Sirnaomics

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Opening new frontiers in immuno-oncology with RNAi therapeutics

Biopharmaceutical firm Sirnaomics is developing RNAi-based therapies to target proteins in diseases including liver cancer, squamous cell carcinoma, and non-small cell lung cancer.

Sirnaomics is pioneering the use of RNA therapeutics in the treatment of cancer. Using its polypeptide nanoparticle (PNP) delivery platform, the biotech delivered the first positive phase 2a clinical trial of RNA interference (RNAi) technology in a cancer indication. The study validated the combination of two siRNA inhibitors dosed simultaneously in one product, opening the door to the progression of sibling compounds and initiation of checkpoint inhibitor combination trials.

PNP provides high delivery and packaging efficiency, simple and stable formulation, and the ability to target cells beyond the hepatocytes of the liver. In its two lead cancer assets, STP705 and STP707, Sirnaomics is using the technology to deliver two siRNA oligonucleotides to knock down TGF-β1 and COX-2 gene expression.

TGF-β1 and COX-2 are gatekeeper targets for oncology. TGF-β1 regulates a range of cellular processes, including proliferation, and COX-2 is a proinflammatory and proliferative mediator. In 2018, researchers found TGF-β, which is elevated in the tumor microenvironment, reduces the ability of T cells to penetrate tumors, thereby reducing the effect of immuno-oncology agents.

Building on the findings, Sirnaomics studied intravenous doses of the combination of the TGF-β1/COX-2 siRNAs in STP707 in a hepatocellular carcinoma model. The study found the oligonucleotides reached the liver and caused marked tumor regression through extra penetration of CD4 and CD8 positive T cells (Fig. 1). Immunohistochemistry showed the T cells entered the tumor microenvironment much more aggressively after treatment with STP707. Both treatment with the two siRNAs in STP707 or the combination with immune checkpoint inhibitors (at a lower dose of STP707) completely abolished hepatocellular carcinoma after 3 to 7 doses twice a week (bi-weekly).

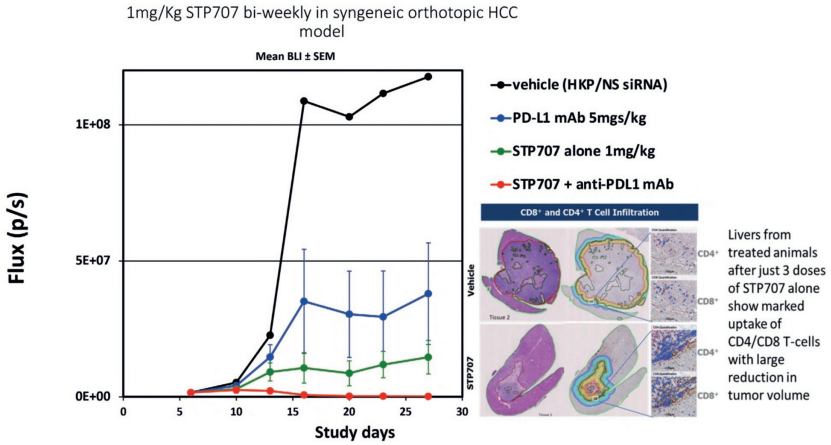

Fig. 1 | A graph showing the results of a study that targeted tumor proteins using siRNAs STP707 alone, or in combination with immune checkpoint inhibitors. mAb, monoclonal antibody; HCC, hepatocellular carcinoma.

The stepwise validation strategy

Sirnaomics has taken a stepwise approach to clinical development of the combination of two siRNAs formulated in one product, starting by validating its approach in humans with the locally administered STP705 and then advancing the systemically delivered STP707.

STP705 is the landmark therapy that provided the first positive cancer phase 2a for RNAi technology. In the phase 2 cutaneous squamous cell carcinoma in situ (isSCC) clinical trial, Sirnaomics showed direct administration of STP705 to diseased tissue silenced expression of TGF-β1 and COX-2. The gene silencing drove suppression of cellular proliferation, tumor progression, and development, with 90% of subjects experiencing complete histological clearance in the two high dose cohorts.

Based on the data, Sirnaomics began a 100-subject phase 2b isSCC clinical trial in the United States in May 2021 to assess the two most efficacious dosing regimens identified in the earlier program against placebo. Initial results data are due in the second half of 2022.

The route of administration and mechanism of action of STP705 suggest the candidate also has a future in the treatment of basal cell carcinoma (BCC). Sirnaomics demonstrated that STP705 triggered such a response in a phase 2 BCC clinical trial. STP705 treatment also has the benefit that it improves the appearance of the skin post—administration in comparison to the alternative procedure which often leaves a scar. Scarring can be an issue because most of the lesions are on exposed regions of the skin, such as the face or upper body.

Sirnaomics' STP705 data validated the targeting of TGF-β1 and COX-2 and the ability of the nanoparticle platform to deliver siRNA to certain cell types. Through the validation, the biotech made the case for the development of STP707, a drug candidate that reaches the same genes but is given systemically and uses a different carrier peptide.

The changes position STP707 to treat solid tumors such as liver cancer, squamous cell carcinoma, and non-small cell lung cancer. Phase 1 clinical trials of the candidate are underway in the United States and China.

Immuno-oncology combinations

The ability of Sirnaomics' unique combination of two siRNAs to increase penetration of CD4/CD8 positive T cells into tumors suggests the molecules will work synergistically with immuno-oncology agents. Sirnaomics provided preclinical validation for that hypothesis when it studied STP707 in combination with anti-PD-L1 monoclonal antibodies in liver cancer models (Fig. 1).

At the original dose (2 milligrams/kilogram), STP707 was able to show single agent action, inhibiting the tumors completely over 7 injections bi-weekly. By halving the STP707 dose, Sirnaomics was able to show the molecule works synergistically with anti-PD-L1 antibodies, driving the biotech to make checkpoint inhibitor combination trials part of its strategy.

As Sirnaomics executes the strategy, it will deliver data readouts on STP705 and STP707 over the coming months in preparation for the potential rollout of isSCC trials globally in 2023. Successful delivery of the milestones will confirm Sirnaomics' position as a global leader in the use of RNA to treat cancers and open new frontiers for immuno-oncology drug development.

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