PRECLINICAL DEVELOPMENT of miR-10b ANTAGONIST FOR THE TREATMENT OF GLIOBLASTOMA

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Abstract

Glioblastoma (GBM) is the most aggressive primary brain cancer with a median survival of 15 months after diagnosis. miR-10b is highly expressed in all GBM molecular subtypes whereas its expression in normal brain cells is nearly undetectable. Herein we report the status of the preclinical development of oligonucleotide antagonists of miR-10b for the treatment of GBM.

A library of 218 anti-miR-10b oligonucleotides with various lengths and chemical modifications was prepared and screened using a luciferase-based cellular miR-10b activity assay and liver slice assay (to assess potential off-target inflammatory effects). Compounds were profiled in vitro using multiple functional assays including selective inhibition of cell viability and induction of apoptosis comparing GBM cell lines and other cell lines lacking miR-10b expression. Nineteen compounds were selected for further evaluation in a xenograft mouse GBM model using human LN229 GBM cells injected intracranially. An anti-miR-10b lead compound exhibited consistent efficacy in vitro and in vivo in all screening assays. A single intratumoral injection of anti-miR-10b lead compound significantly increased median survival of tumor-bearing animals by 18%, while combination treatment with temozolomide (TMZ) extended median survival by 150% (TMZ alone increased median survival by 27%). This anti-miR-10b lead compound exhibits favorable physicochemical properties and in vivo safety profile, which support its further development toward clinical testing. Preliminary mechanistic studies indicate that inhibition of miR-10b in GBM cell lines increased apoptosis/cell death-related and decreased proliferation-related gene expression and had synergistic inhibitory effects with TMZ on tumor cell viability.

Design of Anti-miR-10b Library

- Benchmark with tool compound: CACAGGTTCAGGOTA
- The library includes 218 new anti-miR-10b compounds.
- Length varies from 9 to 30 nucleotides.
- Stabilization chemistries include phosphorothioate (PS), backbone modification and sugar modifications like 2'-O-methyl, 2'-O-methoxymethyl, 2'-fluoro, and 2'-O-(4,4-di-tert-butylphenyl)ethynyl.
- Structure modifications include long miR, short miR, linker miR, seed miR, and prodrug miR.

Unmet Medical Need in GBM

- GBM is the most malignant form of gliomas.
- GBM preferentially affects adults of ages 45-65.
- ~14,000 new cases each year in US and Europe.
- ~15 months median survival with the current standard of care therapy: surgical resection, radiation, and chemotherapy.
- Major treatment hurdles: drug delivery and molecular heterogeneity.

miR-10b is Selectively Up-regulated in GBM

Heterogeneity3.

miR-10b ANTAGONIST FOR THE TREATMENT OF GLIOBLASTOMA

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References