

Drug-like Molecular Degraders of the Oncogenic RNA-Binding Protein HuR

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Background*:
The RNA-binding protein Hu antigen R (HuR) regulates the stability and translation of oncogenic mRNAs involved in cell proliferation, survival, and metastasis. HuR is overexpressed in many cancers, yet its conformational flexibility has hindered efforts to inhibit its function with traditional small molecules. Targeted protein degradation—via PROTACs or molecular glues—offers a promising strategy to overcome these limitations and achieve selective HuR elimination.

Methods*:
We designed and synthesized a focused library of HuR-targeting degraders using two parallel strategies: (1) cereblon-recruiting PROTACs and (2) molecular glues based on fumarate-derived RNF126 recruiters. Binding affinity was measured by fluorescence polarization, and drug-likeness and pharmacokinetics were predicted using the ADMETlab 3.0 platform. Cellular activity was assessed in 2D and 3D cancer models using Western blotting, RT-qPCR, and functional assays including apoptosis, cytotoxicity, proliferation, and spheroid growth.

Results*:
Two lead compounds, MG-HuR2 (molecular glue) and PRO-HuR3 (PROTAC), bound HuR with nanomolar affinity and induced proteasome-dependent degradation. Both exhibited a biphasic dose-response curve, with high efficacy at low nanomolar and high micromolar concentrations, but diminished activity at intermediate doses—consistent with a “hook effect” from dual-pocket HuR engagement, confirmed by molecular docking. HuR degradation led to significant downregulation of downstream oncogenes including *Bcl2* and *FOXQ1*. MG-HuR2 demonstrated favorable drug-like properties and strong anticancer activity, including suppression of tumor spheroid growth.

Conclusion*:
This work presents the first drug-like HuR degraders capable of efficient knockdown and potent anticancer effects. MG-HuR2 emerges as a promising molecular glue with excellent pharmacological properties and therapeutic potential. These findings highlight RNA-binding protein degradation as a viable strategy in oncology.