Patent Review

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Recent advances in antimultiple myeloma drug development

Multiple myeloma (MM) is the second most common hematological malignancy and is characterized by the aberrant proliferation of terminally differentiated plasma B cells with impairment in apoptosis capacity. Particularly, osteolytic bone diseases and renal failure resulting from hyperparaproteinemia and hypercalcemia have been the major serious sequelae that are inextricably linked with MM tumor progression. Despite the introduction of new treatment regimens, problematic neuropathy, thrombocytopenia, drug resistance and high MM relapse rates continue to plague the current therapies. New chemical agents are in development on the basis of understanding several signaling pathways and molecular mechanisms like tumor necrosis factor-α, proteasome, PI3K and MARKs. This review focuses on the most recent patents and clinical trials in the development of new medicine for the treatment of multiple myeloma. Furthermore, the important signaling pathways involved in the proliferation, survival and apoptosis of myeloma cells will be discussed.

Nuozhou Wang[1], Patrick Bartlow[1], Qin Ouyang[1] & Xiang-Qun Xie*[,1,2]

[1]Department of Pharmaceutical Sciences, Computational Chemical Genomics Screening Center, School of Pharmacy & Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA 15260, USA

[2]Department of Computational & System Biology & Department of Structural Biology, University of Pittsburgh, Pittsburgh, PA 15260, USA

*Author for correspondence:
Tel.: +1 412 383 5276
Fax: +1 412 383 7436
xix15@pitt.edu

Background

Multiple myeloma (MM) is the second most common progressive hematological malignancy in the USA, and is characterized by abnormal monoclonal plasma cells accumulated in the bone marrow and destructive bone lesions [1]. In the USA alone, there were 10,710 deaths related to MM and 21,700 new cases in 2012. By 2013, new MM cases rose to 22,350 [2]. MM comprises 1% of malignant tumors and is the second most common form of blood cancer following lymphomas [3]. It is treated as an elderly disease, as the median age of affected individuals is 70 in the USA and 72 in Europe [4]. MM remains an incurable disease, with a median survival of 3–4 years after conventional treatments [5]. Commonly observed in advanced MM patients are excess bone marrow plasma cells and monoclonal protein, hypercalcemia, anemia, osteolytic bone lesions, renal disease, immunodeficiency and peripheral neuropathy [6,7].

In the 1960s, the chemotherapeutic agent melphalan and corticosteroid prednisone were adopted to prolong survival of MM patients. In the 1980s, it was determined that MM evolves from premalignant stages termed **monoclonal gammopathy of undetermined significance** and **smoldering MM** [8,9]. As such, the selection of treatment became dependent on the stage of MM experienced by the patient. By the early 1990s, the standard MM treatment combined high-doses of chemotherapy, followed by autologous hematopoietic stem cell transplantation [10]. Unfortunately, as it is commonly known, such chemotherapies kill both tumor cells and normal cells alike, in this case leading to bone marrow depression and immunosuppression. More recently, however, research has uncovered a new understanding of the bone marrow microenvironment and characteristic molecular mechanisms, resulting in a paradigm shift for the treatment of MM from nonspecific chemotherapy to novel drugs that target bone marrow microenvironments [11]. Since 1998, a combined regimen of thalidomide, bortezomib and lenalidomide has been widely used to treat MM [12].

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Key terms

Monoclonal gammopathy of undetermined significance: Condition in which an abnormal protein (monoclonal protein or monoclonal immunoglobulin) is in the blood with no clinical symptoms. It can progress over years to other disorders such as multiple myeloma.

Smoldering multiple myeloma: Asymptomatic plasma cell disorder that is characterized by the presence of a serum monoclonal protein at a concentration of ≥30 g/l and/or clonal bone marrow plasma cells ≥10% and the absence of end-organ damage. It has a high risk of progression to multiple myeloma.

Immunomodulatory drugs: Therapeutic agents that are structural and functional analogs of thalidomide that can suppress the immune system, inhibiting lymphocyte functions, especially T and NK cells.

Among the new medications, bortezomib, approved by the US FDA in 2003, is the first representative synthetic proteasome inhibitor that can inhibit tumor survival pathways and prevent degradation of pro-apoptotic proteins for the treatment of newly diagnosed MM [13,14]. Unfortunately, bortezomib has low oral bioavailability and severe toxic side effects such as diarrhea, fatigue and insomnia that have restricted the dosage [15,16]. Thalidomide is among the first-in-class **immunomodulatory drugs** (IMiDs) for the treatment of all stages of MM and was approved by the FDA in 2006 to treat newly diagnosed MM [17]. The anticancer mechanisms of IMiDs include inhibition of angiogenesis and the secretion of cytokines, immunomodulation of regulatory T cells, disruption of interactions between plasma cells and the bone marrow microenvironment, as well as direct antitumor effects [18,19]. Thalidomide, however, is associated with toxicities such as thrombocytopenia and side effects that include constipation and neuropathy [20]. Lenalidomide, a more potent and less toxic drug than thalidomide, was adopted in 2006 as a common treatment in combination with dexamethasone for MM patients who have received one prior therapy [21,22].

Although still limited by unwanted side effects and poor long-term efficacy, the newer agents are designed, for the first time, to modulate pathways that most directly influences the progression of MM. Researchers have been encouraged to develop new treatments that also target the bone microenvironment. Indeed, this is the current trend, as both patents and literature citations from SCI-FINDER related to 'MM' have steadily risen in recent years (Figure 1).

Pathophysiology of MM

As a tumors form in postgerminal mature B cells, MM is regulated by expression of various cytokines and signal transduction molecules [23]. Released cytokines, chemokines and growth factors from myeloma cells interact with the microenvironment, causing autocrine and paracrine secretion of insulin-like growth factor 1, interleukin-6 (IL-6), fibroblast growth factor receptor 3 (FGFR3), vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α) and transforming growth factor-β [24]. The bone marrow microenvironment comprises several cell types such as hematopoietic cells, stromal cells, fibroblasts, bone marrow stromal cells (BMSCs), osteoblasts, osteoclasts, endothelial cells and immune cells, as well as noncellular components that include extracellular matrix, cytokines, growth factors and chemokines [23]. The onset of MM is due to the accumulation of abnormal plasma cells in the bone marrow that adhere to extracellular matrix and BMSCs, which play a key role in the pathogenesis of MM [25]. The adherence of MM cells to BMSCs increases induction of the NF-κB signaling pathway that up-regulates the expression of IL-6, which is itself predominant in the development of MM [26]. IL-6 stimulates proliferation and inhibits apoptosis, which in turn enhances drug resistance in myeloma cells [27]. IL-6 can induce the autocrine and paracrine secretion of VEGF, the presence of which can further up-regulate the induction of IL-6 and trigger the MM cells migration by β_1 integrin- and phosphatidylinositol 3-kinase-dependent PKC α [28–30].

Over-activation of the Ras/Raf/MEK/ERK/MAPKK pathway significantly contributes to the proliferation and anti-apoptotic characteristics of MM cells [31]. JAK/STAT3 and PI3K/Akt3 signaling cascades further regulate cytokine-induced survival and inhibition of apoptosis in MM cells. IL-6 triggers the phosphorylation of STAT3 through JAK1, and further stimulates anti-apoptotic genes Bcl-2, Bcl-xL and Mcl-1 downstream [32–34]. Accordingly, inhibition of the JAK/STAT3 pathway is correlated with enhanced apoptosis of MM cells [35]. Cytokines like IGF and VEGF can activate PI3K, stimulating Akt, which mediates various biological processes including increased expression of cyclin D and NF-κB that enhance tumor survival [36]. After CDK-cyclin D functions are carried out, cyclins are polyubiquitinated and degraded via the ubiquitin-proteasome signaling pathway, which is responsible for regulating many cellular events including DNA replication, transcription activation, and cell cycle regulation and apoptosis as mentioned [37]. For an illustration, Figure 2 summarizes all MM patent drugs discussed herein and their associated MM targets. With identification of these putative mechanisms, scientists and clinical researchers have developed various novel agents in an effort to improve the standard treatment of MM.

New MM drugs & patents under development or in clinical trials

TNF-α inhibitors

TNF-α is a multifunctional cytokine associated with various biological activities [38]. TNF can up-regulate

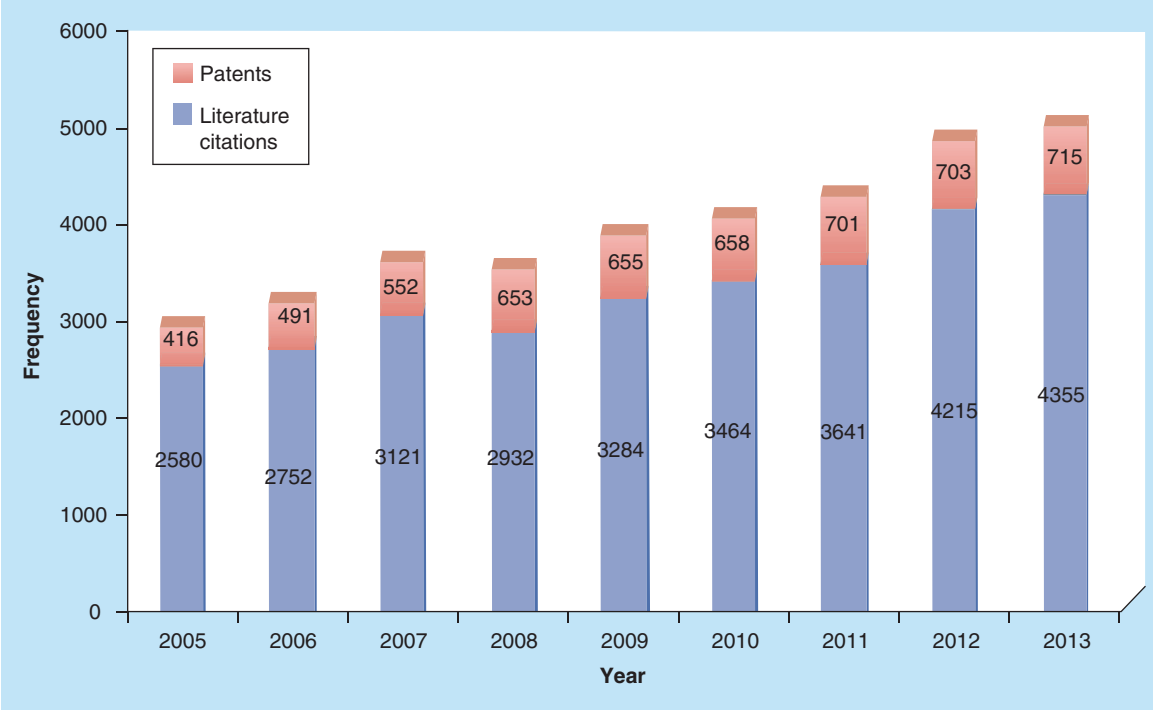


Figure 1. Frequency of patents and literature citations related to 'multiple myeloma' from 2005 to 2013.

IL-6 level under tumoral environment and trigger the JAK/STAT pathways, leading to the activation of NF-κB [39]. It was demonstrated that TNF-α acts as a tumor-promoting factor, which is related to transformation, proliferation, angiogenesis and metastasis in tumor cells [40]. Studies have shown that the concentrations of BAFF and APRIL, two members of the TNF-α family, are enhanced in MM patients [41]. In light of this, the TNF receptor is treated as a potential druggable target for treatment of MM.

Pomalidomide (Table 1), a derivative of thalidomide with oral bioavailability, was approved by the FDA in February 2013 to treat relapsed and refractory MM patients who had received at least two prior therapies. As a novel IMiD, pomalidomide inhibits the interactions between myeloma cells and bone marrow microenvironment, and decreases the production of TNF-α and other cytokines such as IL-6 [42]. Studies showed that pomalidomide potentiated the inhibitory effects on its target cytokines better than thalidomide, which resulted in improved therapeutic effects [43]. However, pomalidomide can potentially cause severe embryo-fetal toxicity and venous thromboembolism. Several pomalidomide-related clinical studies are under way, including those evaluating the safety of pomalidomide in combination with low dose dexamethasone, with or without bortezomib, in patients with relapsed and refractory MM (Phase 3) [44].

Celgene Corporation patented 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dion (lenalidomide) (P-15, Table 2), which is an orally bioavailable immunomodulatory compound. Lenalidomide can promote the degradation of TNF-α mRNA. The IC_{50} of this compound for inhibiting the production of TNF- α in peripheral blood mononuclear cells under the circumstance of LPS-stimulation was 100 nM, representing a marked improvement over thalidomide (194 μM). In preclinical studies, lenalidomide can efficiently overcome drug resistance in MM cells *in vitro* and *in vivo* [45]. Lenalidomide as an oral capsule (Revlimid®) was approved by the FDA in 2006 in combination with dexamethasone for patients with MM who have received one prior therapy [21]. The drug is currently under clinical trials to treat different stages of MM alone or in combination with other drugs [46].

CD40 is a member of TNF-α superfamily, having relatively high expression on the surface of MM cell lines and primary MM cells [69]. Inhibition of the CD40/CD40L interaction can have antimyeloma activity by disrupting key signal transduction pathways in MM or BMSCs. Novartis Vaccines and Diagnostics Inc. filed a patent on anti-CD40 monoclonal antibodies CHIR-12.12 and CHIR-5.9 for the treatment of MM (P-14, Table 2) [60]. The agents have high affinity for CD40 and suppress CD40-ligand mediated survival signals in MM cells [60]. Studies indicated that CHIR-12.12 (5 μg/ml) can inhibit the PI3K/Akt, NF-κB and extracellular signal-regulated kinase activation induced by CD40L (5 μg/ml) [70]. CHIR-12.12 also decreased the

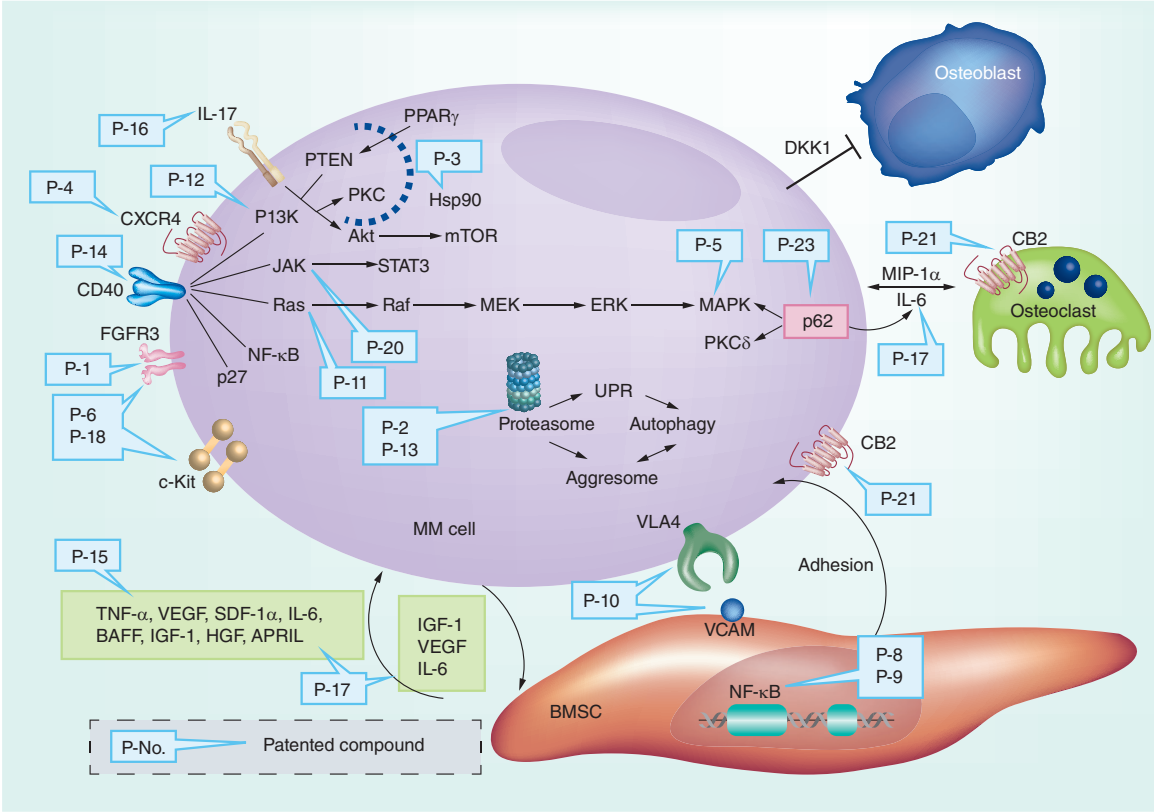


Figure 2. The published patents related to multiple myeloma treatments and their associated targets.
APRIL: A proliferation-inducing ligand; BMSC: Bone marrow stromal cells; CB2: Cannabinoid receptor 2; CD40: TNF receptor superfamily member 5; CXCR4: Chemokine receptor type 4; DKK1: Dickkopf-related protein 1; ERK: Extracellular signal-regulated kinases; FGFR3: Fibroblast growth factor receptor 3; HGF: Hepatocyte growth factor; Hsp90: Heat shock protein 90; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; MEK: Mitogen-activated protein kinase kinase; MIP-1α: Macrophage inflammatory protein-1α; MM cell: Multiple myeloma cell; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositide 3-kinases; PPARγ: Peroxisome proliferator-activated receptor gamma; PTEN: Phosphatase and tensin homolog; SDF-1α: Stromal cell-derived factor 1; STAT3: Signal transducer and activator of transcription 3; UPR: Unfolded protein response; VCAM: Vascular cell adhesion protein 1; VLA4: Very late antigen-4.

adherence of MM cell to BMSCs induced by CD40L, blocking the induction of IL-6 and VEGF [70].

Receptor tyrosine kinases inhibitors

Receptor tyrosine kinases (RTKs) are transmembrane proteins containing an extracellular lectin binding domain and an intracellular catalytic domain, forming a class of targets for the treatment of MM [71]. Several signaling molecules such as MAPKs and PI3K that are responsible for mediating tumor cell growth, progression and metastasis are downstream of RTKs [72]. Of 91 RTKs, 14 have been found to contain mutations in cases of MM, including insulin-like growth factor 1R, epidermal growth factor receptor, neurotrophic tyrosine kinase receptor 1 and neurotrophic tyrosine kinase receptor 2 [73]. These mutations in genes of RTKs highlight their importance in the pathogenesis of MM [73].

Among MM tumors, approximately 15 to 20% are characterized by t(4;14)(p16.3;q32) translocation, which is associated with up-regulation of FGFR3 and myeloma SET domain protein [74]. FGFR3 belongs to FGFR, which is a member of a family of highly related transmembrane RTKs [75]. FGFR3 is associated with the intracellular signaling pathways such as Ras/Raf/MAPK and PI3K/Akt/mTOR, and has effects on tumor cell proliferation and migration [74]. Novartis Pharma Gmbh filed a patent for staurosporine derivatives in 2006 (P-1, Table 2) [47]. Staurosporine derivatives including PKC412 are potential agents for the treatment of curative and prophylactic MM, which target the FGFR3 or Ras signaling pathway and c-fos transcription. c-fos proto-oncogene is a member of the AP-1 family of transcription factors, which play a key role in nuclear response to stimulatory signals that regulate the proliferation and differentiation of cells [76]. PKC412 inhibits the activity of Ras and FGFR3 or c-fos in concentrations ranging from 0.01 to 50 μM, showing significant therapeutic effects [47]. Studies

Table 1. Summary of antimultiple myeloma clinical trial drugs.

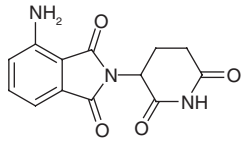
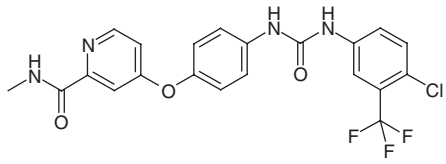
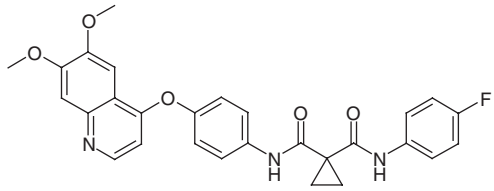
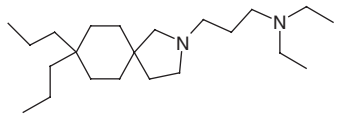
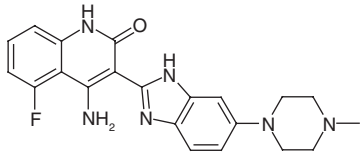
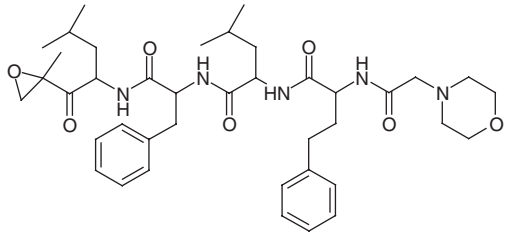
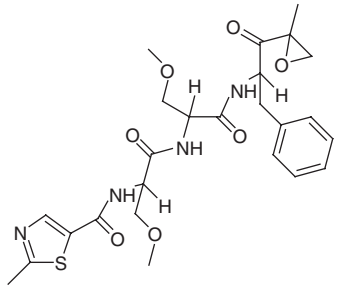
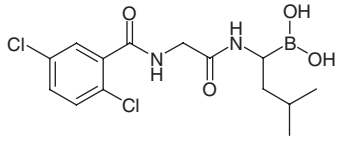
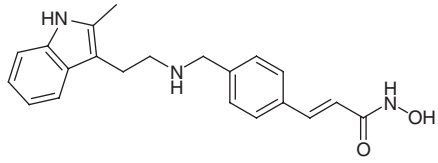
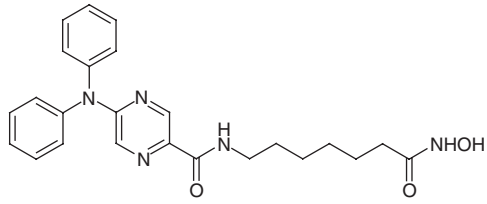
Drug	Structure	Multiple myeloma target	Company	Clinical trial
Pomalidomide		Tumor necrosis factor-α	Celgene Corporation	Phase 1–3
Sorafenib		Vascular endothelial growth factor R2/ Raf-kinase	Bayer/ONYX pharmaceuticals	Phase 2
Cabozantinib		Vascular endothelial growth factor R2/MET	Exelixis, Inc.	Phase 1–2
Atiprimod		Vascular endothelial growth factor	Callisto Pharmaceuticals	Phase 1–2
CHIR-258		Multiple receptor tyrosine kinases	Novartis Pharmaceuticals	Phase 2
Carfilzomib		Proteasome	ONYX pharmaceuticals	Phase 1–3
Oprozomib (ONX-0912)		Proteasome	ONYX pharmaceuticals	Phase 1–2
MLN9708		Proteasome	Millennium	Phase 1–3

Table 1. Summary of antimultiple myeloma clinical trial drugs (cont.).

Drug	Structure	Multiple myeloma target	Company	Clinical trial
Siltuximab	Monoclonal antibody	Interleukin-6	Janssen Research & Development, LLC	Phase 2
Daratumumab	Monoclonal antibody	CD38	Genmab	Phase 1–2
MOR03087	Monoclonal antibody	CD38	MorphoSys	Phase 1–2
BI-505	Monoclonal antibody	CD54	BioInvent	Phase 2
Panobinostat (LBH589)		Histone deacetylase i	Novartis	Phase 1–2
ACY-1215		Histone deacetylase6	Acetylon Pharmaceuticals	Phase 1–2
CC-223	NA	Mammalian target of rapamycin	Celgene Corporation	Phase 1–2
MDX-1338	Monoclonal antibody	CXCR4	Mayo Clinic cancer center	Phase 1
BHQ880	Monoclonal antibody	DKK1	Novartis	Phase 2 (closed)

suggested that PKC412 also suppresses Akt kinase activation and induces apoptosis in myeloma cell lines (RPMI8226S, U266, MM1S and MMIR) [77].

2-amino aryl thiazoles and 2-amino aryl oxazoles are dual c-Kit/FGFR3 inhibitors (P-6, Table 2), making them candidates for the treatment of relapsed or refractory MM over-expressing FGFR3. Studies showed that these agents inhibited enzymatic activity and the phosphorylation of FGFR3 with an IC_{50} below 0.1 and 2 μM, respectively, in MM cell lines expressing FGFR3 [52]. Studies indicated that 30% of MM patients have relatively high expression of c-Kit [78]. It was verified that c-Kit expression is connected to survival pathways, which can modulate MM cell death, suggesting that blocking c-Kit is an ideal strategy to accelerate the death of MM cells [78]. The agents inhibited the proliferation of cells, which expressed mutations of c-Kit in juxtamembrane domain with an IC_{50} of less than 0.1 μM [52].

VEGF, and its receptors VEGFR1, VEGFR2 and VEGF3, have been studied as a target to treat MM, since they are not only essential for angiogenesis but also for triggering growth, survival and migration of MM cells though the MEK/MAPK and PI3K/Akt pathways [79,80]. Elevated levels of VEGF secreted by MM cells will enhance the production of IL-6, promoting the development of MM [81]. Sorafenib (Table 1), a drug initially approved for the treatment of renal and hepatocellular cancer by the FDA in 2007, is a small molecular dual inhibitor of VEGFR 2 and Raf-kinase with oral bioavailability [82]. Administration of sorafenib has been shown to decrease the concentration of plasma VEGF after 8 weeks in patients [83]. Moreover, sorafenib specifically targets Raf kinase by binding to its adenosine triphosphate binding site [84]. A Phase 2 study showed that sorafenib treatment had significant positive effects on two patients among a sample of 11 with relapsed or refractory MM [85].

Cabozantinib (Table 1), developed by Exelixis, Inc., is a small molecule VEGFR2 and MET inhibitor. The signaling pathway of MET is functionally connected to VEGF [86]. The multi-RTK inhibitor cabozantinib is currently under an open label Phase 1–2 clinical trial to study its safety and efficacy for patients with relapsed or refractory myeloma [87].

Atiprimod (Table 1) is a small-molecule drug, belonging to the azaspirane class of cationic amphiphilic drugs with orally bioavailability. It is capable of reducing the production of VEGF and inhibiting

Table 2. Summary of antimultiple myeloma compounds based on selected patents.

Number	Patent	Multiple myeloma agents (targets)	Assignee	Year	Ref.
P-1	WO061199A1	Staurosporine derivatives (FGFR3/c-fos/ Ras)	Novartis Pharma Gmbh	2006	[47]
P-2	WO060676A1	NPI-0052 (Salinosporamide A) (proteasome)	Dana-Farber Cancer Institute	2006	[48]
P-3	WO118953A2	17-allylamino- 17-demethoxy-geldanamycin (17-AGG) or 17-amino geldanamycin (17-AG) (Hsp90)	Kosan Biosciences, Inc.	2006	[49]
P-4	WO116185A2	MDX-1338 (CXCR4)	CBR institute for biomedical research, Inc	2006	[50]
P-5	US079461A1	P38 inhibitor (MAPK)	Scios, Inc.	2006	[51]
P-6	WO026251A2	2-aminoarylthiazoles 2-aminoaryloxazoles (c-Kit/ FGFR3)	AB SCI- ENCE	2007	[52]
P-7	WO059078A1	Dasatinib (multi-kinase)	Dana-Farber Cancer Institute	2007	[53]
P-8	EP-1443927-B1	Carboline derivatives (NF-κB)	Millennium pharmaceuticals, Inc.	2007	[54]
P-9	US7196105	Curcumin (NF-κB)	Research Development Foundation	2007	[55]
P-10	US7211252	Antagonists for Alpha4 intergrin binding agents (VCAM-1, VLA-4)	University of Texas System	2007	[56]
P-11	WO002553 A1	Erastin analogues (Ras)	Prolexys Pharmaceuticals, Inc.	2009	[57]
P-12	WO034414A1	2,3-dihydroimidazo[1,2-c] quinazoline (PI3K/Akt)	Bayer Schering PharmaAktiengesellschaft	2010	[58]
P-13	WO138141A1	[(lR)-l-[[(2S,3R)-3-hydroxy-2-[6-phenyl-pyridine-2- carbonyl)amino]-1-oxobutyl]amino]-3-methylbutylboronic acid (proteasome)	Cephalon, Inc.	2010	[59]
P-14	EP-1684805-B1	CHIR-12.12, CHIR-5.9 (CD40 monoclonal antibodies)	Novartis Vaccines and Diagnostics Inc.	2010	[60]
P-15	US7968569	3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dion (TNF- α)	Celgene Corporation	2011	[45]
P-16	US8012477	IL-17 binding molecule (IL-17)	Novartis AG and Novartis Pharma GmbH	2011	[61]
P-17	US8268807	(E)-3-hydroxy-21-[2′-(N,N-dimethylamino)ethoxy]-19-norpregna-1,3,5(10),17(20)-tetraene (IL-6)	SRI International	2012	[62]
P-18	WO136732 A1	Masitinib (c-Kit/ FGFR3/ PDGFR)	AB SCI- ENCE	2012	[63]
P-19	WO134915A1	Ezatiostat (GSTP1–1)	Telik, Inc.	2012	[64]
P-20	WO149602A1	N-(cyanomethyl)-4-[2-[[4-(4-morpholinyl)phenyl]amino]-4-pyrimidinyl]-benzamide (CYT387) (JAK)	YM BioSciences Australia Pty Ltd	2012	[65]
P-21	WO022919A1	2-((3,4-bis(benzyloxy)benzyl)amino) ethan-1-ol (XRK3) (p62)	Xie, X-Q., *et al.* University of Pittsburgh	2013	[66]
P-22	US0040979	CCR1 antagonists (CCR1)	Millennium Pharmaceuticals,Inc	2013	[67]
P-23	US0172388A1	phenylacetylamide (PAM) (CB2)	Xie, X-Q., *et al.* University of Pittsburgh	2013	[68]

the activation of STAT3, which suggests that it may exhibit potent anti-proliferative and anti-angiogenic activities [88]. A Phase 1–2 clinical study is ongoing to identify the maximum tolerated dose and safety of it in refractory or relapsed MM patients by Callisto Pharmaceuticals [89].

CHIR-258 (Dovitinib) (Table 1) is a benzimidazole-quinoline that targets multiple RTKs including

Key terms

Hsp90: Chaperone protein that assists other proteins in folding properly, stabilizing proteins against heat stress and aiding in protein degradation

Histone deacetylase: Class of enzymes that remove acetyl groups from histone, allowing the histones to bind DNA more tightly and inhibit gene transcription.

FGFR1/3 and VEGF receptors VEGFR1/2, PDGFR, c-kit and Flt3 that are associated with the proliferation of solid MM tumors [90,91]. CHIR-258 can be considered a potent small molecular antitumor drug with oral bioavailability [92]. Preclinical studies demonstrated that daily administration of CHIR-258 suppressed the FGFR3-mediated transduction in KMS-11-luc human MM cells *in vivo*, resulting in significant inhibition of KMS-11-luc tumor growth [92]. The Phase 2 clinical trial to study the safety and efficacy of CHIR-258 for relapsed or refractory MM patients, who are with or without t(4;14) chromosomal translocation, was completed in February 2013 [93].

Dasatinib (P-7, Table 2) is a multi-targeted kinase inhibitor with oral activity, exhibiting inhibitory effects on BCR-ABL, SRC, c-KIT and PDGF-R and ephrin receptor kinases [53]. During preclinical studies, the IC_{50} of dasatinib was found to be within 100 nM in eight out of 15 MM cell lines [53]. Dasatinib is currently in Phase 2 clinical trials for relapsed or plateau phase MM. The patent suggests a combination use of dasatinib and at least one other anti-MM agent such as dexamethasone, bortezomib and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor [53].

Masitinib (P-18, Table 2) is a tyrosine kinase inhibitor that selectively targets c-Kit/FGFR3/PDGFR [94]. It shows no kinase-associated cardiotoxicities at therapeutic doses, making it a much safer drug compared with other kinase-targeted drugs [63,95–96]. It was reported that the inhibition effects of masitinib on PDGF-BB-mediated proliferation and PDGFR-α tyrosine phosphorylation were in the range of 300 ± 5 nM (IC_{50}) [63]. It can inhibit the proliferation of two t(4;14) cell lines, LPI and NCI-H929, by 50% at the dose of 2 μM [63]. Data showed that the combination of masitinib and dexamethasone could decrease the proliferation of MM cell lines *in vitro* [63]. Clinical studies that analyzed the combined administration of masitinib, dexamethasone plus bortezomib demonstrated that the combination therapy is safe and effective for treatment of early stage or first relapsed MM, as evidenced by median progression-free survival and overall survival [63].

Proteasome inhibitors

Proteasomes are multi-enzyme complexes that are responsible for the dysfunctional protein clearance and cell homeostatic maintenance [96]. Tumor cells are sensitive to proteasome inhibitors, which trigger anti-proliferation and pro-apoptotic effects [16]. As mentioned previously, bortezomib is a representative proteasome inhibitor by reversibly blocking the chymotrypsin-like activity of the 20S subunit of the proteasome with limited oral bioavailability and severe side effects [16]. This led to the assessment of other proteasome inhibitors with a more favorable toxicity profile and improved compliance of patients [97]. Carfilzomib (Table 1) is an irreversible, second-in-class proteasome inhibitor for intravenous administration developed by Onyx Pharmaceuticals, Inc. [98]. It was approved by the FDA in July 2012 for the treatment of MM patients who have received at least two prior therapies [99]. The net sales have exceeded US$62M for 2012. Through October 2012, approximately 25% of the estimated 10,000 to 15,000 patients suffering from with third-line or later MM in the USA have been treated with this drug [100]. Compared with bortezomib, carfilzomib targets to chymotrypsin-like proteasome with greater selectivity and less neurotoxicity [101,102]. Clinical trials administering carfilzomib in combination with other agents to cure MM have begun [103].

Oprozomib (ONX-0912) (Table 1), a tripeptide epoxy ketone with oral activity, is now being tested in a Phase 1–2 clinical trial study by Onyx Pharmaceuticals, Inc. [104]. Its anti-MM function is associated with irreversible and specific inhibition of the chymotrypsin-like activities of the proteasome [105]. Oprozomib also induces the activation of caspase-8, caspase-9, caspase-3 and poly (ADP-ribose) polymerase, resulting in a longer duration of effect [16,101].

Another proteasome inhibitor, MLN9708 (Table 1), is an orally bioavailable agent currently in Phase 3 clinical study for the treatment of different stages of MM alone or in combination with other drugs by Millennium Pharmaceuticals, Inc. [106]. Phase 1 and 2 clinical trials of MLN9708 indicated that it was well tolerated and had clinical efficacy with some patients, achieving significant response to the therapy especially at high doses [107]. MLN9708 has greater PDs and PK effects in tissues when compared with bortezomib [108].

Compound [(lR)-I-[[(2S,3R)-3-hydroxy-2-[6-phenyl-pyridine-2- carbonyl)amino]-I-oxobutyl]amino]-3-methylbutylboronic acid (P-13, Table 2), is a reversible proteasome inhibitor in the peptide boronic acid class with oral bioavailability [59]. It has antitumor function in primary MM plasma cells *in vitro* and in RPMI8226 xenografts *in vivo* [59]. This compound shares the same mechanisms of action as bortezomib, inhibiting the chymotrypsin-like activity with little inhibition of the trypsin- and caspase-like activity [59]. When used in combination with bortezomib or melphalan, apoptosis was induced in MM cells. The

combination can inhibit myeloma tumor growth without cytotoxicity to the normal peripheral blood mononuclear cells. The combination can prevent the growth of bortezomib-sensitive LAGκ-1A tumors and significantly delay the progression of bortezomib-resistant LAGκ-1A tumors [59].

NPI-0052 (salinosporamide A) (P-2, Table 2) is a small molecule proteasome inhibitor with oral bioavailability. NPI-0052 can inhibit chymotrypsin-, caspase- and trypsin-like activities of human erythrocyte 20S proteasomes, resulting in apoptosis in various MM cell lines including RMPI-8226, OPM2 and U266 [48]. NPI-0052 can also induce apoptosis in cell lines that are resistant to dexamethasone, bortezomib and thalidomide [48,109]. NPI-0052 is currently under Phase 1 clinical trials by Triphase Research and Development I Corporation [48].

Heat shock protein inhibitor

The molecular chaperone heat shock protein 90 kDa (**Hsp90**) is an attractive target for the treatment of MM. It can interact with a variety of proteins such as erbB2, raf-1 and Akt, which are involved in several functional signaling pathways that govern cell cycle progression and apoptosis [110]. 17-AAG, a semi-synthetic analog of the naturally occurring compound geldanamycin, and 17-AG, a biologically active geldanamycin derivative (P-3, Table 2), were shown to exhibit inhibitory effects on Hsp90 and further induced cell death [49]. When U266 and primary MM cells were treated with 17-AAG, apoptosis increased compared with control cells [111]. 17-AGG has been studied for its anti-MM activity *in vivo* using a model of diffuse Green Fluorescent Protein positive MM lesions in SCID/NOD mice [112]. It was shown that the treatment significantly enhanced the median overall survival [112]. 17-AGG is capable of down-regulating Bcl-2, Mcl-1 and Akt when analyzed anti-apoptotic Bcl-2 family proteins and Akt in MM cells incubated with 17-AGG [111].

Surface antigen monoclonal antibodies

IL-6 mediates autocrine and paracrine growth of MM cells [113]. IL-6 triggers tyrosine kinase JAK1, JAK2 and TYK2, leading to the phosphorylation of signal transducers, STAT1 and STAT2 [114]. It also can activate Ras/Raf/MAPK and PI3K/Akt signaling pathways [115]. Therapeutic strategies targeting IL-6 are under development. Siltuximab (Table 1) is a chimeric, human-murine immunoglobulin monoclonal antibody, which can bind to human IL-6 with high affinity and specificity [116]. Developed by Janssen Research & Development, LLC, siltuximab effectively blocks the IL-6/IL-6R/gp130 signal transduction pathway [116,117]. A Phase 2 trial of siltuximab in high-risk smoldering MM has been launched.

(E)-3-hydroxy-21-[2'-(N,N-dimethylamino) ethoxy]-19-norpregna-1,3,5(10),17(20)-tetraene (P-17, Table 2) has an inhibitory effect on IL-6-induced proliferation in RPMI-8226 and U266 cell lines, as claimed in a patent filed by SRI International [62]. It can also down-regulate p-STAT3 induced by IL-6 [62].

Studies have supported that CD38 is expressed at high levels in all malignant MM cells, suggesting that it is a potential therapeutic antibody target for the treatment of MM [118,119]. A human mAb (daratumumab) (Table 1) is currently under clinical trial Phase 1–2 for MM. Daratumumab is a human lgG1 CD38 mAb, which is capable of binding to a unique epitope of CD38 and kills tumor cells via multiple mechanisms, including anti-tumoral antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [120]. MOR03087 is an anti-CD38 monoclonal antibody, which can bind to CD38 on CD38-positive tumor cells specifically, triggering antibody-dependent cellular cytotoxicity and ultimately cell death [121]. MOR03087 is under an open-label Phase 1–2 clinical trial for its safety and dosing study.

The intercellular adhesion molecule-1 (CD54) is known to be involved in multiple adhesion-dependent leukocyte interactions and immune functions [122]. BI-505 is a humanized immunoglobulin G1 monoclonal antibody that directly targets CD54 (Table 1). It can bind to CD54 with high selectively, leading to the hyper-cross-linking-induced apoptosis and decreased proliferation of tumor cells expressing ICAM-1 [123]. It is currently under Phase 2 clinical trial study to explore its effects on smoldering MM.

Interleukin-17 (IL-17) is a family member of new cytokines that is known to induce expression of several chemokines and cytokines such as IL-6 and ICAM-1 [124]. It was suggested that IL-17 is an important target for the treatment of MM, since molecules that bind to IL-17 are useful in inhibiting the growth of certain solid and hematological tumors [125]. In 2011, Novartis AG and Novartis Pharma GmbH put a patent on record to illustrate a IL-17 binding molecule (P-16, Table 2) [61].

Histone deacetylase inhibitors

Inhibitors of **histone deacetylase** (HDAC) enzymes can be classified as novel anticancer agents. It has been shown that HDAC inhibitors are responsible for regulating gene expression, which can influence apoptosis and cell cycle progression in cancer cells [126]. Panobinostat (LBH589) (Table 1) is a type of HDAC inhibitor with oral bioavailability that induced apoptosis in cancer cells [127]. It further demonstrated antitumor

Key term

Sequestosome-1 (p62): Multidomain and multifunctional protein that acts as a signaling hub for multiple signaling complexes in bone marrow stromal cells.

activity in solid and hematological malignancies in preclinical studies and is currently in Phase 1–2 clinical trials for MM [85,126]. Some researches have reported, however, that panobinostat is nonselective, targeting classes I, II, and IV HDACs with significant toxicity and negative side effects such as gastrointestinal issues and fatigue [84].

ACY-1215 is an orally bioavailable HDAC6 inhibitor (Table 1). Since ACY-1215 selectively inhibit class II HDACs, it has reduced toxic effects on normal cells [128]. Panobinostat and ACY-1215 are currently under clinical trials alone, or in combination with other drugs such as bortezomib and dexamethasone, for MM patients.

PI3K/Akt inhibitor

Enhanced upstream PI3K activation of Akt commonly occurs in late-stage MM [129]. Evidence has shown that inhibition of the PI3K-Akt pathway has potential in preclinical studies of MM, making it a novel target for treatment [36]. 2,3-dihydroimidazo [1,2-c] quinazoline compounds (P-12, Table 2) have potential anti-MM activity via the PI3K/Akt pathway, both as a sole agent or in combination with other active ingredients. Bayer Schering Pharma Aktiengesellschaft filed a patent for the compound, noting that its IC_{50} ranged from 3–100 nM upon inhibition of nine MM cell lines [58].

Mammalian target of rapamycin inhibitor

The mammalian target of rapamycin (mTOR) kinase is responsible for tumor cell proliferation, anti-apoptosis and pro-angiogenesis through regulating the expression of multiple proteins [130]. mTOR is downstream of the PI3K/Akt pathway and has been evaluated for anti-MM drug discovery [131]. CC-223 (Table 1) is an orally available mTOR inhibitor, resulting in the induction of tumor cell apoptosis and decreased proliferation of tumor cells. A Phase 1–2 study began in July 2010 to assess its safety, PKs and efficacy for MM [132].

Ras inhibitor

Mutations of Ras occur in nearly 50% of MM cases and it is a potent activator of multiple downstream signaling pathways like MEK/ERK [133]. Erastin analogues (P-19, Table 2) patented by Prolexys pharmaceuticals Inc. can selectively kill cancer cells that have elevated Ras pathway activity and have no effect on normal cells without elevated Ras activity [57]. Studies showed that 34 of 46 MM cell lines were sensitive to the agent with IC_{50} values of <300 nM for 24 of them [57]. The agent was even effective for the treatment of MM cells resistant to conventional and novel anti-MM agents, and further overcame the protective effect of IL-6 [57].

MAPK inhibitor

A patent for a p38 mitogen-activated protein kinase (MAPK) inhibitors has been put on record (P-5, Table 2) [51]. p38/MAPK is a member of the MAPK family and plays a crucial role in MM as an important regulator of the release of IL-6 and VEGF in BMSCs induced by cytokines and inflammation in the bone marrow microenvironment, enhancing MM cell survival [25]. A potential treatment for MM could thus utilize p38 MAPK inhibitors alone or in combination with other agents. The structures of the p38 MAPK inhibitors indicate that they are derivatives of indole-type compounds containing a mandatory substituent [51,134]. The agents can fully suppress p38 MAPK activity shown by immunodetection of p38 MAPK kinase target HSP-27 [51]. Activated p38 phosphorylates can trigger heat shock protein 27 (HSP-27), resulting in anti-apoptotic effects [135]. The agents blocked phosphorylation of HSP-27 completely in MM cells and in BMSCs [51].

JAK/STAT3 inhibitor

The JAK/STAT3 signaling pathway plays a key role in the development of MM by promoting cell accumulation through its anti-apoptotic activity [136]. CYT387 is a phenylaminopyrimidine compound and a novel JAK-targeted drug that can inhibit JAK1, JAK2, JAK3 and TYK2 kinase activity (P-20, Table 2) [65]. Studies have shown that CYT387 can modulate signaling downstream of IL-6, inhibiting proliferation and disrupting the cycle of MM cells [65]. It is currently in Phase 1–2 evaluation, showing no relevant hematological toxicity. It can be considered as a potential anti-MM drug alone or in combination with other agents [65,137].

NF-κB inhibitors

Transcription factor NF-κB is crucial for the survival and proliferation of MM cells. Numerous tumor cells with enhanced expression of NF-κB are resistant to apoptosis induced by chemotherapy and radiation [138]. NF-κB binds to its inhibitory protein IκB and maintains it in the inactive form in the cytosol [139]. Once IκB is phosphorylated, NF-κB is translocated into the nucleus and stimulates the transcription of specific NF-κB-regulated genes, which control the production of cytokines and chemokines [140]. All MM cell lines showed active IκB kinase and IκBα phosphorylation [55]. Therefore, IκB is a potential target for several diseases. Carboline derivatives (P-8, Table 2) are specific IκB kinase inhibitors, which can inhibit IκBα phosphorylation in MM.1S cells and patient MM cells [139]. The agents can inhibit

the up-regulation of adhesion molecule mediated by NF-κB in cancer cells and block the protective effect of IL-6 against drug-induced apoptosis [54].

Curcumin (P-9, Table 2) is a chemopreventive agent that suppresses IκBα phosphorylation through the inhibition of IκB kinase activity and down-regulation of NF-κB. Curcumin is capable of suppressing constitutive NF-κB activation in all four MM cell lines including U266, MM.1, MM.1R and RPMI 8226 through blocking constitutively active IκB kinase present in MM cells [55]. Curcumin was shown to suppress MM cell proliferation and arrested cells at the G1/S cell cycle phase [55].

Alpha4 intergrin antagonists

Very late antigen-4 (VLA-4) is over-expressed in MM cells, serving as a key adhesion molecule that acts as a receptor for the extracellular matrix protein fibronectin and the cellular counter-receptor VCAM-1 [141]. It is responsible for the adherence of myeloma cells to bone marrow, promoting the development of MM and drug resistance [142]. Studies performed at the University of Texas demonstrated that the VCAM-1/VLA-4 integrin interaction is crucial for the cell–cell interaction between marrow stromal cells and 5TGM1 myeloma cells, leading to increased production of osteoclastogenic and bone resorption activity [56]. A published patent has indicated that antagonist agents that disrupt VCAM-1/VLA-4 binding may serve as potential treatments of MM and myeloma-induced bone resorption (P-10, Table 2) [56].

P62/sequestosome-1 inhibitor

Sequestosome-1 (p62) is a multifunctional protein that facilitates the formation of complexes involved in multiple signaling pathways such as NF-κβ, p38 MAPK and PI3K/Akt [143]. As a key regulator of these signaling pathways, p62 has been shown to play an important role in triggering cell autophagy and apoptosis in tumorgenesis [144]. Studies identified that the ZZ domain of p62 is crucial for BMSC support of MM cells and Osteoclast (OCL) formation. The ZZ domain of p62 can bind to RIP1 protein, interacting with TNF receptor, and activating NF-κB and p38/MAPK signaling [145]. Binding of innate defense regulator peptide (IDR-1) can promote RIP1 complex formation, inhibiting inflammation via p38 and IL6 signaling by interacting with RIP1 [145]. Study of a p62-knockout stromal cell-line showed that the ZZ domain of p62 is required for stromal cell support of MM cell growth, increased IL-6, VCAM-1 expression and OCL formation [66]. Xie *et al.* filed a patent in 2013 for the first p62-ZZ chemical inhibitor compounds (P-21, Table 2) [66]. The small molecule p62-ZZ inhibitor, 2-((3,4-bis(benzyloxy)benzyl) amino)ethan-1-ol (XRK3) had an IC_{50} of <5 μM when tested with MM cell lines. Furthermore, one patented compound demonstrated that it can suppress the expression of VCAM-1 and IL-6 induced by TNF- α in stromal cells by 30 and 90%, compared with the control vehicle [146]. The compounds can block the phosphorylation of PKC-zeta since Phospho-PKK¾ is a unique downstream signal activated by interactions with p62-ZZ domain. Moreover, p62-ZZ inhibitors can block human OCL formation in a dose-dependent way without blocking the differentiation of normal hematopoietic precursors. The compounds involved in the study can treat drug-resistant MM, that is, resistant to one or more of dexamethasone, alkylating agents, anthracyclines, thalidomide, lenalidomide, CC-4047, bortezomib and multi-targeted kinase inhibitors [66].

Other agents

MM patients are known to have elevated levels of bone marrow plasma protein Dickkopf-1 (DKK1) [147]. Evidence further suggests that concentrations of DKK1 are associated with myeloma stage and osteolytic lesions in MM patients [148–150]. The Wnt/β pathway is crucial in osteoblastogenesis and the regulation of bone metabolism [151]. DKK1 can inhibit Wnt/β signaling by binding to LRP5/6, resulting in myeloma bone diseases [152]. Thus, DKK1 can be treated as a potential therapeutic target for MM in the bone marrow microenvironment. Preclinical studies have shown that an anti-DKK1 neutralizing antibody (BHQ880) (Table 1) promoted bone formation and inhibited osteolytic diseases induced by myeloma [153]. Furthermore, BHQ 880 can decrease the level of IL-6 production by BMSCs [154]. Phase 2 clinical study of BHQ880 for the treatment of high risk smoldering MM was complete in October 2013 by Novartis Pharmaceuticals.

Nearly all MM patients suffer from osteolytic bone lesions, as the inherent balance between osteoclast and osteoblast function is disrupted in MM, leading to net bone resorption [155]. Osteoclast-activating factors such as macrophage inflammatory protein-1α and RANK induced by myeloma cells enhance the formation of osteoclasts, and ultimately bone destruction [156]. It has been reported that chemokine receptor CCR1 is employed by macrophage inflammatory protein-1α to form osteoclasts [157]. It is thus suggested that a CCR1 inhibitor could serve as a potential treatment for MM (P-22, Table 2). Studies showed that a CCR1 antagonist could delay the progression of monoclonal gammopathy of undetermined significance or smoldering MM in MM and further

demonstrated that MM cell adhesion to osteoclasts was inhibited [67].

The CXCR4 receptor, a chemokine GPCR receptor, is expressed in human MM cells, influencing their migration to the bone marrow [158]. CXCR4 inhibitors can interfere with the CXCR4/SDF signaling pathway by disrupting CXCR4 binding to chemokine stromal derived factor-1/CXCL12 [159]. Studies demonstrated that the attenuation of CXCR4 expression in 5T33 MM cells completely disrupted the development of MM in recipient mice; thus, a CXCR4 inhibitor such as AMD3100 could serve as a potential therapeutic method to treat MM [50]. MDX-1338 (P-4, Table 2) is an orally bioavailable CXCR4 inhibitor that displayed decreased tumor proliferation and migration [50]. MDX-1338 is currently under Phase 1 clinical study to analyze its safety and toxicity [160].

A recent patent (P-23, Table 2) reported the important role of cannabinoid receptor CB2 in MM cell lines [68]. CB2, of the rhodopsin-family GPCR class, is predominantly expressed in the immune system, particularly in plasma B cells, whose dystregulation is the primary characteristic of MM. This was the first report about CB2 as new anti-MM drug target. In their studies, CB2 was found to be highly expressed in primary CD138+ MM cells and other human MM cells by Western blot and RT-PCR experiments. The discovered CB2 ligands, phenylacetylamide as one example, resulted in significant inhibition of MM growth through cell cycle modulation, mitotic death and cytoskeleton disruption [68]. Importantly, this inhibition was rescued by CB2 gene silencing in the treated MM cells. Furthermore, the reported novel CB2 compounds also exhibit great inhibition of osteoclastogenesis [161,162]. Of course, extensive research studies are still needed to characterize the role of the CB2 receptor in MM cell-signaling pathways in order to facilitate new anti-MM drug targeting CB2.

Ezatiostat (TLK199 or TER 199) (P-11, Table 2) is a potent agent for inhibiting MM cell proliferation and treating MM, either alone or in combination with other anti-myeloma drugs such as bortezomib and cyclophosphamide. Ezatiostat hydrochloride (Telintra), a pharmaceutically acceptable salt of ezatiostat, is a glutathione-analog and a reversible inhibitor of the enzyme glutathione S-transferase P1–1 (GSTP1–1) as well as a therapeutic agent for the treatment of myelodysplastic syndrome [163]. It was shown that Telintra inhibited RPMI8226 MM cell proliferation with an IC_{50} of 33.0 μM [64].

Conclusion & future perspective

Bortezomib, thalidomide and lenalidomide are the representative therapeutic agents to treat MM with specific targets. Extensive research is in progress that utilizes a new understanding of MM cell interactions with the microenvironment and the key signaling pathways. Several anti-MM drugs are undergoing different stages of clinical trials to analyze their efficiency and safety. IMiDs, proteasome inhibitors, p38 inhibitors and other new anti-MM drugs with novel targets have displayed good therapeutic indexes and acceptable toxicity. These new agents will gradually transform the treatment of MM away from administrated high-doses of chemotherapy and towards more rational, selective therapies. It is anticipated that the novel anti-MM agents recently patented will ultimately be groundbreaking in MM research and will lead to future target-specific anti-MM drugs that will benefit millions of patients who suffer from this immune system-related cancer for which there is currently no cure.

Executive summary

Background
- Multiple myeloma (MM) is the second most prevalent blood cancer and remains an incurable disease.
- Novel medications have been approved for the treatment of MM.

Pathophysiology of multiple
- Interaction between MM cells and bone marrow microenvironment play a critical role in promoting the growth of tumor cells and therefore related drug targets have been identified.

New MM drugs & patents under development or in clinical trials
- With understanding of the bone marrow microenvironment and molecular mechanisms, many clinical trial drugs and new patents were developed based on different targets: tumor necrosis factor-α inhibitor, receptor tyrosine kinases inhibitors, heat shock protein inhibitor, surface antigen monoclonal antibodies, histone deacetylase inhibitors, mammalian target of rapamycin inhibitor, Ras inhibitor, MARK inhibitor, JAK/STAT3 inhibitor, NF-κB inhibitors and alpha4 intergrin antagonists.
- Other agents such as DKK1 inhibitors, CCR1 inhibitors and GSTP1–1 inhibitors have been identified, and can be potential anti-MM drugs.

Conclusion & future perspective
- Improved anti-MM drugs will be designed based on new research on MM-associated targets.

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