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Editorial

RNA-based therapies have their day

In both the United States and Europe, regulatory agencies are on the verge of approving the first human therapeutic drug based on RNA interference (RNAi) technology. The investigational drug under consideration, patisiran, is being developed for the treatment of hereditary transthyretin amyloidosis (hATTR amyloidosis). Results from a phase 3 clinical trial (APOLLO; ClinicalTrials.gov number NCT01960348) have just been published in the July 5th, 2018 issue of *The New England Journal of Medicine*, demonstrating promising and clinically-meaningful improvements in both primary and secondary patient endpoints based on alleviation of hATTR amyloidosis symptoms. This debilitating, multi-systemic disease affects an estimated 50,000 people worldwide, and is caused by an accumulation of misfolded transthyretin protein amyloids in tissues throughout the body. Patisiran works by inhibiting the expression of transthyretin within the liver, via RNAi-based targeting of mutant ATTR transcripts—and effectively blocking production of the source of the amyloids.

Since its discovery as a natural cellular defense mechanism 20 years ago, and before the advent of nuclease-based genetic manipulation methods such as CRISPR, RNAi clearly revolutionized the way scientists study gene functionality. RNAi has been hailed as an invaluable basic science research tool due to the relative specificity of silencing and ease of customization. It is these same features that has made RNAi an attractive approach to manipulate gene products in the context of human diseases. Several other late-phase RNAi studies are currently underway, including additional liver-targeted therapeutics such as an antithrombin-lowering drug to treat hemophilia and a drug targeting PCSK9 to treat hypercholesterolemia.

As with many drugs, targeting and delivery of RNAi-based therapies remain as substantial challenges in the field. Several of the more advanced therapeutic candidates in the pipeline are composed of lipid-based nanoparticle formulations or employ N-Acetylgalactosamine conjugation to target the RNA to the liver. Key remaining hurdles include achieving targeted delivery to organs beyond the liver (such as heart, lung and kidney) whilst maintaining stability in the blood, and avoiding glomerular filtration by the kidneys. Once successfully inside a given target cell, additional challenges include avoiding endosomal degradation and unwanted stimulation of innate signaling pathways.

A recent paper in the June 2018 issue of *Science Advances* showed successful multi-organ, endothelial cell-targeted delivery of siRNA in non-human primates using nanoparticles formed from an ionizable low-molecular weight polymer, 7C1. With these and other lipid- and polymer-based delivery systems in development, there is hope for moving RNAi treatments beyond the liver to address a wide range of diseases with known genetic etiology, including cardiovascular and metabolic diseases. RNAi-based treatment of solid tumors is also being explored, with the aim of modulating specific gene-products involved with immune response, growth factors, and tumor metabolism. In addition to delivery, avoiding non-specific toxicity and ensuring intracellular stability, accumulation, and potency specifically within the target cells are also high priorities.

There are some interesting recent advances on the potency front, however, and these findings should help researchers working on RNA therapies including and beyond RNAi-based systems. A recent article published on August 3rd in the journal *Science* highlights a reagent system which allows for more uniform chirality in the synthesis of nucleotide-based drugs, due to improved stereo-control of the phosphorothioate linkages along the RNA backbone. This is important from a therapeutic perspective, because the "shape", or chirality, of a given RNA-based therapeutic can potentially affect its potency and effectiveness, and even perhaps its safety.

Chirality may be especially important when considering another class of RNA-based drugs known as cyclic dinucleotides, or CDNs. CDNs have shown encouraging results in preclinical models for helping to turn a tumor from being immunologically "cold" to immunologically "hot" by binding to and stimulating a key component of the innate immune response within the cell called stimulator of interferon genes (STING). The premise is that by kickstarting the innate response within the tumor via STING activation, this will in turn lead to activation of the adaptive (T-cell based) immune response to the tumor, which should in theory help make T cell-based immunotherapies such as checkpoint inhibitors work more effectively. CDN-based STING agonists are now entering phase 1 clinical trials (both alone, or in combination with checkpoint inhibitors) for several cutaneously accessible tumors.

EBioMedicine will be following the development of these and other RNA-based therapies with great interest. This field shows immense promise for collaborative and translational synergy amongst several biomedical-, and even materials-science fields. As always, we hope to be a home for these collaborations and discussions, and would love to hear your ideas on how to move this field forward.

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