PRESS RELEASE

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Národní 1009/3, 110 00 Prague 1
www.avcr.cz

PREVENT RATHER THAN INHIBIT ACTIVATION. SCIENTISTS HAVE FOUND A NEW WAY TO TREAT GROWTH DISORDERS

Approximately ten children are born every year in the Czech Republic with achondroplasia, the most common form of genetic growth disorder in humans. Scientists from the Institute of Animal Physiology and Genetics CAS, Masaryk University and the International Clinical Research Centre (ICRC) of St. Anne's University Hospital in Brno have described a new approach to the treatment of this disease. The study was published in the prestigious *Science Translational Medicine* journal.

"We have found out that the impaired bone growth leading to achondroplasia can be partially reversed by using a synthetic ribonucleic acid molecule called RNA aptamer," says Pavel Krejčí from the Institute of Animal Physiology and Genetics CAS, describing the study results.

Why do we (not) grow?

After birth, a person's limbs gradually lengthen, which contributes significantly to the person's resulting height. The most crucial role in this process is played by bone growth and that is precisely what is inhibited in achondroplasia. The reason behind this is a mutation in the gene for the FGFR3 cell receptor, which makes it more sensitive to the signals that trigger the receptor. This makes the receptor more active, which in turn results in slower growth. *"The reason lies in the inhibited proliferation of cartilage cells, which is essential for bone growth,"* says the co-author of the study, Michaela Bosáková from the Institute of Animal Physiology and Genetics CAS, explaining the bone growth principle.

More effective treatment

Media contact:

Eliška Zvolánková
External Relations Division CAS
press@avcr.cz
+420 739 535 007

Barbora Vošlajerová
Institute of Animal Physiology and Genetics CAS
voslajerova@iapg.cas.cz
+420 608 242 415

Whereas most of the tested drugs for treatment of achondroplasia focus on reducing the effects of the overactive FGFR3 receptor, Pavel Krejčí's team came up with a conceptually different approach. *"We have shown that the RNA aptamer binding to the triggering signal of the FGFR3 receptor prevents its activation in cartilage cells. "Administration of this aptamer to mouse models with achondroplasia restored cartilage division and maturation and enhanced bone growth,"* Michael Bosáková recounts the specific results.

> *"The therapy must be both safe, with negative effects reduced to an absolute minimum, as well as effective in the long term."*

Ongoing clinical trials for the treatment of achondroplasia show promising preliminary outcomes. *"The treatment of achondroplasia extends over quite a long time and covers the entire period of active human growth, around fifteen years actually. The therapy must therefore be both safe, with negative effects reduced to an absolute minimum, as well as effective in the long term,"* Krejčí describes the principles of treatment.

General limitations of a long-term treatment usually include the development of drug resistance, which cannot be ruled out in achondroplasia either. *"We believe that the RNA aptamer could serve as a suitable first-line treatment method for achondroplasia. At the same time, due to its distinct mechanism of action, it also allows for combination with other therapeutics, which could ultimately lead to an even more effective treatment,"* Krejčí highlights the advantages of their approach. The RNA aptamer recently entered the phase I clinical trial in Japan and a study in the United States is also being planned.

The University of Tokyo and the University of Ósaka also participated in the research. The study was published in the prestigious Science Translational Medicine journal, established by the American Association for the Advancement of Science.

Further information:

RNDr. Pavel Krejčí, PhD.
Institute of Animal Physiology and Genetics CAS and Masaryk University
St. Anne's University Hospital – International Clinical Research Centre (ICRC)
krejcip@med.muni.cz
+420 725 306 371

Mgr. Michaela Bosáková, PhD.
Institute of Animal Physiology and Genetics CAS and Masaryk University
St. Anne's University Hospital – International Clinical Research Centre (ICRC)
bosakovam@med.muni.cz
+420 732 810 025

Link to the publication: to be delivered

Czech Registry of Achondroplasia, the registry includes a link to a video showing how the cartilage cells divide and stop growing after the activation of FGFR3. Research - ReACH (achondroplasia-registry.cz)

Achondroplasia is a rare genetic bone growth disorder affecting 1-2 in 10,000 new-born children. From a genetics point of view, it is a disease with an autosomal dominant pattern of inheritance meaning that only one copy of the altered FGFR3 gene is sufficient to cause the disease. Yet up to 90% of children with achondroplasia are born to parents of normal stature as a result of new spontaneous mutations. One of the main risk factors for these new mutations to occur is increased paternal age. Average adult height in people with achondroplasia is 125 cm and their life is affected by additional bone changes leading to deformities of the limbs and spine as well as sleep-

related disturbances and frequent obesity. So far, the disease remains untreatable, rehabilitation and management of the accompanying health issues being the important factors. Hormonal treatment is sometimes used to stimulate growth and, in extreme cases, even surgical limb lengthening.

Photo gallery:

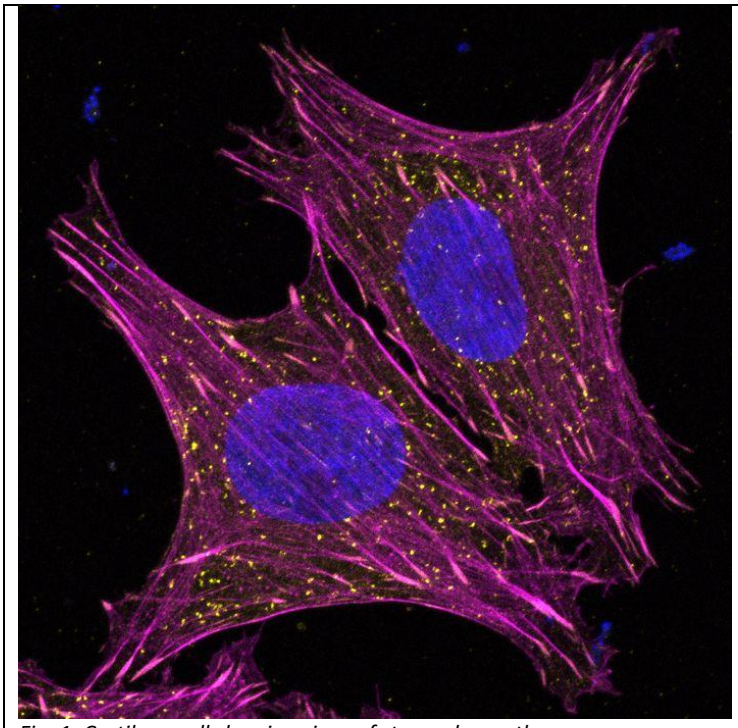

Fig. 1: Cartilage cell showing signs of stopped growth
Photo M. Bosáková

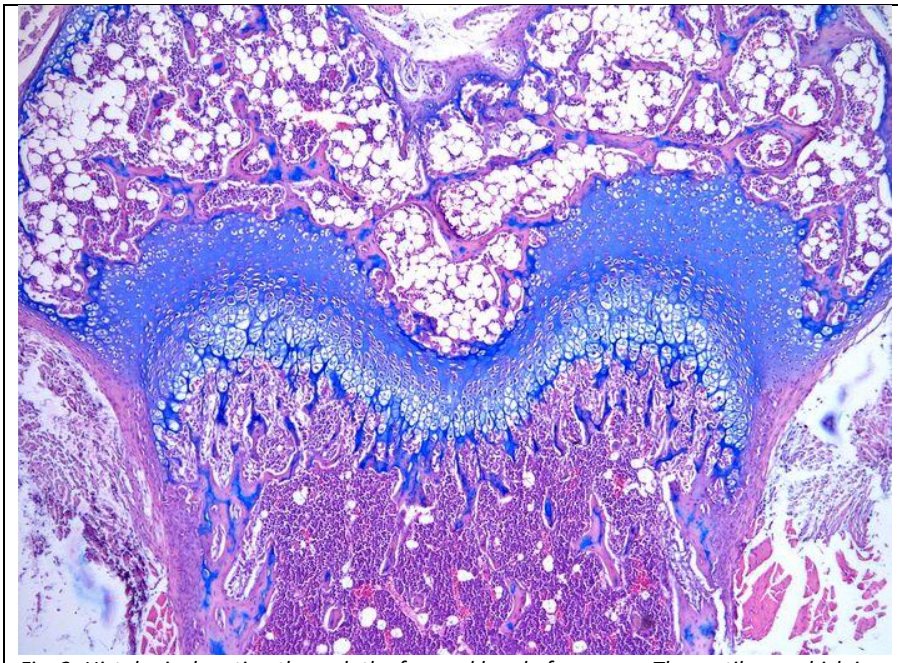

Fig. 2: Histological section through the femoral head of a mouse. The cartilage, which is shortened in achondroplasia, is stained blue.
Photo M. Buchtová