FGFR3-selective inhibitor TYRA-300 increases bone length in a mouse model of hypochondroplasia

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Background

Hypochondroplasia (HCH) is a form of human skeletal dysplasia characterized by disproportionate short stature, affecting ~1 in 30,000 births[1].

The skeletal features tend to be milder than those seen in achondroplasia (ACH), yet individuals with HCH may experience functional limitations, require orthopedic surgeries, and be more prone to ear infections and sleep apnea[1].

Mutations in FGFR3 cause HCH, most commonly an N540K mutation in ~70-80% of cases[1,2,3,4].

FGFR3 is expressed in growth plate chondrocytes and osteoblasts where it functions to regulate endochondral bone formation[5].

The N540K mutation, as well as other mutations, results in increased FGFR3 activity, which impairs chondrogenesis in the growth plate, inhibiting long bone elongation[5].

TREATMENT

There is currently no approved therapy for people with HCH.

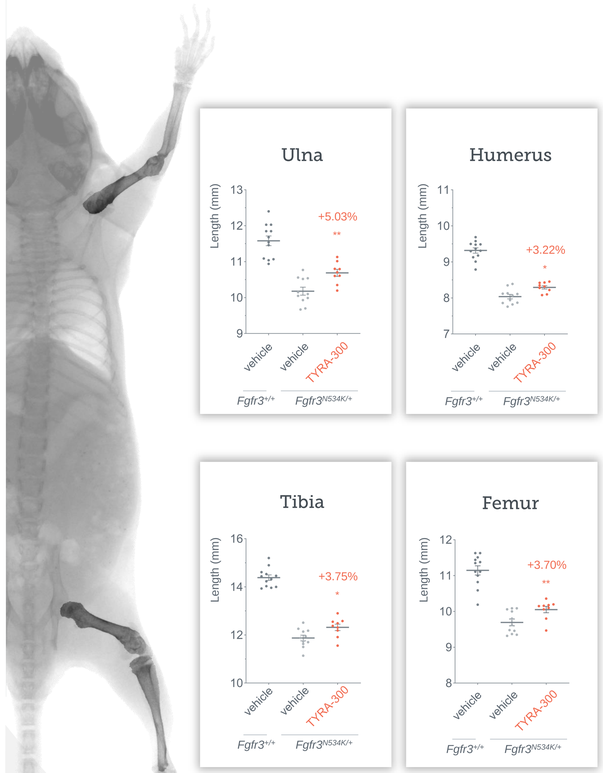
TYRA-300 is an oral, highly selective FGFR3 inhibitor currently undergoing a Phase 1 clinical trial, SURF301[6] (Study in Untreated and Resistant FGFR3+ Advanced Solid Tumors), which may provide a favorable therapeutic window with respect to anticipated toxicities compared to pan-FGFR inhibitors based on its specificity profile.

TYRA-300 has previously demonstrated increases in growth and bone length in an ***Fgfr3***$^{Y367C/+}$ mouse model mimicking ACH[7].

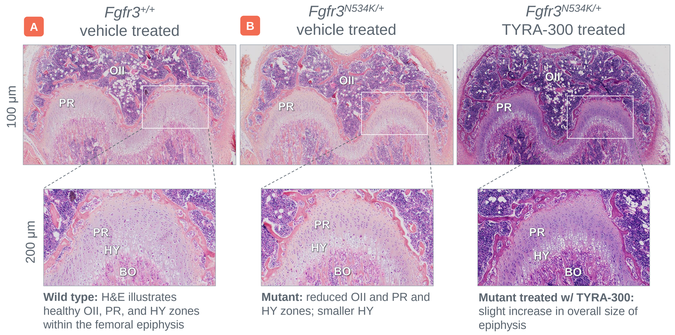
To assess the potential of TYRA-300 in HCH, it was evaluated in the ***Fgfr3***$^{N534K/+}$ mouse model[8].

Results

TYRA-300 increased bone growth of the appendicular skeleton in the *Fgfr3*$^{N534K/+}$ mouse model of HCH



Mann Whitney test vs. vehicle
** p < 0.01
* p < 0.05



Wild type: H&E illustrates healthy OII, PR, and HY zones within the femoral epiphysis

Mutant: reduced OII and PR and HY zones; smaller HY

Mutant treated w/ TYRA-300: slight increase in overall size of epiphysis

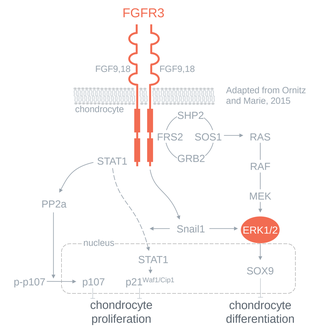
Mice were treated with 1.8 mg/kg (SQ) TYRA-300 from day 3 to day 24 after birth, which resulted in statistically significant increases in long bone length (left).

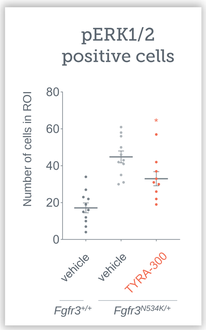
On the final day of the study, the distal femurs were collected for histological analysis of the epiphyses (above). The H&E images demonstrated that TYRA-300 increased the size of the epiphysis and resulted in slight improvement in the growth plate architecture.

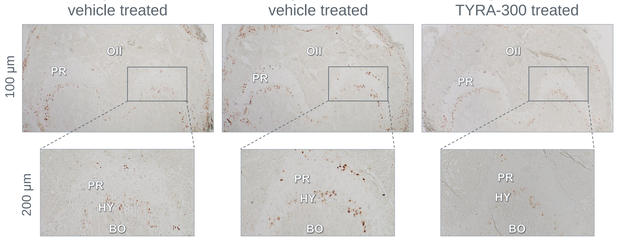
H&E: hematoxylin and eosin stain, PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone.

Results

TYRA-300 decreased FGFR3 signaling within the growth plate







Wild type: pERK is expressed by HY

Mutant: increased expression of pERK in HY

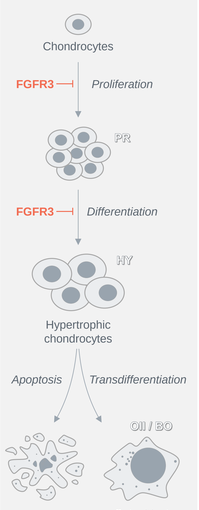
Mutant treated w/ TYRA-300: decrease in pERK; expression similar to WT

Immunohistochemical staining of the distal femurs confirmed that FGFR3 activation is reduced within the growth plate after treatment.

pERK: phosphorylated ERK1/2, PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone, ROI: region of interest.

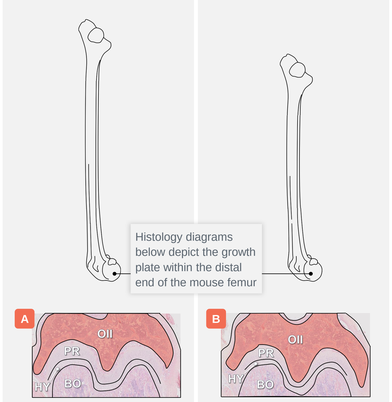
FGFR3 in Bone Growth

FGFR3 plays an inhibitory role in the regulation of chondrocyte proliferation and differentiation.



Wild Type (normal FGFR3)

Mutant (activated FGFR3)



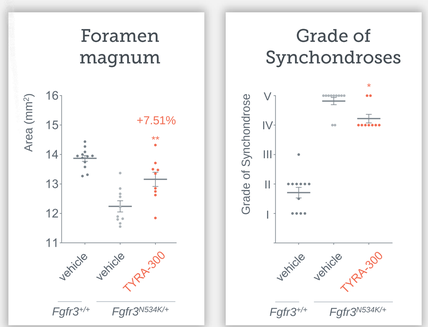
These illustrations correspond to the histological sections at right. They illustrate the differences between zones of chondrocyte proliferation and differentiation in the Wild Type (A) and Mutant (B) in which FGFR3 is over-activated.

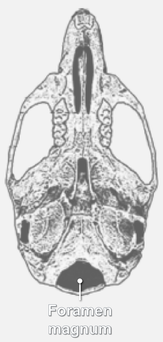
PR: Proliferating chondrocytes form clonal columns of cells that differentiate into prehypertrophic chondrocytes and then HY.

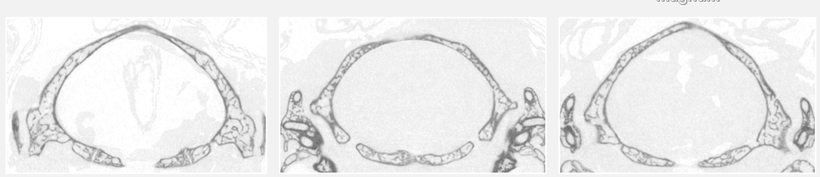
HY: Hypertrophic chondrocytes are master regulators of endochondral ossification. They undergo apoptosis or further differentiate into osteoblasts.

OII / BO: secondary ossification center / bone. Consisting of osteoblasts, the OII serves as protection for the growth plate.

TYRA-300 increased the size of the foramen magnum and improved the synchondroses







Fgfr3$^{+/+}$ vehicle treated

Fgfr3$^{N534K/+}$ vehicle treated

Fgfr3$^{N534K/+}$ TYRA-300 treated

Grades explained
- **I:** borders of synchondroses completely separated;
- **II:** clear separation with some areas of possible bone bridging;
- **III:** bony bridge between the two borders;
- **IV:** completely fused with remnants of margin (cartilage);
- **V:** completely fused synchondroses

µCT images collected at the end of the study after 21 days of dosing from day 3 to day 24 after birth. Images were used for calculation of the area of the foramen magnum, as well as scoring the grade of synchondroses.

Conclusions

TYRA-300 increased long bone length in the ***Fgfr3***$^{N534K/+}$ mouse model of HCH.

Improvements in the foramen magnum area and synchondroses were observed with TYRA-300.

Histological staining indicated that TYRA-300 reduced FGFR3 signaling within growth plate chondrocytes.

The FDA granted TYRA-300 Orphan Drug Designation and Rare Pediatric Disease Designation for ACH.

Using the data from SURF-301 and additional preclinical data, TYRA expects to submit an IND to initiate a Phase 2 study in pediatric ACH: BEACH-301.

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The authors would like to thank Todd Harris, Michael Bober, and Hiroomi Tada for their insights and helpful discussion. We also thank Rob Wishnowsky of Cruxio, Inc., and Melissandre Pache for their contributions to the poster.

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