Pharmacological Profile of INT-1B3, a Novel Synthetic microRNA 193a-3p Mimic for Therapeutic Intervention in Oncology
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Introduction

MicroRNAs (miRNAs) are a family of naturally-occurring small, non-coding RNAs and serve as small snippets of genetic material that regulate gene expression. As a result, miRNAs modulate a wide range of biological processes including: cell cycle control and apoptosis, cancer signaling and differentiation, cell adhesion, and motility. Due to the inherent ability of miRNAs to concurrently target multiple pathways, their therapeutic potential to be used as anti-cancer drugs is attractive.

Currently, we are investigating the mode of action and development of a novel synthetic miRNA 193a-3p mimic (INT-1B3), functioning as a tumor suppressor in variety of cancers, targeting multiple hallmarkers of cancer, and representing potential new approach to immunotherapy as our therapeutic candidate.

Concluding Remarks

➢ Identification of a novel LNP formulation for efficient in vivo delivery of functional miRNA in experimental tumors upon systemic administration
➢ Anti-tumor activity (tumor growth inhibition) demonstrated in human tumor xenograft models
➢ Pronounced immune-oncology characteristics, with modulation of immunosuppressive tumor microenvironment and T-cell dependent-long term immunity against cancer cells
➢ Selection of INT-1B3 as Interna’s development candidate for therapeutic intervention in HCC, melanoma and/or TNBC

Future prospective:
- Confirmatory studies in various syngeneic tumor models
- IND-CTA-enabling activities (CMC and pharmacology)
- IND/CTA preparation

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Results

INT-1B3 mode of actions in vitro settings

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Focus (on-treatment vs. control)</th>
<th>Reactive effect (on-treatment vs. control)</th>
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<tbody>
<tr>
<td>INT-1B3</td>
<td>Cytotoxicity</td>
<td>Apoptosis</td>
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INT-1B3 has been tested in cell-based assays in a variety of cell lines. Different concentrations (1, 3, 10 nM) of INT-1B3 were taken along with proper controls (untreated, mock and scrambled). The 10 nM dose served concentration for in vitro assays are shown in the table. The data points in the graph represent the trend observed at that concentration. The 72 and 96 h post-transfection, results have been summarized.

INT-1B3 anti-tumor activity

Experimental design

A) Tumor growth inhibition

- Tumor growth inhibition of orthotopic implanted A549 tumors

B) Target engagement in tumor samples

- miRNA expression analysis in tumor samples

INT-1B3 targets pivotal oncogenes to induce cell death and apoptosis

- A549 and SNU449 tumor cell lines

- *p < 0.05

- **p < 0.01

- ***p < 0.001

INT-1B3 targets pivotal oncogenes to induce cell death and apoptosis

A vast number of predicted INT-1B3 target genes based on our in vitro miRNA array data and online databases were tested and outlined using a variety of cell lines. This graph shows a large panels of oncogenes target by INT-1B3 and are 50% or more-downregulated compared to the untreated control. Different concentrations of INT-1B3 (0.5, 1 and 10 nM) and proper controls were tested at different time points (24, 48, and 72 h). The INT-1B3 results are shown and results have been corrected to mock.

Cell line: A549 Lung cancer (NSCLC); SNU449 Liver cancer (HCC)
Target gene: APC, EMT, Survivin, and TIMM4 (in cell cycle and cell proliferation; KDR, Oncogene, NTRK3 (CD73); Enzyme involved in adenosine generation pathways)

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