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Future of personalized therapy targeting aberrant signaling pathways in multiple myeloma

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Abstract

Multiple myeloma (MM) is genetically complex disease. Identification of mutations and aberrant signaling pathways that contribute to the progression of MM and drug resistance has potential to lead to specific targets and personalized treatment. Aberrant signal pathways include: RAS pathway activation due to RAS or BRAF mutations (targeted by vermurafenib alone or combined with cobimetinib), BCL2 overexpression especially in t(11:14) (targeted by venetoclax), JAK2 pathway activation (targeted by ruxolitinib), NF-kB pathway activation (treated with DANFIN

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combined with bortezomib), MDM2 overexpression (targeted by DS-3032b) and targeting the PI3K/mTOR pathway (targeted by BEZ235). Cyclin D1 (CCND1), and MYC are also emerging as key potential targets. In addition, histone deacetylase (HDAC) inhibitors are already in use for the treatment of MM in combination therapy and targeted inhibition of FGFR3 (AZD4547) is effective in myeloma cells with t(4;14) translocation. Bromodomain and extra terminal (BET) protein antagonists decrease the expression of MYC and have displayed promising anti-myeloma activity. A better understanding of the alterations in signaling pathways that promote MM progression will further inform the development of precision therapy for patients.

Keywords

Multiple Myeloma; Intracellular pathway; Signaling pathways; Mutations; Personalized therapy

Introduction:

Multiple myeloma (MM) is a genetically complex B-cell malignancy. Clonal plasma cells acquire increasing levels of genetic aberrations including copy number variations, point mutations, gene deletions, and translocations. Clinical guidelines define disease risk stratification based on cytogenetic aberrations and secondary mutational events in plasma cell populations of MM patients. Cytogenetic aberrations in MM can be divided into two main groups: hyperdiploid MM (H-MM) and non-hyperdiploid MM (NH-MM). H-MM are characterized by trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. NH-MM harbor IGH translocations, mainly t (4;14), t (6;14), t (11;14), t (14;16), and t (14;20).[1,2,3] Secondary mutational events contribute to tumor progression and include MYC rearrangements, copy number variations (CNV), del(13q), dup(1q), del(1p) del(17p) and somatic mutations in KRAS, NRAS, BRAF, and P53 among many others.

MM is clinically divided into high, intermediate and standard risk based on interphase fluorescence in situ hybridization (I-FISH). High risk MM (HRMM) patients have del (17p), t(14;16), t(14;20), t(4;14), del 13, plasma cell labeling index (PCLI), a measure of plasma cell proliferation ≥ 3% and gene expression profiling (GEP) shows a high risk signature. The intermediate risk category includes t(14;4), and 1q gain. Standard risk patients carry t(11;14) and t(6;14) mutations.[4,5] For disease staging, the International Myeloma Working Group (IMWG) combined the International Staging System (ISS) with chromosomal abnormalities detected by I-FISH after CD138 and serum lactate dehydrogenase (LDH) sorting for newly diagnosed MM (NDMM) and proposed a revised (R) staging system named R-ISS[6]. The Mayo Clinic's mSMART risk stratification guidelines [5] rely on I-FISH and serum biomarkers (LDH, β_2 microglobulin), however, many characterized aberrations are not adequately surveyed by these methods. The use of other sequencing and array technologies to identify changes to the genomic landscape such as whole exome sequencing (WES), whole genome sequencing (WGS), single nucleotide polymorphism (SNP) arrays, gene expression profiling (GEP), array comparative genomic hybridization (aCGH), in addition to historical genetic testing methods could identify new subgroups and novel targetable pathways in MM. Research identifying aberrant molecular pathways enhances our

understanding of the mechanisms of disease in MM and offers opportunity for the development of new, more targeted therapeutic strategies.

Methods

We performed a focused review of the literature to compile current clinical data regarding novel genetic mutations, disrupted intracellular pathways, cancer driving aberrations and response to targeted therapies to summarize the potential for the advancement of personalized and precision therapy against MM.

Literature Search

We searched PubMed, and Clinicaltrials.gov for only English language studies. We did not limit our search to time period. We also cross checked bibliographies manually to avoid missing potential studies. We retrieved preclinical studies, phase I/II trials and data from clinicaltrials.gov on complete or still recruiting trials. We based our electronic database search on keywords like multiple myeloma, cytogenetics, molecular profiling, mutations, disrupted pathways and prognosis. A sample search strategy is “(multiple myeloma [MeSH Terms]) AND factor NF-kb, transcription [MeSH Terms]) AND “drug therapy” [MeSH Subheading])”. The final updated search was performed on 03/16/2018.

Eligibility Criteria

We included 1) Preclinical studies, 2) Case report & series, 3) Phase 1 or higher clinical trials, and 4) studies that had efficacy outcomes clearly documented. We excluded studies in which no objective efficacy outcomes were reported.

Results

The literature search yielded a total of 827 articles. Relevant articles which focused on the effect of drug therapy on MM cell lines and patients with specific mutation and aberrant intracellular pathways yielded 49 preclinical studies, case reports, case series and clinical trials. We present the summary of findings from these articles here and in Table 1.

A) Developing Targets: Signaling pathways against which specific agents have been tested in clinical trials

Apoptosis in MM—BCL-2 proteins that regulate cell death are grouped according to their pro-apoptotic (i.e. BAX, BAK, BAD, BIK) or anti-apoptotic (i.e. BCL-2, BCL-XL, BCL-W, MCL-1) activity. MM cell lines and primary patient samples, with t(11;14), detected in up to 20% MM patients, have upregulation of cyclin D1, high BCL-2, low BCL-XL, and low MCL-1 profile.[7] Patients with MM often have overexpression of BCL-2 or MCL-1, which makes them resistant to apoptosis.[8] Therefore, inhibitors that target these anti-apoptotic proteins have been the focus of several studies.

BCL2 inhibition—Kumar *et al.* conducted a phase 1 study on 66 patients with relapsed refractory MM (RRMM) using venetoclax, a BCL-2 inhibitor. Venetoclax given weekly in dose-escalation (300, 600, 900, or 1200 mg) had an acceptable toxicity profile. The overall

response rate (ORR) was 21% (14/66) and 15% achieved a partial response (PR) or better. The best response (12/14 [86%]) was seen in patients with t(11;14), a translocation that is associated with high levels of BCL-2. Those with t(11;14) had an ORR of 40% and PR of 27%.[9] Moreau *et al.* in an open-label phase 1b study on 66 patients with RRMM used venetoclax in combination with the proteasome inhibitor bortezomib and dexamethasone, a steroid that has been reported to increase the expression of proapoptotic protein BIM.[8] The treatment was well tolerated when considering adverse events, with an ORR of 67% (44/66) and a PR rate of 42% or better. The median time to progression was 9.5 months and the duration of response was 9.7 months.[8]

Ras/Raf/Mek/Erk—The RAS/RAF/MEK/ERK pathway is an important regulator of gene expression, cell survival, proliferation, migration and angiogenesis. KRAS/NRAS/BRAF mutations are detectable in up to 50% of MM patients[10] and 45-81% of RRMM patients.[11] RAS mutations are linked to a more aggressive clinical course leading to shorter survival.[12] t(4;14) translocation can cause increased expression of FGFR3 which also stimulates RAS/MAPK pathway.[13] IL-6 also triggers growth of cells via the RAS/MAPK pathway.[14] Xu *et al.*[15] noted a dominant mutation cluster in *RAS/RAF* genes in samples taken from MM patients, identifying RAS/RAF/MEK/ERK signaling as a therapeutic target. In comparison with NDMM, RRMM patients have statistically significant higher overall incidence of *RAS/BRAF* mutations (p =0.011), which are mostly driven by a higher prevalence of *NRAS* mutations (p =0.010). Mulligan *et al*[16] observed that *NRAS* but not *KRAS*-mutant MM had significantly lower response rates (P = .016) and a shorter time to progression (P = .012) following treatment with bortezomib monotherapy. These data indicate that an important component of bortezomib's antitumor activity acts at a level upstream of NRAS survival signaling and thus cannot effectively kill myeloma cells with this mutation. MEK inhibitors can kill MM cell lines that have MAF oncogenes and are resistant to other chemotherapeutic agents like lenalidomide, pomalidomide, bortezomib and dexamethasone by re-sensitizing MM cells to these agents.[17–19]

BRAF and MEK inhibition—Selumetinib and sorafenib are two agents under investigation for use in MM with mutations in the Ras/Raf/Mek/Erk pathway. In a phase II trial of the MEK1/2 inhibitor selumetinib (AZD6244) for treating RRMM as a single-agent, AZD6244 resulted in minimal improvement with only 2 out of 36 heavily pretreated RRMM patients achieving very good partial response (VGPR).[20] Another phase II trial for assessing the efficacy of sorafenib, a multi-kinase inhibitor, in RRMM patients showed 50% overall survival (95% CI 27-73%) at 12 months and median progression-free survival of 1.2 months (95% CI 1.0-5.4). [21]

Approximately 4% of patients with MM have *BRAF* mutations.[22,23] Patients who harbor an activating V600E mutation in the BRAF kinase have an aggressive clinical course, higher incidence of extra-medullary disease and shorter overall survival (OS).[24] *BRAF* mutations are highly prevalent in melanoma and hairy cell leukemia and treatment with vemurafenib, a BRAF inhibitor, has shown to have clinical benefit.[25,26] Andrulis *et al* reported a RRMM patient with *BRAF* V600E who was refractory to all approved treatments, but responded rapidly and had a durable response as stable remission to vermurafenib.[24] Larger scale trials

are needed to further explore the role of *BRAF* mutation inhibitors for treatment of MM patients harboring the V600E mutation.

Cobimetinib ($C_{21}H_{21}F_3IN_3O_2$) is an FDA approved drug to treat melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cobimetinib is a reversible, non-ATP-competitive MEK1/MEK2/MAPK. In a case report of RRMM with V600E mutation, Mey *et al.* reported a rapid and sustained response with a combination of vemurafenib and cobimetinib.[27] A phase III study of combined inhibition of BRAF (vemurafenib) and MEK (cobimetinib) showed a statistically significant ($p<0.001$) improvement in progression-free survival (PFS) of patients with BRAF-mutated melanoma, compared to the usage of vemurafenib alone. The usage of vemurafenib alone showed progression-free survival (PFS) of 6.2 months, while the combination showed 9.9 months of progression-free survival, total of a 16-week difference.[28] A phase Ib/II clinical trial is currently underway using cobimetinib as a single agent and in combination with venetoclax with or without atezolizumab in patients with RRMM.[29]

FGFR3 inhibition—FGFR3 mutations have been identified in MM.[30] t(4;14) brings FGFR3 under the control of Ig heavy chain promoter, causing aberrant expression of FGFR3.[30,31] Myeloma cell lines with t(4;14) chromosomal translocation are very sensitive to FGFR3 targeted inhibition.[31] Monoclonal antibodies bind to the FGFR extracellular domain, compete with FGFs and as a result block FGF-FGFR association. Monoclonal antibodies targeting FGFR3 have been shown to have significant inhibitor effect on cellular proliferation in t(4;14) positive multiple myeloma cases.[32] MFGR1877S, is a human anti-FGFR3 monoclonal antibody which was studied in a phase I trial. It was found to be well-tolerated overall in patients with multiple RRMM. No objective responses were observed; however, stable disease was observed in 3 out of 14 patients for 3–4 cycles.[33]

Dovitinib (TKI258) is a well-studied second-generation non-selective FGFR inhibitor. Among its other actions, it has been shown to inhibit the cellular activity of FGFR3 in t(4;14) MM in pre-clinical studies.[34] In a phase II, open label, non-randomized trial, dovitinib did not demonstrate single-agent activity in RRMM, but may stabilize disease in some t(4;14)-positive patients.[35]

BGJ398 is a potent, pan-FGFR inhibitor which demonstrated preclinical antitumor activity in RT112 bladder cancer xenograft models overexpressing wild-type FGFR3. In a study of t(4;14)-positive myeloma cells, [36] enhanced expression of FGFR3 was observed. However, the cells were not sensitive to FGFR inhibitors (neither dovitinib nor BGJ398). While preclinical data was promising, this study concluded that single agent activity is modest and often independent of FGFR status.

AZD4547 is a selective, small molecule, oral FGFR (FGFR 1-3) inhibitor which has shown to be a potent inhibitor of proliferation in cell lines with activation of the FGFR pathway and also in tumor xenograft models [37]. Inhibition by AZD4547 is also shown to cause a significant dose-dependent tumor growth inhibition and increased survival in gastric cancer carrying an FGFR2 gene amplification.[38] A Phase I, open label, multicenter study that assessed the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of

ascending doses of AZD4547 in patients with advanced solid tumors was completed in March 2015.[39] It is currently in phase II trials, aimed to define its role in targeted therapy directed by genetic testing in patients with advanced refractory solid tumors, lymphomas, or MM.[40]

CDK inhibition—Dysregulation of cyclin D is an early and unifying event in MM pathogenesis.[41] Post-transcriptional modifications play an important role in regulating *CCND2* expression.[42] Overexpression of cyclin D1 is seen in up to 60% of MM cells, which is associated with either t(11;14)(q13;q32), polysomy of chromosome 11 or induced expression from interaction of MM tumor cells with the surrounding bone marrow stroma.[43,44] CCND1 overexpression is historically associated with poor prognosis in MM.[45,46] In a small series of patients, CCND1 overexpression conferred improved response to bortezomib therapy.[47,48] In a study of 45 relapsed MM patients who received bortezomib, CCND1 expression was associated with better prognosis (OR, −2.21; $p = 0.07$).[49] In a study of 74 NDMM patients who received high-dose chemotherapy with autologous stem cell transplant (ASCT), patients who overexpressed cyclin-D1 had significantly longer duration of remission in comparison with patients who did not (41 vs. 26 months, respectively; $p = 0.02$) resulting in longer median event-free survival (33 vs. 24 months, respectively; $p = 0.055$). The risk for progression after bortezomib treatment was significantly decreased (HR 0.102, 95% CI 0.021-0.498, $p = 0.0048$) and progression-free survival prolonged ($p = 0.0011$).[50] Palbociclib ($C_{24}H_{29}N_7O_2$), an FDA approved drug to treat breast cancer works by selectively inhibiting CDK4/6. In a phase II study, to evaluate the safety and efficacy of palbociclib in combination with bortezomib and dexamethasone in RRMM, objective responses were achieved in 5 (20%) patients and 11 (44%) achieved stable disease.[51]

PI3K/mTOR inhibition—The PI3K/AKT/mTOR pathway guards tumor growth and is involved in proliferation, survival and drug resistance in MM cells. This pathway also mediates the formation and activity of bone-forming osteoblasts and bone-resorbing osteoclasts.[52] IL-6 can directly activate the proliferative effects of PI3K[53]and activate AKT hence playing an important role in MM pathogenesis.[54,55]

Dysregulated activation of mTOR signaling pathway is considered to be associated with drug resistance and poor prognosis of many cancers, including MM. [56] mTOR coordinates cell growth and proliferation in response to inputs from growth factors, nutrient status and energy stress, thus regulating cell cycle progress and survival.[56] mTORC1 is a key modulator in MM cell proliferation, tumor development and chemoresistance. Disruption of this signaling could lead to MM cell apoptosis, tumor regression, and improved survival of MM patients.[57]

Feng *et al.* researched the effects of an organic compound, silybin, which decreased proliferation and ultimately led to apoptosis of MM cell lines by inhibiting the expression of PI3K, p-AKT and mTOR.[58] With *in vitro* studies, a novel PI3K and mTOR inhibitor, BEZ235, showed potent antitumor effects as well as decreased osteoclast and increased osteoblast production and activity, respectively. This property of BEZ235 can be utilized against osteolytic lesions in MM patients.[52] Oral PI3K/AKT inhibitors C98 and C96, have also been shown to inhibit proliferation and induce apoptosis of MM cells in both *in vitro*

and xenograft studies. Importantly, the agents were very well tolerated in the animal studies.[59,60]

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is an anti-microbial drug, metal chelator, and potential anticancer drug. Clioquinol inhibits mTOR activity by disrupting the integrity of mTORC1 in MM.[57] In preclinical studies, Clioquinol induced autophagy in leukemia and myeloma cells. Clioquinol has been shown to induce autophagy in association with the increase of the PI3KC3/Beclin 1 complex and dissociation of Beclin 1/Bcl-2.[61] A phase I trial of Clioquinol was performed in patients with advanced hematological malignancies, including MM, identifying neuropathy and abdominal pain as dose limiting toxicities (NCT00963495).

A novel small molecule SC-06 also disrupts the mTOR signaling pathway, inducing cell apoptosis. In preclinical studies, SC06 showed promising results by disrupting mTOR signaling thus decreasing tumor volume in mouse xenograft models of MM.[56] There have been no clinical trials to date with SC-06.

Histone deacetylase inhibition—Histone deacetylases (HDAC) modulate the organization of chromatin, thereby functioning as a controller over gene transcription. In MM, HDAC function is dysregulated, sometimes resulting in the upregulation of oncogenes. HDAC inhibitors represent a new therapeutic class in MM treatment that have the potential to control proliferation, differentiation, cell cycle arrest, and apoptosis. HDAC inhibitors are continuing to emerge as a promising therapy to inhibit MMSET complex assembly, because MMSET associates with HDACs in a large complex.[62–64] Several preclinical investigations and clinical trials have demonstrated the antimyeloma activity of HDAC inhibitors.[65] In preclinical settings, HDAC inhibitors (panobinostat, vorinostat and romidepsin) showed remarkable anti-MM activities as single agents. However, they showed only modest clinical activity in cases of relapsed or refractory MM.[66–68] HDAC inhibitors have been clinically evaluated in combination with other agents, especially with proteasome inhibitors. Clinical efficacy of vorinostat has been studied in combination with bortezomib in phase I trials,[69,70] and subsequently in phase II and III trials (Vorinostat Clinical Trials in Hematologic and Solid Malignancies or VANTAGE trials).[71,72] In the phase II VANTAGE 095 trial, 17 % ORR and 31% clinical benefit rate (CBR) were observed. The phase III VANTAGE 088 trial showed only a modest statistically significant difference in median progression free survival (PFS). The combination of panobinostat with bortezomib has been studied in RRMM patients in a phase Ib study[73] and later in phase II and III.[74,75] In phase II PANORAMA trial, the ORR was 34.5 % and the CBR was 52.7 %. In the randomized, double-blind phase III PANORAMA trial, the combination of panobinostat with bortezomib improved median PFS. The results of the phase III PANORAMA trial resulted in the FDA approval of panobinostat in combination with bortezomib and dexamethasone. A HDAC6 selective inhibitor ricolinostat has also been studied as monotherapy and in combination with bortezomib and dexamethasone.[76,77] This combination showed ORR of 29% and CBR of 39% while in bortezomib refractory patients, ORR was 14% in all combination doses.[77]

B) Emerging Targets: Pathways for which only preclinical data exist, but there is a potential to develop future targeted therapies.

JAK-STAT inhibition—JAK2 (Janus kinase 2) is a tyrosine kinase that binds to cytokine receptors. It is thought that autocrine and paracrine IL-6 leads to upregulation of the JAK2 pathway.[78] Upon binding of cytokine IL-6 to the receptor, the receptor will dimerize and allow JAK2 to cross phosphorylate the receptors. Once phosphorylated these act as docking site for STAT3 to bind and influence gene expression as a transcription factor.[79] Inhibition of the IL-6 receptor and STAT3 pathway has been reported to induce apoptosis in various myeloma cell lines.[80,81] JAK2 pathway activation in MM leads to increased BCL-XL expression, which protects cells from chemotherapy-induced cell death.[82] Interestingly, the *JAK2* V617F mutation which is commonly found in myeloproliferative diseases was not found in 93 MM cases.[83] JAK pathway inhibitors, including ruxolitinib, act by binding to the cytokine receptor and preventing JAK2 association, thereby decreasing activity.[84] Zhang *et al* identified a JAK2/STAT3 inhibitor, SC99, that displays potent activity against MM cells by decreasing their proliferation and increasing MM cell apoptosis in both *in vitro* and MM xenograft models in mice.[85]

Proteasome inhibition of NF-κB pathway—The NF-kB pathway is primarily involved in DNA transcription, production of cytokines, cell proliferation and ultimately cell survival. NF-kB is thought to play an important role in the pathogenesis of MM, as the pathway becomes constitutively active, a potential mechanism by which tumor cells function independently of the marrow microenvironment.[86] Dysregulation of the NF-kB pathway has led to the enhanced proliferation of cancerous cells and an increased likelihood of tumor development. Additionally, NF-kB pathway activation leads to MM lytic bone disease by activating osteoclasts.[87,88] NF-kB also regulates cyclin D1expression.[89,90]

Proteasome inhibitors[91], which partially act by inhibiting NF-kB, have shown great clinical success in NDMM as well as RRMM.[92] DANFIN (N,N'-bis-(2,4-dimethyl-phenyl)-ethane-1,2-diamine) has also been shown to inhibit NF-κB activation and signaling. In preclinical studies, Uematsu *et al.* treated a MM xenograft mouse model with DANFIN plus bortezomib; this combination decreased tumor weight by more than 60% and enhanced the apoptosis of MM cells.[93]

MDM2 inhibition—*TP53* is a tumor suppressor gene that promotes normal cellular proliferation, differentiation and apoptosis. Murine double minute (MDM) 2 is a pleiotropic protein that functions as an E3 ubiquitin ligase that limits the accumulation and function of TP53.[94] It does so by helping ubiquitination of TP53 and thus facilitating its proteasome-mediated degradation. It also binds to TP53 amino acids 15–29, thereby limiting TP53 transcription.[94] MDM2 is a rational target for *TP53* mutated MM.[95] Over-expression of MDM2 is seen in 0-20% of MM patient population [96–98] and its overexpression is associated with increased proliferation and survival of myeloma cells, partly due to down-regulation of cyclin-dependent kinase inhibitor p21.[99] Nutlins are potent and selective small molecule antagonists of MDM2. They function by binding to MDM2 in the p53 binding pocket, releasing p53 from negative control. Preclinical data have demonstrated nutlin-induced

apoptosis in MM cells, supporting further investigation of this therapeutic intervention in MM[100].

c-MYC/WNT—Pathologic activation of c-MYC has a key role in cancer development by upregulating the transcriptional program of the cell, enhancing cell proliferation.[101,102] Amplification, translocation or rearrangement of MYC is among the most common genetic alterations observed in cancer genomes, including MM[103,104] where activation is found in more than 60% of patient-derived MM cells.[105] Increased activity of MYC upregulates ribosomal biogenesis and translation.

MYC inhibition—With a high-throughput screen, Manier *et al.* determined rocaglate derivatives are active against MM. Rocaglates are plant-derived cytotoxic compounds known to inhibit protein synthesis and can repress translation of specific messenger RNAs. Rocaglates inhibit a specific translation oncogenic program related to high expression of MYC, with potent *in vitro* and *in vivo* activity in preclinical studies. Due to their specificity, targeting dysregulated translation initiation with rocaglates rather than targeting the elongation machinery with other translation inhibitors might be less toxic to normal tissues.[106]

WNT inhibition—Deletion or mutation of the tumor suppressor gene encoding the deubiquitinating enzyme CYLD is a common genomic aberration in MM. CYLD acts as a negative regulator of NF-κB and WNTβ-catenin signaling and loss of CYLD sensitizes MM cells to NF-κB-stimuli and WNT ligands. In NDMM, low CYLD expression is strongly correlated with proliferation and a WNT signaling-gene expression signature.[107] In a preclinical study, Schmmel et al demonstrated that targeting WNT signaling with ethacrynic acid and ciclopirox olamine with piceatannol had a synergistic effect, increasing cytotoxicity in myeloma cells with minimal effect on healthy cells.[108] Given these early preclinical results, targeting the WNT pathway is a potential therapeutic strategy in MM with loss of CYLD activity.

Histone methyltransferase inhibition—MMSET, also known as Wolf-Hirschhorn syndrome candidate 1 (WHSC1) or nuclear receptor-binding SET domain 2 (NSD2), is a member of the nuclear receptor binding SET domain (NSD) histone methyltransferase (HMT) family, which also includes NSD1 and NSD3.[109–111] NSDs are histone modifiers that maintain chromatin, methylating histone H3 lysine 36 (H3K36) and histone H4 lysine 20 (H4K20). Multiple myeloma SET domain (MMSET) is specifically over-expressed in 15% of MM cases due to chromosomal translocation of t (4;14); putting the MMSET locus under the control of the Ig heavy chain promoter.[112] As a lysine histone methyltransferase, MMSET regulates the methylation of histones, thereby causing global changes to the chromatin state and subsequent gene expression in t(4;14) MM cells.

Min *et al.* showed that MMSET stimulates cell growth and enhances the expression of cMYC protein in t(4;14) cells.[112] Various studies have shown that when MMSET expression is inhibited, there is reduction of proliferation, induction of apoptosis and alteration of cell adhesion.[113–115] Due to alternative splicing and differential promoter usage, the MMSET locus produces several different transcripts and is also overexpressed in many other cancers

including: pediatric acute lymphoblastic leukemia, lung, prostate, bladder and other solid tumors.[116]

Di Luccio *et al.* discovered a small molecule, LEM-06, which inhibits the H3K36 methylation action of MMSET by putatively blocking the histone binding pocket.[117] Tisi *et al.* demonstrated that N-alkyl sinefungin derivatives also assert low level inhibition of MMSET. [116] Though these compounds have not yet progressed to clinical trial, preclinical research suggests the feasibility of these products or their derivatives to inhibit epigenetic remodeling mechanisms driving MM progression.

BET inhibition—The bromodomain and extra terminal (BET) family of proteins can bind to acetylated chromatin and regulate gene transcription. These molecules were first studied in myeloma and were found to repress c-MYC expression which resulted in significant downregulation of c-MYC regulated genes. A bromodomain (BRD) is an approximately 110 amino acid protein domain that recognizes acetylated lysine residues, such as those on the N-terminal tails of histones and is responsible for transducing the signal carried by acetylated lysine residues and recruiting different molecular partners, including chromatin factors and transcriptional machinery.[118] Histone acetylation is a critical process of chromatin remodeling that underlies the open chromatin architecture dynamics and activation of transcription.[119,120] Histone acetyltransferases (HATs) and histone deacetylases (HDACs) catalyze the addition and removal of acetyl groups on lysine residues of histones and other regulatory proteins, then BRDs recognize the relaxed chromatin segments and bind to the acetylated nucleosomes, transcription factors and co-activators.[121122,123]

Given this, inhibitors of BRDs have demonstrated positive effects in both solid and hematologic malignancies.[124] The selective small molecule bromodomain inhibitor, JQ-1 has shown to selectively inhibit the interaction between BET proteins and acetylated chromatin, resulting in dissociation. It was demonstrated to inhibit proliferation when tested against a panel of 25 MM cell lines and primary MM samples. The molecule was similarly tested in a xenograft mouse model of MM where treatment with JQ-1 resulted in decreased tumor burden, reduced immunoglobulin expression and increased overall survival.[125] Jake *et al.* showed that BET inhibition by JQ-1 downregulates MYC and inhibits MM cell proliferation including MM cell lines that are resistant to FDA approved drugs like dexamethasone and melphalan.[125] Another BET inhibitor, CPI-0610, is currently in phase I testing and preliminary results show that human MM cell lines are sensitive to BET inhibition. CPI-0610 induces apoptosis, G_1 cell cycle arrest and caspase-dependent cell death associated with inhibition of MYC, IKZF1 and IRF4.[126,127] Boi et al. demonstrated the antiproliferative activity of BET inhibitor OTX015, in a preclinical study using multiple myeloma cells.[128] OTX015 acts via binding to BRD motifs and is currently in phase I trials.[129,130]

BET inhibition by CPI203 increases lenalidomide/dexamethasone efficacy in MM cell lines. Anti-myeloma activity of CPI203 is independent of cell sensitivity to lenalidomide and involves MYC and IKZF1 downregulation.[131] There is a synergistic effect of CPI-203 on cell death induction which is followed by the reduced expression of MYC and IRF4.[132] CPI-203 and bortezomib have been shown to have synergistic effects in drug resistant

myeloma.[133] In MM cells, a novel inhibitor CG13250 is capable of suppressing the MYC transcription by impeding BRD4 binding to the MYC promoter.[134]

Epigenetic Remodeling—The dysregulation of epigenetics is increasingly recognized in the pathogenesis of hematological malignancies and recently a number of epigenetic therapies targeting DNA methylation, acetylation, and posttranslational histone modification have been introduced in clinical practice.[135]

Conclusion

Recent advancements in preclinical and clinical research have identified novel aberrant molecular pathways in MM and by targeting these pathways, we could develop treatment modalities for achieving better results with less side effects. Targets for further clinical development include BCL-2, MDM2, KRAS, NRAS, BRAF MEK, JAK-STAT, NF-**k**B, c-MYC/Wnt, PI3K/Akt/mTOR, Cyclin D, MMSET and BET. Cobimetinib (MEK) and vorinostat (Histone deacetylase inhibitor) are currently in phase 3 drug testing. Phase 2 trials of Selumetinib (MEK1/2 inhibitor) and palbociclib (CDK4/6 inhibitor) are underway while venetoclax (a BCL-2 inhibitor) is in phase 1 testing. In various preclinical studies, vemurafenib (BRAF inhibitor), SC99 (JAK2/STAT3 inhibitor), DANFIN (NF-κB), BEZ235 (P13K and mTOR inhibitor), and clioquinol (mTOR inhibitor) displayed potent anti-myeloma activity. Monoclonal antibodies targeting FGFR also have potential in the treatment of MM. Development of targeted therapies against these pathways offer promise for the future of precision and personalized treatment of MM.

Biography:

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Table 1.
Emerging therapies targeting novel aberrant pathways in Multiple Myeloma.

Abbreviations: **BCL-2**=B cell lymphoma-2, **JAK-STAT**=Janus kinase Signal Transducer and Activator of Transcription proteins, **MEK**=Mitogen activated protein kinase kinase, **FGFR**=fibroblast growth factor receptor, **NF-KB**=nuclear factor kappa light chain enhancer of activated B cells, **mTOR**=mammalian target of rapamycin, **MM**=multiple myeloma, **NSD2**=nuclear receptor binding SET domain2, **BET**=bromodomain and extra terminal, **BRD**=bromodomain, **MYC**=Myeloctomatosis (oncogene), **HDAC**=histone deacetylase

Pathway	Drug Name	Mechanism of action	Clinical Trial
BCL-2 overexpression			
	venetoclax (ABT-199)	BCL-2 inhibitor	NCT01794520
JAK-STAT			
	ruxolitinib	JAK2 inhibitor	NCT00639002
	SC99	JAK2/STAT3 inhibitor	
NF-KB			
	DANFIN	Proteasome inhibitor-inhibits NF-KB activation and signaling	
Ras/Raf/Mek/Erk			
	selumetinib (AZD6244)	MEK 1/2 inhibitor -blocks the MEK immediately downstream of BRAF	NCT01085214
	sorafenib	Multi kinase inhibitor-inhibits cell surface TKIs and downstream intracellular serine/threonine kinases	
	vemurafenib	BRAF inhibitor	NCT01524978
	cobimetinib	BRAF inhibitor	NCT03312530
FGFR mutation			
	MFGR1877S	Anti-FGFR monoclonal antibody	
	dovitinib (TKI258)	Non selective FGFR inhibitor	NCT02465060
	BGJ398	Non selective FGFR inhibitor	
	AZD4547	FGFR (1-3) inhibitor	
Cyclin D			
	palbociclib	CDK4/6 inhibitor	
PI3K/AKT/mTOR			
	clioquinol	Hydroxyquinoline, downregulates expression of mTOR, inducing autophagy in MM cells	NCT00963495
	SC-06	Disrupts mTOR signaling pathway by downregulating Raptor, a key component of mTORC1 signaling	
	BEZ235	mTOR inhibitor	
	C98	PI3K/AKT inhibitor	
	C96	PI3K/AKT inhibitor	
Epigenetic regulation			
	LEM06	MMSET/NSD2 inhibitor (histone methyl transferase inhibitor)	
	JQ-1	BET inhibitor	
	CPI-0601	BET inhibitor	

Pathway	Drug Name	Mechanism of action	Clinical Trial
	OTX015/MK8628	BET inhibitor	NCT01713582
	CPI-203	BET inhibitor	
	CGI13250	Suppresses MYC transcription by blocking BRD4 binding to MYC promoter	
	panobinostat	HDAC inhibitor	NCT01651039 NCT01023308
	vorinostat	HDAC inhibitor	NCT00773838
	romidepsin	HDAC inhibitor	NCT00066638 NCT01755975
	ricolinostat	HDAC inhibitor	NCT01323751