Mouse 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 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-β mRNA expression following gynmotic delivery of selected TGF-β oligonucleotides constructs in mouse Renca RCC cell-based assays

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 genetic 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. and to a lesser extent in Balb/c nude mice.
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.