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Molecular therapy for multiple myeloma

Giovanni Martinelli, Patrizia Tosi, Emanuela Ottaviani, Simona Soverini, Sante Tura
Institute of Hematology and Medical Oncology Seràgnoli, University of Bologna, Italy

Correspondence: Dr. Giovanni Martinelli, Molecular Biology Unit, Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, via Massarenti 9, 40138 Bologna, Italy.
Phone: international +39.051.6364075.
Fax: international +39.051.6364037.
E-mail: gmartino@kaiser.alma.unibo.it

Background and Objectives. Several molecular and cytogenetic advances have suggested novel therapeutic strategies that could help reach an eventual cure for multiple myeloma (MM).

Evidence and Information Sources. Identification of novel, *MM-specific* molecular targets should pave the way for drugs that can specifically attack the neoplastic cells while sparing the normal ones. Drugs that alter the marrow microenvironment – such as bisphosphonates, proteasome inhibitors (e.g. PS-341/LDP341), lactacystin or LLNV compounds – induce apoptosis or G1 growth arrest and alter the adhesion of MM cells to marrow stroma. These drugs that modify the microenvironment have a more solid scientific basis and may, therefore, have more realistic implications in MM treatment. Of these, novel vascular endothelial growth factor (VEGF) inhibitors, such as SU5416 and SU6668, block tumor-cell adhesion and could disrupt MM cell proliferation. Similarly, tyrosine kinase inhibitors (TKI) such as fibroblast growth factor receptor (FGFR) inhibitors, may serve when the *FGFR3* gene is overexpressed due to the t(4;14)(p16.3;q32) and/or is activated by point mutations. In cases carrying the translocation and expressing the *IgH/WHSC1-MMSET* hybrid transcripts, histone deacetylase (HDAC) inhibitors could be useful, but their possible clinical use needs to be supported by more biological studies. Tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL) induces apoptosis in MM cell lines and primary cells. The proliferative signaling pathway of FGFR3 is mediated by Ras (Ras-activating mutations are frequently found in MM), which presents a possible target for farnesyltransferase inhibitors (used alone or in association with IFN-α).

Perspectives. In several of these options, preclinical studies have proved encouraging, and clinical trials are now getting underway.

Key words: multiple myeloma, therapy, proteasome inhibitors, TRAIL, VEGF inhibitors, FTI.

Multiple myeloma (MM) affects terminally differentiated B-cells (plasma cells) and runs a progressive clinical course, the median survival of patients treated with conventional chemotherapy usually being 3 to 4 years.[1] Most patients with MM have symptomatic disease at diagnosis and require therapy. Recent advances in the management of MM include the use of high-dose chemo(radio)therapy followed by autologous or allogeneic transplantation of hematopoietic stem cells.[2] Although such strategies improve the clinical outcome and lengthen survival, stringently defined complete remission (CR) is achieved in only 20-40% of patients, most of whom subsequently relapse.[2-4]

In the last few years, molecular biology studies have provided new important insights into the pathogenesis of MM. The precursor cell in MM appears to be a cytoplasmic my+ B cell that has undergone antigen selection and somatic hypermutation in the lymph node, but which has not yet switched isotype class.[5,6]

Several advances have been reported in MM, mostly in the field of biological knowledge. In particular, the survival and proliferation of MM cells are largely dependent on a supportive microenvironment. Interleukin-6 (IL-6), present in the bone marrow microenvironment, is known for its ability to support cell growth and protect MM cells from the apoptotic effects of corticosteroids. Therapy targeting IL-6 (or its pathway), may be of oncoming promise on MM cells. Furthermore, angiogenesis is also prominent in the pathogenesis of MM. Vascular endothelial growth factor (VEGF) is one of the important endogenous factors that promote angiogenesis. An understanding of the process of angiogenesis in myeloma is necessary, because its inhibition offers promising prognostic and therapeutic implications. In addition to immunomodulatory and cytokine-modulatory properties, thalidomide has antiangiogenic activity. It has been investigated in a number of cancers including multiple myeloma. Its role has been best explored in myeloma, in which, at daily doses of

100 to 800 mg, is remarkably active, causing clinically meaningful responses in one-third of extensively pretreated patients (*Tosi et al. manuscript submitted*). It also acts synergistically with corticosteroids and chemotherapy in myeloma.

The bisphosphonates provide effective therapy for the skeletal complications of multiple myeloma. Although the earliest bisphosphonates had poor bioavailability and relatively low potency, newer compounds such as pamidronate and zoledronic acid have greater potency. Bisphosphonates block the development of monocytes into osteoclasts and are thought to promote apoptosis of osteoclasts. These agents prevent osteoclasts from moving to the bone surface and seem to inhibit the production of bone-resorbing cytokines such as interleukin-6 by bone marrow (BM) stromal cells. In addition, bisphosphonates seem to have a direct antimyeloma effect by inducing apoptosis of malignant plasma cells.

Although cytogenetic analysis is only sometimes successful, it has been demonstrated that translocations involving the immunoglobulin (Ig) loci, predominantly involving the switch regions of the heavy chain locus (*IGH*) at 14q32, are an almost universal event in MM.[6] A large array of chromosomal partners may be involved, including 4pl6.3, 6p25, 11q13, and l6q23, where the *FGFR3* and *WHSC1/MMSET*, *MUM1/IRF4*, *cyclin D1* and *c-MAF* putative target genes are located, respectively.[7-12] Each of these genes can be structurally and/or functionally deregulated by the translocation. Multiple partner chromosomes have been described.[5,7,8] Some of the translocations have been cloned and the oncogenes involved have been partially characterized. For example, the translocation involving the 4p16.3 breakpoints[7-9] occurs 50-100Kb centromeric to the fibroblast growth factor receptor 3 (*FGFR3*) gene[13] and within the 5' regions of a novel gene called *WHSC1/MMSET*.[9,14]

Microenviroment modifiers: bisphosphonates and proteasome inhibitors

MM cells accumulate in the BM microenvironment, where they specifically adhere both to extracellular matrix (ECM) proteins and BM stromal cells (BMSCs).[15] Subsequent changes in the profile of cell-adhesion molecules are associated with migration of tumor cells into the peripheral blood during progressive disease. One of the functional consequences of their initial adhesion within the BM microenvironment is that the MM cells are resistant to apoptosis. Bisphosphonates (such as zoledronic acid and ibandronate)[16] (Table 1a), which are also employed in current forms of MM therapy, block adhesion and could thus confer sensitivity to treatment by overcoming cell-adhesion-mediated drug resistance.[17]

A further consequence of MM cell adhesion is augmented transcription of IL-6 - which is both a growth and survival factor for MM cells - leading to high levels of secretion in BMSCs.[18] The upregulation of IL-6 seems to depend partially on the presence of the transcription factor NFκB.[18] Moreover, tumor cell secretion of cytokines, such as transforming growth factor β (TGFβ), further promotes IL-6 transcription and secretion in BMSCs.[19] Another promising therapeutic approach could thus take advantage of the particular characteristics of proteasome inhibitors.

Proteasome inhibitors induce apoptosis of tumor cells even with accumulation of p21, p27 and Bax.[20] These novel drugs have been shown to be capable of inhibiting activation of NFκB[21] and inducing apoptosis[22-24] in MM cells that are resistant to conventional therapy. Indeed, recent studies suggest that proteasome inhibitors such as PS-341/LDP341, lactacystin or LLNV compounds[20,25] could have a role in inhibiting the NFκB-dependent upregulation of IL-6 in BMSCs and the related paracrine growth of adherent MM cells.[24,25] Moreover, proteasome inhibitors are synergistic with dexamethasone, at least in an asthma model.[20] PS-341 in particular has demonstrated marked *in vivo* antitumor activity in several human and murine models, and is effective in both MM-derived cell lines and primary MM cells.[20] Phase I clinical tests on PS-341 are nearing completion and its toxicity profile appears acceptable.[20]

Tyrosine kinase (TK) inhibitors

Receptor TKs (RTKs) are a family of enzymes that play crucial roles in the proliferation, survival, differentiation and metabolism of cells. RTKs can be divided into several subfamilies. A large superfamily of RTKs includes a series of growth factor receptors, such as fibroblast growth factor receptors (FGF-Rs), platelet-derived growth factor receptor (PDGF-R) and vascular endothelial growth factor receptor (VEGF-R) (Figures 1 and 2). All these RTKs are commonly expressed on endothelial cells, except for VEGF which exhibits more restricted expression on endothelial cells than on other cell types, and is not generally found on MM cells.

The FGF family of soluble growth factors are structurally related proteins with a high heparin-binding affinity that exhibit a variety of biological functions following binding to membrane FGF-Rs.

Table 1a. Different categories of drugs and their mechanisms of activity and specificity.

Category: Microenviroment modifiers: bisphosphonates and proteasome inhibitors

Drug	*Mechanism of action*
Bisphosphonates	Block adhesion and could thus confer sensitivity to treatment by overcoming cell-adhesion-mediated drug resistance; induce tumor cell apoptosis[16, 17]
Zoledronic acid (ZOMETA)	Inhibits osteoclast hyperactivity and induces tumor cell apoptosis
Ibandronate	Blocks adhesion and could thus confer sensitivity to treatment, and inhibits osteoclast hyperactivity and induces tumor cell apoptosis
Proteasome inhibitors	Induce apoptosis of tumor cells even with accumulation of p21, p27 and Bax[20-25]
PS-341/LDP341	Marked *in vivo* antitumor activity in several human and murine models[20]
Lactacystin	Marked *in vivo* antitumor activity in several human and murine models[25]
LLNV	Marked *in vivo* antitumor activity in several human and murine models[25]

Table 1b. Different categories of drugs and their mechanisms of activity and specificity.

Category: Tyrosine kinase (TK) inhibitors

Drug	*Mechanism of action*
Quinazolines	Inhibitors of EGF-R, Her-2,PDGF-R, VEGF-R, FGF-Rs and CSF-1R TKs[27]
SU9902	Inhibits VEGF-R and FGFR-I
SU9803	Inhibits VEGF-R and FGFR-I
ZD4190	Inhibits VEGF-R[27]
ZD6474	Inhibits VEGF-R[28]
Pyridopyrimidines	Inhibit EGF-R, PDGF-R, c-Src TKs, and FGF-Rs
PD166285	Inhibits FGFR-I, PDGF-R and c-Src kinases[28, 29]
PD173074	Inhibits effect on FGFR-I[30]
STI571 (GLIVEC)	PDGF-R, c-kit and ABL-specific TK inhibitor[31]

Table 1c. Different categories of drugs and their mechanisms of activity and specificity.

Category: Histone deacetylase (HDAC) inhibitors

Drug	*Mechanism of action*
Depsipeptide FR901228	Histone deacetylase inhibition[36]
SAHA	Histone deacetylase inhibition[37]

Table 1d. Different categories of drugs and their mechanisms of activity and specificity.

Category: TRAIL

Drug	*Mechanism of action*
Apo-2 ligand (Apo2L)	Induces apoptosis in sensitive target cells like another TNF-family member, the Fas/APO-1/CD95 ligand (CD95L)[48,49]

(continue in next page)

Table 1e. Different categories of drugs and their mechanisms of activity and specificity.

Category: VEGF inhibitors

Drug	*Mechanism of action*
Thalidomide	Anti-angiogenic agent in MM[50-53]
SU5416	Inhibitor affecting the VEGF-R RTK[32]
SU6668	RTK inhibitor associated with Flk-1, FGF-R1 and PDGF-R, and has been shown to inhibit both VEGF- and FGF-dependent proliferation[32]

Table 1f. Different categories of drugs and their mechanisms of activity and specificity.

Category: FTI inhibitors

Drug	*Mechanism of action*
CAAX peptidomimetics, farnesyldiphosfonate analogs and bi-substrate analogs	Inhibit tumor cell growth *in vitro* as well as *in vivo*[55-57]
SCH-66336	Inhibits farnesyltransferase[60]
R115777	Inhibits farnesyltransferase[61]

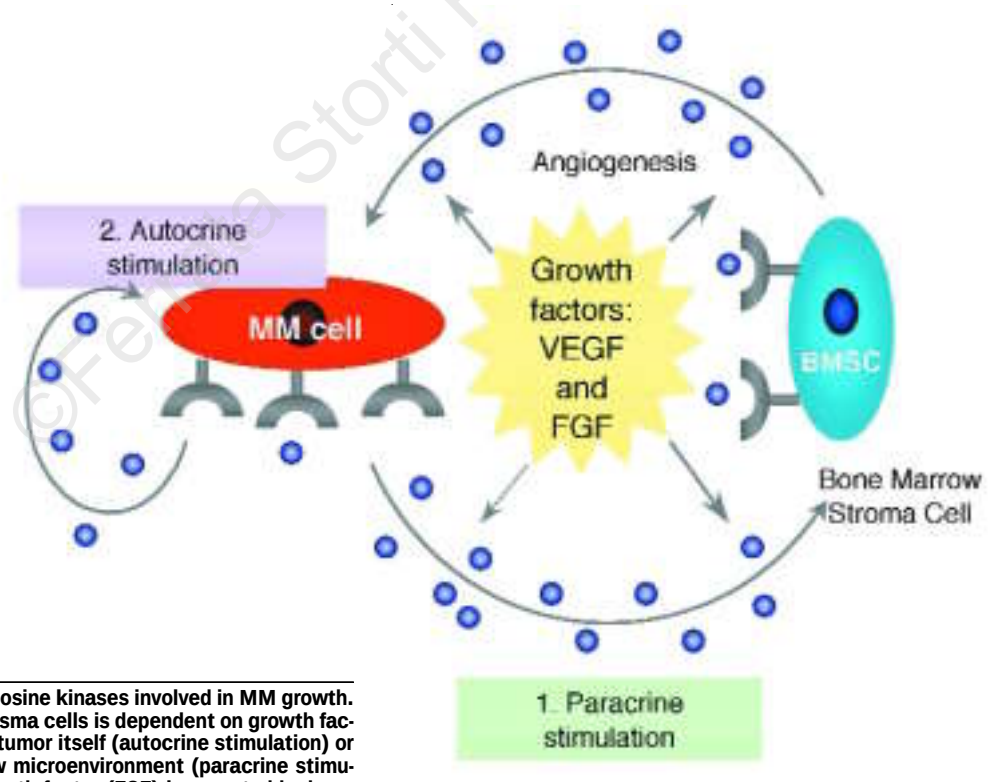

Figure 1. Receptor tyrosine kinases involved in MM growth. The growth of MM plasma cells is dependent on growth factors derived from the tumor itself (autocrine stimulation) or from the bone marrow microenvironment (paracrine stimulation). Fibroblast growth factor (FGF) is secreted by bone marrow stromal cells, leading to enhanced growth and survival. Vascular endothelial growth factor (VEGF), is secreted both by BMSC and MM cells. VEGF and FGF can stimulate the branching, extension and survival of endothelial cells, resulting in the formation of new blood vessels during tumor angiogenesis.

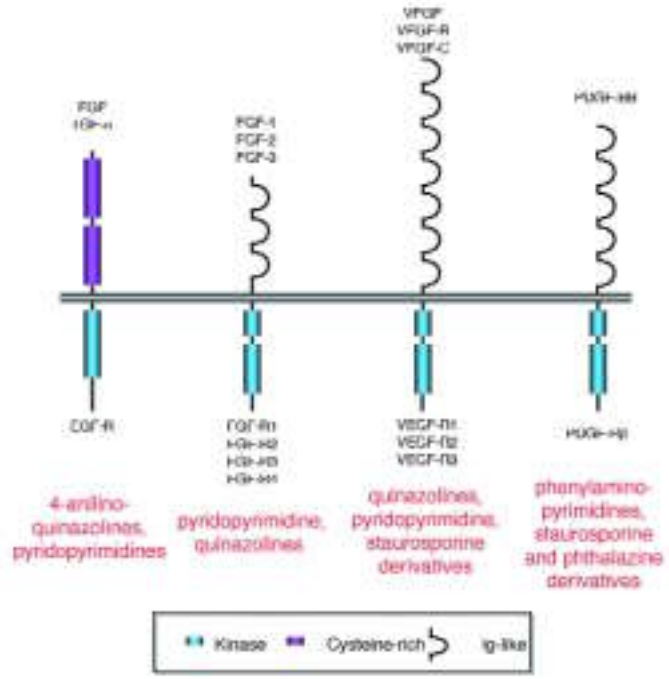

Figure 2. Receptor tyrosine kinases regarded as candidate therapeutic targets. RTKs share a common structure with highly conserved homology motifs. They all have an extracellular domain with cystein-rich or Ig-like motifs, and an intra-cellular kinase domain. Some RTKs (i.e., VEGF-R, PDGF-R, FGF-Rs, EGF-R) have been strongly implicated as therapeutic targets. Examples of the synthetic inhibitors already developed are indicated in red.

FGF-Rs are expressed on many cell types and can be grouped into four subtypes (FGF-R1 to FGF-R4). The ability of the FGF-R to bind their related mitogenic FGFs leads to the activation of complex signaling pathways.[13,14]

In MM patients a consistent involvement of FGFR-3 in cell transformation has been suggested. In the presence of the t(4;14) translocation found in MM patients, the *FGFR3* gene is overexpressed,[26] and activating point mutations have been found in the deregulated gene in some MM cell lines and primary tumors.[7,8,26] This suggests that the *FGFR3* gene may play a critical role in the malignant transformation and/or progression of MM.

During the past decade, various small-molecule FGF-R1 kinase inhibitors have been isolated as potential therapeutic agents for solid tumors (Table 1b). With regard to the mechanism of action, most of these agents compete for binding with ATP in the vicinity of the intracellular catalytic core of FGFRs: they include SU9902 and SU9803 by SUGEN, both exerting a similar TK inhibition on either VEGF or FGFR-1.

With regard to specificity of action, most of these TK inhibitors shared inhibitory activity with similar receptors (such as FGFR-1 and FGFR-3) or classes of receptors (but with different efficacy). In this regard, quinazolines were synthesized and found to be inhibitors of EGF-R, Her-2, PDGF-R, VEGF-R, FGF-Rs and CSF-1R TKs.[27] Pyridopyrimidines were found to inhibit EGF-R, PDGF-R, c-Src TKs, and FGF-Rs. The quinazoline-derived compound ZD4190 was found to inhibit VEGF-R but to be inactive against FGF-R.[27] In addition, ZD6474[28] – a compound more compatible with once-daily oral dosing – exhibits nanomolar inhibition of VEGF receptors, but with sub-micromolar potencies against EGF-R and FGF-R1. This drug, which is currently being assessed in phase I clinical trials for the treatment of solid tumors, could be used in MM patients in the future.

As with 4-phenylamido-quinazolines, pyridopyrimidines were first discovered as highly selective and potent inhibitors of RTKs. These compounds are selective for FGF-Rs and for EGF-R, PDGF-R, and c-Src kinases. PD166285 exhibits nanomolar inhibition of FGFR-1, PDGF-R and c-Src kinases.[28,29] Modification of the substituents on core resulted in inhibitors with different kinase selectivity profiles. For example, PD173074 exerts a strong and selective inhibitory effect on FGFR-1 without affecting other TK activities associated with PDGF-R, EGF-R and c-Src. In particular, the compound specifically inhibits FGF-stimulated growth and formation of microcapillaries and has anti-angiogenic and antitumor activity.[30] It is therefore reasonable to suppose that PD173074 will soon become available for phase I clinical studies, as is the case with STI571 – produced by Novartis as GLIVEC®, an ABL-specific TK inhibitor (but STI571 is also effective at nanomolar concentrations on

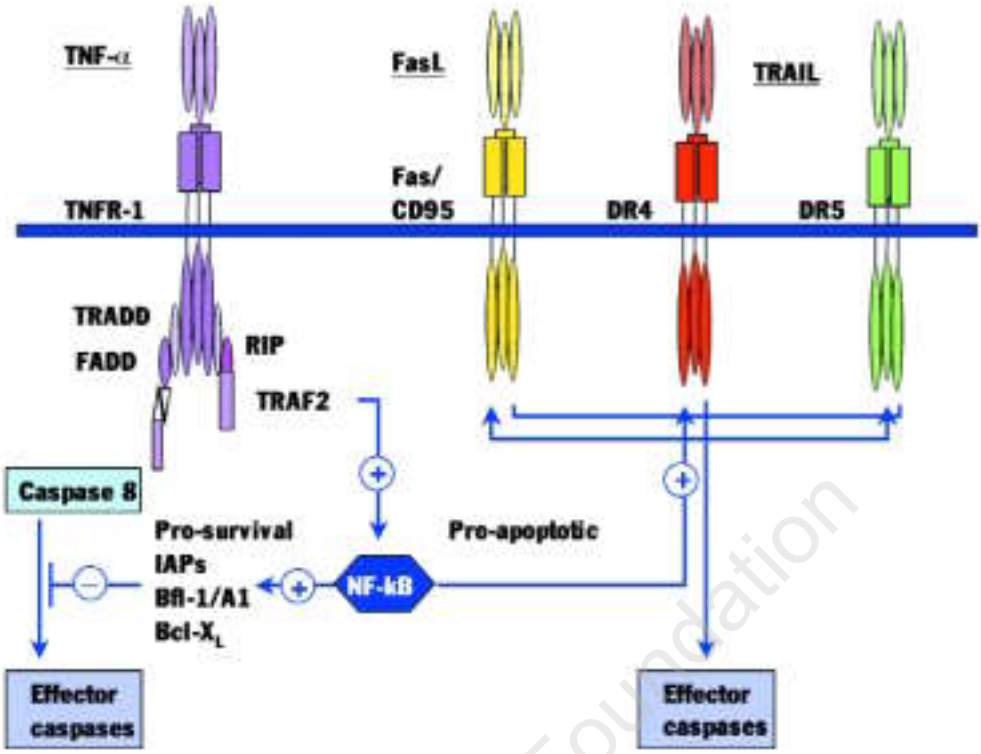

Figure 3. Apo-2L/TRAIL-induced apoptosis. Molecular mechanisms underlying the pro-apoptotic action of TRAIL and other TNFα family members (see text for details).

c-KIT and PDGFR) that has already entered clinical studies in Philadelphia-positive chronic myeloid leukemia patients.[31]

Recent data demonstrating that the deregulated FGFR3 protein is involved in the MAPK activation pathway point to the possibility of molecular-based therapeutic approaches aimed at opposing the role of FGFR3 in neoplastic processes. Although no specific FGFR-3 inhibitor have yet been reported, FGFR inhibitors are widely considered to be good candidates for the treatment of a subset of MM patients. For example, 3-substituted indolin-2-one inhibitors have been identified as inhibitors of various RTK including VEGF-R, FGF-R, and PDGF-R;[32,33] these are discussed in the section on VEGF which follows.

Histone deacetylase (HDAC) inhibitors

The question of how post-translational modification of histones – and particularly their acetylation – affects chromatin structure and transcriptional regulation has attracted considerable attention. Many transcription activators form complexes with histone acetyltransferases, which are thought to facilitate transcription by loosening the interactions between histones and DNA.[34,35] *Vice versa*, the removal of acetyl groups from histones is thought to cause tighter nucleosomal packaging of DNA, and many transcriptional repressors interact with HDAC, either directly or through adaptor proteins. Such interactions have also been described for transcription factors involved in leukemias.[35] The body of data highlighting the importance of histone acetylation pattern disruption in the development of both solid and hematological neoplasms suggests that HDAC inhibitors could provide a promising new therapeutic opportunity (Table 1c).

In the context of MM, a possible target for HDAC inhibitors is offered by the product of the *WHSC1/MMSET* gene. This gene, which has been proposed as a candidate for Wolf-Hirschhorn malformation syndrome,[13] is deregulated by the t(4;14) in a subset of MM patients. The breakpoints on 4p16.3 fall within the 5' introns of the gene, result-

ing in the formation of IgH/MMSET fusion transcripts.[14] The latter could provide a marker for the identification of MM patients carrying the t(4;14) translocation. Whereas *WHSC1/MMSET* is generally expressed at relatively low levels in MM cell lines, in the presence of the t(4;14) it tends to be overexpressed due to juxtaposition with powerful IgH enhancers. *WHSC1/MMSET* is normally expressed in early developmental stages, particularly in rapidly growing tissues.[9,13] The functional role of its protein product is currently unknown. However, amino acid sequence analysis has revealed the presence of a SET domain, two zinc finger motifs and a PWWP domain,[14] all of which are usually found in proteins involved in transcriptional regulation and/or chromatin remodeling. If *WHSCH1/MMSET* also turns out to exert these functions, it could represent an attractive target for HDAC inhibitors, such as FR901228 (Depsipeptide)[36] or SAHA.[37]

TRAIL

The recently cloned TNFα-related apoptosis-inducing ligand (TRAIL)[38-40] – also known as the Apo-2 ligand (Apo2L) – has been found to induce apoptosis in sensitive target cells as does another TNF-family member, the Fas/APO-1/CD95 ligand (CD95L),[41-43] The two ligands share similarities in terms of target selectivity and intracellular signaling pathway(s). Recent results indicate that TRAIL seems to complement the activity of the CD95 system, as it allows otherwise resistant cells to undergo apoptosis triggered by specific extracellular ligands.[44] Otherwise, TRAIL actively suppresses human mammary adenocarcinoma growth in mice without any of the strongly toxic effects associated with *in vivo* use of TNF or the Fas ligand (CD95L).[45] It thus seems to be a more promising candidate for clinical trials (Table 1d).

TRAIL can trigger apoptosis by binding specific molecules termed death receptors (DRs), which in turn activate caspase-8 and the caspase cascade. The best-characterized DRs and their cognate ligands include TNFR1/TNF-α, Fas/FasL, DR4/TRAIL-R1, DR5/TRAIL-R2 and DR3/Apo3L[45] (Figure 3). The intracellular signaling that links TRAIL/DRs to caspase-8 remains unclear. However, studies of Fas and TNFR1 signaling pathways show that DRs bind, through a stretch of 80 amino acids called the *death domain* (DD), to the adapter protein FADD.[46] This can occur either directly, as in Fas-induced apoptosis, or indirectly, via another adapter protein named TRADD,[47] as in TNFR1-induced apoptosis. FADD, in turn, interacts with caspase-8 via its DD. This subsequently activates downstream effector caspases that lead to apoptosis, such as caspases-3, -6, and -7. TRAIL was found to be a potent inducer of apoptosis in primary MM cells and also to be non-cytotoxic for hematopoietic stem cells.[48] The amount of apoptosis correlated with the time and dose of TRAIL treatment.[49] Prior chemotherapy drives overexpression of DR4 and DR5 on cells surface, thereby priming the effect of TRAIL, which can thus be considered an attractive candidate for sequential chemotherapy protocols.

VEGF inhibitors

Recent studies suggest that adhesion of MM cells to BMSCs upregulates VEGF secretion by BMSCs and tumor cells.[50-53] This increase in VEGF may partially account for increased angiogenesis in human myeloma BM. It is under evaluation whether VEGF is also a growth and/or survival factor for MM cells (but preliminary studies[54] suggest that VEGF induces MAPK activation and proliferation of some MM cells, and that VEGF receptor inhibitors are able to block tumor cell proliferation) (Table 1e). Angiogenesis is critical for MM progression.[52] In recent years, considerable efforts in the development of anti-angiogenic cancer drugs have been directed at growth factors and growth factor receptors involved in endothelial cell proliferation. For instance, based upon its anti-angiogenic activity, thalidomide[50-52] (as well as fumagilins) was recently reported to be very effective in the treatment of MM patients, including those refractory to conventional therapy.[52] Although thalidomide may act as an anti-angiogenic agent in MM, the drug (and/or its *in vivo* metabolites) has many other potential mechanisms of action.[53]

Other efforts have been made to discover anti-angiogenic drugs that target VEGF and one of its receptors, VEGF-R2 (i.e. flk-1) as well as bFGF and its receptor. Many small angiogenesis-inhibitor molecules have been identified.[32] In particular, selective inhibitors affecting the VEGF-R RTK (not expressed on MM cells but expressed by BMSC) have been discovered, including SU5416 and SU6668 (SUGEN San Diego, CA, USA). These two drugs are currently in late and early clinical evaluations, respectively, for the treatment of solid tumors. In addition, SU6668 was shown to be localized in the ATP binding sites of the FGF-R1 catalytic core[32] – and FGF-R1 is similar to FGF-R3. This suggests that SU6668 exerts effects on both VEGF-R and FGF-R, two important RTKs involved in the pathogenesis of MM. Indeed, SU6668 has been identified as an RTK inhibitor associated with Flk-1, FGF-R1 and PDGF-R, and has been shown to inhibit both VEGF- and FGF-depen-

Table 2. Drugs already in clinical trials and biopharmaceutical companies involved in these trials.

Drug	*Status*	*Manufacturer*
Zd6474	Phase I	Astrazeneca
Pd173074	Phase I	Pfizer
Sti571 (Glivec)	Phase III	Novartis Pharma Ag
Fr901228 (Depsipeptide)	Phase I	Developmental Therapeutics Program, Division Of Cancer Treatment, National Cancer Institute
Saha (Suberoylanilide Hydroxamic Acid)	Phase I	Dewitt Wallace Research Laboratories
Zoledronic Acid (Zometa)	Phase III	Novartis Pharma Ag
Ibandronate (Bondronat)	Phase I-II	Roche
Ps-341/Ldp341	Phase II	Proscript - Millenium
Apo2l/Trail	Candidate for clinical trials	Genentech - Immunex
Su5416	Phase III	Sugen
Su6668	Phase I	Sugen
Sch-66336	Phase I	Schering-Plough
R115777	Phase I-II	Janssen-Cilag

dent proliferation.[32] It is now known that SU6668 is a potent antiangiogenic and antitumoral agent capable of inducing regression of established tumors in the hematopoietic NIH 3T3 cell line.[54] Thus, SU6668 appears to be another attractive candidate for MM therapy (Table 2).

FTI inhibitors

The proliferative pathway of FGFR3 is mediated by Ras signaling.[55-57] Furthermore, the Ras-activating mutation is frequent in MM patients at diagnosis and, even to a greater extent, in advanced disease.[58] For these reasons, the Ras protein is another potential target for specific therapy[59] – either alone or in association with IFN-α – in sensitive, refractory, or relapsed MM patients. Membrane association of Ras protein is required for its biological functions. The critical step of Ras post-translational modification is mediated by the cytosolic enzyme farnesyltransferase (Ftase), which catalyzes farnesylation on the sulfur of the cysteine residue in the CAAX motif of the Ras protein. New anti-tumor agents have been designed which target this enzyme. Several potent Ftase inhibitors (FTIs) have been described (Table 1f), including both natural products and synthetic compounds.[59] They can be divided into three main classes, namely, CAAX peptidomimetics, farnesyldiphosfonate analogs and bi-substrate analogs. These FTIs are all potent inhibitors of tumor cell growth *in vitro* as well as *in vivo;* potential candidates for clinical treatment include SCH-66336 and R115777.[60,61] However, the potential of FTIs, either alone or in association with specific FGFR3 TK inhibitors or IFN-α therapy, for the treatment of MM is currently unknown.

Conclusions

Any or all these perspective therapies could offer great promise for improving the outcomes of MM patients.[62,63] There is now much optimism about the possibility of finding selective anticancer drugs that should eliminate the cytotoxic effects associated with conventional chemotherapy for MM. This hope is based on the identification of various novel molecular targets that are *MM-specific*. This should pave the way for drugs that can specifically attack the neoplastic cells while sparing the normal ones. Thus far, encouraging results have been obtained with several of these novel agents only at the preclinical level. This hope is based on the identification of various novel molecular targets that are *MM specific*. (Table 2). The clinical phase is now getting underway.

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