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MUR PNRR National Center for Gene Therapy and Drugs based on RNA Technology

Spoke 6: RNA drug development

# veRNAdì

## A webinar series about RNA

to share projects and competences,
increase networking, discuss issues
and new ideas, and disseminate results

*Every last Friday of the month*

*https://rb.gy/y40y6*

## XVIII veRNAdì: October 31 2025, 15:30

## Selective targeting of RNAs in Medicinal Chemistry: a balance between pairing and structure recognition

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An ever-increasing interest in nucleic acids for therapeutic applications is emerging. Among several tested designs, a relevant fraction of the so-far approved nucleic-acid-targeted therapeutics share a common molecular mode of action based on the pairing of two nucleic acid strands. This outcome is closely related to the reliable prediction of the energetics associated with strand pairing, which can be derived directly from the target primary sequence. This promising strategy not only accelerates the design of selective oligonucleotide-based drugs but also enables their adaptation to a wide range of diseases and emerging mutations. Nonetheless, it still faces important limitations, primarily related to oligonucleotide stability and biodistribution. An additional, frequently underestimated issue concerns the structural features of both the target and the drug. For example, RNA chains can easily accommodate folded domains that hinder the complementary binding site on the RNA target. This structural issue is further complicated by the potential occurrence of so-called "non-canonical nucleic acid arrangements" which depend on both the primary sequence and environmental conditions. Unfortunately, the predictive capability for these arrangements remains unsatisfactory. However, this structural polymorphism can open novel opportunities for targeted therapies. Indeed, the divergent three-dimensional features of nucleic acid structures are frequently associated with unique recognition by specific cellular components. Moreover, non-canonical nucleic acid folding can be spatially and temporally regulated by the cellular environment, allowing fine-tuned control of selected functions. Last but not least, these structures arise only at specific, well-defined regions of nucleic acids. These observations envisage their exploitation as targets for therapeutic interventions. Here, we will present how different experimental approaches can provide a comprehensive understanding of the functions of these structural elements at the molecular level, and how this knowledge can be used to develop a variety of strategies to ultimately modulate selected cellular pathways.