Title
Seeking Convergence and Cure with New Myeloma Therapies

Journal
Trends in Cancer, 4(8)

ISSN
2405-8033

Authors
Choudhry, Priya
Galligan, Derek
Wiita, Arun P

Publication Date
2018-08-01

DOI
10.1016/j.trecan.2018.05.005

Peer reviewed

Published in final edited form as:

Trends Cancer. 2018 August ; 4(8): 567–582. doi:10.1016/j.trecan.2018.05.005.

Seeking convergence and cure with new myeloma therapies

Priya Choudhry[1,3,*], **Derek Galligan**[2,3,*], and **Arun P. Wiita**[1,3,4]

[1]Dept. of Laboratory Medicine, University of California, San Francisco, CA

[2]Dept. of Medicine, University of California, San Francisco, CA

[3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA

Abstract

For over a decade, the mainstay of multiple myeloma therapy has been small molecules that directly attack malignant plasma cell biology. However, potent immunotherapies have recently emerged, transforming the myeloma therapeutic landscape. Here we first review new promising strategies to target plasma cells through protein homeostasis and epigenetic modulators. We then discuss emerging immunotherapy strategies that are leading to dramatic results in patients. Finally, we focus on recent preclinical data suggesting that enforcing cell-surface antigen expression through small molecules may enhance immunotherapy efficacy and avoid resistance. We argue that these emerging observations point the way toward potential convergence between drug classes. With recent rapid progress we may finally be on the verge of the “C” word: a cure for myeloma.

Keywords

immunotherapy; myeloma; cell surface; epigenetics; protein homeostasis; CAR-T

The Rapid Evolution of Clinical Myeloma Therapy

Multiple myeloma is a malignancy of plasma cells primarily localized to the bone marrow. It is the second most common hematologic malignancy in the United States with ~30,000 new cases diagnosed/year (1). While myeloma remains without a definitive cure, since the FDA approval of bortezomib (Velcade) in 2003, therapeutic regimens in multiple myeloma have undergone a rapid evolution. This proteasome inhibitor - now joined in the clinic by carfilzomib (Kyprolis), ixazomib (Ninlaro), and others in development - appears to have many mechanisms of efficacy both directly on the plasma cell and surrounding tumor microenvironment (2). However, the primary mechanism of action is thought to directly

Correspondence: arun.wiita@ucsf.edu (Arun P. Wiita).
*Equal contribution

Conflicts of Interest

A.P.W. has received research support from Cleave Biosciences, Quadriga BioSciences, Sutro BioPharma, and TeneoBio.

target the biology of the plasma cell. By disrupting degradation of misfolded proteins in these cellular “immunoglobulin factories”, the unfolded protein response is induced and ultimately leads to plasma cell apoptosis (3–5). The introduction of the thalidomide analogs – thalidomide (Thalomid), Lenalidomide (Revlimid), and pomalidomide (Pomalyst) - led to further increases in overall and event-free survival (6). These agents also disrupt protein homeostasis of plasma cells by re-targeting the ubiquitin ligase cereblon to degrade the proliferative transcription factors Ikaros (IZKF1) and Aiolos (IZKF3) (7, 8). These “immunomodulatory” drugs (IMiDs) also carry numerous effects on the immune microenvironment which contribute to anti-tumor effects (9).

These two drug classes, often administered in combination with dexamethasone, and used in series with autologous stem cell transplantation, have formed the backbone of myeloma therapeutic strategies for over a decade. Between 2006 and 2012, median survival in myeloma increased from less than 4 years to nearly 7 years (10). This major progress in overall survival does not reflect two new monoclonal antibodies approved by the FDA in late 2016: daratumumab (Darzalex), targeting the plasma cell-surface antigen CD38, and elotuzumab (Empliciti), targeting the antigen SLAMF7.

Daratumumab in particular has shown extremely promising clinical findings, with significant single-agent activity in highly refractory myeloma patients (11) and exceptional responses when in combination with lenalidomide and dexamethasone (12). Elotuzumab has shown limited single-agent responses (13) but has shown promise in combination regimens (14). Though long-term survival data are not yet available, many anticipate that these new agents may extend median lifespan beyond a decade. As myeloma is typically diagnosed in older individuals, this means that some patients can now address myeloma as a chronic disease. This is remarkable advance and a far cry from the death sentence that a myeloma diagnosis used to be.

Together, the advent of these existing small molecule therapies and new monoclonal antibodies has raised significant hope in the myeloma field. However, a sobering fact is that despite all these advances, the vast majority of myeloma patients unfortunately still become refractory to any given therapy. A major finding emerging from genomic studies of myeloma is the presence of multiple subclonal populations within any patient’s tumor (15). In this context, one therapy may eliminate the vast majority of cells, but a subclonal, resistant population will eventually be selected for and lead to re-establishment of disease. Combination therapies have therefore become a mainstay in myeloma treatment, potentially allowing for attack on multiple clones at once, but unfortunately still not to the point of eliminating all disease. This dynamic is even further complicated by the presence of the elusive myeloma “stem cell”, which appears to be of B-cell origin and may lack many phenotypic and biological features of more differentiated plasma cells (16). These myeloma stem cells may also be more therapy-resistant, meaning that entirely different strategies may be necessary to eliminate this nidus of disease (17). Given this clinical and biological context, there remains significant interest in the development of additional, new therapies for myeloma. Furthermore, the search for a definitive cure continues.

Here we provide an overview of some of the most promising new developments in myeloma therapy. In particular we focus on new strategies to target protein homeostasis in multiple myeloma as well as the conceptually related approach of targeting transcription through epigenetic modifiers. We then move onto an area where the greatest excitement currently resides: immunotherapy targeting specific antigens expressed on malignant plasma cells. Finally, we focus on the convergent use of small molecules to modulate cell surface antigen expression, potentially avoiding immunotherapy resistance and getting us ever closer to cure.

Beyond Proteasome Inhibitors: New Strategies to Target Protein Homeostasis

Protein homeostasis is defined by the mechanisms which maintain and control protein synthesis, folding, localization, and degradation within the cell. Proteasome inhibitors are highly effective in treating myeloma but show little clinical effect versus almost all other tested cancer types (18). This empirical finding has established myeloma as the paradigm indication for any therapeutics that disrupt protein homeostasis. In recent years a number of new, promising small molecules have emerged that target different aspects of this fundamental process (Figure 1).

One protein homeostasis-targeting agent that has advanced to Phase III trials in myeloma is plitidepsin (Aplidin). This natural product is a direct inhibitor of eukaryotic translation elongation factor 1 (19, 20), the central protein responsible for continuous translation of essentially all mRNAs. Given this mechanism of action, the ability to achieve an adequate therapeutic index remains an open question. However, the translation initiation inhibitor omacetaxine (Synribo) has been approved for chronic myeloid leukemia, raising the potential for clinical utility of plitidepsin in myeloma.

Another critical node of protein homeostasis is p97/VCP. This multi-functional AAA+ ATPase has the best-characterized function of extracting misfolded proteins from the endoplasmic reticulum and shuttling them to the proteasome for degradation (21). We showed that a highly active p97 targeting agent, CB-5083 (22), induced a potent unfolded protein response and showed promising preclinical results in myeloma (23). Unfortunately this molecule failed in Phase I trials due to unexpected off-target ocular toxicity. However, p97 remains an intriguing hub for disrupting protein homeostasis and should continue to be explored with new small molecule designs.

Another approach with promising preclinical data in myeloma is inhibition of the proteasome-associated deubiquitylases (“DUBs”) including USP7, USP14, and UCHL5 (24) (25). These enzymes are required to remove ubiquitin from substrates prior to proteasomal degradation, and their inhibition leads to proteotoxic stress and cell death. Unfortunately, these molecules have not entered into clinical trials due to widespread off-target activity of available agents. The recent description of new, more specific DUB inhibitors (26) may revive this strategy.

Selinexor targets a different aspect of protein homeostasis: localization. This inhibitor of the nucleor exportin XPO1 is thought to prevent the shuttling of tumor suppressor proteins from

the nucleus to cytosol (27). Tumors are therefore forced to activate apoptotic pathways that would otherwise be evaded. Selinexor is in various stages of clinical trials for a range of cancers; initial clinical results in myeloma have suggested modest efficacy (28).

Venetoclax (Venclexta) has a different mechanism of action related to protein localization. This agent, already approved for use in chronic lymphocytic leukemia, is a specific inhibitor of the anti-apoptotic Bcl-family member Bcl-2. Venetoclax inhibition allows for pro-apoptotic Bax and Bak to co-localize in the mitochondrial membrane and form the apoptotic "pore" (29). Venetoclax has shown particular clinical efficacy in t(11;14) myeloma, where Bcl-2 is highly expressed (30, 31). Tumors that express high levels of the alternative anti-apoptotic Bcl-family member Mcl-1 tend to be resistant to venetoclax (32). Recently three highly selective small molecule Mcl-1 inhibitors have been described (33)[i],[ii] and shown to have promising preclinical data in myeloma models.

Finally, one exciting conceptual advance, though still in early preclinical stages, is to use an IMiD-like strategy to degrade any chosen protein in the cell. In this approach, small molecules are designed to repurpose ubiquitin ligases (not limited to cereblon, though this is the first target in development) to target specific oncoproteins for degradation (34). Ideally these approaches will degrade central nodes in tumor cell survival, analogous to IZKF1 and IZKF3 for the currently-used IMiDs, leading to plasma cell death. Much remains to be done but it is an exciting strategy to follow.

Targeting Epigenetic Modifiers to Alter Oncogenic Transcription

Myeloma oncogenesis is characterized by transcriptional dysregulation as well as dysfunction of protein homeostasis. The most canonical example is activation of the c-*myc* oncogene, which drives a diverse pro-growth transcriptional program in >50% of myeloma cases (35). This biology suggests that altering pro-proliferative transcription in myeloma may be of therapeutic benefit.

Inhibition of histone deacetylases (HDACs), enzymes which remove acetyl marks from histone tails as well as other protein substrates, may cause widespread transcriptional alteration (36). There are four different classes of HDACs and numerous HDAC inhibitors currently in myeloma clinical trials (see Table 1). However, most of these molecules are not specific to a single HDAC class and their overall anti-tumor mechanism of action is not well-understood. Panobinostat (Farydak), a pan-HDAC inhibitor, was FDA-approved in 2015 after data demonstrated improved outcomes in relapsed-refractory disease when co-administered with bortezomib and dexamethasone (37), despite very limited monotherapy activity (38). However, clinical uptake of this agent has been sparse due to relatively limited survival benefits at toxicity-limiting doses, particularly gastrointestinal and hematopoietic. Therefore, development of agents with an improved therapeutic index is desired. Of HDAC subtypes, HDAC6 is of particular interest as it functions in the cytosol to facilitate protein degradation via the aggresome. Inhibition of this proteostasis mechanism appears synergistic

[i]**RESOURCES:**
http://cancerres.aacrjournals.org/content/77/13_Supplement/2027,
[ii]http://cancerres.aacrjournals.org/content/77/13_Supplement/DDT01-02

with proteasome inhibitors in myeloma (39). Given this proposed mechanism, the HDAC6-selective inhibitor ricolinostat was studied in a Phase I/II combination trial. The findings showed somewhat reduced toxicities compared to panobinostat as well as a favorable overall response rate (40). Other HDAC inhibitors of note under clinical investigation in myeloma include romidepsin (Istodax) and vorinostat (Zolinza), both of which are approved for cutaneous T-cell lymphoma. If any of these drugs are approved for myeloma, it remains to be seen whether these agents will achieve wider clinical use than panobinostat.

The family of bromodomain-containing proteins bind acetylated lysines on histones and recruit transcriptional co-activators. Provocative preclinical data suggested that the BET inhibitor JQ1 could effectively provide a way to "turn off" the BRD4-mediated superenhancer driving c-*myc* expression in myeloma, providing a mechanism to inhibit this "undruggable" transcription factor (41). However, it is becoming clear that BET inhibitors inhibit transcription of far more genes than just c-*myc* (42). Since the initial description of JQ1, numerous other BET inhibitors have been developed. One published phase I trial of OTX015 did not show any response in 12 myeloma patients at the maximal tolerated dose (43). Currently there are several other BET inhibitors in clinical trials for myeloma, but the role of these agents in myeloma remains uncertain.

Briefly, MMSET is a histone acetyltransferase overexpressed in t(4;14) myeloma and inhibitors have been developed and preclinically evaluated (44). Other epigenetic strategies to briefly note include inhibitors of EZH2 ("enhancer of zeste-2"), a transcriptional regulator overexpressed in myeloma and numerous other cancers (45, 46). Notably, the EZH2 inhibitor tazemetostat has shown strong responses in B-cell lymphomas (47). However, it is worth noting that myeloma patients carry activating mutations in EZH2 much less frequently than lymphoma patients. It therefore remains to be seen if this different genetic background leads to differential efficacy in myeloma. Another avenue is DNA methyltransferase inhibitors, such as 5-azacitidine (Vidaza) (48, 49), which is currently approved for acute myeloid leukemia and myelodysplastic syndromes. However, investigation of these agents in myeloma is still in preclinical or early clinical phases.

Emerging Immunotherapies: Checkpoint Blockade and Targeting Tumor-Specific Antigens

Like many cancers, progression of myeloma is intricately linked to the composition of the immune microenvironment. Also like other cancers, harnessing the immune system to treat myeloma has been a major goal of recent translational and clinical research. Two major modalities have been most heavily investigated and will be discussed here: checkpoint blockade and tumor antigen-specific immunotherapy. Immune checkpoint blockade, removing the "brakes" on cytotoxic T-cell activity, using monoclonal antibodies toward CTLA-4 (ipilimumab/Yervoy) or PD-1 on T-cells (pembrolizumab/Keytruda, nivolumab/Opdivo), or PD-L1 on tumor cells (atezolizumab/Tecentriq, durvalumab/Imfinzi, avelumab/Bavencio), have been FDA-approved for numerous other malignancies and shown at least a subset of long-term responders (50–52). However, in myeloma monotherapy, initial clinical responses were more muted (53),[iii]. Combination regimens with IMiDs appeared more

effective in a Phase II trial (54), possibly due to synergistic modulation of the immune microenvironment. Based on these findings, it was surprising when in 2017 multiple checkpoint inhibitor studies in combination with IMiDs were halted due to concern of increased initial mortality. Notably, phase III checkpoint blockade trials in other malignancies have shown similar patterns of early increased mortality with later increased survival (55, 56). Fortunately, some of these studies were recently allowed to re-open and will eventually reveal the true utility of these agents in myeloma.

As noted above, tumor-antigen specific immunotherapy is currently led by daratumumab and elotuzumab, both of which target antigens that are highly expressed on malignant plasma cells (CD38 and SLAMF7, respectively). However, they are far from alone. Dozens of additional tumor antigen-specific molecules are following them in preclinical and clinical development. There are four major classes of antigen-specific immunotherapies under active investigation in myeloma (see Figure 2): monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptor engineered T-cells (CAR-Ts).

As myeloma is a malignancy of plasma cells, a unique, terminal stage of B-cell differentiation, there appear to be a number of expressed antigens with relative specificity for this tumor. These serve as handles that allow, to varying degrees, relatively selective targeting of myeloma tumor while largely avoiding “on-target, off-tissue” toxicity. Other relatively tumor-specific antigens currently under investigation in myeloma include B-cell maturation antigen (BCMA, gene *TNFRSF17*), CD138/Syndecan-1, CD307/FcRH5, SLAMF1/CD150, SLAMF2/CD48, SLAMF6/CD352, CD229, CD200, CD40 (57–59). Our group has recently participated in development of promising ADCs targeting CD74, a B-lineage specific marker[iv], and CD46, a complement inhibitor marker (60), both of which are highly expressed in myeloma. Other cell-surface antigens that are not very specific to plasma cells but have been investigated using immunotherapies developed for other indications include CD44v6, CD70, and CD56 (61). This category also includes CD19, which is not expressed on plasma cells but may be a modality to eliminate the putatative myeloma stem cell (62).

Of these markers, BCMA is currently the antigen generating the most excitement. BCMA is expressed only on late-stage B-cells and plasma cells, including on the large majority of patient malignant plasma cells (63). Therefore, BCMA offers very high selectivity with minimal anticipated toxicity on other tissues. All four modalities outlined in Fig. 2 are currently in development to target BCMA. mAbs, bispecific antibodies, and ADCs have all demonstrated strong preclinical efficacy (64–66) and some are advancing into clinical trials. However, much of the greatest hope has been placed on engineered CAR-T-cells targeting BCMA in myeloma. These “living drugs” have the potential to replicate and persist for long periods within patients and provide the theoretical possibility of long term disease control or even cure (58). Last year the results of two Phase I trials showed remarkable findings: one BCMA CAR-T from Nanjing Legend showed 100% overall response rate (ORR) as an early

[iii] http://www.bloodjournal.org/content/124/21/291
[iv] https://ash.confex.com/ash/2017/webprogram/Paper104213.htm

line of therapy[v], and another from Bluebird Bio in heavily refractory patients showing an ORR of 94%, with 9 of 10 patients evaluated showing no evidence of minimal residual disease up to a median follow-up of 40 weeks[vi]. While these results are still early, they provide the possibility that BCMA-targeting CAR-Ts may form the basis of a cure for myeloma, at least in some patients.

Due to space constraints, we cannot review here all current immunotherapy trials in myeloma targeting cell surface antigens, though two recent reviews examined progress in CAR-T cells (58, 61). Furthermore, nor can we include other approaches such as dendritic cell or peptide vaccines, TCR-engineered cells, or NK-based therapies (reviewed in (67)). However, the dozens of trials registered at clinicaltrials.gov, examining an array of myeloma immunotherapy options, underscores the rapid expansion of this field.

Reversing Antigen Escape through Forced Expression

Despite significant survival benefits, resistance to daratumumab is increasingly recognized as a widespread issue. Informative studies from van de Donk and colleagues demonstrated that daratumumab resistance may be mediated by loss of CD38 protein expression at the cell surface (68). This observation of “antigen escape” dovetailed with *in vitro* data suggesting that daratumumab efficacy dropped in parallel with antigen density (69). Furthermore, patients with higher CD38 antigen expression on plasma cells had better clinical outcomes (68). In an important series of experiments, the same group demonstrated that the small molecule all-trans retinoic acid (ATRA), previously known to induce CD38 expression in myeloid cells, could also induce CD38 expression in plasma cells (69). ATRA binds to and activates a specific transcription factor, the retinoic acid receptor, which has a response element at the CD38 locus (70). Increasing antigen expression via epigenetic modulation led to restored sensitivity of plasma cells to daratumumab-mediated antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (69). Combination clinical trials examining the efficacy of ATRA and daratumumab are now underway (NCT02751255).

We believe these experiments may establish a generalizable template for reversing resistance to antigen-specific immunotherapy. In support of this hypothesis, evidence from B-cell malignancies suggests that antigen escape is a primary mode of acquired resistance to many antigen-specific immunotherapies. An informative case study comes from the CD20-targeting mAb rituximab (Rituxan). While the mechanisms of resistance can be highly diverse, ranging from transcriptional repression to increased CD20 endocytosis to increased expression of other cell surface proteins inhibiting ADCC or CDC (71), the large majority of these mechanisms could likely be reversed or at least partially ameliorated by increasing CD20 expression. Furthermore, resistance to CD19-targeted therapy in B-cell acute lymphoblastic leukemia can be mediated by diverse mechanisms leading to antigen or epitope loss at the cell surface (72, 73). Emerging Phase I results from CD22-targeting CAR-Ts in B-ALL also have demonstrated antigen loss at relapse in patients who initially

[v] https://meetinglibrary.asco.org/record/153928/abstract
[vi] https://ash.confex.com/ash/2017/webprogram/Paper107984.html

responded (74). Importantly, in myeloma patients who initially showed partial response or better, relapses following a Novartis CAR-T targeting BCMA were characterized by decreased BCMA at the tumor cell surface[vii].

While other tumor-extrinsic factors also clearly influence efficacy of antigen-specific immunotherapies - for instance, in the case of mAbs, Fc-gamma receptor alleles on NK cells (75) or depletion of CD38-expressing NK cells (76), or, in the case of CART cells, the presence of T-regulatory cells and myeloid-derived suppressor cells in the immune microenvironment, leading to failure of CAR-T proliferation (77) - it stands to reason that ensuring sufficient antigen expression on the tumor is a minimum requirement to get strong clinical responses. Similarly, one could imagine developing strategies to enforce particular antigen expression specifically on myeloma stem cells, allowing for elimination of this disease-renewing population. Therefore, given the hope of antigen specific immunotherapy to finally lead to a cure for myeloma, any mechanism to enforce expression of the target antigen will be a critical part of our therapeutic arsenal.

Seeking Convergence between Small Molecules and Immunotherapies

In the case of daratumumab resistance, potential explanations for CD38 loss include the uptake of cell-surface antigens by other lymphoid cells (78) or shedding of CD38 on microvesicles[viii]. However, the true primary mechanism of antigen loss in patients remains unresolved. We also do not definitively know if a heterogeneous population of tumor cells loses CD38, or, alternatively, high-expressing cells are rapidly eliminated to select a subset of distinct low-expressing clones. If the latter, this may open the opportunity to specifically eliminate these low-CD38 clones if they exhibit additional vulnerabilities not seen in the broader population. The suggestion that CD38 expression may correlate with other cell-surface antigens was underscored by increases in the CDC-inhibitory molecules CD55 and CD59 on daratumumab-resistant patient plasma cells with decreased CD38 (68).

Similarly, the mechanism for the recently-described loss of BCMA expression after CAR-T therapy still remains to be investigated. But, to some degree, regardless of the mechanism, small molecules which increase antigen expression at the cell surface are likely to show clinical utility. To this end, emerging evidence suggests that epigenetic modulation with ATRA is just the tip of the iceberg. Already, others have demonstrated that the HDAC inhibitors panobinostat (79) and ricolinostat[ix], as well as the Vitamin D analog inecalcitol[x], can increase CD38 expression. In parallel, others have recently demonstrated that CD22 expression can be upregulated in B-cell malignancies by the protein kinase C modulator bryostatin-1, leading to increased preclinical CAR-T efficacy[xi] . Furthermore, a recent study in B-cell tumors suggested that HDAC6 inhibition can increase CD20 expression through a mechanism of translational regulation (80). In addition, gamma-secretase inhibitors can block proteolytic shedding of BCMA on normal plasma cells to enforce cell-surface

[vii] https://ash.confex.com/ash/2017/webprogram/Paper106279.html
[viii] http://www.bloodjournal.org/content/126/23/1849
[ix] https://ash.confex.com/ash/2017/webprogram/Paper105500.html
[x] https://ash.confex.com/ash/2017/webprogram/Paper101424.html
[xi] https://ash.confex.com/ash/2017/webprogram/Paper100688.html

expression (81). These findings suggest that for other immunotherapy targets, altering protein homeostasis may also play a critical role in either leading to increased translation, increased translocation to the cell surface, decreased extracellular shedding, or decreased lysosomal degradation (Figure 3).

Overall, we anticipate the potential for significant and rational convergence of small molecules and antigen-specific immunotherapies. To this end, novel small molecules could be screened using either cell line or primary patient cell models to identify surface-level effects on immunotherapy targets. This approach could be applied both to the modalities we discuss here as well as other emerging small molecule strategies. Importantly, RNA-only analyses will not be enough, given the multiple layers of regulation between the genome and cell-surface protein expression (Figure 3). To assess cell-surface protein expression, these assays could be done on an antigen-by-antigen basis using flow cytometry. However, methods such as cell-surface proteomics (82) may prove even more powerful in this regard. We have shown that the plasma cell proteome can be extensively remodeled in response to bortezomib (83, 84) and similar dynamics are likely true for other drugs. Unbiased cell-surface proteomics can survey numerous known antigens simultaneously as well as reveal novel immunotherapy targets that appear in response to drug-induced cell surface remodeling. Furthermore, high-throughput functional genomics methods may be fruitful to elucidate targetable mechanisms that regulate cell-surface trafficking of immunotherapy targets (85). Broader approaches to understand the tumor cell surface, both at baseline and after drug perturbation, may also be important for engaging another potential strategy for overcoming antigen escape: “dual-targeting” engineered T-cells (74, 86) that can simultaneously recognize two antigens at the cell surface to lead to tumor death. Ideally, small molecules modulating cell-surface expression may be implemented to reverse resistance after initial therapy, make baseline-resistant patients sensitive, or as co-therapies to drive deeper remissions. These strategies must take into account modulation of the tumor microenvironment as well (87). While increasing antigen expression may not be effective for every immunotherapy target in myeloma, the balance of evidence thus far, across hematologic malignancies, suggests that it will be relevant for the majority of them.

Considerations in Clinical Practice

Given that essentially all myeloma therapies are given as combinations, two major considerations for the practicing oncologist are 1) combined toxicities across agents and 2) decision-making for therapeutic strategies offered to patients. In terms of toxicities, even if certain agents (whether only small molecules, or small molecules and immunotherapies), show promising preclinical or even clinical combination benefits, it is critical to note that combined toxicity may significant reduce the number of patients who can tolerate such a regimen, greatly limiting utility. In terms of decision-making, whether in the up-front or relapsed setting, the significant recent increase in the number of FDA-approved therapies, not to mention the myriad emerging therapies described here, can make prescribing the “best” therapy for a given patient exceedingly difficult if not impossible. A few crude examples exist, such as the increased efficacy of venetoclax in tumors carrying the t(11;14) translocation (30). However, going forward, biomarker-driven or other “decision support

tools" for precision medicine would be of significant utility in guiding myeloma practice to match each patient's disease.

Concluding Remarks

These are exciting times in myeloma therapy. There are now three major pillars of clinical myeloma therapy: proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, which have together made a remarkable impact on patient survival. The advent of engineered cellular therapies targeted to specific tumor antigens, particularly BCMA, gives promise of potentially reaching a cure, at least for some patients, within the near future. Rational strategies to enhance immunotherapy efficacy and reverse resistance, including harnessing the cellular biology of epigenetic modification and protein homeostasis, may play a critical role in achieving this goal (see Outstanding Questions).

Outstanding Questions

- Can BCMA-targeting CAR-T cells truly lead to the first unqualified cure in a subset of myeloma patients?
- Will emerging immunotherapies be used as front-line therapies or reserved for patients who are refractory to standard small molecule-based regimens?
- What is the future of small molecule therapeutic development in myeloma in the age of tumor-antigen specific immunotherapy?
- Can we develop rational combinations of small molecules and immunotherapies to reach deeper remissions or cures for even more patients?
- With so many current and emerging options for myeloma therapy, how do we best match a given patient's disease with the regimen that will lead to longest survival with least toxicity?

Acknowledgments

We would like to thank Drs. Jeffrey Wolf, Tom Martin, Nina Shah, and Sandy Wong for helpful discussions. Related work in A.P.W.'s group is supported by a Damon Runyon Cancer Research Foundation-Dale Frey Breakthrough Award (DFS 14–15), an NIH New Innovator Award (DP2OD022552), a Translational Network Award from the Multiple Myeloma Research Foundation, a Research Grant from the Gabrielle's Angel Foundation for Cancer Research, and the National Cancer Institute (K08CA184116). We apologize to colleagues whose work we were unable to cite due to space limitations.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1):7–30. [PubMed: 29313949]
2. Gandolfi S, et al. The proteasome and proteasome inhibitors in multiple myeloma. Cancer Met Rev. 2017; 36(4):561–584.
3. Meister S, et al. Extensive immunoglobulin production sensitizes myeloma cells for proteasome inhibition. Cancer Res. 2007; 67(4):1783–1792. [PubMed: 17308121]
4. Obeng EA, et al. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood. 2006; 107(12):4907–4916. [PubMed: 16507771]

5. Wang Q, et al. ERAD inhibitors integrate ER stress with an epigenetic mechanism to activate BH3-only protein NOXA in cancer cells. Proc Natl Acad Sci USA. 2009; 106(7):2200–2205. [PubMed: 19164757]
6. Dimopoulos MA, Richardson PG, Moreau P, Anderson KC. Current treatment landscape for relapsed and/or refractory multiple myeloma. Nat Rev Clin Oncol. 2015; 12(1):42–54. [PubMed: 25421279]
7. Kronke J, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science. 2014; 343(6168):301–305. [PubMed: 24292625]
8. Lu G, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science. 2014; 343(6168):305–309. [PubMed: 24292623]
9. Kortum KM, Zhu YX, Shi CX, Jedlowski P, Stewart AK. Cereblon binding molecules in multiple myeloma. Blood Rev. 2015; 29(5):329–334. [PubMed: 25843596]
10. Fonseca R, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia. 2017; 31(9):1915–1921. [PubMed: 28008176]
11. Usmani SZ, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood. 2016; 128(1):37–44. [PubMed: 27216216]
12. Dimopoulos MA, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016; 375(14):1319–1331. [PubMed: 27705267]
13. Zonder JA, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood. 2012; 120(3):552–559. [PubMed: 22184404]
14. Lonial S, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015; 373(7):621–631. [PubMed: 26035255]
15. Lohr JG, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell. 2014; 25(1):91–101. [PubMed: 24434212]
16. Johnsen HE, et al. The myeloma stem cell concept, revisited: from phenomenology to operational terms. Haematologica. 2016; 101(12):1451–1459. [PubMed: 27903712]
17. Abe M, Harada T, Matsumoto T. Concise review: Defining and targeting myeloma stem cell-like cells. Stem Cells. 2014; 32(5):1067–1073. [PubMed: 24449391]
18. Manasanch EE, Orlowski RZ. Proteasome inhibitors in cancer therapy. Nat Rev Clin Oncol. 2017; 14(7):417–433. [PubMed: 28117417]
19. Carelli JD, et al. Ternatin and improved synthetic variants kill cancer cells by targeting the elongation factor-1A ternary complex. eLife. 2015; 4:e10222. [PubMed: 26651998]
20. Losada A, et al. Translation Elongation Factor eEF1A2 is a Novel Anticancer Target for the Marine Natural Product Plitidepsin. Sci Rep. 2016; 6:35100. [PubMed: 27713531]
21. Meyer H, Bug M, Bremer S. Emerging functions of the VCP/p97 AAA-ATPase in the ubiquitin system. Nat Cell Biol. 2012; 14(2):117–123. [PubMed: 22298039]
22. Anderson DJ, et al. Targeting the AAA ATPase p97 as an Approach to Treat Cancer through Disruption of Protein Homeostasis. Cancer Cell. 2015; 28(5):653–665. [PubMed: 26555175]
23. Le Moigne R, et al. The p97 inhibitor CB-5083 is a unique disrupter of protein homeostasis in models of Multiple Myeloma. Mol Cancer Therap. 2017; 16(11):2375–2386. [PubMed: 28878026]
24. Chauhan D, et al. A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. Cancer Cell. 2012; 22(3):345–358. [PubMed: 22975377]
25. Tian Z, et al. A novel small molecule inhibitor of deubiquitylating enzyme USP14 and UCHL5 induces apoptosis in multiple myeloma and overcomes bortezomib resistance. Blood. 2014; 123(5):706–716. [PubMed: 24319254]
26. Gavory G, et al. Discovery and characterization of highly potent and selective allosteric USP7 inhibitors. Nat Chem Biol. 2018; 14(2):118–125. [PubMed: 29200206]
27. Gravina GL, et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014; 7:85. [PubMed: 25476752]
28. Chen C, et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom's macroglobulinemia. Blood. 2018; 131(8):855–863. [PubMed: 29203585]

29. Ruefli-Brasse A, Reed JC. Therapeutics targeting Bcl-2 in hematological malignancies. Biochem J. 2017; 474(21):3643–3657. [PubMed: 29061914]
30. Kumar S, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. Blood. 2017; 130(22):2401–2409. [PubMed: 29018077]
31. Moreau P, et al. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. Blood. 2017; 130(22):2392–2400. [PubMed: 28847998]
32. Touzeau C, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma. Leukemia. 2014; 28(1):210–212. [PubMed: 23860449]
33. Kotschy A, et al. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. Nature. 2016; 538(7626):477–482. [PubMed: 27760111]
34. Matyskiela ME, et al. A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. Nature. 2016; 535(7611):252–257. [PubMed: 27338790]
35. Affer M, et al. Promiscuous MYC locus rearrangements hijack enhancers but mostly super-enhancers to dysregulate MYC expression in multiple myeloma. Leukemia. 2014; 28(8):1725–1735. [PubMed: 24518206]
36. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res. 2007; 5(10):981–989. [PubMed: 17951399]
37. San-Miguel JF, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014; 15(11): 1195–1206. [PubMed: 25242045]
38. Wolf JL, et al. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012; 53(9):1820–1823. [PubMed: 22288662]
39. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. Mol Cancer Therap. 2011; 10(11):2034–2042. [PubMed: 22072815]
40. Vogl DT, et al. Ricolinostat, the First Selective Histone Deacetylase 6 Inhibitor, in Combination with Bortezomib and Dexamethasone for Relapsed or Refractory Multiple Myeloma. Clin Cancer Res. 2017; 23(13):3307–3315. [PubMed: 28053023]
41. Delmore JE, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell. 2011; 146(6):904–917. [PubMed: 21889194]
42. Abedin SM, Boddy CS, Munshi HG. BET inhibitors in the treatment of hematologic malignancies: current insights and future prospects. Onco Targets Ther. 2016; 9:5943–5953. [PubMed: 27729803]
43. Amorim S, et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. Lancet Hematol. 2016; 3(4):e196–204.
44. Tisi D, et al. Structure of the Epigenetic Oncogene MMSET and Inhibition by N-Alkyl Sinefungin Derivatives. ACS Chem Biol. 2016; 11(11):3093–3105. [PubMed: 27571355]
45. Alzrigat M, et al. EZH2 inhibition in multiple myeloma downregulates myeloma associated oncogenes and upregulates microRNAs with potential tumor suppressor functions. Oncotarget. 2017; 8(6):10213–10224. [PubMed: 28052011]
46. Hernando H, et al. EZH2 Inhibition Blocks Multiple Myeloma Cell Growth through Upregulation of Epithelial Tumor Suppressor Genes. Mol Cancer Therap. 2016; 15(2):287–298. [PubMed: 26590165]
47. Italiano A, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. Lancet Oncol. 2018; 19(5):649–659. [PubMed: 29650362]
48. Khong T, Sharkey J, Spencer A. The effect of azacitidine on interleukin-6 signaling and nuclear factor-kappaB activation and its in vitro and in vivo activity against multiple myeloma. Haematologica. 2008; 93(6):860–869. [PubMed: 18443271]

49. Moreaux J, et al. DNA methylation score is predictive of myeloma cell sensitivity to 5-azacitidine. Br J Hematol. 2014; 164(4):613–616.
50. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363(8):711–723. [PubMed: 20525992]
51. Rizvi NA, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015; 16(3):257–265. [PubMed: 25704439]
52. Topalian SL, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012; 366(26):2443–2454. [PubMed: 22658127]
53. Berger R, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. Clin Cancer Res. 2008; 14(10):3044–3051. [PubMed: 18483370]
54. Badros A, et al. Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory multiple myeloma. Blood. 2017; 130(10):1189–1197. [PubMed: 28461396]
55. Bellmunt J, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017; 376(11):1015–1026. [PubMed: 28212060]
56. Borghaei H, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373(17):1627–1639. [PubMed: 26412456]
57. Al-Hujaily EM, Oldham RA, Hari P, Medin JA. Development of Novel Immunotherapies for Multiple Myeloma. Int J Mol Sci. 2016; 17(9)
58. Mikkilineni L, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for multiple myeloma. Blood. 2017; 130(24):2594–2602. [PubMed: 28928126]
59. Muccio VE, et al. Multiple myeloma: New surface antigens for the characterization of plasma cells in the era of novel agents. Cytometry B Clin Cytom. 2016; 90(1):81–90. [PubMed: 26287276]
60. Sherbenou DW, et al. Antibody-drug conjugate targeting CD46 eliminates multiple myeloma cells. J Clin Invest. 2016; 126(12):4640–4653. [PubMed: 27841764]
61. Atanackovic D, Radhakrishnan SV, Bhardwaj N, Luetkens T. Chimeric Antigen Receptor (CAR) therapy for multiple myeloma. Br J Hematol. 2016; 172(5):685–698.
62. Garfall AL, et al. Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. N Engl J Med. 2015; 373(11):1040–1047. [PubMed: 26352815]
63. Carpenter RO, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res. 2013; 19(8):2048–2060. [PubMed: 23344265]
64. Seckinger A, et al. Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. Cancer Cell. 2017; 31(3):396–410. [PubMed: 28262554]
65. Ryan MC, et al. Antibody targeting of B-cell maturation antigen on malignant plasma cells. Mol Cancer Therap. 2007; 6(11):3009–3018. [PubMed: 18025285]
66. Tai YT, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014; 123(20):3128–3138. [PubMed: 24569262]
67. Boussi L, Niesvizky R. Advances in immunotherapy in multiple myeloma. Curr Opin Oncol. 2017; 29(6):460–466. [PubMed: 28877078]
68. Nijhof IS, et al. CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. Blood. 2016; 128(7):959–970. [PubMed: 27307294]
69. Nijhof IS, et al. Upregulation of CD38 expression on multiple myeloma cells by all-trans retinoic acid improves the efficacy of daratumumab. Leukemia. 2015; 29(10):2039–2049. [PubMed: 25975191]
70. Drach J, et al. Retinoic acid-induced expression of CD38 antigen in myeloid cells is mediated through retinoic acid receptor-alpha. Cancer Res. 1994; 54(7):1746–1752. [PubMed: 7511050]
71. Seyfizadeh N, Seyfizadeh N, Hasenkamp J, Huerta-Yepez S. A molecular perspective on rituximab: A monoclonal antibody for B cell non Hodgkin lymphoma and other affections. Crit Rev Oncol Hematol. 2016; 97:275–290. [PubMed: 26443686]

72. Jacoby E, et al. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. Nat Commun. 2016; 7:12320. [PubMed: 27460500]

73. Sotillo E, et al. Convergence of Acquired Mutations and Alternative Splicing of CD19 Enables Resistance to CART-19 Immunotherapy. Cancer Discov. 2015; 5(12):1282–1295. [PubMed: 26516065]

74. Fry TJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018; 24(1):20–28. [PubMed: 29155426]

75. Jakubowiak A, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. Blood. 2016; 127(23):2833–2840. [PubMed: 27091875]

76. Casneuf T, et al. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. Blood Adv. 2017; 1(23):2105–2114. [PubMed: 29296857]

77. Maus MV, June CH. Making Better Chimeric Antigen Receptors for Adoptive T-cell Therapy. Clin Cancer Res. 2016; 22(8):1875–1884. [PubMed: 27084741]

78. Krejcik J, et al. Monocytes and Granulocytes Reduce CD38 Expression Levels on Myeloma Cells in Patients Treated with Daratumumab. Clin Cancer Res. 2017; 23(24):7498–7511. [PubMed: 29025767]

79. Garcia-Guerrero E, et al. Panobinostat induces CD38 upregulation and augments the antimyeloma efficacy of daratumumab. Blood. 2017; 129(25):3386–3388. [PubMed: 28476749]

80. Bobrowicz M, et al. HDAC6 inhibition upregulates CD20 levels and increases the efficacy of anti-CD20 monoclonal antibodies. Blood. 2017; 130(14):1628–1638. [PubMed: 28830887]

81. Laurent SA, et al. gamma-Secretase directly sheds the survival receptor BCMA from plasma cells. Nat Commun. 2015; 6:7333. [PubMed: 26065893]

82. Wollscheid B, et al. Mass-spectrometric identification and relative quantification of N-linked cell surface glycoproteins. Nat Biotechnol. 2009; 27(4):378–386. [PubMed: 19349973]

83. Liu TY, et al. Time-Resolved Proteomics Extends Ribosome Profiling-Based Measurements of Protein Synthesis Dynamics. Cell Syst. 2017; 4(6):636–644. e639. [PubMed: 28578850]

84. Wiita AP, et al. Global cellular response to chemotherapy-induced apoptosis. eLife. 2013; 2:e01236. [PubMed: 24171104]

85. Burr ML, et al. CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. Nature. 2017; 549(7670):101–105. [PubMed: 28813417]

86. Roybal KT, et al. Precision Tumor Recognition by T Cells With Combinatorial Antigen-Sensing Circuits. Cell. 2016; 164(4):770–779. [PubMed: 26830879]

87. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017; 168(4):707–723. [PubMed: 28187290]

Trends

- Myeloma clinical therapy has undergone enormous changes over the past decade, leading to significantly improved patient outcomes
- Promising new small molecule approaches are being developed to target protein homeostasis and epigenetic regulation in myeloma
- Immunotherapy approaches, particularly CAR-T cells, are leading to remarkable responses in patients
- Rational combinations of small molecules and immunotherapies may allow modulation of surface antigen expression, avoidance of resistance, and ultimately lead to a cure

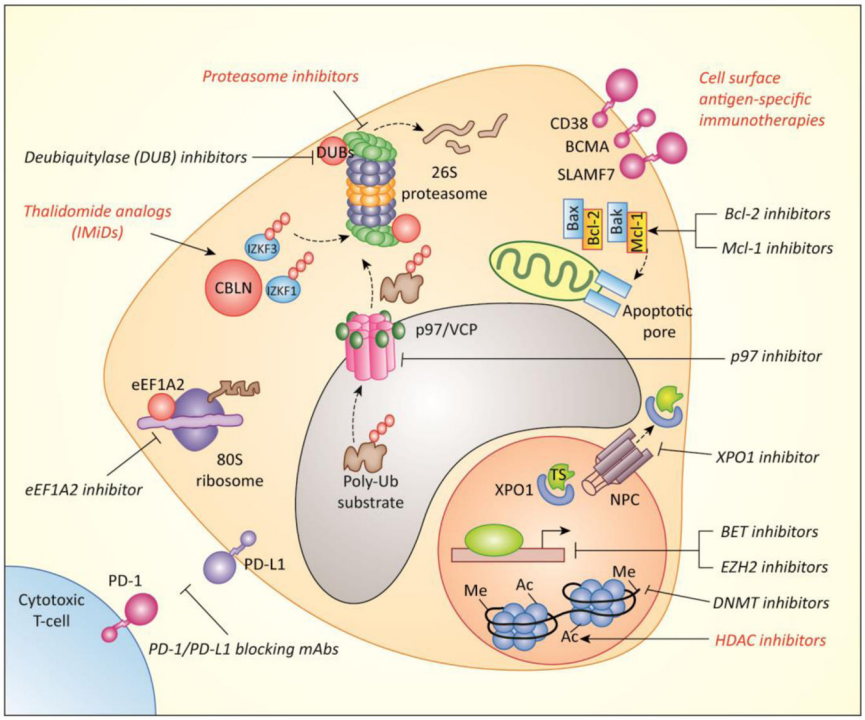

Figure 1, Key Figure. Attacking Malignant Plasma Cells Through Proteostasis, Epigenetics, and the Cell Surface

Nodes to attack protein homeostasis by increasing unfolded protein stress include direct inhibition of the proteasome, inhibition of proteasome-associated deubiquitylases (DUBs), and direct inhibition of VCP/p97. Other approaches to therapeutically modulating protein homeostasis include cereblon (CBLN) re-targeting via the immunomodulatory thalidomide analogs (IMiDs), inhibition of translation elongation via eukaryotic elongation factor 1A1 (eEF1A2), inhibition of nuclear pore complex (NPC) export of tumor suppressors via XPO1, and activation of apoptosis at the mitochondrion by inhibition of Bcl-2 or Mcl-1. Nodes to modulate myeloma epigenetics include chromatin post-translational modifications through DNA methyltransferase (DNMT) inhibitors and histone deacetylases (HDACs) as well as transcription factor activation via BET bromodomain inhibitors and EZH2 inhibitors. Specific cell surface antigens can be targeted via checkpoint blockade either on myeloma plasma cells (PD-L1) or on cytotoxic T-cells (PD-1) using monoclonal antibodies. Other tumor cell-surface antigens such as CD38 and SLAMF7, which have FDA-approved mAbs, or BCMA, under intense clinical investigation, can be targeted with numerous different modalities, as outlined in Figure 2. Drug classes with at least one FDA-approved member are noted in red.

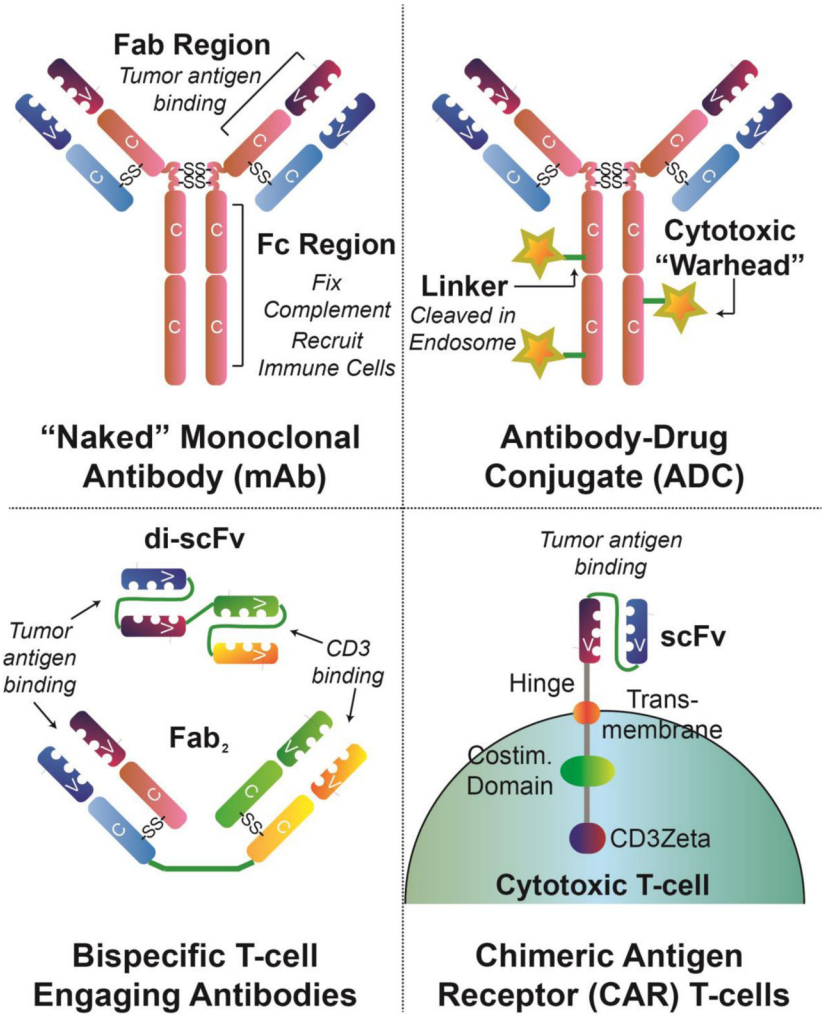

Figure 2. Modalities of Myeloma Cell Surface Antigen-Specific Immunotherapy

Monoclonal antibodies (mAbs) (*top left*) are comprised of tumor antigen-binding variable regions of the both the heavy and light chain as well as one constant immunoglobulin domain from each chain, comprising the Fab region, as well as the constant Fc region of the heavy chain which can recruit cytotoxic NK cells and macrophages as well as fix complement to lead to tumor cell death. Antibody drug conjugates (ADCs) (*top right*) are typically mAbs with chemical linkers to general cytotoxic warheads such as alkylating agents or microtubule destabilizers. Specificity for tumor kill is achieved after antigen binding, internalization into the endosome (see Fig. 3), and specific cleavage of the linker and warhead release only in that specialized environment. Bispecific T-cell engaging antibodies (*bottom left*) can come in many versions. The goal of all varieties is to bring the tumor cell in close proximity to a cytotoxic T-cell, which is then activated due to CD3 engagement. Two examples are shown here. One is a dual single-chain variable fragment (scFv) comprising just the variable fragments derived from both a tumor-antigen binding Fab and a CD3-binding Fab, linked into a single polypeptide chain. Another is two full Fab domains connected via a peptide linker (Fab_2). Among other options not shown include full immunoglobulins resembling mAbs but with Fabs toward different antigens, or inclusion of

chains of multiple scFvs or Fabs to increase avidity for target. Chimeric antigen receptor (CAR) T-cells are gene-engineered products derived from patient T-cells. These cells are transduced with a lentiviral construct encoding a scFv directed toward the tumor antigen as well as a cloned hinge region, transmembrane region, costimulatory domain, and T-cell activation domain derived from CD3Zeta, expanded, and then re-introduced back into the patient as “living drugs”.

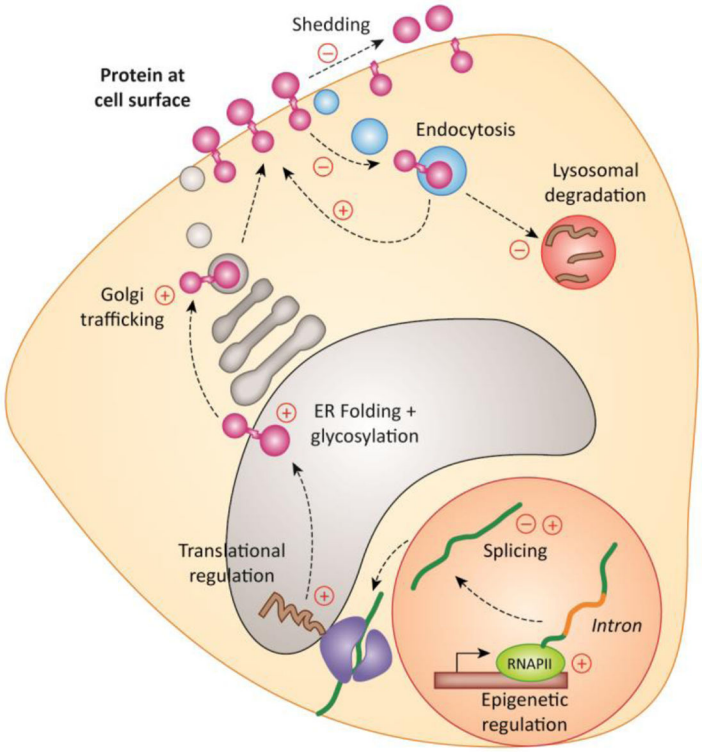

Figure 3. Manipulating Cell Surface Antigens with Small Molecules

The complex regulation of cell-surface proteins provides multiple opportunities to enforce immunotherapy target expression. At the RNA level, enhancing transcription through epigenetic regulation or modulating splicing to enforce expression of an isoform with a specific epitope are potential goals. Protein-level increases can be achieved by enhancing protein synthesis, folding, and glycosylation within the ER. As many membrane proteins also have intracellular components, enhancing trafficking to the cell surface via the trans-Golgi network would be particularly desirable. Once at the cell-surface, the goal is to keep proteins there. This aim could be achieved by inhibiting proteolytic shedding of extracellular domains, inhibiting endocytosis, enhancing recycling back to the cell surface when endocytosis does occur, or inhibiting lysosomal degradation after endocytosis. From a discovery perspective, this complex regulation emphasizes that transcriptome and even total cell proteome studies will only tell part of the story at the cell surface. Instead, enrichment-based membrane proteomics methods are the preferred approach. Red ”+” symbols = opportunity to increase biological process with small molecules; “−“ = opportunity to decrease.

Table 1

Notable clinical trials of emerging myeloma therapies.

Target	Agent Class	Molecule Name	Single Agent (S) or Combi nation (C)	Phase	NCT number	Reference
HDAC	Small molecule	Panobinostat	S	II	NCT00621244	
			C	III	NCT01023308	PMID26631116
			C	II	NCT01083602	PMID23950178
			C	I/II	NCT01496118	PMID25710456
		Ricolinostat	C	I/II	NCT01323751	PMID28053023
			C	I/II	NCT01583283	
			C	I/II	NCT01997840	
			C	I	NCT02189343	
			C	I	NCT02400242	
		Suberoylanilide hydroxamic acid	C	II	NCT00773838	
			C	I	NCT00111813	
			C	I	NCT00310024	
			C	I	NCT00858234	
		Belinostat	C	II	NCT00131261	
		Entinostat	S	I	NCT00015925	
		Romidepsin	C	II	NCT00765102	
		Vorinostat	C	III	NCT00773747	
			C	IIb	NCT00773838	PMID27025160
			C	IIb	NCT01502085	PMID27859001
BET	Small molecule	CPI-0610	S	I	NCT02157636	
		RO6870810	S/C	I	NCT03068351	
		ABBV-075	S/C	I	NCT02391480	
		I-BET-762/GSK525762	S	II	NCT01943851	

Target	Agent Class	Molecule Name	Single Agent (S) or Combi nation (C)	Phase	NCT number	Reference
		OTX015/MK-8628	S	I	NCT01713582	
HMT	Small molecule	GSK2816126	S	II	NCT02082977	
DNMT	Small molecule	5-Azacytidine	S	II	NCT00412919	
			C	I/II	NCT01155583	
			C	I	NCT01050790	
CD38	mAb	Daratumumab	S	I/II	NCT00574288	PMID26308596
			S	I/II	NCT01985126	PMID26778538
			C	III	NCT02136134	PMID27557302
			C	III	NCT02076009	ASH2017 Session 653–739
		Isatuximab	S	II	NCT01084252	ASCO2016; 8005
			C	I	NCT01749969	PMID28483761
			C	I	NCT02283775	ASH2017 Session 653
			C	I	NCT02332850	ASH2014 abstract (*Blood*, 128(22), 2111)
		MOR202	S/C	I/II	NCT01421186	ASH2014 abstract (*Blood*, 128(22), 1152)
SLAMF7	mAb	Elotuzumab	S	I	NCT00742560	
			C	II	NCT01478048	PMID27091875
			C	III	NCT01239797	PMID28677826, PMID28249893
			C	II	NCT02654132	ASCO2016; TPS8066
BCMA	Bispecific	BI 836909	S	I	NCT02514239	PMID28025583
		JNJ-64007957	S	II	NCT03145181	
		PF-06863135	S	I	NCT03269136	
	ADC	GSK2857916	S	I	NCT02064387	
	CAR-T	Anti-BCMA CART	S	I	NCT02215967	PMID27412889

Target	Agent Class	Molecule Name	Single Agent (S) or Combi nation (C)	Phase	NCT number	Reference
		BB2121	S	I	NCT02658929	ASH2017 Session 653
			S	II	NCT03361748	
		BB21217	S	I	NCT03274219	
		KITE-585	S	I	NCT03318861	
		FCARH143	S	I	NCT03338972	
		CART-BCMA	S	I	NCT02546167	ASH2017 Session 653
		LCAR-B38M	S	I	N/A (Chinese study)	ASH2017 Session 653
	mAb/auto T cell	SEA-BCMA/ACTR087	C	I	NCT03266692	
CD56	Bispecific Ab	JNJ-64007957	S	I	NCT03145181	
		PF-06863135	S	I	NCT03269136	
	ADC	IMGN901/Lorvotuzumab	C	I	NCT00991562	
CD138	ADC	BT062/Indatuximab Ravtansine	S	I/II	NCT01001442, NCT00723359	
			C	I/II	NCT01638936	
	CAR-T	CART-138	S	I/II	NCT01886976	
		CART-138/BCMA	C	I/II	NCT03196414	
CD74	mAb	Milatuzumab	S	I/II	NCT00421525	
	ADC	Milatuzumab-doxorubicin/hLL 1-DOX/IMMU-110	C	I/II	NCT01101594	
PD-1	mAb	pembrolizumab	C	II	NCT02289222	PMID28461396
			C	II	NCT02036502	ASCO2016;8010
			C	III	NCT02576977	
			C	III	NCT02579863	

Target	Agent Class	Molecule Name	Single Agent (S) or Combi nation (C)	Phase	NCT number	Reference
		nivolumab	C	II	NCT03292263	
			C	II	NCT02903381	
			C	I	NCT01794507	PMID28847998
eEIF1A 2	small molecule	plitidespin	C	III	NCT01102426	ASH2017 Session 653
Bcl-2	small molecule	venetoclax	C	I/II	NCT01794520	PMID29018077
			C	II	NCT02899052	
			C	II	NCT01794507	
			C	III	NCT02755597	
MCL-1	small molecule	AMG-176	S	I	NCT02675452	
		MIK-665	S	I	NCT02992483	
XPO-1	small molecule	selinexor	S	I	NCT01607892	PMID29203585
			C	III	NCT03110562	

Abbreviations: ASH=American Society for Hematology. ASCO = American Society for Clinical Oncology. HDAC = histone deacetylase. BET = bromo- and extra-terminal domain. HMT = histone methyltransferase. DNMT = DNA methyltransferase. mAb = monoclonal antibody. ADC = antibody-drug conjugate. CAR-T = chimeric antigen receptor T-cell.