines and immunoactive substance, impairing the normal function of lymphocytes, and accelerating the invasion of tumor cells. Therefore, the interruption of APN activity will be potential for the control of various diseases associated with APN including invasion and metastasis of tumor cells, viral infection, leukemia, rheumatoid arthritis, angiogenesis, diabetic nephropathy and central nervous system diseases as well, such as Alzheimer’s disease, by building up the immunopotency of the body, disturbing the growth and metastasis of tumor cells. The structures of inhibitors targeting to APN, among which bestatins 27 have been marketed for a long time; probestin 28 is designed based on the proline which exists abundantly in collagen; the AHPA scaffold derivatives, represented by 29 and 30, which have been synthesized in our lab and found to have highly selective activity with \( \text{IC}_{50} \) ranging from 16 – 200 nM against APN [52,53]. In recent \textit{in vitro} studies, bestatin 27 is shown to inhibit the invasion of human metastatic tumor cells and induce apoptosis in human non small lung cancer cell lines. In tumor-bearing mice, it inhibited metastases or tumor growth and prolonged the survival of patients with acute adult nonlymphocytic leukemia who also received chemotherapy and had an immunomodulatory effect in patients with lymphoma after autologous bone marrow transplantation [54]. A multicenter, double blind, randomized phase-III clinical trial of bestatin in patients with completely resected stage-I squamous cell lung carcinoma has just been completed in 2003 [55].
D. The Drug Discovery Based on Histone Deacetylase (HDACs) as Target

It has been described recently that changes in the chromosome structure with modified histone protein play a significant role in the regulation of gene expression in eukaryotes. These modifications include methylation, ethylation, phosphorylation and ubiquitination as well, among which enzymes mediating the ethylation of chromosome are closely associated with tumorigenesis. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) participate in controlling the degree of ethylation of chromosomes and affect the process of cell physiological function, such as transcription, cell cycle, the differentiation of gene, DNA replication and simultaneously involve the development of tumorigenesis [56-58]. There is a balance between HATs and HDACs in regulating the function of normal cells. However, the activity of HDACs is upregulated in cancer cells, resulting in destruction of the balance and closure of the expression of anti-oncogene. Consequently, the strategy of inhibiting the activity of HDACs will have potential to enhance the ethylation of HDACs substrate, such as histone, inducing the sensitive promoter of histone ethylation to activate the expression of antioncogene, such as p21, p27, Rb gene. Therefore, the suppressing activity of HDACs to gene expression provides with a novel target for the treatment of cancer. The classes of compounds that are identified as HDAC inhibitors include: Electrophilic Ketone derivatives, SAHA for which a Phase-I clinical trial perform to evaluate the safety, pharmacokinetics, and biological activity and it is concluded that SAHA is well tolerated, inhibits the biological target in vivo, and has antitumor activity in solid and hematological tumors [59].

E. The Drug Discovery Based on Heat Shock Protein 90 (HSP90) as Target

The heat shock protein90 (HSP90) is a molecular chaperone that is increasingly attracting the interests of oncologists and pharmacologists. This is due to its essential role in maintaining the conformational stability and function of a number of key oncogenic ‘client’ proteins involved in
signaling pathways crucial for the development and maintenance of the tumor phenotype [60]. The chaperone plays a critical role in mediating the physiology of cells exposed to the environment. Therefore, agents that can interfere with the function of HSP90 may thus be potentially used for tumor diagnosis. Kamal and co-workers [61] suggested that there is no difference in the expression level between normal cells and tumor cells. The most striking is that the latter are more sensitive to the HSP90 inhibitors compared to the former, due to the binding state of HSP90; that is in tumor cells HSP90 complexes with a number of cofactors and thus the conformation of HSP90 is converted into a state which is facilitated to bind with the HSP90 inhibitors, while in the former HSP90 exists in a single form and the conformation is not a favorable one for it in normal cells to bind to the HSP90 inhibitors. As a result, HSP90 in normal cells is not sensitive to the HSP90 inhibitors. Keeping the above description, HSP90 has currently been considered as a target to design anticancer agents. The ansamycins or geldanamycin \textsuperscript{32} derived from \textit{nocardia} and its derivative 17AAG \textsuperscript{33} were found to bind to the N-terminal pocket of HSP90 and thus inhibited its function. In addition, 17AAG is currently undergoing a phase I clinical trial and the primary side effects include plague, nausea, vomit, liver toxicity.

\textbf{F. The Drug Discovery Based on Cyclooxygenase-2 (COX-2) as Target}

Cyclooxygenase-2 (COX-2), the rate controlling enzyme that catalyzes the conversion of arachidonic acid (AA) to different endogenous prostaglandins (PG), is involved in several physiological and pathological pathways, such as inflammation, fever, bleeding and blotting as well. It is evident that COX-2 sub-cells locate in the endoplasm and karyotheca, the PG produced enter the nucleus regulating the transcription of target gene and play a significant role in the process of tumorigenesis in different tumors. The whole process is mediated by CUGBP-2, a cytidine-uridineguanosine binding protein-2. In cancer cells, the gene expressing CUGBP-2 is closed, resulting in the enhancement of COX-2 activity, producing the PG excessively, and promoting the gene expression associated with angiogenesis. As a result, COX-2 becomes a potential target for the prevention of tumor [62]. It has been discovered that the action of COX-2 involved in tumorigenesis include: (a) stimulating the proliferation through PGI2; (b) inhibiting tumor cells apoptosis. This process is associated with an anti-apoptotic, anti-oxidation protein, Bcl-2; (c) Stimulating angiogenesis of tumor cells; (d) The production of PG enhances the invasive and metastatic activity, which is linked to the enhancement in MMP-2 activity and the levels of MTMMP mRNA, promoting the degradation of ECM and increasing the possibility of metastasis; (e) The PGE2 produced inhibit the proliferation of T or B-lymphocytes and cytotoxic reaction of NK cells [63]. Currently, a number of COX-2 inhibitors have been evaluated in all kinds of clinical trials for the treatment of cancer, including Celecoxib \textsuperscript{34}, Rofecoxib \textsuperscript{35}, NS-398 \textsuperscript{36}, among which \textsuperscript{34} is combined with Isotreinoin for the treatment of recurrent and deteriorated malignant neuroglioma in a phase II clinical trial [24]. Rofecoxib induced growth arrest and apoptosis of HCA-7 cells occurred only at concentrations significantly higher than the IC50 for COX-2 inhibition. Rofecoxib \textsuperscript{35} may negatively regulate angiogenesis in human CRC liver metastases. The absence of a significant, direct effect of rofecoxib on epithelial cells in liver metastases \textit{in vivo} mirrors the lack of activity on human CRC cells at pharmacologically relevant concentrations \textit{in vitro} [64].
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G. The Drug Discovery Based on Endothelin Receptor (ETR) as Target
Endothelin (ET) is a kind of biologically active peptide excreted by endothelial cells, composed of 21 amino acids. During metastasis, ET act as a promoter, facilitating cells differentiation and mitosis and mediating the proliferation of cancer cells [24,65]. It has been described that ET receptors (ETR) are expressed on cancer cells. The synthesis of DNA and active pro-factor of angiogenesis are induced when ET and ETR combine with each other. ET-1, a survival/antiapoptosis factor, is produced by tumor vessel system including protein kinase C (PKC) route and extracellular signal mediating route. To date, two receptors with a 25% homology have been cloned, represented by ETA and ETB respectively [66]. The former receptor is a dominating target for ETR antagonist. Atrasentan/ABT-627 37 is a pyridoline-3-carbonyl derivative [24], which can inhibit ETA receptor selectively. A phase-I clinical trial is underway for the treatment of gland carcinoma, for which the primary adverse effects include rhinitis, headache, fatigue and edema. Several other clinical trials from phase-I to phase III have been reported in recent years for the treatment of refractory prostate cancer [67-69].

H. Other Anticancer Targets
Presently, other novel targets and corresponding inhibitors are being paid more attention for anticancer drugs including: (a) the antagonist targeting VEGFR [24,34]; (b) the proteasome antagonist targeting Ubiquitin and Proteasome systems [24,70]; (c) the inhibiting substance targeting nuclear transcript factor NF-kB and not all of these can be described here.

CHEMOGENOMICS
Chemogenomics represents a new approach to target identification and drug development with the potential for dramatically accelerating the process of NDD. Chemogenomics combines the latest tools of genomics and chemistry; its strength lies in eliminating the bottleneck that currently occurs in target identification and NDD and bridging a drug discovery gap by measuring the broad, conditional effects of chemical libraries on whole biological systems or by screening large chemical libraries quickly and efficiently against selected targets. Chemogenomics together with chemoinformatics that generate knowledge through data integration will concurrently identify and validate therapeutic targets and detect drug candidates to rapidly and effectively generate new treatments for many human diseases. However, a detailed description of the rational concepts, goals and strategies and the future prospects of chemogenomics and the unique or mainly technical challenges that it faces are beyond the scope of this review. Interested readers are referred to the many excellent reviews on this new discipline [71-73] as well as to the references therein. The application of this method, particularly to cancer research and therapy is reviewed briefly in this review. Chemogenomics strategies are increasingly being harnessed by various fields of medical research, especially those related to cancer or immune, inflammatory and hormone disease, in attempts to develop new targeted therapies as rapidly as possible such as HDACs [74,75], Methionine Aminopeptidase Type-2 (MetAP2) [76], HSP90 [77], Ras-Raf. [78] and so on. In general, chemogenomics approaches can be used for three different purposes in disease research. Firstly, chemogenomics can be used to identify new drug targets and might allow their biological functions to be understood. The application of chemogenomics to cancer and angiogenesis research, for example, has identified HSP90 molecular chaperone as targets of radicicol, an antifungal antibiotic that has anti-tumor and anti-neoplastic activity. Secondly, chemogenomics approaches are applied to discover, in a high-throughput fashion, new chemical candidates for molecular
targets and phenotypes of interest. Hundreds of novel drug-like ligands have been identified for various molecular targets in the past few years through chemogenomics. These targets relate to different disease areas, such as cancer, asthma, and hyperthyroidism. Finally, chemogenomics can also be used to understand the mechanism of drug action, which also includes finding genetic markers of drug susceptibility. A specific example is that sequential chemogenomics has led to the initial identification of HDACs and the subsequent development of HDAC inhibitors, such as 19 and 21. Clinical testing of these compounds has already begun in patients with peripheral and cutaneous T-cell lymphoma, acute myeloid leukemia and advanced solid cancers. Predictive chemogenomics strategies have been extensively used in cancer research to determine the relationship between genes, compounds and phenotypes. Using this approach, it has been possible to generate integrated databases of compound–gene interactions by experimental profiling. And libraries of thousands of anticancer compounds have been indirectly screened against the genomes of cancer cell lines. However, no longer is a single drug designed for a single protein target; rather, through chemogenomics, multiple drugs can be designed to target multiple-gene families. With this approach, biophysical and chemical information gained on one protein can be applied to structurally similar targets in the same family. Metalloproteinases represented by MMP and APN all have the HEXXXH conserved motif that can interact with the critical zinc ion in the active site. As a result, anticancer drugs design strategy can resort to design small molecules containing zinc-binding group (ZBG), thereby targeting all metalloproteinases associated with various diseases. On the other hand, small molecule leads, identified for one member of a gene family, can also be used to elucidate the function and biological role of another member of that family whose function is not known, as well as enabling simultaneous measurement of their potency and selectivity. Furthermore, families of related proteins can be considered together as potential drugs targets rather than any single member, that is, with the aid of chemogenomics multiple functions, drugs targeting to a gene family in which each protein has different biological and potential therapeutic function will be designed for the treatment of a large quantity of diseases.

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ABBREVIATIONS
AA = Arachidonic Acid
ADCC = Antibody Dependent Cell Mediated Cytotoxicity
AHPA = 3-amino-2-hydroxy-4-phenyl butyric acid
APN = Aminopeptidase N
APNIs = Aminopeptidase N Inhibitors
bFGF = basic Fibroblast Growth Factor
COX-2 = Cyclooxygenase-2
CML = Chronic Myelocytic Leukemia
CUGBP = Cytidine-Uridine-Guanosine binding protein
3D-QSAR = Three dimensional quantitative structure activity relationship
ECM = Extracellular Matrix
EGF = Endothelial Growth Factor
EGFR = Endothelial Growth Factor Receptor
ET = Endothelin
GBM = Glioblastoma multiform
FTase = Farnesyltransferase
HATs = Histone Acetyltransferases
HDACs = Histone Deacetylase
HSP90 = Heat Shock Protein 90
HTS = High Throughput Screening
MAPK = Mitogen Activated Protein Kinase
mAbs = Monoclonal Antibodies
MetAP2 = Methionine Aminopeptidase Type-2
MMPIs = Matrix Metalloproteinase Inhibitors
MMPs = Matrix Metalloproteinase
NDD = New Drug Discovery
NSCLC = Non-Small Cell Lung Cancer
PG = Prostaglandins
TIMP = Tissue Inhibitors of Matrix Metalloproteinase
TK = Tyrosine Kinase
PKC = Protein Kinase C
PI-3K = Phosphatidylinositol-3-Kinase
VEGF = Vascular Endothelial Growth Factor
VEGFR = Vascular Endothelial Growth Factor Receptor