Molecular Therapy
Nucleic Acids
Commentary

siRNA goes after diseases of the bone

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Genomic medicine has revolutionized medicine with several FDA-approved drugs and many more in clinical development. siRNA is one important class of genomic medicines that has received intense interest since the approval in 2018 of Onpattro for amyloidosis. In addition, the use of GalNAC conjugated delivery to hepatocytes has resulted in numerous preclinical and clinical development programs and 5 approved drugs.[1] There are several advantages to siRNA and include more rapid drug development timelines and higher specificity relative to small molecule or antibody drugs. One major limitation to achieving the full potential of siRNA is extrahepatic delivery. Several academic labs and pharmaceutical companies are working on this problem with various delivery methods. Promising methods for delivery to extrahepatic tissues include direct conjugation[2] or by non-viral delivery.[3] siRNA can be directly conjugated to an antibody, lipid, or other targeting moiety. Another approach is to encapsulate the siRNA in a nanoparticle, such as a lipid nanoparticle or exosome. Both methods have pros and cons associated with them, which include safety considerations and tissue exposure. Even though these methods help to increase the delivery to extrahepatic tissues, most of the dose still goes to the liver.

Targeting cells of the bone has been pursued since the last century with important implications in treating skeletal diseases. There have been significant strides made in targeting bone, but challenges still exist. A few approaches have been used to some effect, which include engineered exosomes with a bone-targeting peptide[4] or nanoparticles with bisphosphonates or aptamers.[5] However, several limitations exist such as systemically delivered nanoparticles being trapped in the liver and spleen and the low vascular perfusion of bone. In addition, there has been work on targeting specific cells of the bone, such as osteoblasts and osteoclasts. One group used aptamer-conjugated nanoparticles to selectively target osteoblasts.[6] Some additional limitations with current approaches also include safety concerns such as gastrointestinal distress or calcium toxicity. Better approaches to selectively target bone for the delivery of siRNAs to treat skeletal diseases are warranted.

The article in a recent issue of *Molecular therapy – Nucleic Acids* by Maurizi et al.[7] shows a promising approach to target diseases of the bone. In this paper, the authors developed a nanoparticle formulation to deliver siRNAs to bone for the treatment of autosomal dominant osteopetrosis (ADO). ADO is one of 400 rare bone diseases with only a few having any therapies. A single mutant gene has been identified as the cause for several of these diseases, which makes the use of more recent developments in genomic medicine, such as siRNA, optimal therapeutic modalities. ADO is caused by mutations in the CLCN7, which is a chloride channel, and it results in a range of symptoms from asymptomatic to bone pain and fractures. Several treatments exist but do not treat the underlying genetics of the disease, which siRNA would be able to do.

The nanoparticle used in the study by Maurizi et al. circumvents some of the current limitations for selective bone targeting. The novel use of a silicon-based drug delivery system allows for, at least in rodents, robust encapsulation of siRNAs and a good safety profile. One limitation of this study was the most robust siRNAs reduced the mutant gene by only 50%. This may be due to the use of unmodified siRNAs, which have been shown to be less potent than fully chemically modified versions. Currently, FDA-approved drugs have shown that fully chemically modified siRNAs are more resistant to degradation by endonucleases, decrease immunogenicity, bind to the RISC complex more tightly, and have minimal toxicity.[1,8] The nanoparticle formulation does protect the siRNAs from serum degradation and helps with cellular uptake. However, the observed 50% reduction in the mutant version of the CLCN7 gene was sufficient to observe a phenotypic improvement in the mouse model. Increasing the ultimate incorporation of siRNA into the RISC complex may increase the total reduction in the amount of the mutant protein. Understanding how these particles are internalized and possibly the use of endosomal escape agents may increase the total reduction of the pathogenic protein. One other consideration is the number of doses the authors used in their *in vivo* studies. They injected the animals 3 times every week for up to 4 weeks. Current siRNAs that are FDA approved are injected every 3 months.[1] The low duration of effect could have several reasons and requires additional work to optimize as this platform is developed further.

Another limitation of this study was that only 15% of the injected dose reached the bone, with half the dose being trapped in the liver. Next generations of this delivery platform will hopefully increase the injected dose that reaches the bone. One advantage of this approach was that the authors observed no major safety signals, such as no changes in animal behavior or body weight. The authors only reported on rodent studies and short-term dosing studies. It will be of interest to see how this new delivery platform behaves with more chronic dosing in larger animals and ultimately human studies. Even though silicon-based nanoparticles have been used before, the safety aspects are incompletely understood with the studies drawing inconsistent results. The long-term safety of silicon-based nanoparticles should be further explored.

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Rare diseases in general, and skeletal diseases specifically, need better treatments to improve the quality of life for those people suffering from them. The application of genomic medicine, such as siRNA, holds great promise in the treatment of these indications. But delivery has always been a hurdle to fully realize the potential of genomic medicine. The article by Maurizi et al. adds to the tissues that siRNA can reach and the indications that can be treated. Beyond using this platform to deliver treatments for skeletal diseases, it could potentially be used for bone regeneration applications. It will be interesting to see how this new bone-targeting delivery platform stands up to the rigors of clinical development.

DECLARATION OF INTERESTS

I am an employee of and own stock in Abbvie.

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