Development of RNA-Targeting Therapies for Malignant Brain Tumors

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Dr. Krichevsky's lab focuses on small regulatory RNA molecules, microRNAs, their role in brain tumors, and potential as novel therapeutic targets and biomarkers. RNA-mediated intracellular communication between brain tumors and normal cells of their microenvironment is also a main focus of research. Dr. Krichevsky's goal is to develop basic RNA research toward a cure for glioblastoma (GBM) and other brain tumors.

Until recently, biomedical research has entirely focused on proteins and protein-coding genes as building blocks and enzymatic factors underlying human physiology and pathology. Consequently, all current precision medicine approaches are based on protein targeting. However, in recent years it became clear that the human genome is vastly transcribed to non-protein-coding RNA (ncRNA) that play diverse and multiple regulatory functions. In contrast, only 2% of the genome is protein-coding. Targeting regulatory ncRNA species would expand the repertoire of therapeutic targets and the space for drug development tremendously.

The mission of the Krichevsky lab is to explore diverse types of regulatory RNAs in the most devastating human neurologic diseases, including neurodegenerative diseases (such as Alzheimer's) and malignant brain tumors (such as GBM). Our immediate goal is to target GBM dependencies on molecular circuits controlled by regulatory RNAs. The talk will illustrate the potential of ncRNA targeting using microRNA-10b and associated long ncRNAs as an example. Possible therapeutic strategies rely on antisense oligonucleotides and CRISPR-Cas9 gene editing and will pave the road for similar approaches for other malignancies and neurologic disorders.

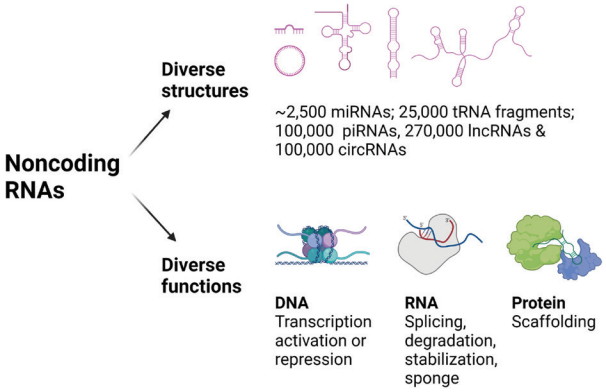

Figure 1. Hundreds of thousands of non-coding RNAs, short and long, with diverse regulatory functions, are expressed from the human genome.

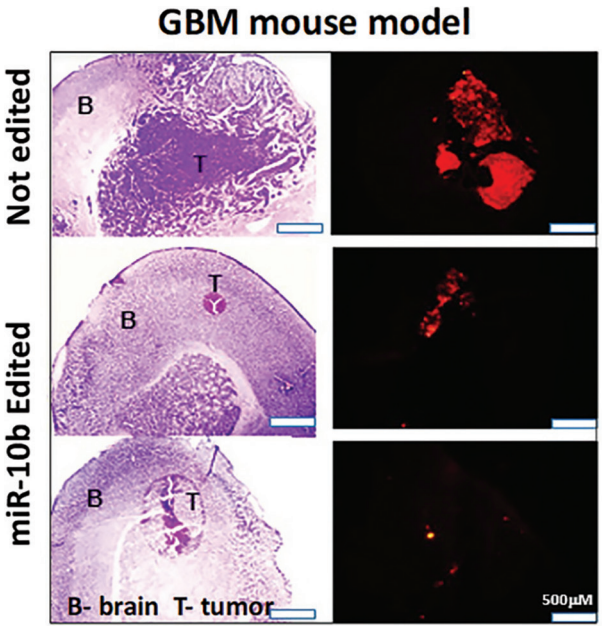

Figure 2. Gene editing of essential miRNA-10b in orthotopic glioblastoma in vivo reduces tumor growth and extends animal survival (El Fatimy … Krichevsky, Mol Therapy 2017).