TransCode Therapeutics, Inc.
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TRANSCODE THERAPEUTICS™

Delivering on the promise of RNA therapeutics in oncology

TransCode Therapeutics has developed an iron oxide nanoparticle–based therapeutic RNA delivery system that maximizes targeted tumor uptake while minimizing clearance. With a lead candidate in metastasis and several preclinical programs targeting other cancers, the company is rapidly expanding its portfolio.

RNA oncology company TransCode Therapeutics has developed a modular, iron oxide nanoparticle–based nanocarrier system for the delivery of RNA therapeutics to tumors. The platform overcomes issues of stability, efficiency, and immunogenicity faced by existing lipid and liposomal nanoparticle platforms while optimizing targeting of and accumulation in tumor cells and metastatic sites.

The company's lead therapeutic candidate, TTX-MC138, targets microRNA-10b (miRNA-10b), a master regulator of metastatic cell viability in a range of cancers, including breast, pancreatic, ovarian, colon cancer, glioblastomas, and others. TTX-MC138 is entering an exploratory investigational new drug (IND) application in the first half of 2022. TransCode plans to finalize IND-enabling studies for TTX-MC138 in the second half of 2022.

The company's other preclinical programs include two solid tumor programs—TTX-siPDL1, a small interfering RNA (siRNA)–based modulator of programmed death-ligand 1 (PD-L1), and TTX-siLin28b, an siRNA-based inhibitor of RNA-binding protein LIN28B. TransCode also has three cancer agnostic programs—TTX-RIGA, an RNA-based agonist of the retinoic acid-inducible gene I (RIG-I)–driven immune response in the tumor microenvironment; TTX-CRISPR, a CRISPR/Cas9-based therapy platform for the repair or deletion of cancer-causing genes inside tumor cells; and TTX-mRNA, an mRNA-based platform for the development of cancer vaccines that activate cytotoxic immune responses against tumor cells.

"While RNA therapeutics could potentially have a tremendous impact on cancer patients, the necessary step of RNA delivery has remained a formidable hurdle for translation," said Michael Dudley, co-founder, and CEO of TransCode. "We believe our TTX delivery platform could finally help resolve this challenge and launch tremendous opportunities across a range of indications."

A therapeutic (re)purpose

The therapeutic potential of RNA in oncology remains an unrealized promise due to the difficulty in safely and effectively delivering RNA oligonucleotides to tumors. TransCode is now closer to solving this challenge by means of an ingenious exercise in repurposing. The company has developed an RNA delivery platform, the TTX platform, which leverages an iron oxide nanoparticle already approved as a clinical cancer imaging agent and a treatment for iron deficiency anemia as the physical carrier.

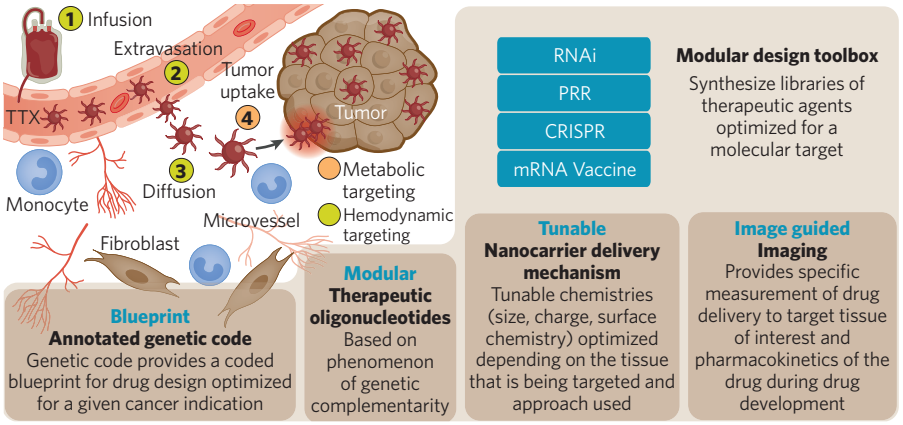

Fig. 1 | The TTX delivery system. The mode of action (top left) of the delivery system and its benefits. PRR, pattern recognition receptors; RNAi, RNA interference.

The TTX delivery system is built around a core iron oxide nanoparticle that minimizes kidney and liver clearance, which translates into a long circulation half-life that allows for efficient accumulation in tumor cells and metastatic sites (Fig. 1). These particles have an excellent clinical safety record of low toxicity and low immunogenicity, and their built-in imaging capabilities have the bonus of enabling quantification of the particles' delivery to target organs. The iron oxide cores are functionalized with amino groups to provide stable links through disulfide bonds to the therapeutic oligonucleotides of interest. The core iron oxide–oligonucleotide complex is further coated with dextran, a glucose polymer, to protect the oligonucleotides from degradation and to provide overall stability to the particle.

The small hydrodynamic size and positive charge of the resulting nanoparticles allows them to infiltrate the tumor microvasculature, extravasate into the interstitium of tumors and metastases, and be readily taken up by the cells. The coating with dextran further facilitates the rapid uptake of the particles by exploiting the high avidity of cancer cells for glucose, a process analogous to the mechanism behind the systemic loading of metastatic cancer cells with fluorodeoxyglucose for diagnostic PET imaging. The combined result of a hydrodynamically favored distribution and a metabolically triggered uptake result in the enhanced ability of TransCode's nanoparticles to access genetic targets inside tumor cells.

A modular approach for new RNA therapies

The TransCode TTX platform for RNA cancer therapeutic development is modular by design, both at the level of the core nanoparticle and of the therapeutic loading. The size, charge, and surface chemistry of the core nanoparticle can be tuned to optimize the particles for the intended target and therapeutic load. The therapeutic load can also be adapted to the specific application being developed, ranging from siRNAs, antisense oligonucleotides, and non-coding RNA mimics to mRNA–based cancer vaccines and CRISPR–based gene repair and replacement platforms. The platform can further be used for developing RNA-targeted radiolabeled therapeutics and diagnostics and other custom products targeting known and novel genetic biomarkers.

"With TTX-MC138 going into first-in-human studies later this year, and several of our other development programs rapidly advancing to the pre-IND stages, we feel we are getting closer to our goal of overcoming the obstacles of RNA delivery in oncology," said Dudley. "We are looking forward to further unlocking its therapeutic potential to develop solutions for patients worldwide."

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