The Evolving Landscape of Multiple Myeloma

Multiple myeloma (MM) is a persistent hematological malignancy that continues to be incurable, marked by the clonal proliferation of plasma cells within the bone marrow, which results in suppressed hematopoiesis and osteolytic lesions (Ding et al., 2021). The treatment landscape for MM has undergone a significant transformation in recent decades. The shift has been from traditional chemotherapy and hematopoietic stem cell transplantation to more innovative targeted therapies and immunotherapy (Anderson, 2000), leading to substantial improvements in patient outcomes (Podar&Jger, 2017). This evolution in therapeutic approaches has provided new avenues for managing this complex disease (Anderson, 2000). This review aims to synthesize existing knowledge on MM pathogenesis and shed light on the crucial role of immunotherapies.
Specifically, it will explore chimeric antigen receptor (CAR) T-cells, bispecific antibodies, and monoclonal antibodies, while simultaneously investigating emerging novel targets and personalized medicine strategies. The ultimate goal is to effectively address relapsed/refractory disease and enhance long-term survival for MM patients.

Current Immunotherapeutic Strategies in Multiple Myeloma

The advent of chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of multiple myeloma (MM), particularly for patients with relapsed/refractory MM (RRMM). Early clinical trials involving CAR-T cells targeting B-cell maturation antigen (BCMA) have shown significant anti-MM activity (Ding et al., 2021). This led to the approval of autologous BCMA-directed CAR-T cell therapy by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2021 (Mirvis & Benjamin, 2024). Beyond BCMA, a range of other promising targets are under investigation, including CD138, CD38, CS1, CD19, light chain, CD56, CD44v6, Lewis Y, NY-ESO-1, and CD229 (Ding et al., 2021). While initial response rates in heavily pretreated MM patients have been impressive, challenges such as relapse, high manufacturing costs, and impaired T-cell fitness due to prior treatments persist (Mirvis & Benjamin, 2024).

Bispecific antibodies (BsAbs) and antibody-drug conjugates (ADCs) represent another critical advancement in immunotherapy for MM. BsAbs are engineered to simultaneously bind to the CD3 subunit on T-cells and an antigen on tumor cells, thereby activating T-cell-mediated killing (Tacchetti et al., 2024). Two BCMAtargetingBsAbs, teclistamab and elranatamab, and one GPRC5D-targeting BsAb, talquetamab, have received regulatory approval for heavily pretreated RRMM patients (Braun et al., 2024; Tacchetti et al., 2024). These agents have demonstrated impressive clinical activity as monotherapy, achieving overall response rates exceeding 60% and

complete response rates between 25% and 50%, with a median progression-free survival of approximately one year in patients with a median of four to six prior lines of therapy (Tacchetti et al., 2024). ADCs, such as belantamabmafodotin (targeting BCMA), deliver cytotoxic agents directly to tumor cells and have shown activity in heavily pretreated MM patients (Davis et al., 2022; Luca et al., 2023). Emerging research explores novel antigen targets like Fc receptor homologue 5 (FcRH5) and signaling lymphocyte activation molecule family member 7 (SLAMF7), as well as innovative structures like trispecific antibodies, to further enhance efficacy and safety (Braun et al., 2024; Mirvis & Benjamin, 2024).

Monoclonal antibodies (mAbs) against CD38 (daratumumab, isatuximab) and SLAMF7 (elotuzumab) have significantly improved patient outcomes through various mechanisms, including direct cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and immunomodulation (Luca et al., 2023). Daratumumab, a novel human monoclonal antibody binding CD38, has dramatically improved outcomes both as monotherapy and in combination with traditional regimens. Originally approved for RRMM, daratumumab is now widely incorporated into frontline therapy for newly diagnosed MM patients, regardless of transplant eligibility, with promising results and a tolerable side-effect profile (Dima et al., 2020). Isatuximab, also targeting CD38, and elotuzumab, targeting SLAMF7, have similarly become integral components of treatment strategies for relapsed/refractory MM (Luca et al., 2023; Musto & Rocca, 2020). These mAbs represent crucial tools in the evolving treatment landscape, with ongoing efforts to identify optimal combinations and manage potential toxicities (Musto & Rocca, 2020).

Therapy Type	Key Targets	Mechanism of Action	Efficacy in MM (Relapsed/Refractory)	Regulatory Status (Examples)
CAR-T Cell Therapy	BCMA, CD138, CD38, CS1, CD19, Light chain, CD56,	Genetically engineered T-cells recognize tumor	Significant anti-MM activity, and kill impressive	BCMA-targeting CART approved by FDA/EMA

Therapy Type	Key Targets	Mechanism of Action	Efficacy in MM (Relapsed/Refractory)	Regulatory Status (Examples)
	CD44v6, Lewis Y, NY-ESO-1, CD229	cells	initial response rates (BCMAtargeting)	(2021) (Mirvis & Benjamin, 2024)
Bispecific Antibodies	BCMA, GPRC5D, FcRH5, CD19, SLAMF7	Bridge T-cells to tumor cells, activating Tcell mediated killing	Impressive clinical activity, ORR >60%, CR 2550%, median PFS ~1 year (with 4-6 prior lines)	Teclistamab (BCMA), Elranatamab (BCMA), Talquetamab (GPRC5D) approved by EMA/FDA (Braun et al., 2024; Tacchetti et al., 2024)
Antibody-Drug Conjugates (ADCs)	BCMA	Deliver cytotoxic agents directly to tumor cells	Demonstrated activity in pretreated patients (Luca et al., 2023)	Belantamab mafodotin (BCMA) heavily approved
Monoclonal Antibodies	CD38, SLAMF7, BCMA	Direct cytotoxicity, ADCC, CDC, immunomodulation	Daratumumab/isatuximab improved outcomes as monotherapy (Luca et al., 2023) or in combination; elotuzumab also effective	Daratumumab, Isatuximab, Elotuzumab approved

Novel Targets and Mechanisms of Action for Immunotherapy

Beyond established targets like BCMA, ongoing research is actively identifying new antigens for multiple myeloma (MM) immunotherapy. G protein-coupled receptor, class C group 5 member D (GPRC5D), for instance, has emerged as a promising therapeutic target for relapsed/refractory MM due to its expression on malignant plasma cells and limited presence in normal tissues (Xia et al., 2023). GPRC5Dtargeted CAR-T and CAR-NK cell therapies, as well as bispecific T-cell engagers, have shown remarkable anti-tumor activities (Xia et al., 2023), with GPRC5Dtargeted CARs demonstrating enhanced antigen-dependent activation and effective lysis of MM cells in

preclinical models (Smith et al., 2018). The rational selection of such highly selective and stably expressed tumor targets is crucial for successful CAR therapy in MM (Bezborodova et al., 2025).

Further innovative targets under investigation include Fc receptor-like 5 (FCRL5) and Leukocyte Immunoglobulin-Like Receptor B4 (LILRB4). FCRL5, considerably upregulated in MM, has shown promise as a CAR-T cell target, with FCRL5-directed CAR-T cells incorporating interleukin-15 (IL-15) exhibiting potent anti-tumor efficacy and improved survival in MM xenograft models (Yu et al., 2024). LILRB4 is another identified biomarker and immunotherapy target for high-risk MM, capable of dual targeting tumor cells and myeloid-derived suppressive cells (MDSCs) within the tumor microenvironment (Gong et al., 2024). A TCR-based CAR cell, LILRB4STAR-T, has demonstrated effective elimination of tumor cells and impeded MDSC function (Gong et al., 2024). Other novel targets, such as ILT3, have been identified through high-throughput screening, showing therapeutic relevance with a bispecific engager that demonstrated potent killing effects in vitro and prolonged survival in mice (Meo et al., 2023). Intercellular Adhesion Molecule 1 (ICAM1) is also being explored, with an anti-ICAM1 antibody-drug conjugate (ADC) showing potent anti-myeloma cytotoxicity in vitro and in vivo, particularly in daratumumabrefractory patients with decreased CD38 expression (Sherbenou et al., 2020).

List of Emerging Immunotherapy Targets

- **GPRC5D:** An orphan receptor expressed on malignant plasma cells with limited expression in normal tissue, targeted by CAR-T cells and bispecific Tcell engagers (Smith et al., 2018; Xia et al., 2023).
- **FCRL5:** Considerably upregulated in MM, FCRL5-directed CAR-T cells, especially with IL-15 integration, exhibit potent anti-tumor activity (Yu et al., 2024).
- **LILRB4:** A biomarker for high-risk MM, this target allows for dual targeting of tumor cells and immunosuppressive MDSCs, with LILRB4-STAR-T cells showing efficacy (Gong et al., 2024).
- **ILT3:** Identified through mass spectrometry and RNA sequencing, a bispecific engager targeting ILT3 has shown potent killing effects against MM cells (Meo et al., 2023).
- **ICAM1:** Highly expressed on myeloma cells, an anti-ICAM1 antibody-drug conjugate has demonstrated potent anti-myeloma cytotoxicity, particularly in daratumumab-refractory patients (Sherbenou et al., 2020).

Overcoming Resistance and Managing Toxicities in Immunotherapy

Despite the significant advancements in multiple myeloma (MM) immunotherapy, challenges remain, particularly in overcoming treatment resistance and managing associated toxicities. Resistance to CAR-T cell therapy often involves the loss or downregulation of target antigens like B-cell maturation antigen (BCMA), necessitating strategies such as multispecific CAR constructs and combinations of novel targets (Schans et al., 2020). An immunosuppressive tumor

microenvironment, characterized by increased numbers of monocytes expressing immune checkpoint molecule CD39 and suppressed CD8+ T-cell and natural killer cell function, also contributes to resistance to CAR T-cell therapies (Rade et al., 2024). Furthermore, T-cell exhaustion can impede the long-term efficacy of CAR Tcell treatments, highlighting the need for strategies to maintain T-cell fitness and functionality (Schans et al., 2020). The development of immunogenic cell death (ICD)-inducing therapies, which can overcome the non-immunogenic nature of apoptosis, offers a promising avenue for improving immune responses against MM cells (Valle et al., 2019).

Managing toxicities such as cytokine release syndrome (CRS) and neurotoxicity remains a critical concern in CAR-T cell therapy, demanding tailored management strategies and a deeper understanding of their pathophysiology (X. Zhou et al., 2020). These severe adverse events have been observed in clinical trials and can even lead to toxic death, emphasizing the need for improved understanding and established management protocols (X. Zhou et al., 2020).

Mechanism of Resistance	Therapy Type(s) Affected	Description	Implications for Overcoming Resistance

Target Antigen Loss/Downregulation	CAR-T cell, Bispecific Antibodies, Monoclonal Antibodies	Malignant cells reduce or cease expression of the targeted surface antigen (e.g., BCMA, CD38, GPRC5D)	Develop multispecific CAR constructs; identify novel, stably expressed targets; dynamic monitoring of antigen expression (Munawar et al., 2023, 2024; Schans et al., 2020)
Immunosuppressive Tumor Microenvironment (TME)	CAR-T cell, Bispecific Antibodies	High numbers of immunosuppressive cells (e.g., CD39+ monocytes) suppressed immunotherapies effector cell with agents that function (CD8+ T modulate the cells, NK cells) TME; enhance CAR within the TME T-cell functionality and durability	Target immune checkpoints on CAR T-cells; combine and

Genetic alterations in MM cells also play a crucial role in treatment resistance. For example, specific mutations in KRAS (e.g., G12A) can lead to a significant reduction in the surface expression of key immunotherapeutic targets such as BCMA, SLAMF7, and CD38 (Munawar et al., 2023). Similarly, TP53 double-hit situations (inactivating hotspot mutation R282W in a TP53 deletion background) have been linked to a further decrease in BCMA expression and altered cell morphology, potentially explaining reduced susceptibility to BCMA-targeting therapies (Munawar et al., 2023). Recent findings also suggest that G protein-coupled receptor class C group 5 member D (GPRC5D) alterations are associated with the downregulation of CD38 at a post-transcriptional level, leading to reduced sensitivity to CD38-targeting antibodies like daratumumab (Munawar et al., 2024). These findings underscore the importance of dynamically monitoring target antigen expression and considering the impact of secondary genomic events for personalized therapeutic approaches. In the context of bispecific antibodies, resistance can similarly emerge from various factors, including antigen loss, T-cell exhaustion, and high disease burden (Devasia et al., 2024). Ongoing research aims to optimize these therapies and investigate their sequencing to overcome these hurdles (Devasia et al., 2024).

Mechanism of Resistance	Therapy Type(s) Affected	Description	Implications for Overcoming Resistance
			Schans et al., 2020)
T-cell Exhaustion	CAR-T cell, Bispecific Antibodies	T-cells become dysfunctional and lose their ability to effectively kill tumor cells due to chronic antigen exposure or prior treatments	Improve T-cell fitness and persistence; develop nextgeneration CAR Tcells with enhanced proliferative and cytotoxic capacity; combine with Tcell checkpoint inhibitors (Schans et al., 2020)
Genetic Alterations (e.g., KRAS mutations, TP53 double-hit, GPRC5D alterations)	CAR-T cell, Bispecific Antibodies, Monoclonal Antibodies	Secondary genetic events impact surface antigen expression (e.g., reduced BCMA, SLAMF7, CD38) or lead to acquired resistance	Pre-treatment genomic profiling; dynamic monitoring of antigen expression; consider alternative targets or combination therapies based on genetic landscape
			(Rade et al., 2024; (Munawar et al., 2023, 2024)

Targeting the Tumor Microenvironment and Emerging Novel Agents

The bone marrow microenvironment (BMM) plays a pivotal and complex role in the pathogenesis of multiple myeloma (MM), significantly influencing disease progression, drug resistance, and relapse (Solimando et al., 2020). A comprehensive understanding of the MM-bone marrow microenvironment is crucial to tailor personalized approaches, bridging the gap from bench to bedside (Solimando et al., 2020).

Novel small-molecule inhibitors are emerging as promising agents, particularly for relapsed/refractory MM. For instance, the DEAD-box RNA helicase protein 5 (DDX5), an

oncoprotein overexpressed in approximately 75% of MM patients, is being targeted by novel camptothecinanalogs like FL118 and its derivatives (e.g., FL77-32) (Pfitzer et al., 2025). These DDX5 inhibitors induce apoptosis and downregulate myeloma drivers such as MYC and NFkB, showing potent cytotoxicity in a panel of human MM cell lines and ex vivo in primary bone marrow samples (Pfitzer et al., 2025). Another DEAD-box helicase protein, DDX3X, has been identified as a potential c-Myc downstream target in MM, promoting cell survival and proteasome inhibitor resistance by modulating stress granule assembly and MAPKAPK2 translation (Jiang et al., 2024). Inhibition of DDX3X, either genetically or pharmacologically, significantly enhances apoptosis and decreases tumor growth in combination with bortezomib in MM xenograft models (Jiang et al., 2024). These findings underscore the potential of targeting DDX5 and DDX3X to overcome drug resistance and improve outcomes in MM (Jiang et al., 2024; Pfitzer et al., 2025).

Beyond small molecules, innovative therapeutic avenues include engineered oncolytic viruses and strategies to mitigate treatment-induced genomic damage. An oncolytic vaccinia virus variant, BCMA T-cell engager armed neutralization escape variant (BCMA-TEA-VVNEV), has been developed to evade neutralizing antibodies and effectively infect MM cell lines, enhancing tumor lysis and T-cell activation (L. Zhou et al., 2024). This modified virus holds promise for systemic delivery and improved immune-mediated targeting of MM cells, representing a dual approach to eradicate residual tumor cells (L. Zhou et al., 2024). Furthermore, given that genotoxic agents used in MM chemotherapy can induce DNA damage and lead to new driver genomic abnormalities that contribute to drug resistance and relapse, understanding these mechanisms is crucial (Gourzons et al., 2019). Adopting precision medicine and developing biomarkers to limit mutagenic effects and prevent drug-induced DNA damage holds potential for improving disease management (Gourzons et al., 2019).

Mechanism	Target	Development Phase	:—	:—	:—
DDX5 helicase inhibition	DEAD-box protein 5 (Jiang et al., 2024)	Preclinical (Pfitzer et al., 2025)	DDX3X DEAD-box helicase inhibition	Preclinical	RNA (Pfitzer et al., 2025)

		Development Phase			
Mechanism	Target protein 5 (DDX5)	:—	:—	(DDX3X)	:—
Oncolytic virus (BCMA-TEA-VVNEV)	BCMA, T-cell activation	Preclinical (L. Zhou et al., 2024)	Prevention of druginduced DNA damage	DNA repair pathways, genomic stability	Research/ Early Preclinical (Gourzons et al., 2019)

Personalized Medicine and Future Directions

Genetic and molecular profiling are increasingly relevant for risk stratification and to guide treatment decisions in multiple myeloma (MM). Techniques such as fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) provide critical insights into patient-specific genetic aberrations (Marcon et al., 2023). These advancements allow for a more precise understanding of the disease, moving beyond broad categorizations to identify specific subtypes and their implications for therapy (Landgren & Rajkumar, 2016). For instance, experts advocate for revising the Revised International Staging System (R-ISS) to include chromosome 1 abnormality, TP53 mutation/deletion, circulating plasma cells by next generation flow, and extramedullary plasmacytomas to better define highrisk MM (Marcon et al., 2023). This detailed genetic profiling is vital for developing rational and individualized treatment strategies (Landgren & Rajkumar, 2016).

Minimal residual disease (MRD) assessment has emerged as a key tool for monitoring treatment response, predicting relapse, and informing adaptive treatment strategies. MRD negativity has shown a strong correlation with improved progression-free survival and overall survival (Landgren & Rajkumar, 2016). The International Myeloma Working Group (IMWG) response criteria now include MRD negativity as the deepest level of response in MM (Landgren & Rajkumar, 2016). While the application of MRD assessment in guiding treatment strategies is still evolving, particularly within real-world data settings (Marcon et al., 2023), its robust prognostic value allows clinicians to tailor treatment intensity and duration, aiming for sustained remissions and preventing overtreatment or undertreatment. This is particularly important given the heterogeneous nature of MM and the continuous lines of therapy many patients receive throughout their disease trajectory (Chakraborty &Majhail, 2020).

Addressing challenges related to treatment access, managing therapy-related toxicities, considering patient frailty in treatment selection, and investing in further research are crucial for optimizing care and improving outcomes for all MM patients. The availability of novel treatment classes has significantly improved outcomes, yet median survival in relapsed/refractory MM remains approximately 32 months, underscoring the need for continued optimization (Alhuraiji et al., 2025). High treatment costs and limited healthcare infrastructure in some regions, such as India and Ukraine, pose significant barriers to accessing innovative therapies like bortezomib and stem cell transplantation (Nait et al., 2016). Moreover, managing treatment-related complications, including infection and secondary cancers, is a critical component of survivorship care (Chakraborty &Majhail, 2020). Recognizing the high

prevalence of frailty among elderly MM patients, effective assessment strategies are needed to tailor treatment intensity, avoiding both overtreatment and undertreatment (Larocca & Palumbo, 2015). Continued research into novel treatment modalities, improved supportive care, and cost-effective strategies, including high-quality generics, is essential to bridge existing gaps and ensure equitable access to advanced MM care globally (Nait et al., 2016).

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