FGFR3 Selective Inhibitor TYRA-300 Increases Bone Length in a Mouse Model of Hypochondroplasia

Pharmachon, June 2024

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2. Tyra Biosciences, Carlsbad, CA

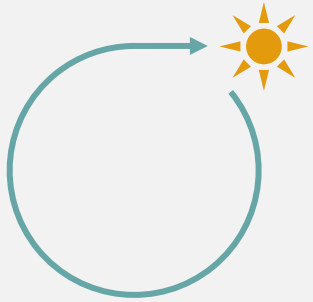
Disclosures

Employee and shareholder at TYRA Biosciences

TYRA's unique approach creates purpose-built drugs

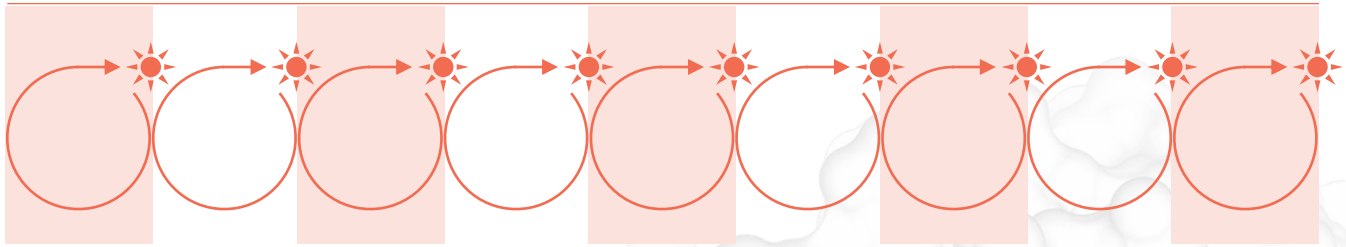
DESIGN CYCLE

Chemistry design



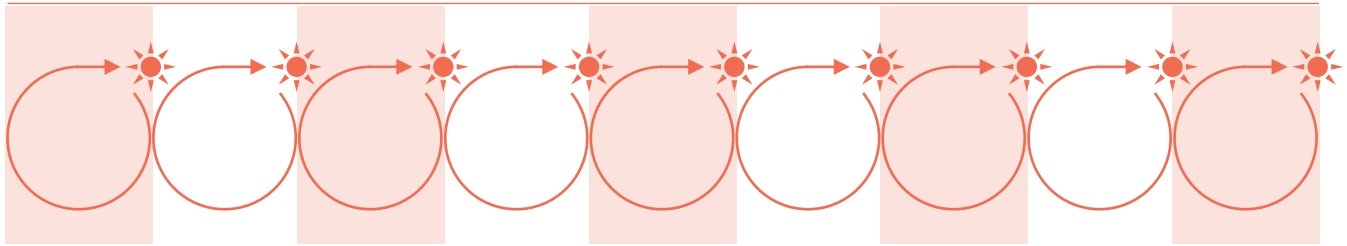
Crystallography
Cell-based assays
In vivo models

SNAP CHEMISTRY DESIGN



TYRA's unique approach creates purpose-built drugs

SNAP CHEMISTRY DESIGN

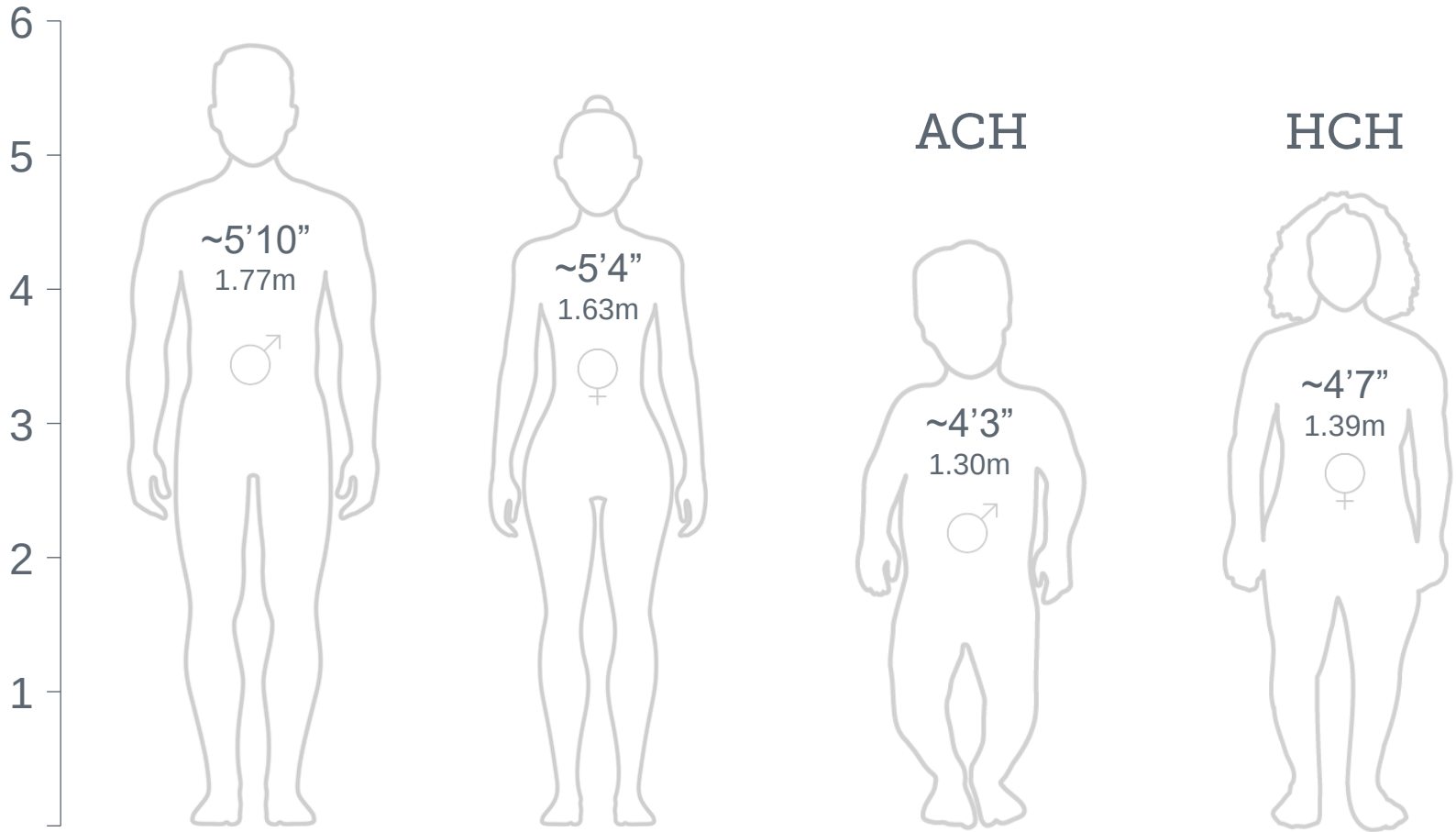


FGFR3

Inhibiting FGFR3 may benefit people with skeletal dysplasias

FGFR3

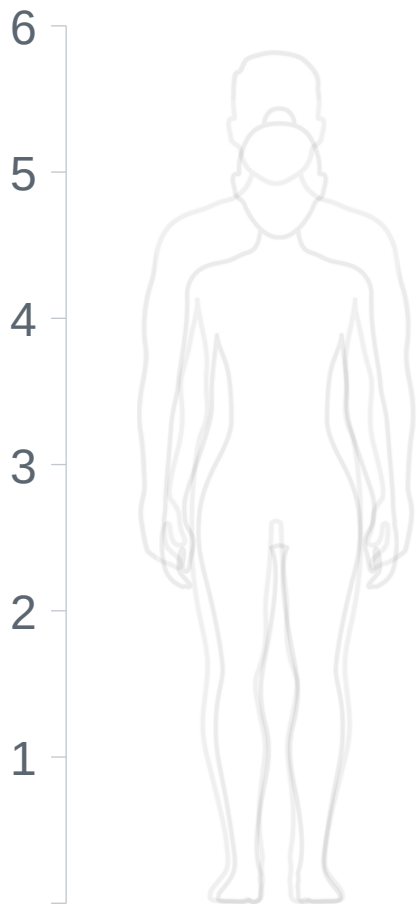
Over-activation of this protein in bone growth plates underlies both ACH and HCH



We designed TYRA-300 to purposefully inhibit FGFR3

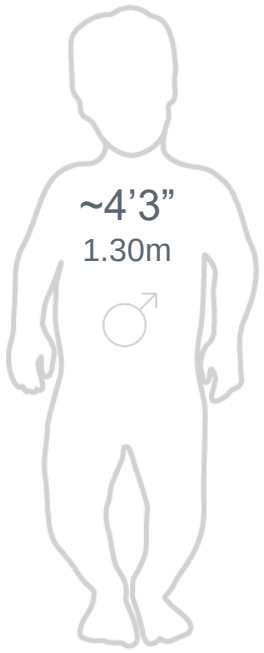
FGFR3

We developed our molecule to specifically inhibit the alteration driving FGFR3-related skeletal dysplasias.



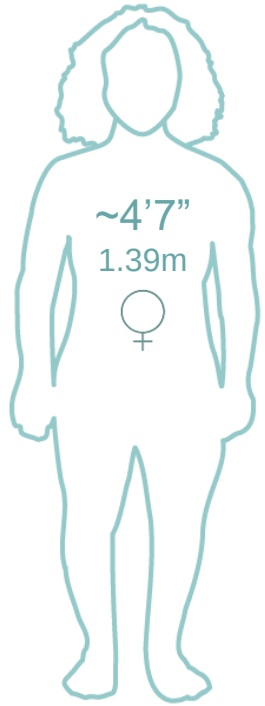
ACH

~99% FGFR3
Alteration: G380R



HCH

~70-80% FGFR3
Alteration: N540K



Like ACH, HCH results in disproportionate long bones

The proximal long bones are more affected than distal bones*

*Arm: humerus
Leg: femur

MECHANISM

FGFR3 inhibits cells that promote bone growth

Over-activation of FGFR3 decreases bone growth in ACH and HCH[1]

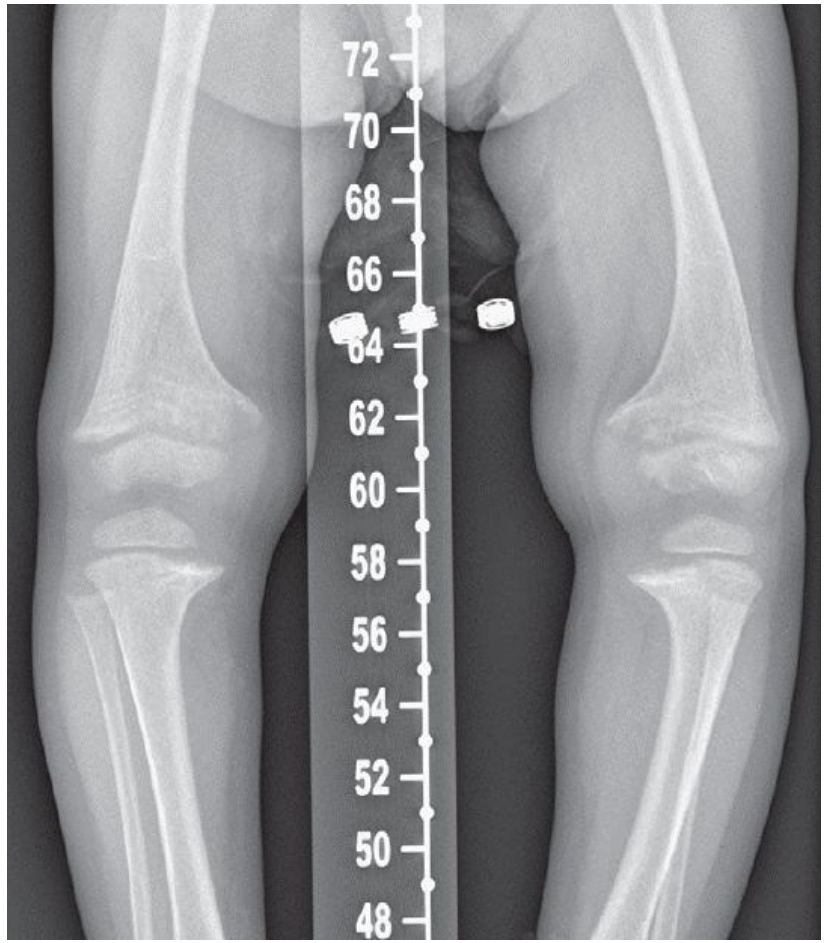
CHALLENGES

Skeletal features and functional limitations similar to those seen in ACH, but milder[2]

Additional (examples): orthopedic surgery, ear infections, sleep apnea

1. Ornitz and Legeai-Mallet, 2017; 2. Bober et al., 1999

There is currently no approved therapeutic option for HCH

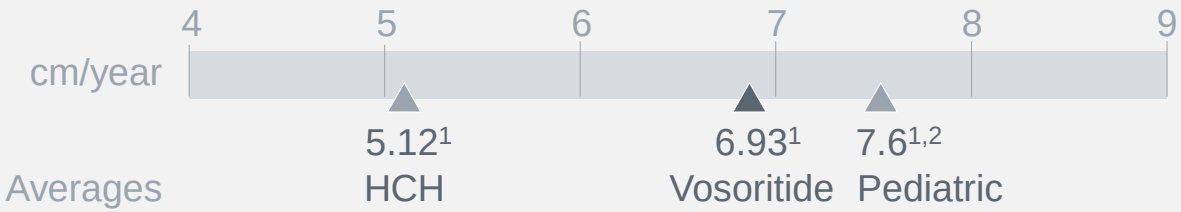


Vosoritide

(CNP analog)

Daily injection, Ph 2

Annual Height Velocity (AHV)



1. Phase 2 Data, Dauber et al., 2024; 2. Merck Manuals (12mo to 10yrs)

Pan-FGFR inhibitors have exhibited toxicity in cancer treatment

FGFR1: HYPERPHOSPHATEMIA

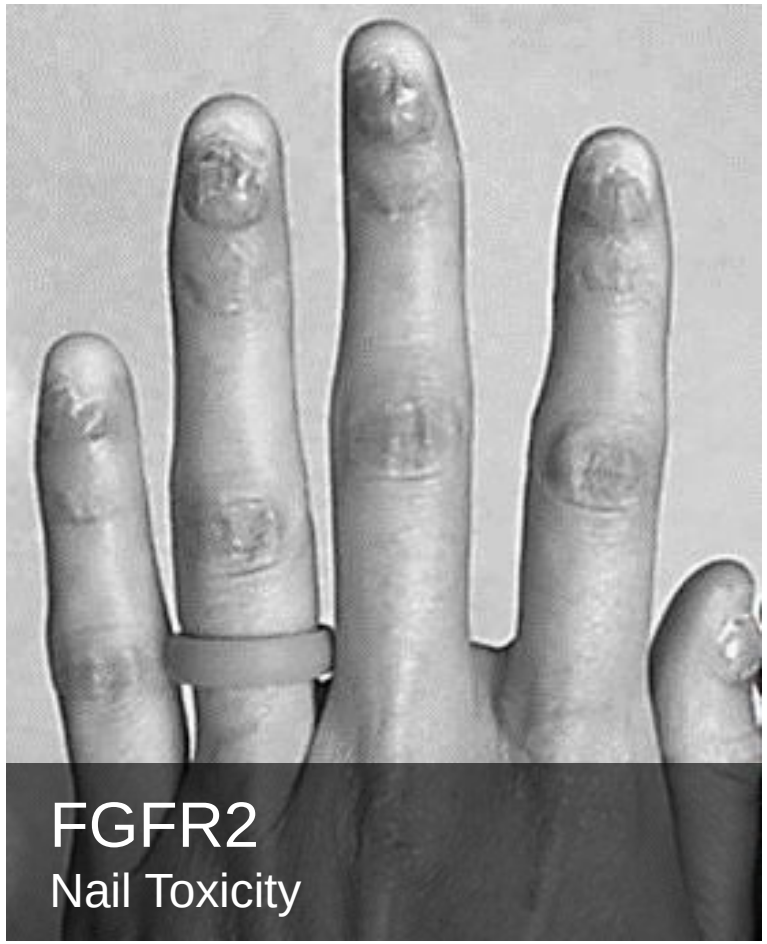
PAN-FGFR INHIBITORS	% PATIENTS AFFECTED
PEMAZYRE (pemigatinib[1])	60%
LYTGOBI (futibatinib[2])	88%
BALVERSA (erdafitinib[2])	76%
TRUSELTIQ (infigratinib[1])	82%

1. FGFR1-3 inhibitor 2. FGFR1-4 inhibitor
Source: PEMAZYRE (pemigatinib) label, FIGHT-202 data, accessed 04/15/24; LYTGOBI (futibatinib) label, pooled data, accessed 04/15/24; BALVERSA (erdafitinib) label, BLC3001 Cohort 1 data, accessed 04/15/24; TRUSELTIQ (infigratinib) label, pooled data, accessed 04/15/24; Chan, 2022; Kim, 2019; Hollebecque, 2022 (ESMO)

Pan-FGFR inhibitors have exhibited toxicity in cancer treatment

OTHER TOXICITIES

FGFR1
Hyperphosphatemia

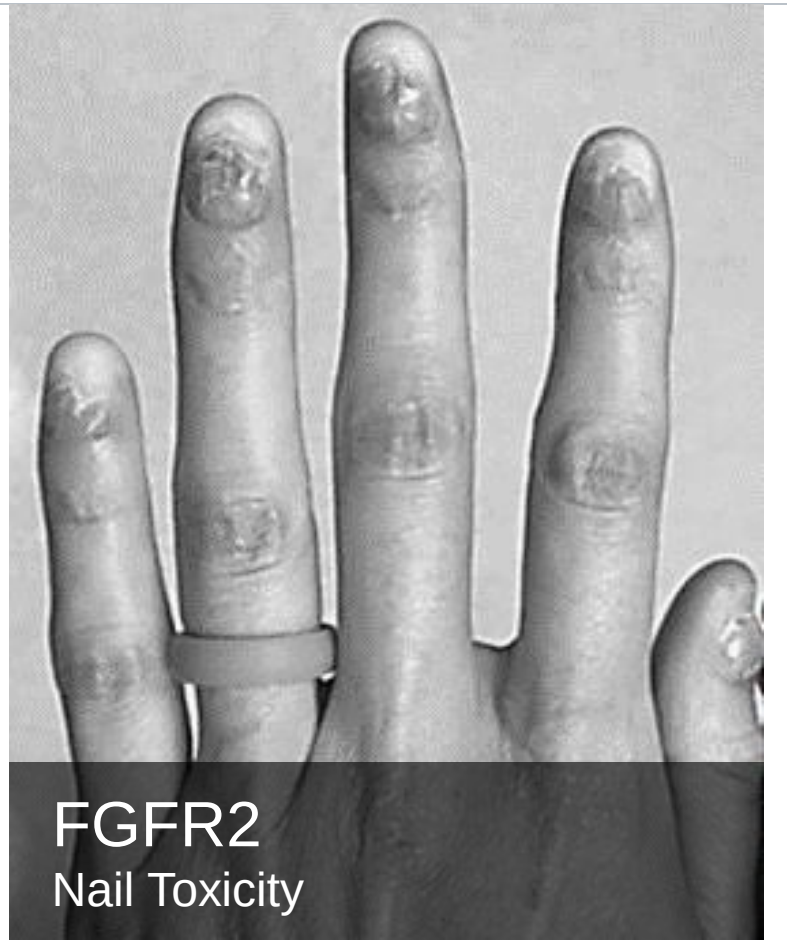


FGFR2
Nail Toxicity

Source: PEMAZYRE (pemigatinib) label, FIGHT-202 data, accessed 04/15/24; LYTGOBI (futibatinib) label, pooled data, accessed 04/15/24; BALVERSA (erdafitinib) label, BLC3001 Cohort 1 data, accessed 04/15/24; TRUSELTIQ (infigratinib) label, pooled data, accessed 04/15/24; Chan, 2022; Kim, 2019; Hollebecque, 2022 (ESMO)

Pan-FGFR inhibitors have exhibited toxicity in oncology

FGFR1
Hyperphosphatemia



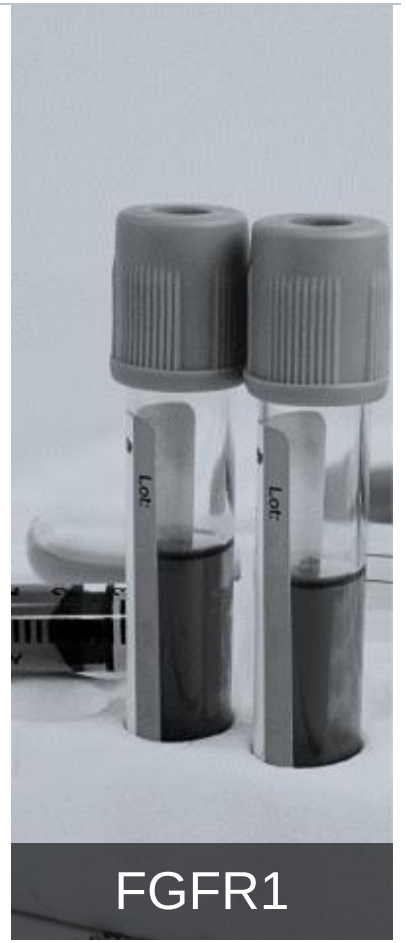
FGFR2
Nail Toxicity

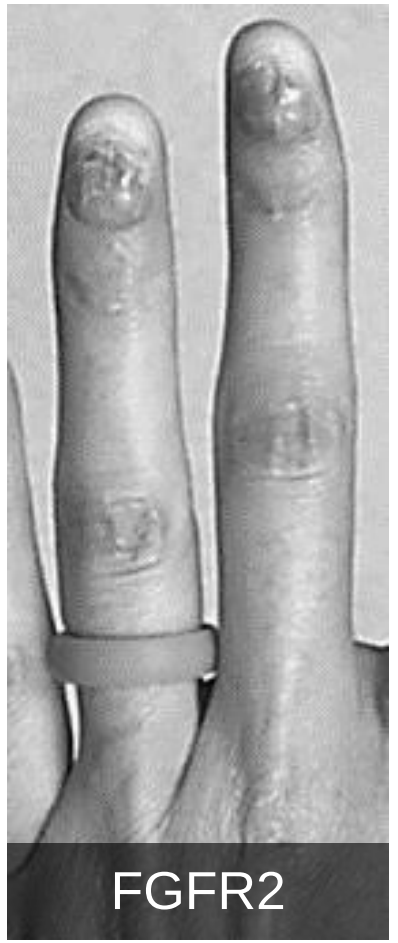
FGFR4
Diarrhea

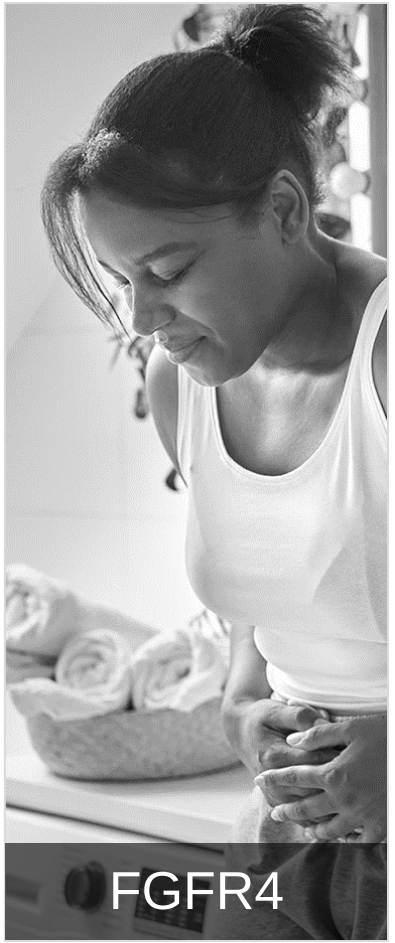
Source: PEMAZYRE (pemigatinib) label, FIGHT-202 data, accessed 04/15/24; LYTGOBI (futibatinib) label, pooled data, accessed 04/15/24; BALVERSA (erdafitinib) label, BLC3001 Cohort 1 data, accessed 04/15/24; TRUSELTIQ (infigratinib) label, pooled data, accessed 04/15/24; Chan, 2022; Kim, 2019; Hollebecque, 2022 (ESMO)

Pan-FGFRi side effects led to dose reductions & discontinuations

PAN-FGFR INHIBITOR	% PATIENTS DOSE REDUCTIONS & DISCONTINUATIONS
PEMAZYRE (pemigatinib[1])	23%
LYTGOBI (futibatinib[2])	63%
BALVERSA (erdafitinib[2])	83%
TRUSELTIQ (infigratinib[1])	75%







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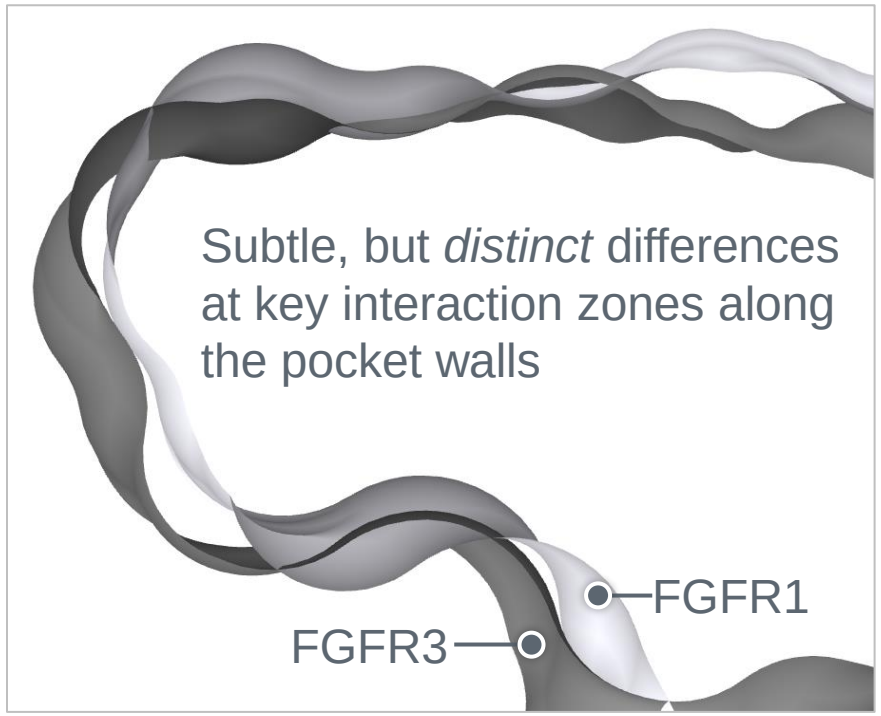
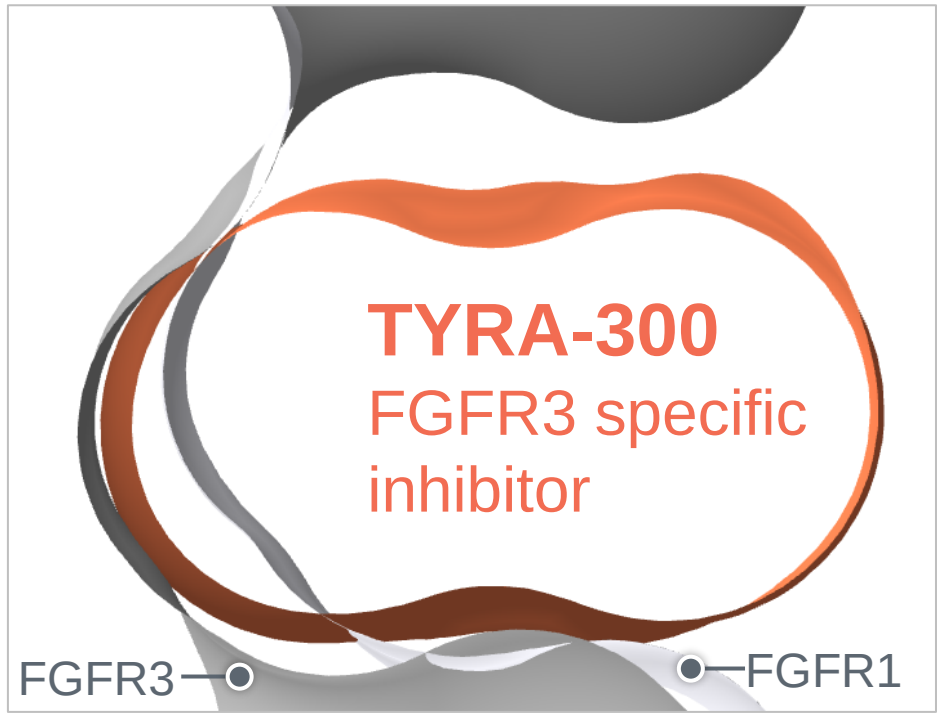
The challenge: similar structures of FGFR family members



MOLECULAR MODEL

dozens of high-resolution crystal structures

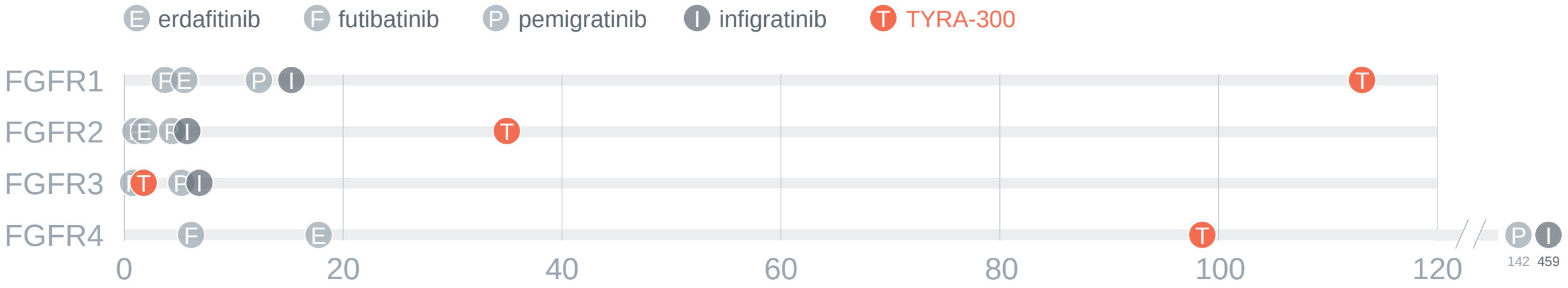


CRYSTALLOGRAPHY

3.0Å cross-sections

TYRA-300 was more selective for FGFR3 than pan-FGFR inhibitors

Selectivity observed for TYRA-300 vs. approved or late-stage clinical compounds: *in vitro* Ba/F3 Cellular IC_{50} (nM)



All experiments conducted under identical conditions, tested in duplicate.

TYRA-300 inhibits the human FGFR3 alteration, N540K

The FGFR3 N540K alteration accounts for 70-80% of HCH

	TYRA-300
Strength of binding IC_{50} (nM)	
FGFR3 Wild Type	24.1
FGFR3 N540K	73.5

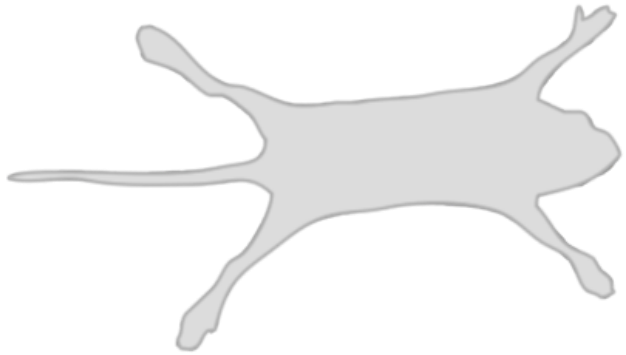
NanoBRET™ binding assay

The first mouse model of HCH was recently developed

HCH Mouse

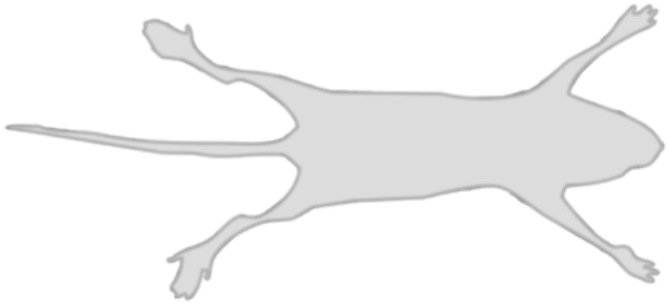
(Fgfr3 $^{Asn534Lys/+}$)[1]

Same alteration in humans



WT Mouse

Mouse without HCH



Developed by Legeai-Mallet lab

Collaborative evaluation

- Daily subcu. injections: 3−24 days old
- Dose: 1.8 mg/kg/day

1. Loisey et al., JCI Insight, 2023

The first mouse model of HCH was recently developed

HCH Mouse

WT Mouse

1. Loisey et al., JCI Insight, 2023

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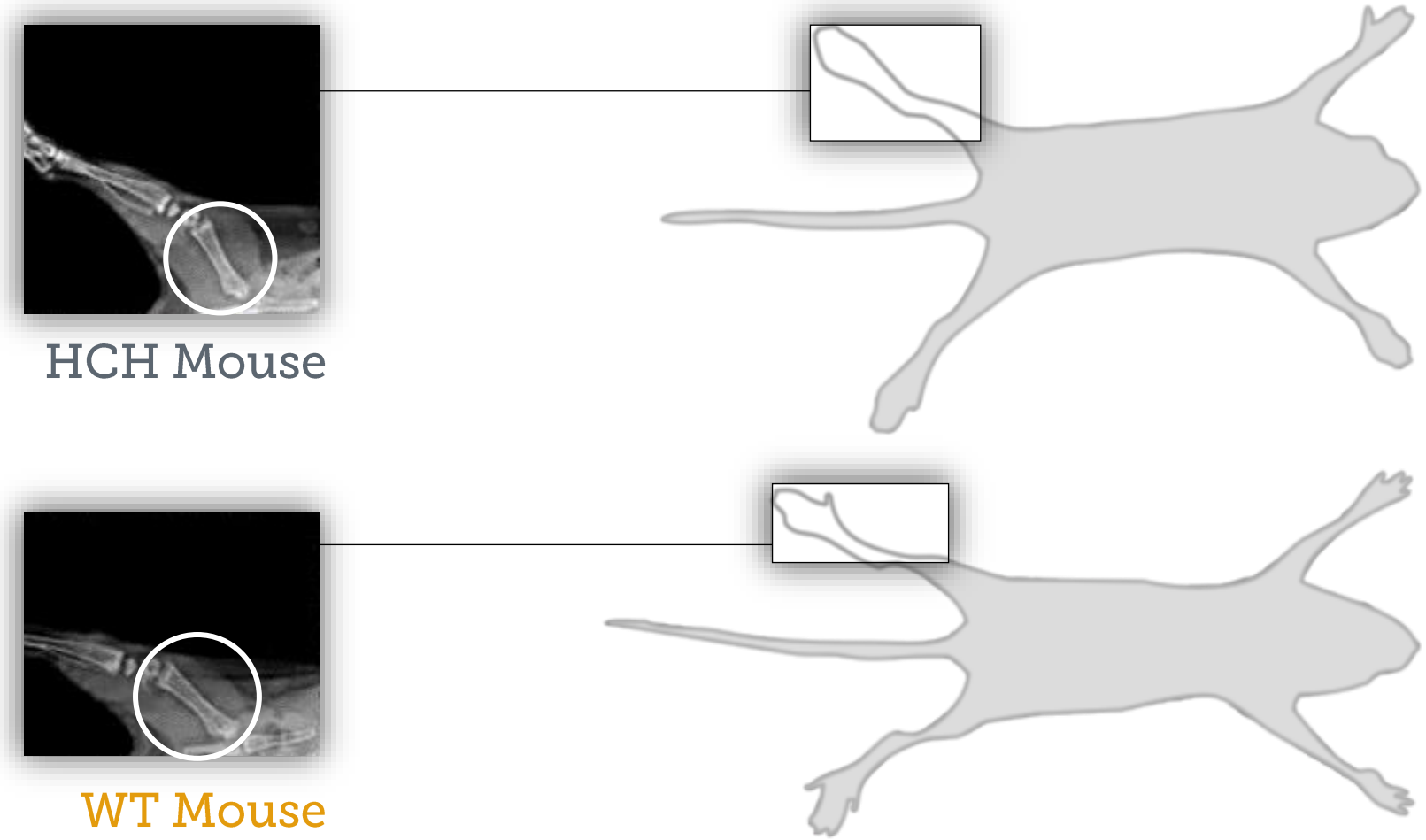
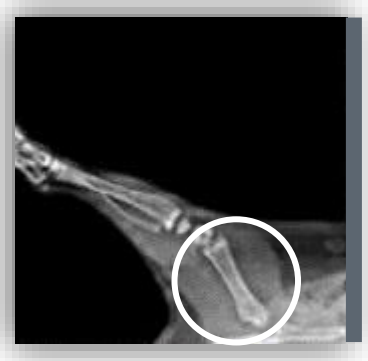
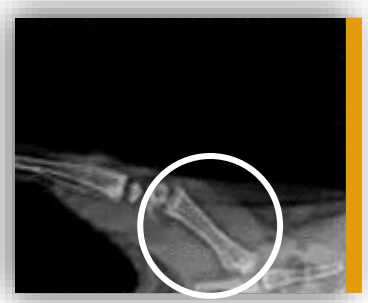


1. Loisey et al., JCI Insight, 2023

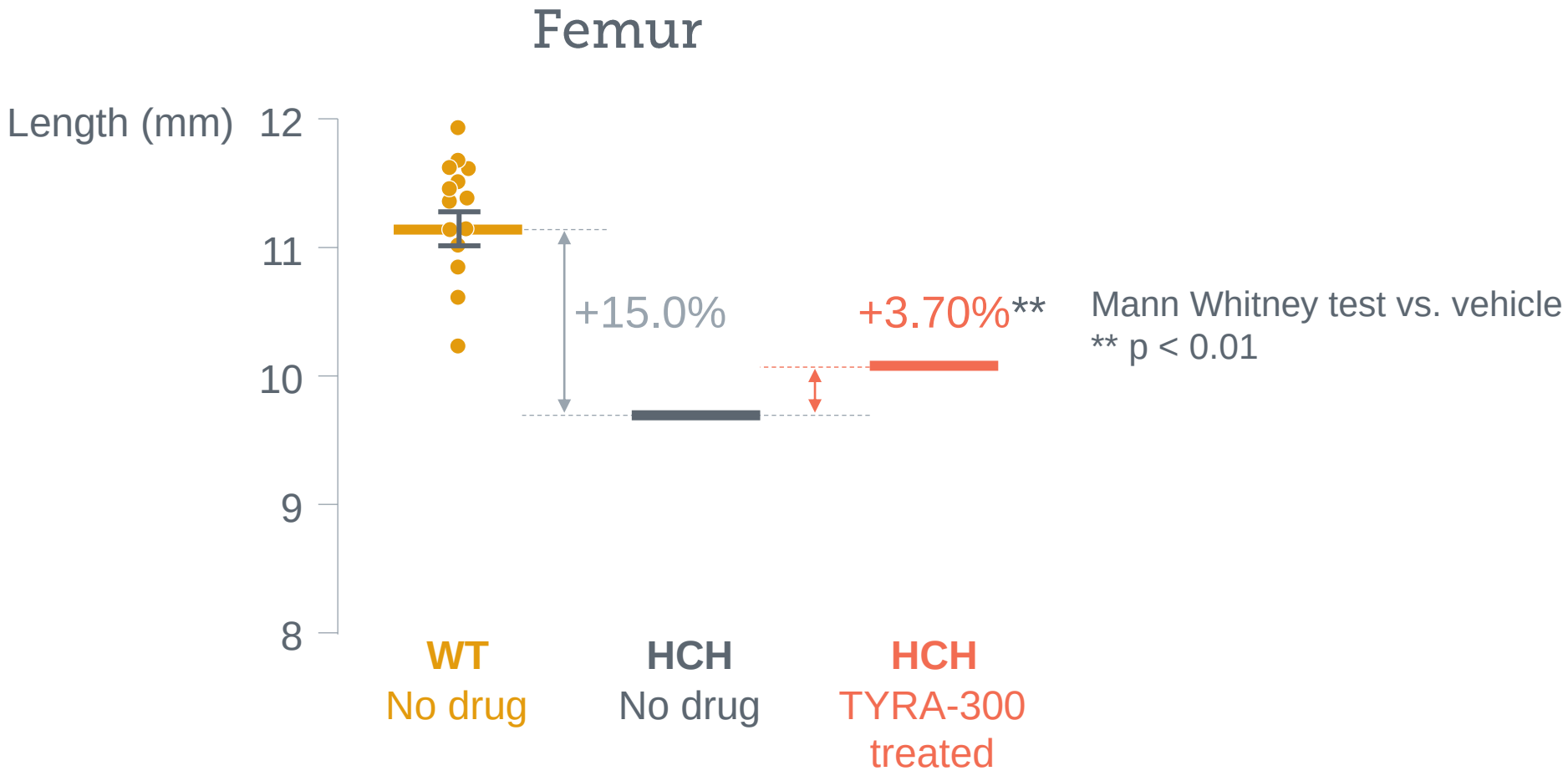
Here’s how we compare WT, HCH, and treated-HCH



HCH Mouse



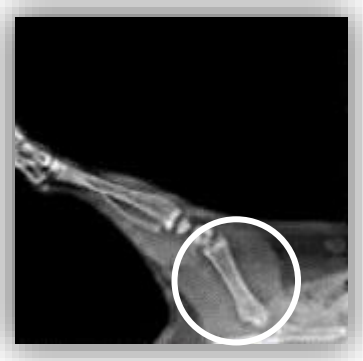
WT Mouse



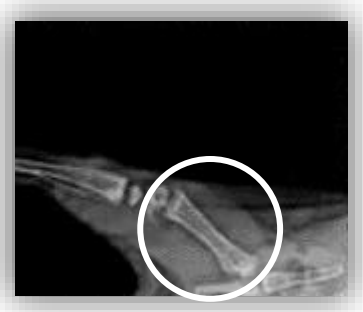
Mann Whitney test vs. vehicle
** p < 0.01

Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France
Daily subcutaneous injection of TYRA-300 at 1.8 mg/kg/day for 21 days starting at Day 3

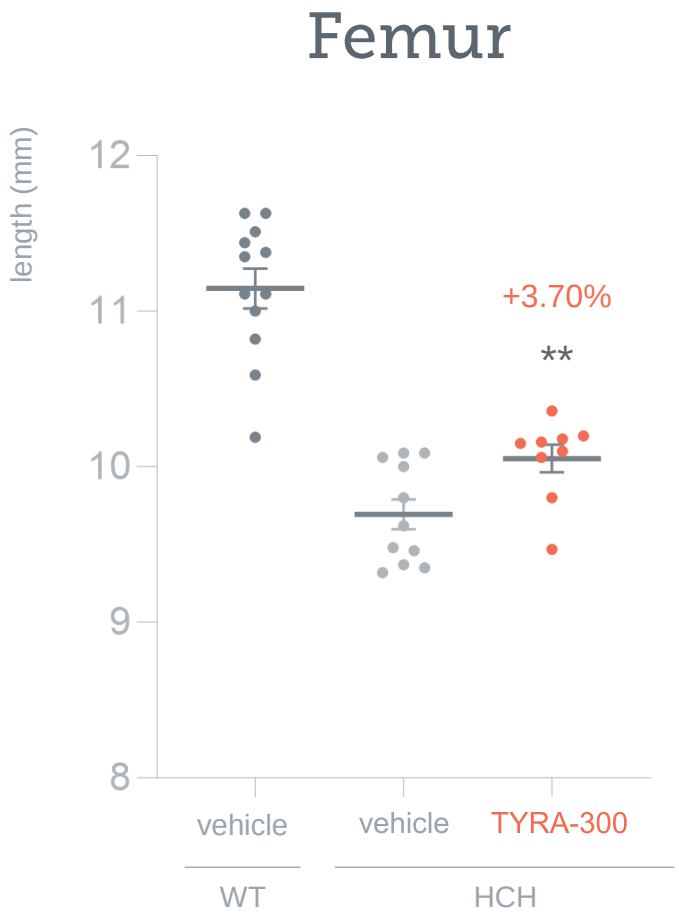
TYRA-300 increased the length of the long bones



HCH Mouse



WT Mouse



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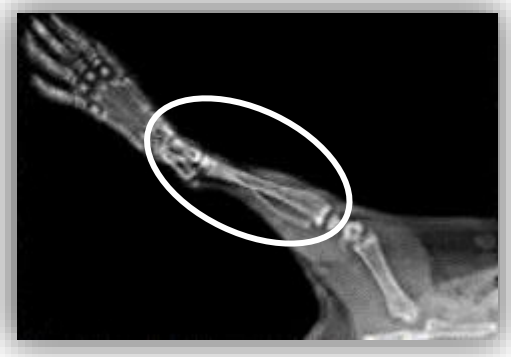
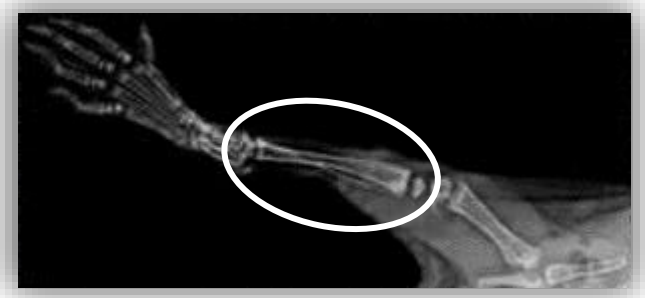
Mann Whitney test vs. vehicle ** $p < 0.01$, * $p < 0.05$

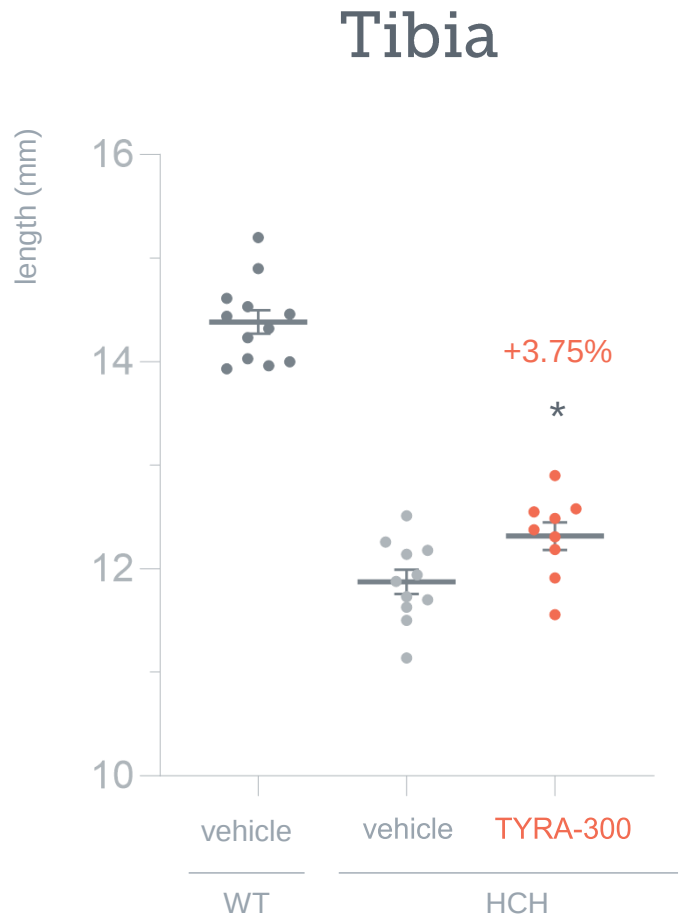
TYRA-300 increased the length of the long bones



HCH Mouse



WT Mouse



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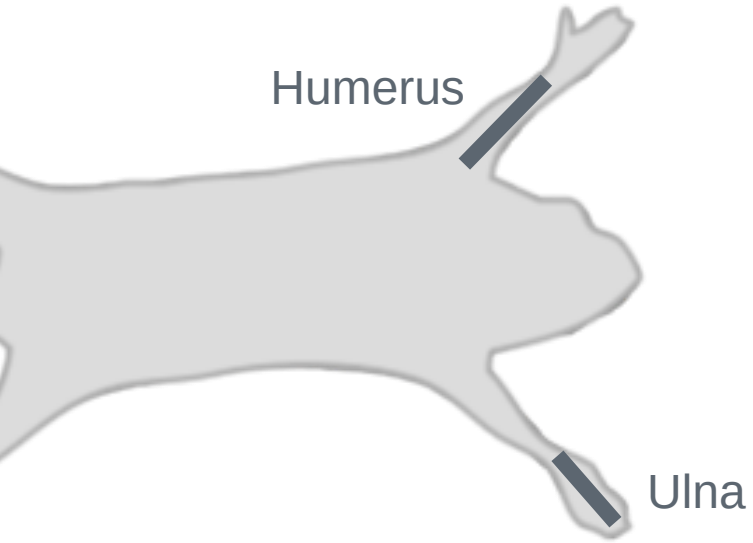

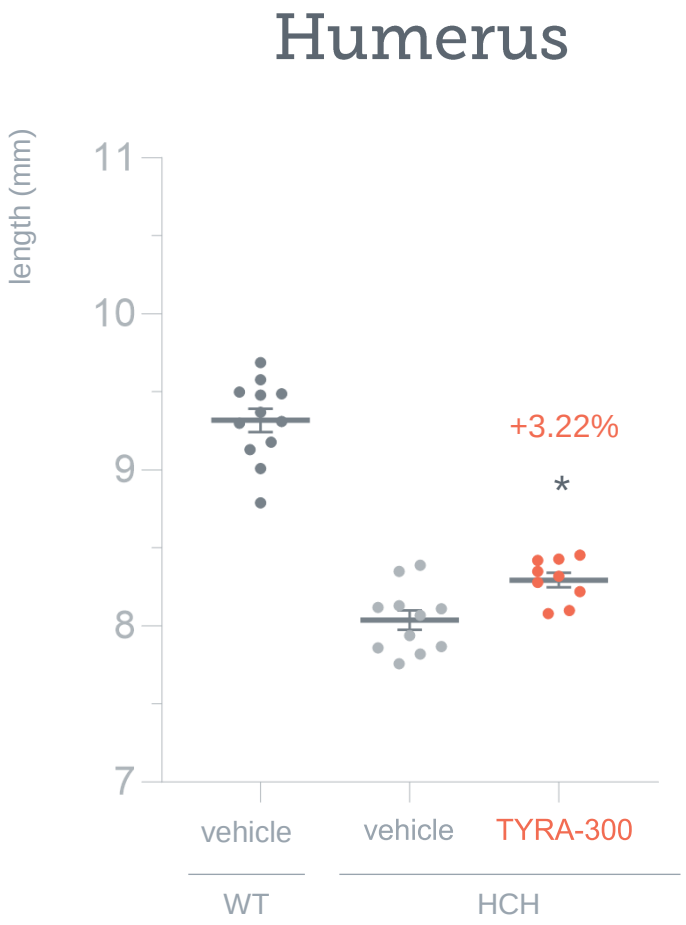

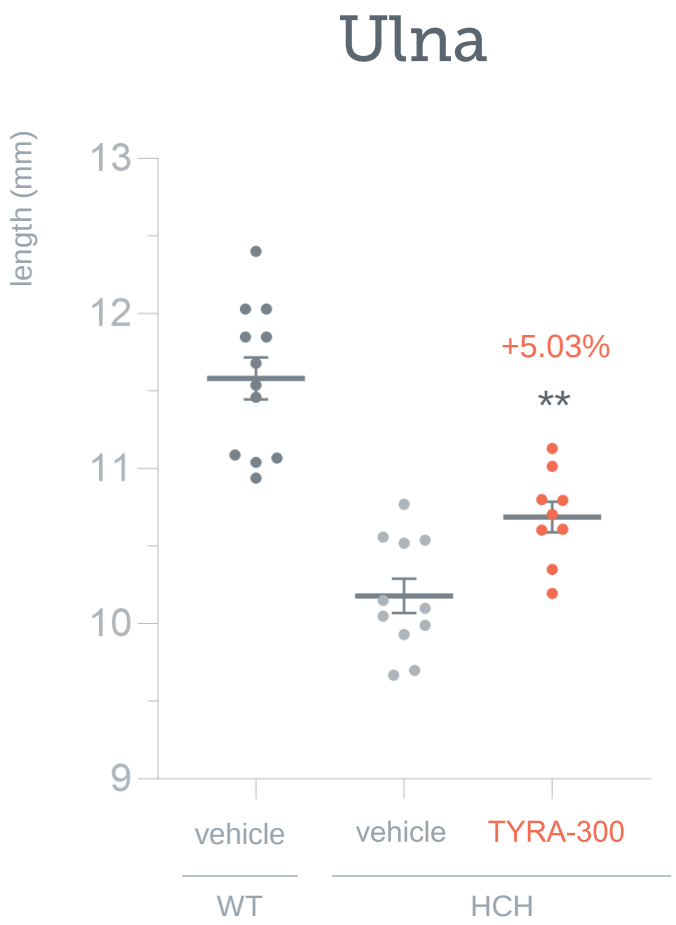

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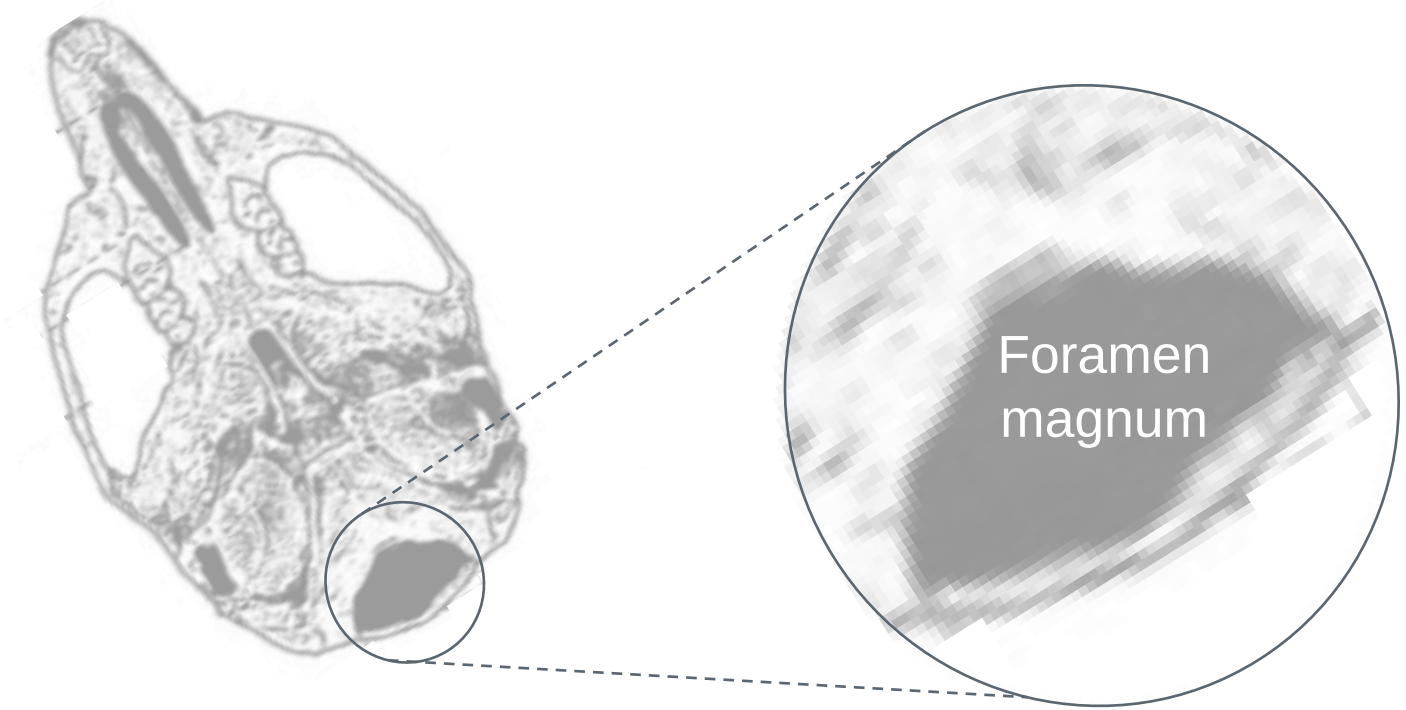
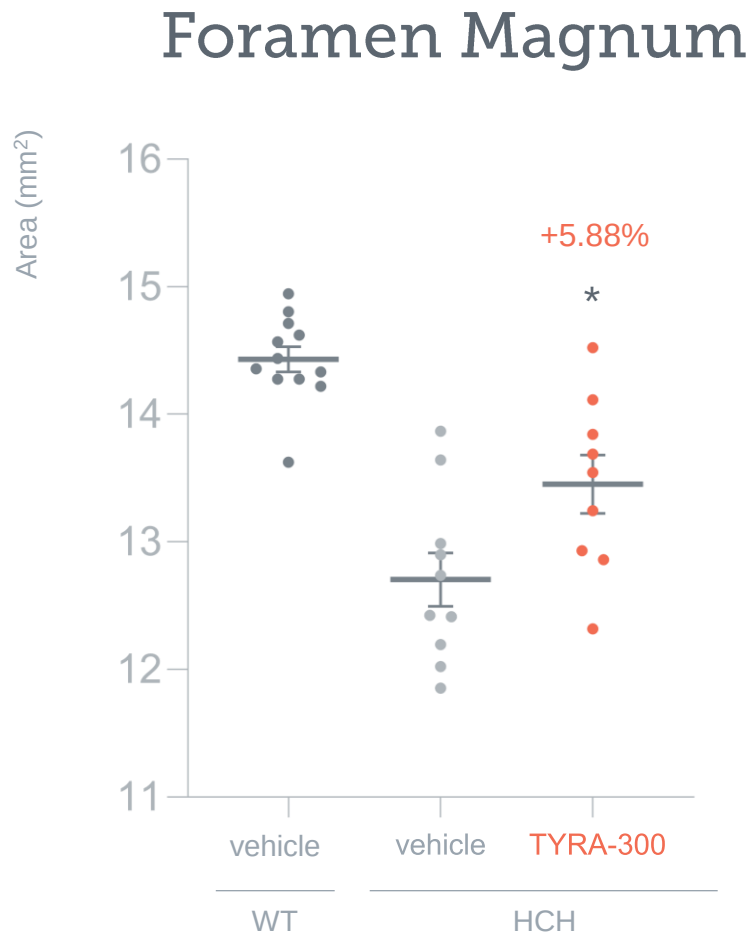
Mann Whitney test vs. vehicle ** $p < 0.01$, * $p < 0.05$

TYRA-300 increased the size of the foramen magnum





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

Here are our key pre-clinical conclusions about TYRA-300

1. Demonstrated specific binding for FGFR3
2.
3.
4.

Fold Selectivity for FGFR3

	TYRA-300
FGFR1	63x
FGFR2	19x
FGFR4	55x

Here are our key pre-clinical conclusions about TYRA-300

1. Demonstrated significant selectivity for FGFR3
2. Exhibited binding against FGFR3 N540K
3.
4.

	TYRA-300
FGFR3 Wild Type	24.1
FGFR3 N540K	73.5

Here are our key pre-clinical conclusions about TYRA-300

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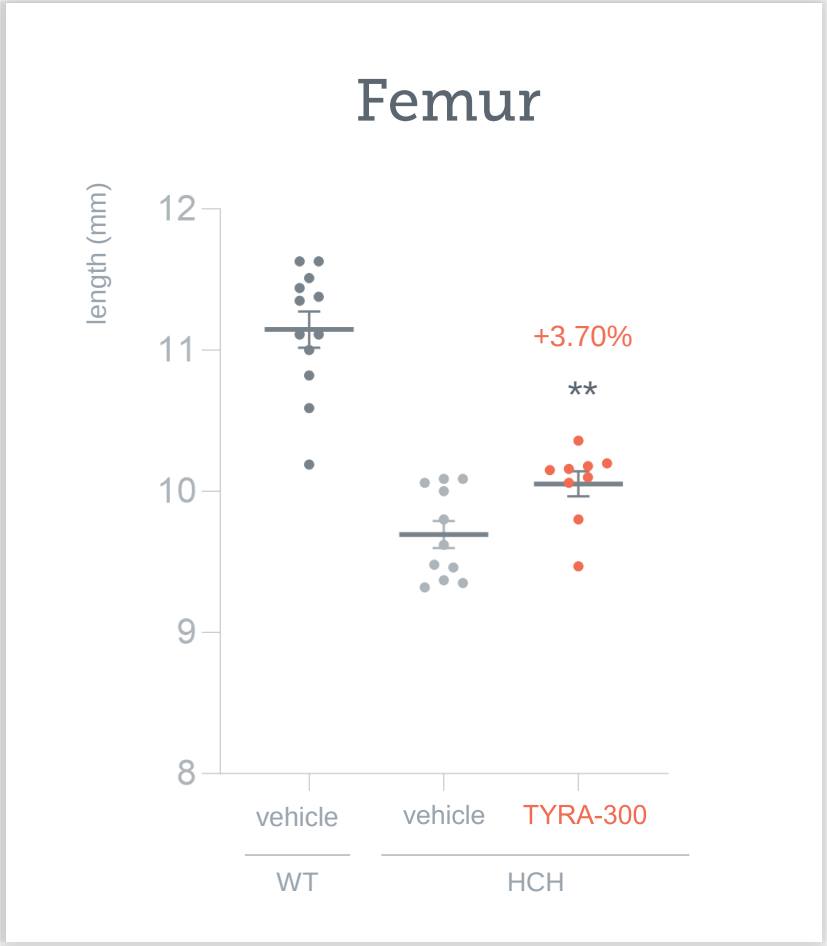
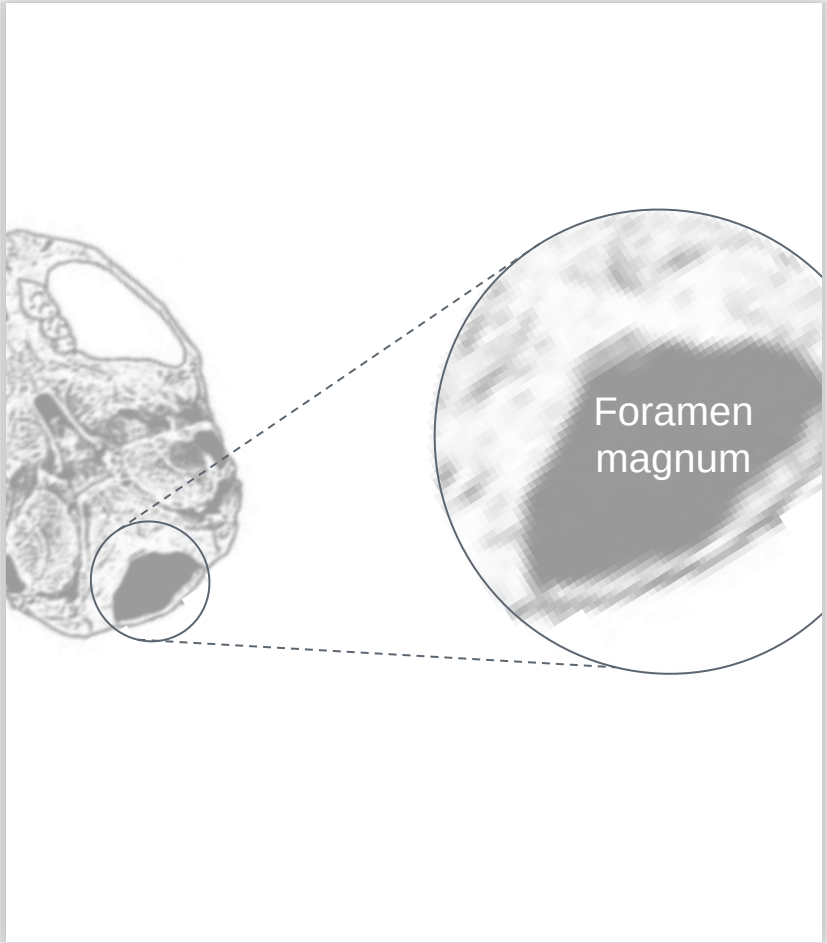
2. Exhibited binding against FGFR3 N540K
3. Increased bone length in the HCH mouse model
4.



Here are our key pre-clinical conclusions about TYRA-300

1. Demonstrated significant selectivity for FGFR3
2. Exhibited binding against FGFR3 N540K
3. Increased bone length in the HCH mouse model
4. Increased the area of the foramen magnum

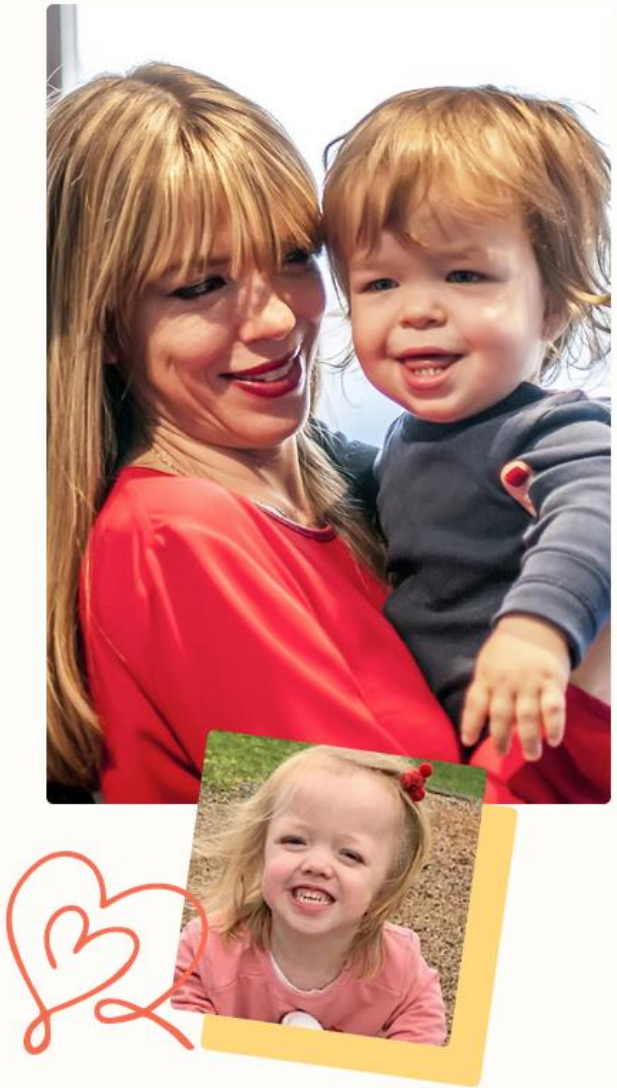


Understanding achondroplasia

Children with achondroplasia live long, active, and meaningful lives. Achondroplasia is the most common form of dwarfism and is caused by an alteration in the fibroblast growth factor receptor-3 gene (*FGFR3*).

Learn more about achondroplasia and its impact.

ABOUT ACHONDROPLASIA



Learn more at achondroplasia.bio