

Splicing Modulation as an Unintended NMD Inhibition Pathway with Therapeutic Potential in Cancer

Fernando Pastor
Therapeutic Innovation Program, CIMA, **University of Navarra**, Pamplona; CIBERONC, Madrid, Spain
Authors*:
Martin Barainka1, Angelina Zheleva1, Angela Pérez-Cervera1, Helena Villanueva1, Daniel Meraviglia-Crivelli1, Beatriz Moreno1,2, Fernando Pastor1,4

Affiliations*:
1 Therapeutic Innovation Program, CIMA, University of Navarra, Pamplona, Spain.

2 Department of Pathology, University of Navarra, Pamplona, Spain.

3 Instituto de Investigaciones Sanitarias de Navarra (IdiSNA), Pamplona, Spain.

4 CIBERONC, Madrid, Spain.

Background:
Nonsense-mediated mRNA decay (NMD) is an essential RNA quality control pathway that degrades transcripts containing premature termination codons (PTCs), which often result from transcriptional errors or genetic mutations. While the role of NMD in modulating tumor antigenicity and immune evasion is increasingly recognized, its interaction with splicing remains poorly understood.

Methods:
We investigated the effects of the splicing-modulatory compounds MS023 and indisulam on NMD activity and tumor immunogenicity. Mechanistic studies were performed to assess intron retention in the SMG1 transcript, SMG1 protein expression, and overall NMD function. Cytotoxic effects were evaluated in microsatellite instability (MSI) tumor models, and expression analyses in patient tumors were conducted to assess correlations between SMG1 and key splicing regulators (RBM39, SRSF1, and SRSF2).

Results:
MS023 and indisulam promote intron retention in the SMG1 transcript, resulting in reduced SMG1 protein levels and impaired NMD function. This suppression stabilizes PTC-containing transcripts, expanding the pool of immunogenic neoantigens. Splicing modulation also enhances cytotoxic effects in MSI tumors, which are particularly dependent on NMD for survival. Expression analyses in patient tumors reveal strong positive correlations between SMG1 and key splicing regulators, supporting a functional link between splicing and NMD.

Conclusion:
Splicing modulators act as inadvertent NMD inhibitors that simultaneously increase tumor antigenicity and selectively target NMD-addicted tumors. These findings reveal a novel mechanism linking splicing and NMD, offering a promising strategy for cancer therapy.