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Perspective

# Overcoming Resistance in Multiple Myeloma with Nanomedicine

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## DESCRIPTION

Nanostructures have emerged as a transformative platform in drug delivery, providing new hope for tackling complex and resistant malignancies such as multiple myeloma. As a hematologic cancer originating from plasma cells in the bone marrow, multiple myeloma remains incurable despite advancements in chemotherapeutics, immunomodulators and monoclonal antibodies. Relapse and drug resistance continue to pose significant barriers to long-term remission. In this article, nanostructure-based drug delivery systems provide an innovative approach to enhance therapeutic efficacy while minimizing systemic toxicity.

Conventional chemotherapy suffers from limitations including poor bioavailability, rapid degradation, off-target effects and limited accumulation at the tumor site. Nanostructures ranging from liposomes, polymeric nanoparticles and dendrimers to metallic and inorganic nanocarriers can overcome many of these obstacles. They can encapsulate therapeutic agents, protect them from premature degradation and exploit the Enhanced Permeability and Retention (EPR) effect to achieve targeted delivery to tumor tissues. This is particularly advantageous in multiple myeloma, where the bone marrow microenvironment often acts as a sanctuary, shielding malignant cells from systemic therapies.

One of the compelling advantages of nanostructures is their capacity for surface modification. By attaching ligands, antibodies, or peptides, these carriers can be engineered to recognize specific surface markers overexpressed on myeloma cells, such as *CD38*, *SLAMF7*, or *BCMA*. This active targeting mechanism enables selective delivery, potentially reducing the harmful effects on healthy cells and enhancing the therapeutic index. Additionally, nanostructures can be designed for stimuli-responsive release, allowing drug payloads to be released in response to pH, temperature, or enzymatic conditions unique to the tumor microenvironment. Such precision minimizes systemic toxicity and maximizes local efficacy.

Multidrug resistance is another formidable challenge in multiple myeloma, often resulting from the overexpression of efflux transporters or alterations in apoptotic pathways. Nanocarriers can address this by co-delivering multiple agents with synergistic mechanisms of action or by bypassing efflux pumps through endocytosis-mediated cellular uptake. Moreover, incorporating agents such as *siRNA*, *miRNA*, or *CRISPR-Cas9* components into nanocarriers opens the door to gene-silencing and genome-editing strategies, providing a means to downregulate resistance-associated genes or modulate oncogenic pathways directly within the tumor cells.

Despite the vast potential, clinical translation of nanostructure-based therapies faces important challenges. The complexity of nanoparticle synthesis, scalability, potential immunogenicity and long-term safety are areas that require rigorous evaluation. Additionally, variability in the EPR effect among patients and tumor types can limit the consistency of passive targeting strategies. For nanostructures to become mainstream in multiple myeloma treatment, more data from well-designed clinical trials are necessary to validate their superiority over existing therapies.

Nonetheless, early-phase studies and preclinical models provide encouraging evidence. Nanocarriers encapsulating bortezomib, curcumin, or doxorubicin have shown enhanced anti-myeloma effects with reduced systemic toxicity. Some liposomal formulations are already in clinical use for other cancers, suggesting a viable regulatory pathway. The integration of nanomedicine with existing immunotherapies, such as CAR-T cells or bi-specific antibodies, also opens exciting avenues for combination strategies that may reshape the therapeutic landscape.

In conclusion, nanostructures represent a powerful and flexible drug delivery platform with significant potential in the treatment of multiple myeloma. By enabling targeted, sustained and comprehensive therapeutic delivery, they have the potential to overcome drug resistance, reduce adverse effects and improve patient outcomes.

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