Exicure, Inc.
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Exicure uses its proprietary spherical nucleic acids to treat disease at its genetic source

The clinical-stage biotechnology company has pioneered the development of 3D spherical nucleic acids to treat a broad range of inflammatory disorders affecting multiple organs in the body.

Psoriasis is a common, chronic skin disease that affects at least 100 million individuals worldwide. This inflammatory disease is painful and disabling, causing red, scaly patches to appear on the skin, typically on the elbows, knees, or scalp. The negative impact of this condition on people's lives can be immense. There is no cure, and currently available therapies only manage symptoms. Moreover, the most commonly prescribed biologic significantly increases the patient's risk of infection and elicits the production of antibodies, rendering the treatment ineffective.

Exicure is harnessing the potential of nucleic acid therapeutics to stop psoriasis and other inflammatory conditions at their genetic source. The clinical-stage biotechnology company has pioneered the development of 3D spherical nucleic acid (SNA) technology to safely and effectively penetrate multiple organs and deliver oligonucleotides to specific disease tissues. Exicure's pipeline for inflammatory skin disorders includes two gene regulation therapies that enter the skin after topical application and stop the production of proteins that trigger the inflammatory cascade. The company is also applying the same principles to develop SNA-based therapies for inflammatory conditions affecting the eye, gastrointestinal tract, and lung.

AST-005 successfully completes phase 1 trial

Exicure's most advanced drug candidate is AST-005. This topical treatment consists of an SNA containing antisense oligonucleotides that reduce levels of tumor necrosis factor-α, an inflammatory protein known to have a major role in the development of a variety of inflammatory disorders, including psoriasis. Exicure has now completed its phase 1 clinical trial of AST-005. The trial was a 15-subject micro plaque study wherein over two weeks each subject was dosed with three different strengths of AST-005 as well as both positive and negative controls. A dose response was demonstrated across all three dose strengths of AST-005, with statistically significant knockdown of *TNF* mRNA at the highest dose. This successful knockdown of mRNA in the skin is an important milestone in the history of nucleic acid therapeutics, a field in which the preponderance of clinical targets have been in the liver.

The 3D architecture of SNAs significantly broadens the versatility of nucleic acid therapies. In particular, SNAs enter cells in high quantities through class A scavenger receptors, which reside on the surfaces of many cells throughout the body. This key advantage creates opportunities for nucleic acid therapeutics targeted to organs other than the liver, making SNAs suitable for treating the more than 200 skin diseases with a monogenetic origin, in addition to inflammatory bowel disease, macular degeneration, infectious diseases, and other conditions affecting the immune system.

Moreover, nucleic acid therapies offer a faster, more economical path to drug discovery compared with small molecules or antibody-based drugs. Using computer-based digital design tools, Exicure can go from target identification to investigational new drug (IND) in under 12 months. Exicure's platform combines the fast development times of nucleic acid therapeutics with the fast clinical development times of dermatology drugs. The progression of AST-005 from drug candidate nomination to completion of the phase 1 trial took less than 18 months and cost less than $5 million. Exicure's next clinical candidate is XCUR-17, an antisense drug targeted to *IL17RA*. XCUR-17 is expected to enter a phase 1 trial for psoriasis in 2017.

SNA architecture increases safety and efficacy

SNAs consist of densely packed synthetic nucleic acid sequences radially arranged on the surface of a nanoparticle (**Fig. 1**). Unlike linear forms of nucleic acids, SNAs enter cells without the toxicity associated with lipid- or polymer-based encapsulation or transfection agents. Gene regulation therapies based on the SNA platform combine the specificity of biologics with the safety of topical preparations. Local delivery of the SNA therapeutic eliminates systemic exposure to the drug and reduces the amount of drug required to elicit a therapeutic response. Additionally, unlike currently available nucleic acid therapeutics, SNA-based therapeutics reduce the amount of chemical modification required to produce intracellular stability and thus also limit unwanted inflammatory responses. The 3D architecture of the SNA protects it from cellular proteins that degrade the nucleic acid and inhibit efficacy once the SNA is within the cell.

SNAs: a powerful new therapeutics modality

Beyond offering a more favorable safety profile, SNAs can also be formed with a wide variety of nanoparticle cores and with almost any nucleic acid sequence. This 'third way' of pharmaceutical development can be applied to therapeutic targets that were previously inaccessible to small molecules or antibodies.

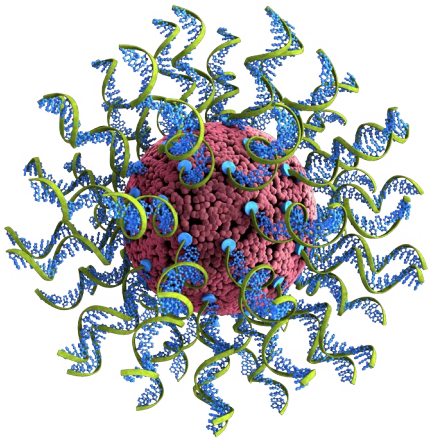

Figure 1: Spherical nucleic acid structure. Synthetic nucleic acid sequences are radially arranged on the surface of a nanoparticle.

Not only has the company harnessed this capability to develop therapeutics for gene silencing therapies, but it is also designing SNAs to upregulate the immune system. Exicure's clinical candidate AST-008 is an SNA targeted at *TLR9* and is designed to be an immune-system agonist in an array of immuno-oncology applications. AST-008 is expected to enter a phase 1a trial in 2017. Currently, Exicure is seeking to further expand its pipeline to realize the vast potential of its 3D SNAs to treat a broad range of diseases with great unmet medical need.

"Exicure now stands poised to capitalize on its proprietary SNA platform by leveraging 20 years of accumulated research and development into the field of nucleic acid therapeutics," said Exicure's CEO, David Giljohann. "We look forward to pairing the attractive economics of nucleic acid therapeutic development with the platform potential of the SNA to rapidly expand our therapeutic offerings."

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