Development of oligonucleotide aptamer therapy for achondroplasia

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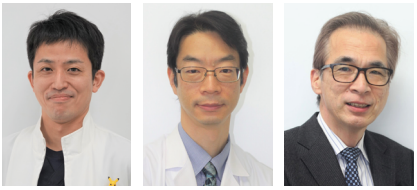

Abstract

Achondroplasia (ACH) is the most prevalent genetic form of dwarfism in humans, caused by activating mutation in *FGFR3* tyrosine kinase. The clinical need for safe and effective inhibitor of FGFR3 is currently unmet, leaving ACH an incurable condition. We evaluated the RBM-007, a RNA aptamer developed to neutralize the FGFR3 cognate ligand, FGF2, for its activity against FGFR3 signaling in cartilage. In cultured chondrocytes and in cartilage xenografts derived from ACH-iPS cells, RBM-007 rescued the proliferation arrest and aberrant chondrocyte differentiation and maturation in the growth plate cartilage. When delivered by subcutaneous injection, RBM-007 restored defective bone growth in mouse model to ACH.

Background & Results

Achondroplasia (ACH) is the most common dwarfism in humans, occurring in 1: 25,000 live births. ACH is caused by mutations in the FGFR3 gene, which encodes a transmembrane receptor tyrosine kinase. No therapy exists for ACH except for growth hormone, which is approved for ACH in Japan and shows limited effect. Although several experimental approaches for targeting FGFR3 are being tested, including small chemical inhibitors of FGFR3 catalytic activity or biomolecules targeting downstream pathways of FGFR3 signaling, there is no definitive therapy for ACH.

In this study, a RNA aptamer named RBM-007 are examined as potential drug for ACH. Aptamers are short RNA or single-stranded DNA oligonucleotides that can bind to their targets like antibodies and are functionally used as antagonists, agonists, or targeting ligands. RBM-007 can bind human FGF2 specifically and does not affect other FGFs.

We show that neutralization of FGF2 ligand by RNA aptamer RBM-007 restores defective bone growth in FGFR3-related skeletal dysplasia in mice. RBM-007 inhibited activation of FGFR3 signaling in cultured chondrocytes in vitro as well as in tibia organ cultures and cartilage xenografts differentiated from hiPSCs derived from individuals with ACH. More importantly, when administered to mice, the RBM-007 restored defective skeletal growth in the ACH model.

Significance of the research and Future perspective

We demonstrate an approach to target FGFR3 signaling in skeletal dysplasia based on a ligand-trap concept. RBM-007 could potentially be used for full restoration of skeletal growth in patients with ACH, although this remains to be tested in future studies.

RBM-007 is already undergoing a clinical evaluation in the United States (NCT03633084 and NCT04200248), and a clinical trial program for ACH treatment was initiated in Japan in July 2020 (JapicCTI-205345).

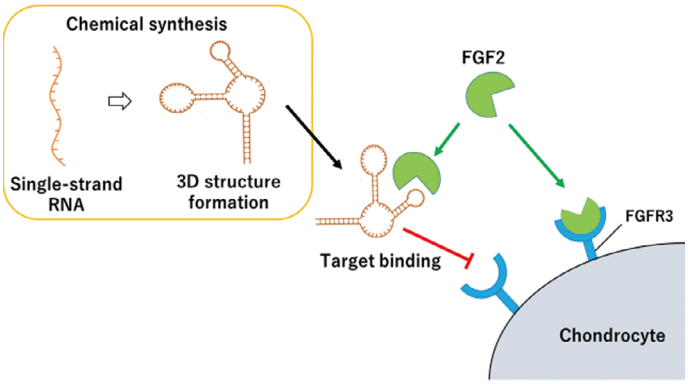

Figure1: The mechanism of RNA aptamer
RBM-007 is composed of 36 nucleotides and binds stably and specifically to FGF2 but not to the other FGFs. RBM-007 confirmed the blocking effect in FGF2 binding to human FGFR3 and suppress signaling pathway induced by FGF2.

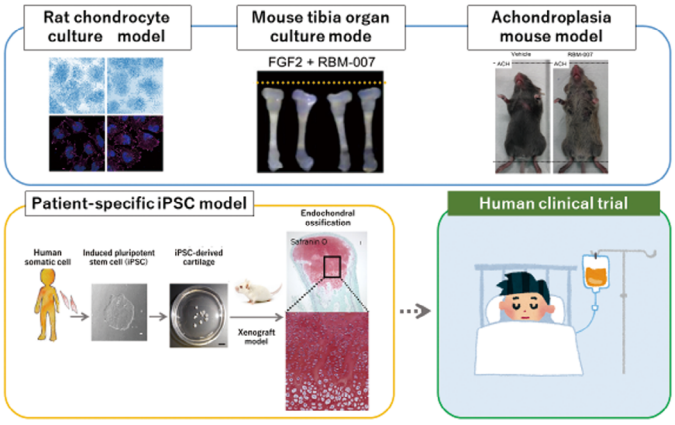

Figure2: Drug discovery process in our research
In addition to traditional *in vitro* and *in vivo* tests using animal model, we evaluated the efficacy of RBM-007 with patient-specific hiPSC models. The clinical trial program for RBM-007 in ACH treatment have been initiated in Japan.

Patent

Treatise Kimura, Takeshi; Bosakova, Michaela; Nonaka, Yosuke et al.
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Keyword achondroplasia, RNA aptamer, patient-specific iPS cells