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Monoclonal Gammopathies & Multiple Myeloma

PARTIAL INHIBITION OF NAMPT RESTORES METABOLIC VULNERABILITY AND SYNERGIZES WITH ANTI-MYELOMA AGENTS IN MULTIPLE MYELOMA

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Background: Multiple myeloma (MM) is a metabolically demanding plasma cell malignancy in which resistance to current therapies remains a major clinical challenge. Nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme of the NAD^+ salvage pathway, sustains cellular energetics and redox balance in tumor cells and is frequently upregulated in MM. We previously reported that complete inhibition of NAMPT disrupts NAD^+ metabolism in malignant and normal cells, leading to dose-limiting toxicities that have hindered clinical development. RPT1F is a novel, first-in-class partial NAMPT inhibitor designed to preserve residual enzymatic activity in healthy cells while selectively disrupting NAD^+ homeostasis in tumor cells. This study aimed to evaluate the efficacy and mechanistic synergy of RPT1F, alone and in combination with standard anti-MM agents, in preclinical models.

Methods: RPT1F was first tested on bone marrow mononuclear cells collected from MM patients to assess selective toxicity toward malignant plasma cells ($CD138^+$) versus normal immune subsets ($CD138^-$), including NK, NKT, B lymphocytes, and $CD8^+$/$CD4^+$ T cells. Anti-tumor activity was then evaluated across a panel of genetically and metabolically heterogeneous MM cell lines. Cell viability, apoptosis, NAD^+/ATP levels, and mitochondrial oxygen consumption rate (OCR) were quantified after 24-hour drug exposure. Combination studies with clinically used anti-MM drugs were performed, and drug synergy was analyzed using Bliss independence modeling.

Results: RPT1F induced a dose-dependent reduction in NAMPT activity and NAD^+ levels, leading to marked disruption of bioenergetic homeostasis in MM cells but not in normal immune cells, where metabolic reserve-maintained viability. Strong anti-myeloma activity was observed across all tested cell lines, irrespective of cytogenetic background. Combination of RPT1F with standard agents produced synergistic cytotoxicity characterized by enhanced oxidative stress and impaired antioxidant defenses.

Conclusions: Partial inhibition of NAMPT with RPT1F offers a novel and safer approach to targeting NAD^+ metabolism in multiple myeloma. The combination of RPT1F with different anti-myeloma drugs effectively overcomes apoptotic and metabolic resistance mechanisms, resulting in selective tumor killing without affecting normal cells. These findings support the clinical development of RPT1F based regimens, particularly in metabolically adaptive or drug-resistant MM, and provide a strong rationale for future phase I trials in relapsed/refractory disease.