Mouse Renca Renal Cell Carcinoma Syngeneic Model to Evaluate Efficacy of Novel Antisense Oligonucleotides Targeting Transforming Growth Factor beta (TGF-β) Isoforms


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Background: Transforming Growth Factor beta (TGF-β) represents a family of cytokines, which function as the primary mediators for TGF-β signaling via TGF-β receptor type II (TβRII) and both non-canonical and canonical downstream signaling pathways. TGF-β is associated with a wide range of biological processes in oncology, including tumor cell invasion, migration, angiogenesis, immunosuppression, as well as regulation of tumor stem cell properties. Hence, optimal preclinical evaluation of efficacy of TGF-β antagonists is challenging. Isarna Therapeutics has designed and developed selective and potent LNA-modified antisense oligonucleotides targeting the various TGF-β isoforms. In order to adequately evaluate selected preclinical development candidates, Oncodesign has developed customized experimental mouse Renca renal cell carcinoma models in syngeneic and/or immunodeficient mice. The Renca cell line was established from a murine transplantable renal adenocarcinoma of spontaneous origin, and has been used under various experimental conditions: (1) subcutaneous tumor model by inoculating cells into the flanks of the animals; (2) the pulmonary metastatic tumor model by an intravenous injection of cells into the tail vein; and (3) the orthotopic tumor model by injecting cells into the renal subcapsule (and subsequent pulmonary metastasis). Outcome of this development program and preliminary results for selected TGF-β antisense oligonucleotides are presented and discussed.

Figure 1: The role of TGF-β in tumor development (multi-modal tumor-promoting effects)

Figure 2: TGF-β and TGF-β2 mRNA expression following gynnotic delivery of selected TGF-β isoforms

Figure 3: Survival of Balb/c mice bearing orthotopic (kidney) mouse Renca RCC tumors

Figure 4: Development of lung metastasis model (i.v. administration of Renca cells) in Balb/c and Balb/c nude mice

Figure 5: Effect of systemic treatment of Balb/c mice with ASPH_0047 (selective TGF-β2 antisense oligonucleotide) on lung metastasis in orthotopic (kidney) mouse Renca RCC model

Figure 6: Effect of systemic treatment of Balb/c mice with ASPH_0047 (selective TGF-β2 antisense oligonucleotide) on lung metastasis in i.v. mouse Renca RCC model

Conclusions:
1. Marked downregulation of TGF-β2 and TGF-β1 mRNA after gynnotic delivery of ASPH_0047 and ASPH_1047, respectively, in mouse Renca RCC cell-based assays
2. Syngeneic Balb/c mice developed significant number of lung metastases when mouse Renca RCC cells were injected i.v. or subcutaneously, or based on lung weight.
3. Confirmed trend in reduction of lung metastasis number (and consequently lung weight) in syngeneic Balb/c mice bearing orthotopic (kidney) mouse Renca RCC tumors and mice injected i.v. with Renca cells following systemic treatment with ASPH_0047, and not control scrambled oligonucleotide.
4. Administration route and/or treatment schedule for ASPH_0047 may require some further optimization (e.g., based on tissue PK data) to increase inter-studies reproducibility and consistency.
5. Fast-growing tumors in syngeneic models make it difficult to study potential immune-related effects of selected oligonucleotides as treatment window spans only 2-3 weeks.

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b. Use of LNA-modified gapmers is performed under a license from Santaris Pharma.