

## Novel Targeted Therapies for Multiple Myeloma

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Although high-dose therapy with stem cell transplant has improved complete responses (CR) and survival, multiple myeloma (MM) remains incurable. Novel therapeutic interventions based on improved understanding of the biology of this disease are therefore needed. Improved understanding of myeloma cell survival in its microenvironment has provided such new targets. We are attempting to derive novel biologically based therapies focused upon targeting the MM cell as well as its BM microenvironment to improve patient outcome.

Myeloma cells interact and adhere to the extracellular matrix and to the bone marrow stromal cells (BMSC) through well defined adhesion molecules. These interactions initiate both adhesion-mediated and cytokine-mediated signaling that allows myeloma cells to proliferate, survive and have anti apoptotic effects against conventional chemotherapies. The cytokines involved in these effects include IL-6, VEGF, TNF- $\alpha$ , and IGF-1 amongst others. The molecular signals mediating these effects include the Ras/Raf MAPK cascade for proliferation and the PI3-K/Akt pathway which provides drug resistance signals. This understanding has now allowed us to evaluate novel therapies that not only directly target myeloma cells but also act on the bone marrow microenvironment, specifically, the molecular and cytokine targets, to overcome drug resistance.

In the past four years, we have used the *in vitro* and *in vivo* animal model systems to define novel therapeutic agents directed at both the MM cell and its microenvironment, and have then translated these studies from bench to bedside in the related clinical trials. Thalidomide and its analogous

immunomodulatory agents (IMiDs), proteasome inhibitor Velcade, and Arsenic trioxide (As<sub>2</sub>O<sub>3</sub>), are three such agents which have already demonstrated marked clinical anti-MM activity even in patients with refractory relapsed MM validating the efficiency of our preclinical models to identify novel therapeutics.

Thalidomide and its more potent analogous Revlimid (CC5013), not only act to inhibit angiogenesis and have modest direct effect on MM cells; but it changes expression of adhesion molecules; abrogates the adhesion of MM cells to BMSCs and thereby block the increased secretion of MM growth and survival factors such as IL-6, TNF- $\alpha$ , VEGF and FGF; and additional immune responses by expansion of NK cell number and function against human MM cells. Efficacy of thalidomide has now been demonstrated not only in relapsed patients, but a randomized study has confirmed superiority of combination of thalidomide with dexamethasone over dexamethasone alone in newly diagnosed myeloma patients; paving way for its use as an induction regimen. Based on preclinical results and a derived clinical Phase I trial of Revlimid (CC5013) demonstrating significant anti-myeloma activity, a phase II trial of Revlimid in patients with relapsed/refracting MM has achieved 10% CR, and 25% PR. Another novel class of agents, the proteasome inhibitor, targeting myeloma cell and its microenvironment, has now been validated in preclinical and clinical studies. A large multicenter phase II trial of Velcade, the first in its class agent, in 202 advanced refractory myeloma patients showed 35% response including CRs. Its activity has now been confirmed in a randomized trial demonstrating superior activity of Velcade

as compared to single agent dexamethasone. The genomic and proteomic studies have now identified newer targets such as hsp90 and histone deacetylase in MM.

The recent cellular and signaling studies are now providing the preclinical rationale for combining these novel agents amongst themselves or with other conventional therapies to enhance efficacy. Preliminary results of studies combining these novel agents are providing high response rates including substantial proportion achieving CR or near CR. These novel therapies represent a new treatment paradigm targeting both tumor cells and their microenvironment to achieve greater tumor cytoreduction resulting in a possible cure.