ItPS Seminars

28th Feb 2025
3pm CEST

Dr. Peter 't Hart

Max-Planck Institute for Molecular Physiology, Dortmund

Stapled peptide modulators of mRNA processing

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The proper processing of mRNA requires various steps, including capping, splicing, polyadenylation, and transport. These processes are regulated by RNA-binding proteins that are often found to be key players in disease and would therefore make interesting therapeutic targets. However, the structure of such proteins lacks well-defined binding pockets, which is why we use hydrocarbon peptide stapling to develop inhibitors. In the first project where we applied this strategy, we targeted the splicing factor PTBP1. By designing a stapled peptide from a helix that was reported to be important for RNA-binding, we could inhibit the protein allosterically. The peptide was found to be highly cell permeable and could modulate a PTBP1-regulated splicing event in HEK293 cells. In the second project, we targeted the deadenylation complex CCR4-NOT, which is required for the removal of poly(A) tails from mRNA. Again, we were able to develop cell-permeable hydrocarbon stapled peptides that target a core component (CNOT9) of the complex, which not only inhibited RNA-binding but also deadenylation in vitro. Treatment of HeLa cells with an optimized peptide led to stabilization of poly(A) tails. Both projects demonstrate that these challenging targets can be addressed using peptide modalities, creating the possibility to modulate mRNA processing as a novel therapeutic strategy.

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