TYRA-300 Demonstrates Significant Increases in Bone Length and Foramen Magnum Area in a Mouse Model of FGFR3-Related Skeletal Dysplasia

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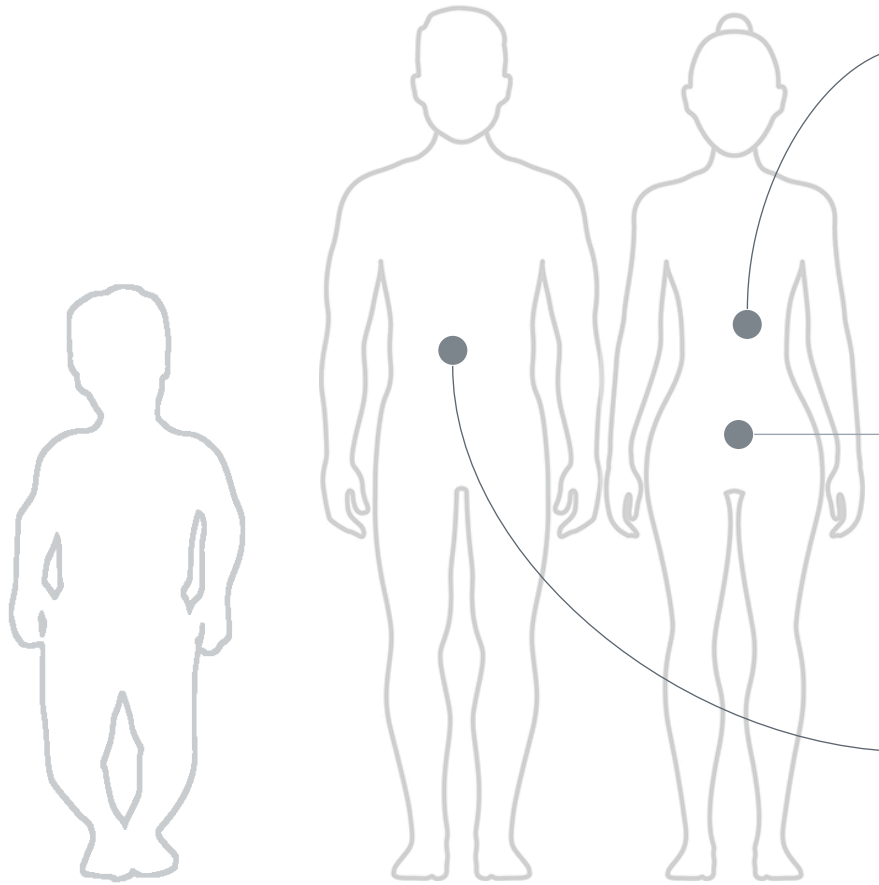
FGFR alterations are implicated in many clinical conditions

ACHONDROPLASIA (ACH)
~99% FGFR3 | ~3,000/yr (US)

OTHER FGFR3-RELATED SKELETAL DYSPLASIAS
~40,000/yr (US)



HEPATOCELLULAR CARCINOMA (HCC)
~30% FGF19 | ~9,000/yr (US)

UROTHELIAL CARCINOMA (UC)
~50% FGFR3 | ~40,000/yr (US)

INTRAHEPATIC CHOLANGIOCARCINOMA (ICC)
~10–20% FGFR2 | ~1,700/yr (US)

Oncology figures represent 2022 US incidence across all stages of the disease; skeletal dysplasias represent 2022 US pediatric prevalence

ACH is the most common cause of disproportionate short stature

MECHANISM

FGFR3 G380R gain of function mutation accounts for ~99% of ACH[1,2]

FGFR3 inhibits chondrocyte proliferation and differentiation, resulting in decreased longitudinal bone growth[2]

COMPLICATIONS

Infants can face serious complications related to critical foramen magnum stenosis[1,3]

Additionally: Pain, multiple surgeries, and functional limitations (e.g., reach, stride)

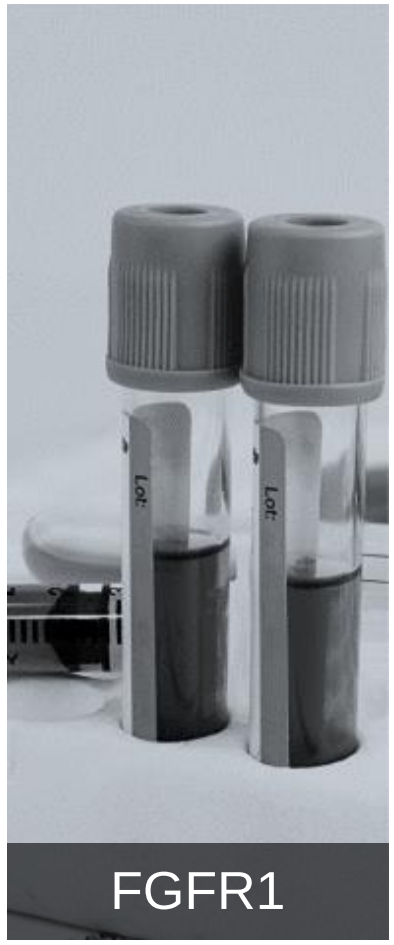
THERAPIES

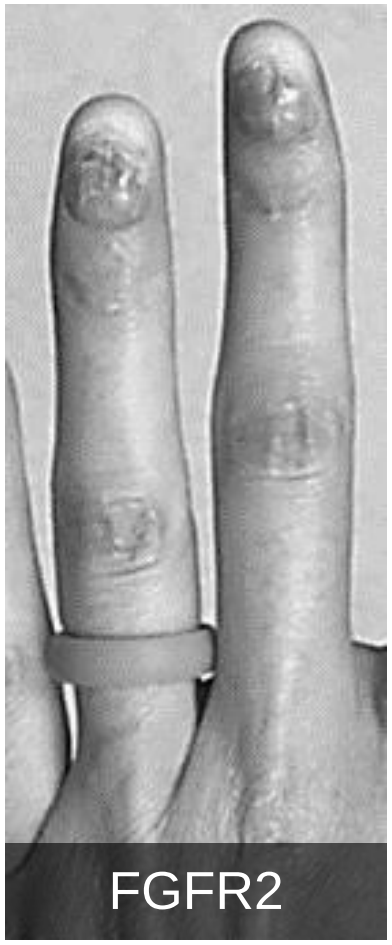
Vosoritide (CNP analog) is a once daily injectable approved by the US FDA

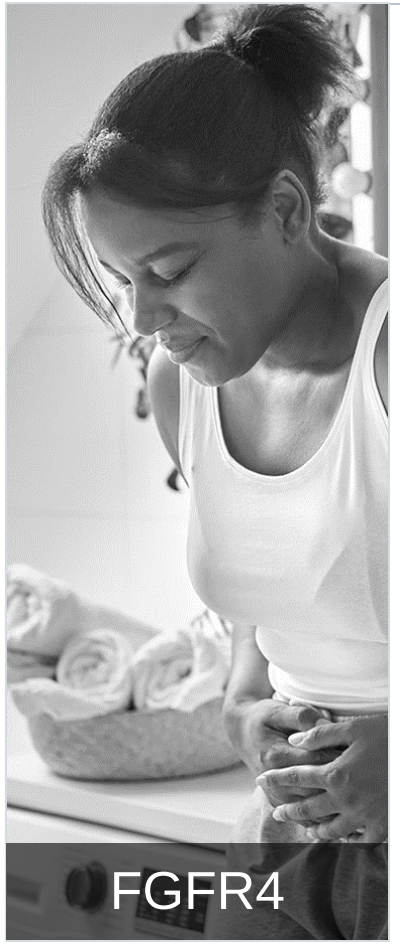
Infigratinib (pan-FGFR1/2/3 inhibitor) is a once daily oral currently in clinical trials for ACH

1. Pauli et al., 2019; 2. Ornitz and Legeai-Mallet, 2017; 3. Hecht et al., 1987

Pan-FGFRi side effects led to dose reductions & discontinuations


FGFR1


FGFR2

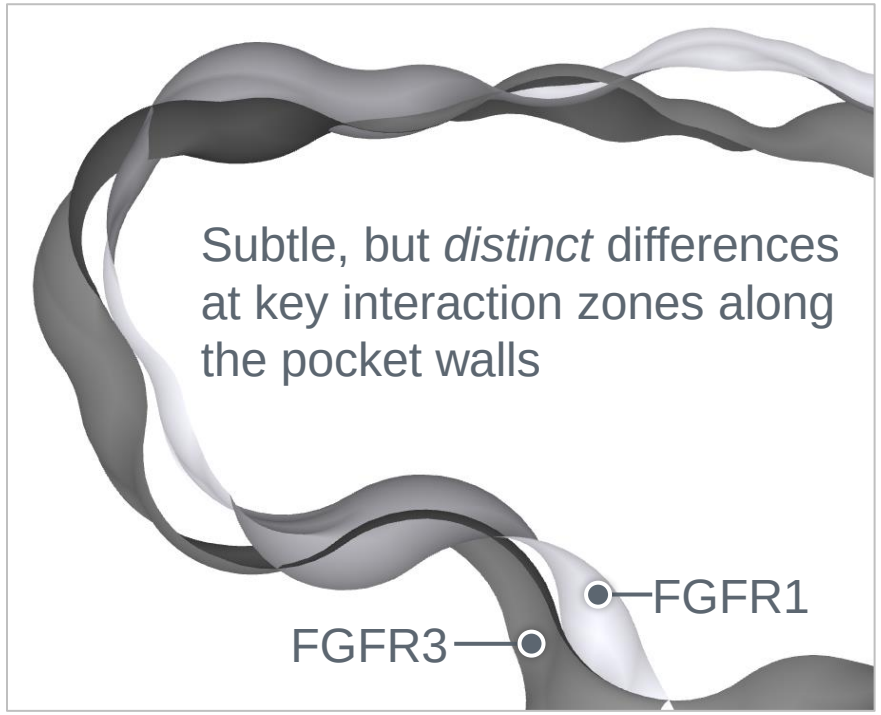

FGFR4

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

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)

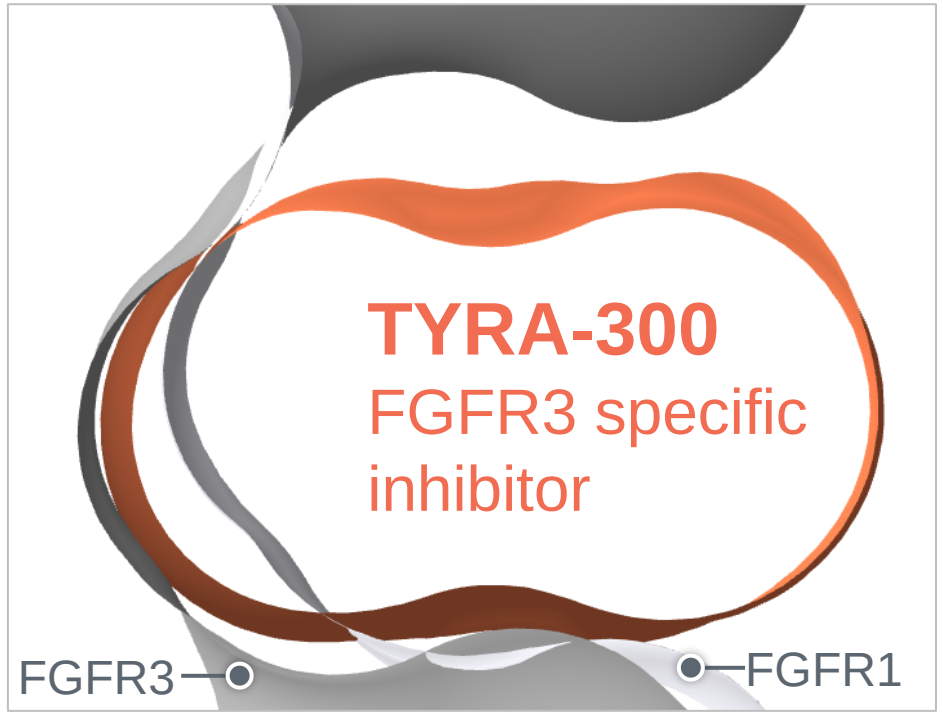
The challenge: FGFR family active sites are nearly identical

FGFR isoform selectivity



MOLECULAR MODEL

dozens of high-resolution crystal structures

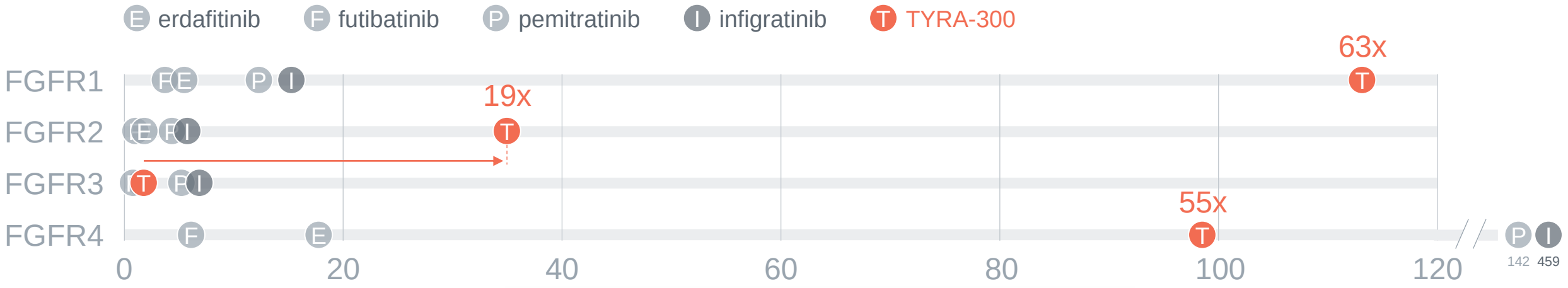


CRYSTALLOGRAPHY

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)



	E	F	P	I
FGFR1	4.2x	4.9x	2.4x	2.2x
FGFR2	1.4x	1.3x	0.8x	0.8x
FGFR4	14x	7.6x	27x	67x

All experiments conducted under identical conditions, tested in duplicate.

TYRA-300 increased bone growth in the *Fgfr3*$^{Y367C/+}$ mouse model

17.9%

Increase in naso-anal length*

*p<0.0001

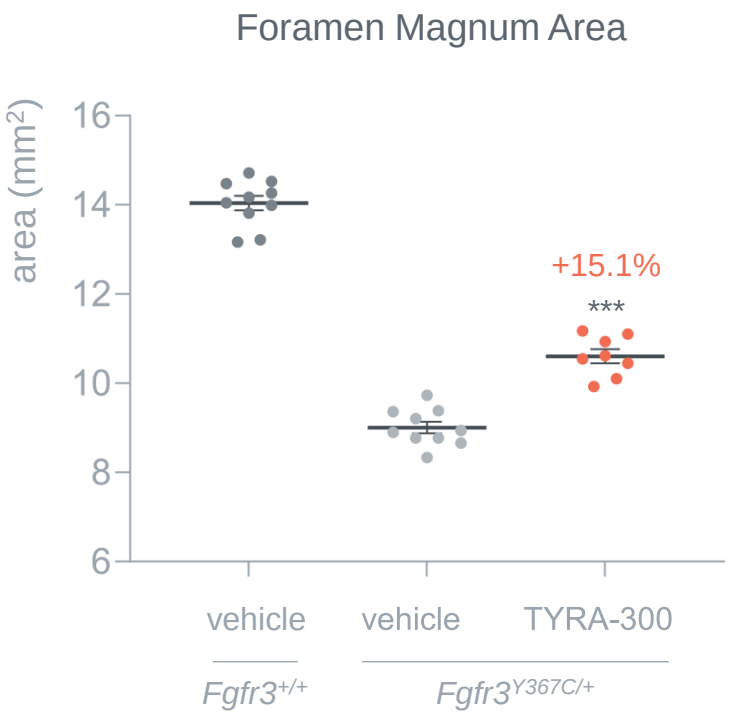
	Dose (mg/kg/day)	Femur	Tibia	L4-L6
TYRA-300	1.2[1]	22.6%*	33.0%*	23.5%*
infigratinib	2.0[2]	20.9%	32.6%	12.1%
infigratinib	0.5[3]	10.4%	16.8%	18.4%

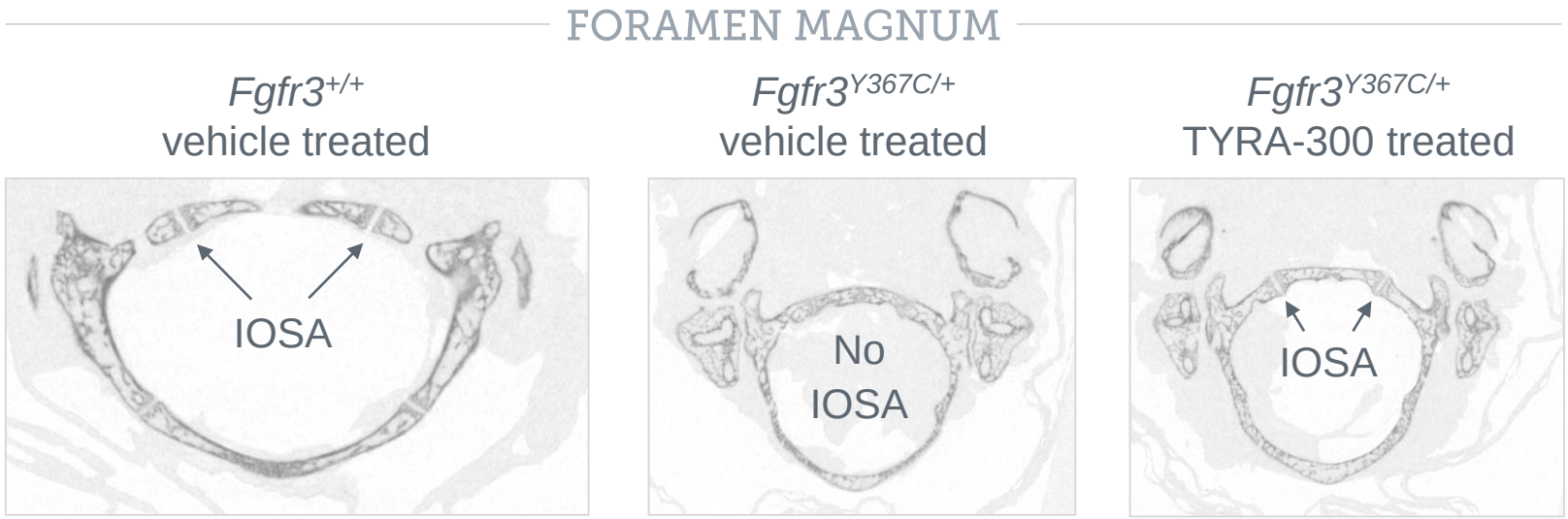
*p<0.0001

Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; data reflects separate experiments for TYRA-300 and infigratinib

1. 15 days subQ starting at day one; n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from dataset when molecular analysis showed chimeric incorporation of mutation;
2. Data from Komra-Ebri et al., 2016 (Legeai-Mallet lab);
3. Data from Demuynck et al., 2024 (Legeai-Mallet lab); 0.667mg/kg/day human equivalent dose for 2.058 mg/kg/day; 0.167mg/kg/day human equivalent dose for 0.514mg/kg/day; infigratinib human recommended phase 3 dose for ACH is 0.25mg/kg/day

TYRA-300 improved the size and shape of the foramen magnum





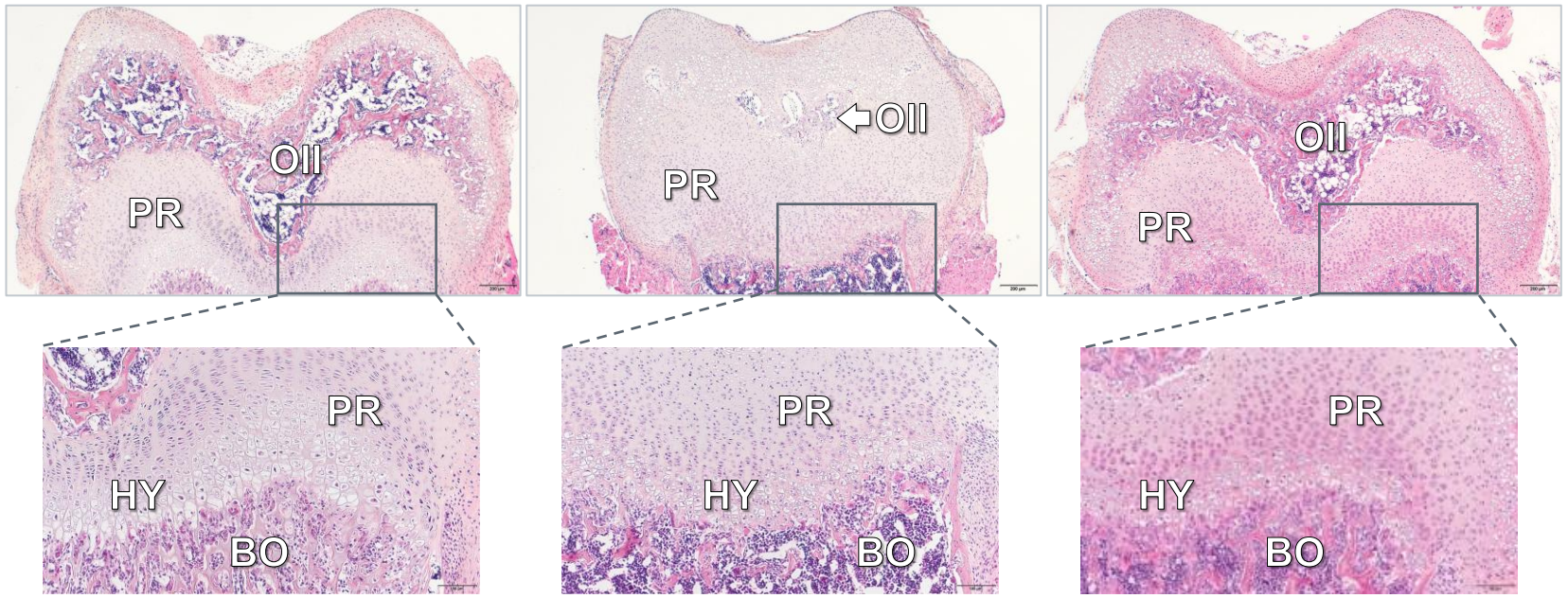
IOSA: intraoccipital synchondrosis anterior

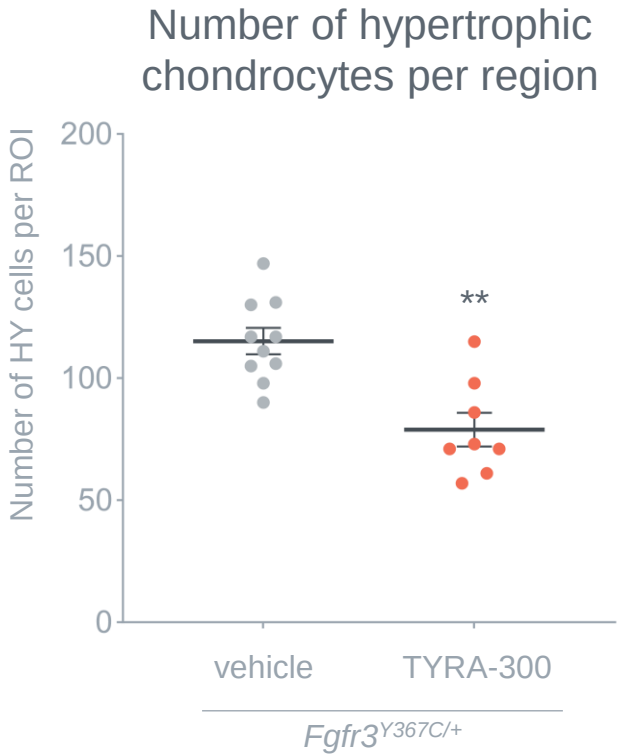
Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; Daily subcutaneous injection of TYRA-300 at 1.2 mg/kg/day for 15 days starting at Day 1; n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from dataset when molecular analysis showed chimeric incorporation of mutation.

Mann Whitney test vs. vehicle
*** $p < 0.001$

TYRA-300 increased chondrocyte proliferation and differentiation

DISTAL FEMUR





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

Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France
Hematoxylin and eosin stains of distal femurs. PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone

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

1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2.
3.
4.

Fold Selectivity for FGFR3

	Infigratinib	TYRA
FGFR1	2.2x	63x
FGFR2	0.8x	19x
FGFR4	67x	55x

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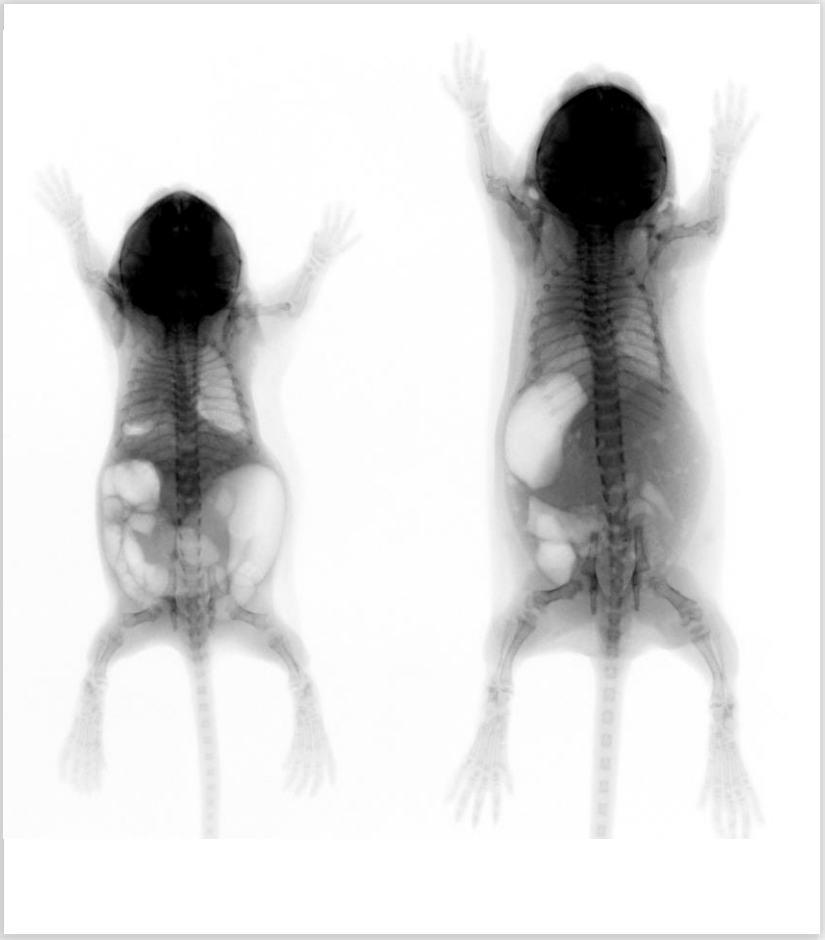

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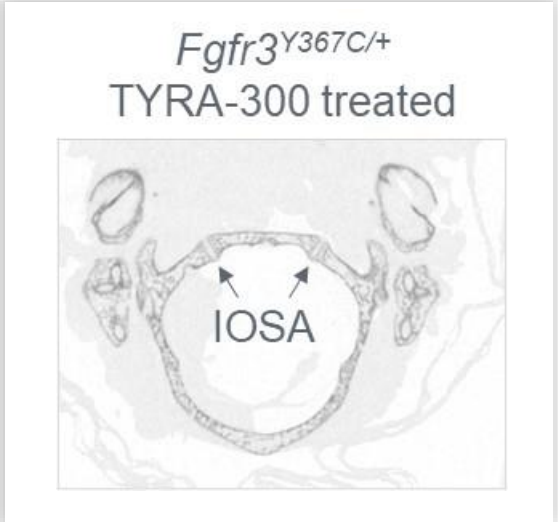

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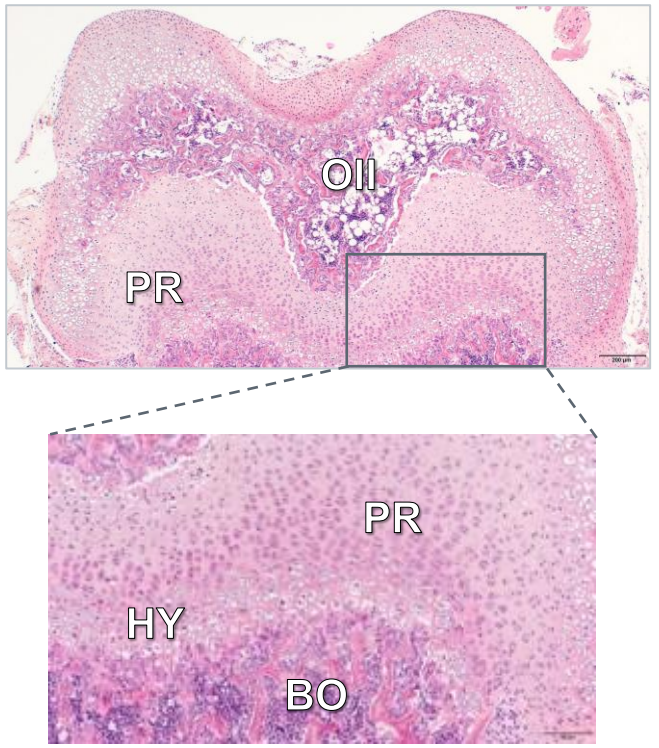
1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2. Increased bone length of the appendicular and axial skeleton in the *Fgfr3*$^{Y367C/+}$ mouse model
3. Improved the size and shape of the skull and foramen magnum
4. Restored growth plate architecture by improving proliferation and differentiation of chondrocytes

Fgfr3$^{Y367C/+}$
TYRA-300 treated



We greatly appreciate our collaborators at the Institut Imagine!

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