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Introduction to Clementia's Multiple Osteochondromas Program: efficacy of PVO in Fsp1-Ext1^{cko} mice ACAR conference

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Executive Medical Director
April 7, 2018

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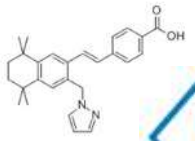
Palovarotene

Retinoic Acid Receptor Gamma (RARγ) Agonist

2003-2013



Roche

- **Oral, small molecule in-licensed from Roche after testing in >800 subjects; >450 dosed chronically up to 2 yrs**
- **Well-tolerated, safety profile was consistent with other retinoids**

Fibrodysplasia Ossificans Progressiva (FOP) 2013-2017

- **Publication of newly discovered role of RARγ agonists in the prevention of heterotopic ossification (HO)**
- **RARγ agonists inhibit BMP signalling and bind nuclear hormone receptors**
- **Company formed to evaluate palovarotene as a potential treatment for FOP**
- **Phase 2 dose ranging study completed**
- **Global Ph 3 MOVE trial in FOP initiated 4Q2017**

Multiple Osteochondroma(MO) 2016-2017

- **Publications identify abnormal BMP signalling in the pathologic changes in mouse models of MO**
- **Clementia collaborated with Yamaguchi to evaluate the effect of palovarotene to inhibit osteochondroma growth**
- **Advisory board of international experts in MO formed to develop a clinical trial**
- **Global Ph 2 MO-Ped trial in MO initiated 1Q2018**

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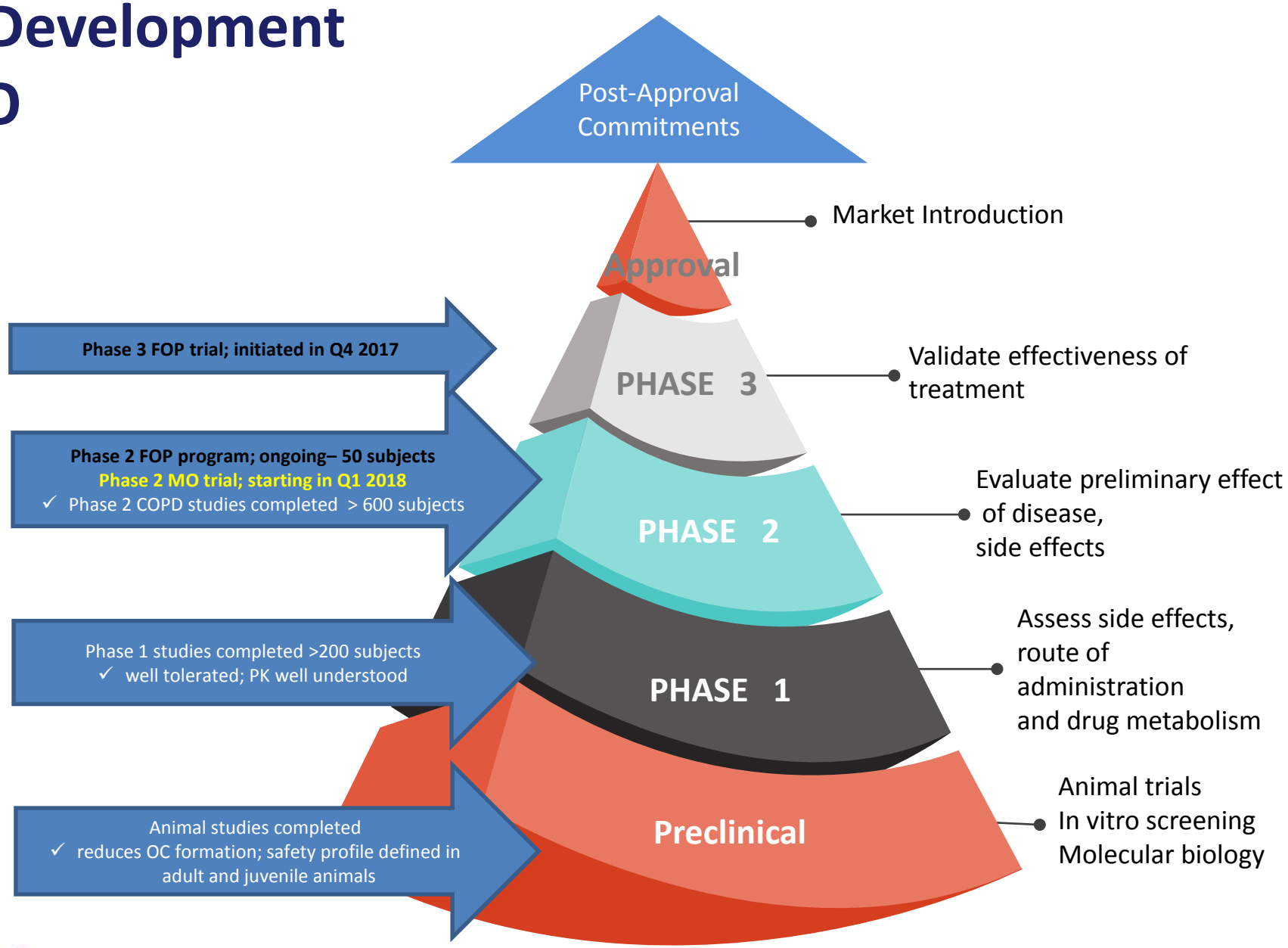
Clementia Team: Highly experienced, dedicated rare disease drug development experts

Palovarotene Development Program in MO



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Palovarotene is an Oral Small Molecule with a Well Characterized Safety Profile

Adverse Events

- Adverse events primarily dose-related mucocutaneous side effects
  - dry skin/mouth/eyes
  - Rash
  - Itching
  - Redness
- Managed with prophylactic treatments, and dose reduction (if necessary)
- No treatment related effects on growth plate or linear height observed to date

Clinical Laboratory ECG

- No treatment related changes in clinical safety labs or ECGs

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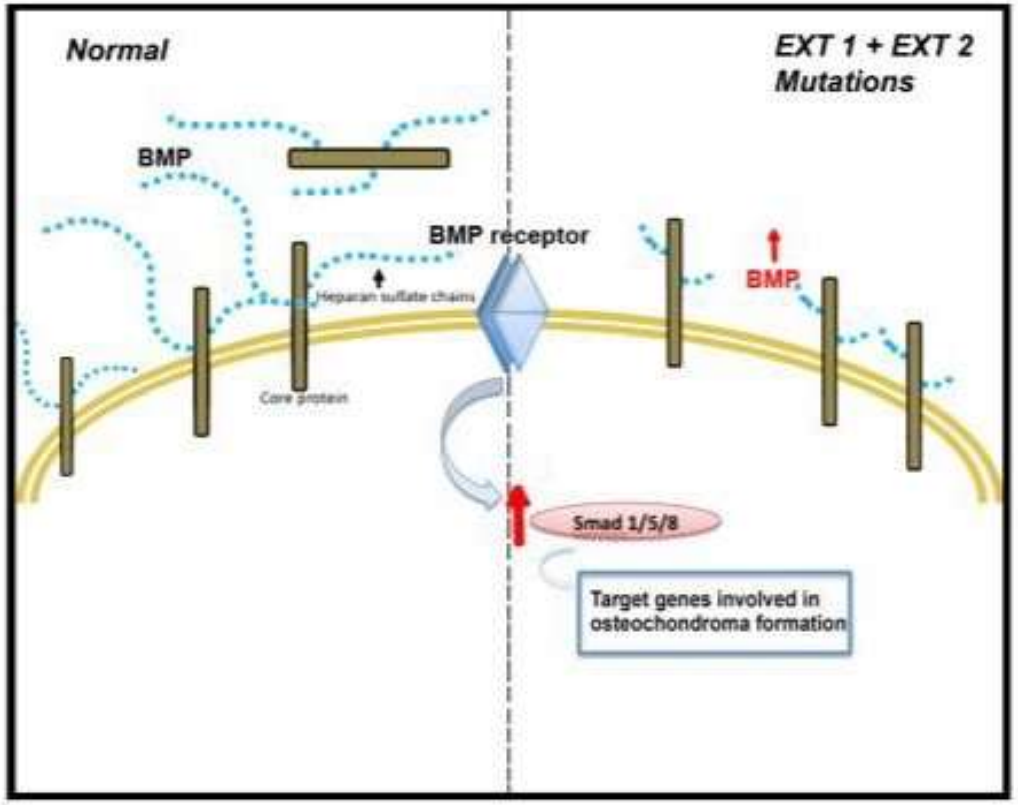
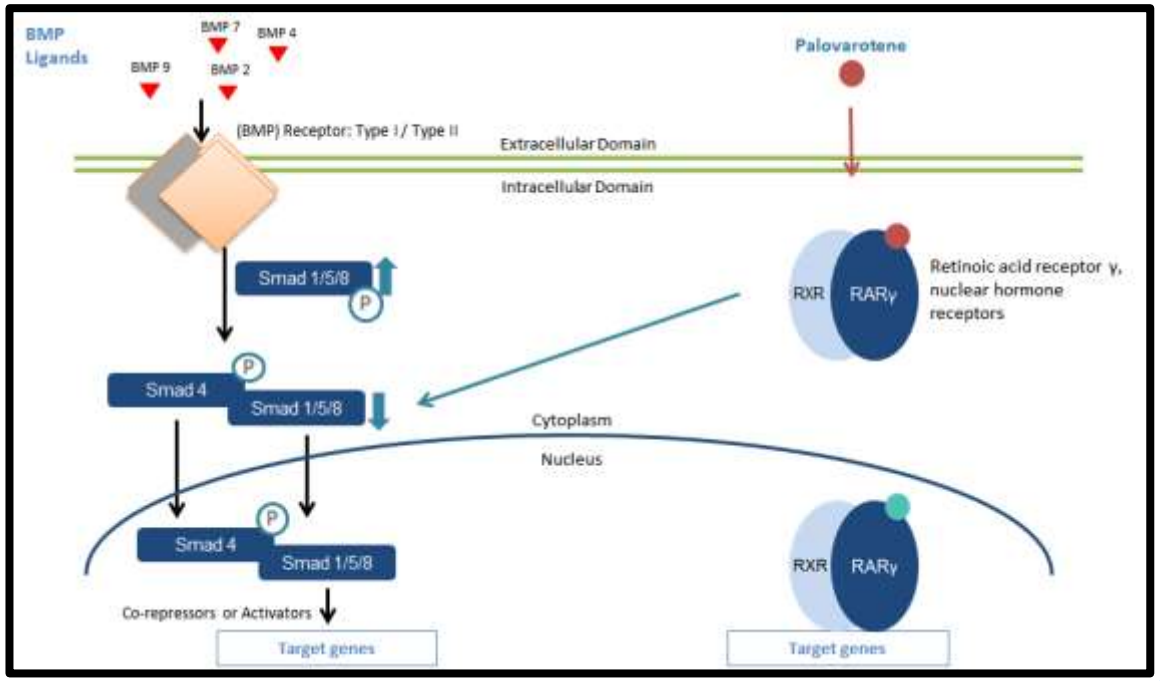
Mechanism of Action

Multiple osteochondromas (MO) mediated by excess BMP signaling



Palovarotene suppresses effects on mediators of BMP signaling



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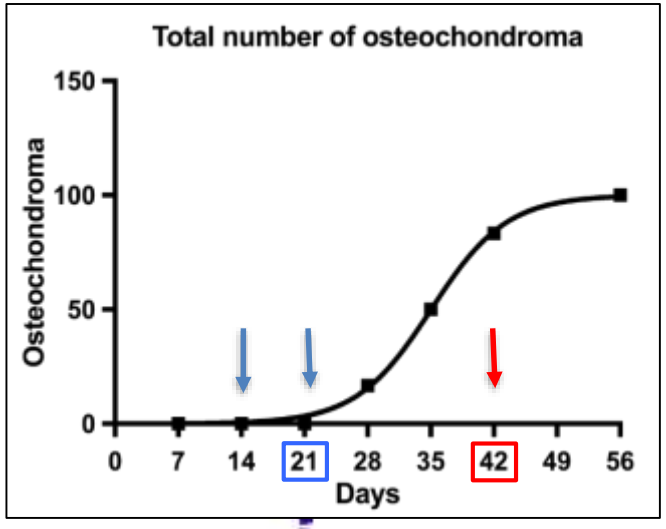
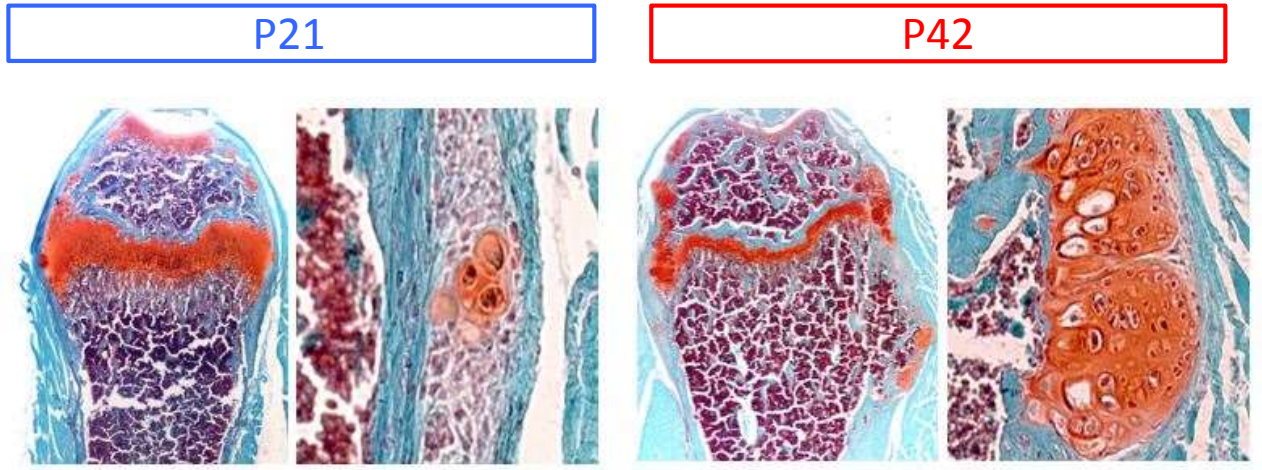
Fsp1-Ext1^{CKO} mouse model of MO

- *Fsp1* is expressed by precursor cells of the mesenchymal lineage, and its expression in developing bone is restricted to the perichondrium and periosteum
- Fsp1-Ext1^{CKO} mouse develops multiple osteochondromas in rib and long bones – *Inubushi et al., JCI 2017*

Time course of osteochondroma formation in *Fsp1*-Ext1^{CKO} mice





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Fsp1-Ext1^{CKO} mice demonstrate many of the pathologic features of MO

12 weeks

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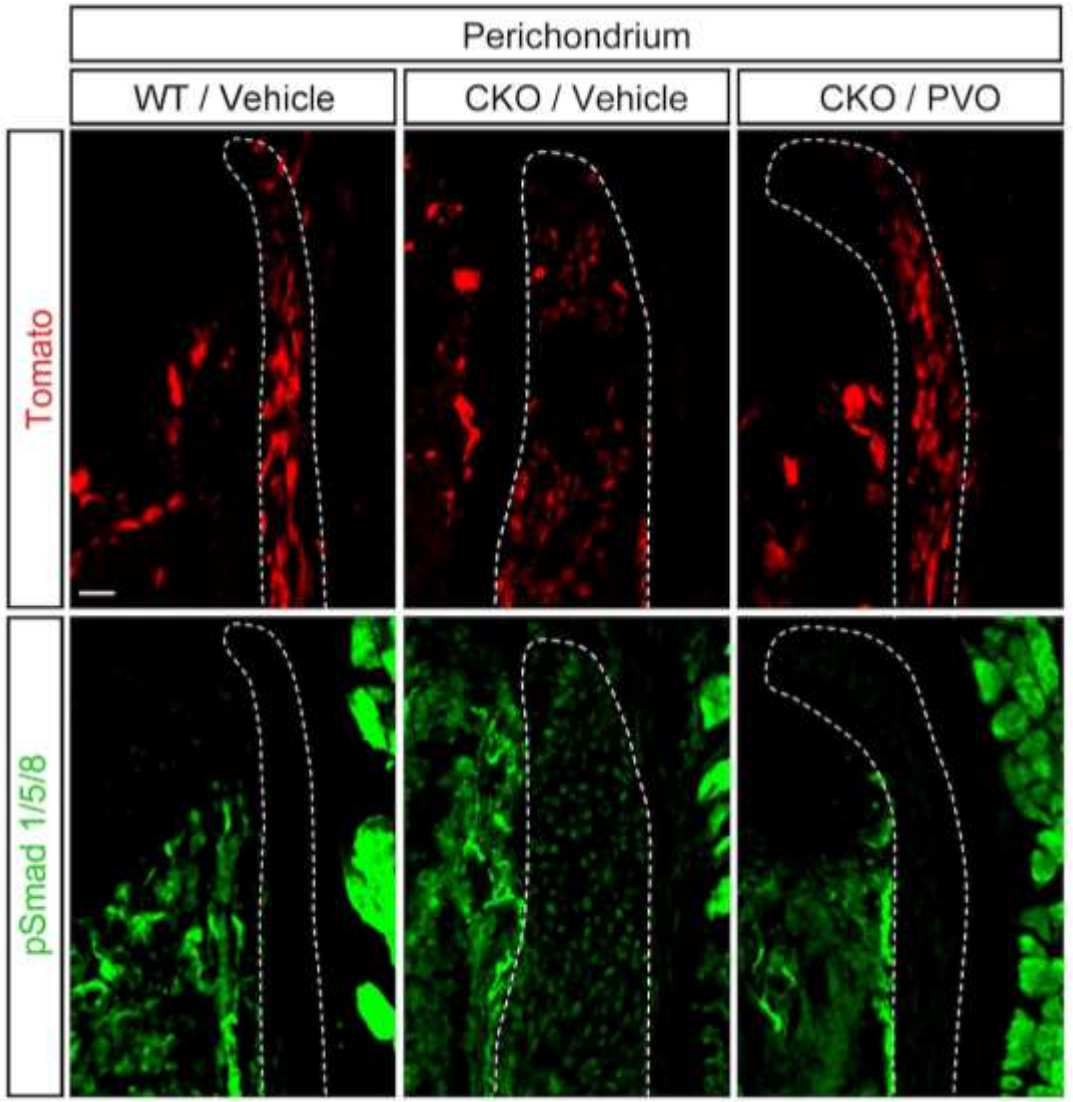
Modified from Inubushi et al.,2017 JCI

Palovarotene reduces Smad 1/5/8 phosphorylation in R26^{Tom}Fsp1-Ext1^{CKO} mice

- Mesenchymal cells marked by Tomato expression in the perichondrium (depicted by dashed line)
- pSmad 1/5/8 expression in the perichondrium
- Fsp1-Ext1^{CKO} mice exhibit excess BMP signaling in developing bone
- Palovarotene at 1.76 mg/kg/day from P21-P31 reduces pSmad 1/5/8 to WT

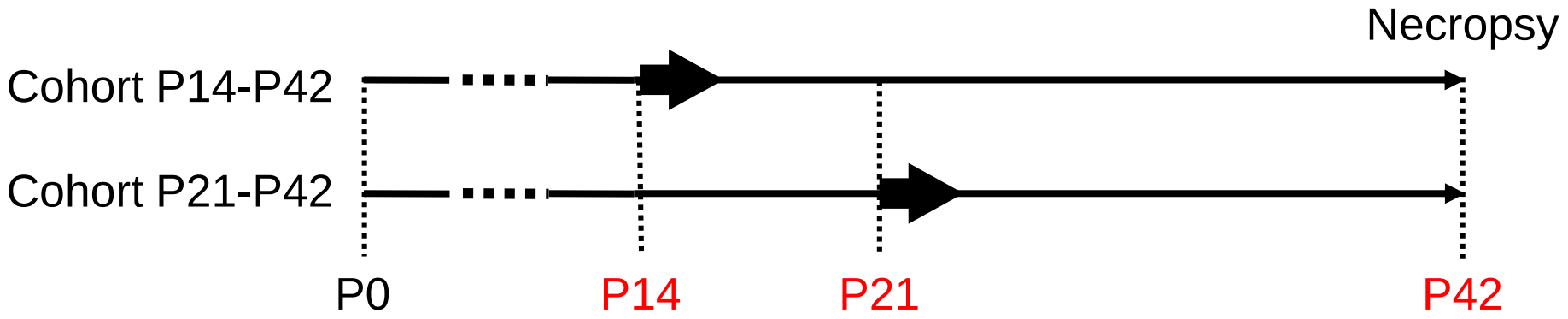


Scale bars, 50 µm

Adapted from Inubushi et al., submitted
Laboratory of Dr. Yu Yamaguchi, Sanford Burnham Prebys Medical Discovery Institute

Study Design – Palovarotene in Fsp1-Ext1^{CKO} mice

- Dosing regimen: daily
- Route of administration: oral gavage
- Dose levels: 0.27, 0.88 and 1.76 mg/kg palovarotene or vehicle
- Treatment schedule



- Sample size: 6 – 11 per group
- Endpoints: Number of OCs, bone length, histology

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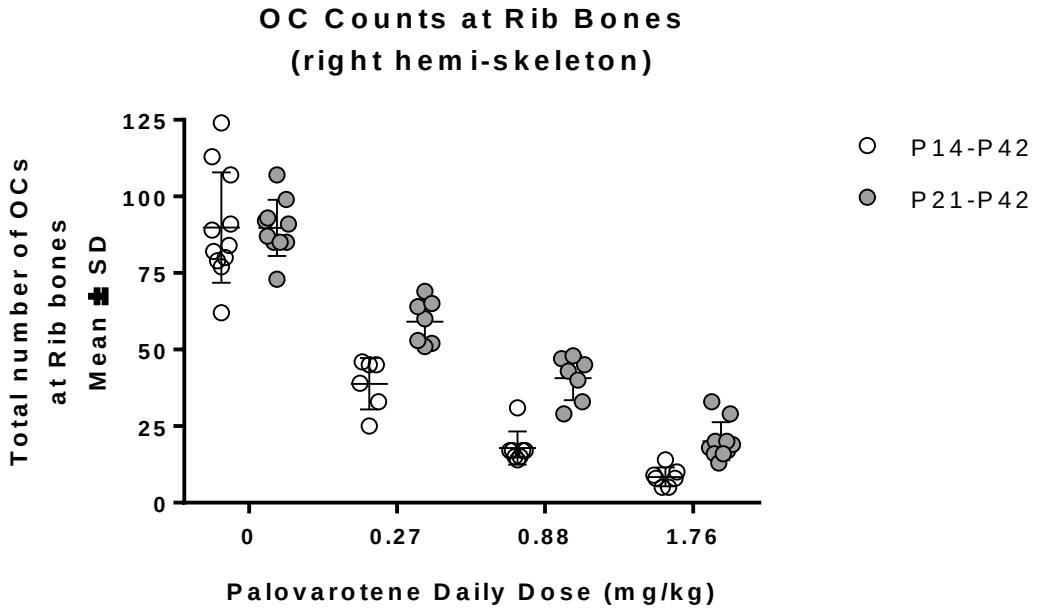
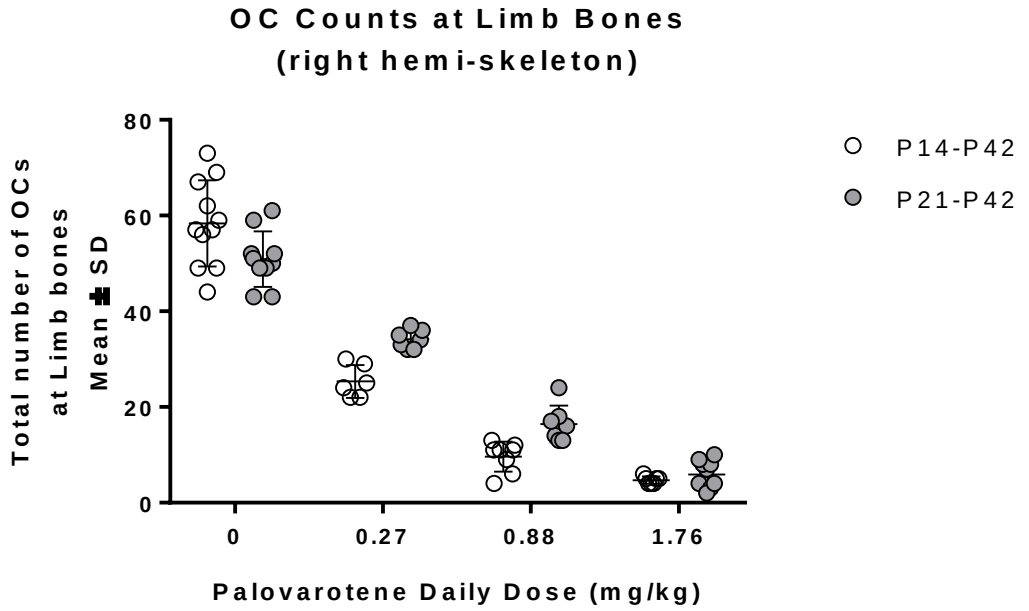
Palovarotene reduces OC formation at rib and long bones in Fsp1-Ext1^{CKO} mice





	EC_{50} (mg/kg)	Mean (SD) % Decrease Vs Vehicle		
PVO (mg/kg)		0.27	0.88	1.76
P14-P42	0.20	57 (9)	80 (6)	91 (3)
P21-P42	0.59	34 (8)	55 (8)	78 (7)

	EC_{50} (mg/kg)	Mean (SD) % Decrease Vs Vehicle		
PVO (mg/kg)		0.27	0.88	1.76
P14-P42	0.20	57 (6)	83 (6)	92 (1)
P21-P42	0.43	33 (4)	68 (8)	88 (6)

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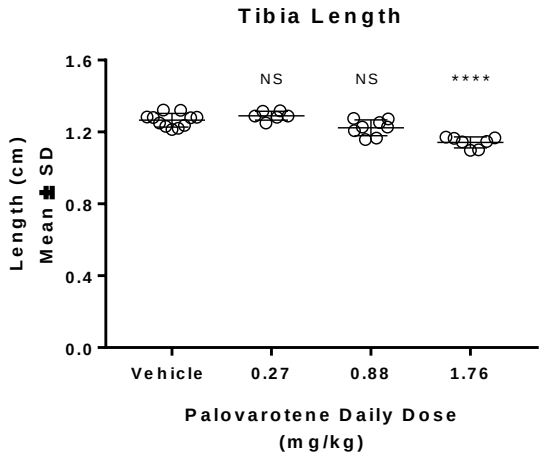
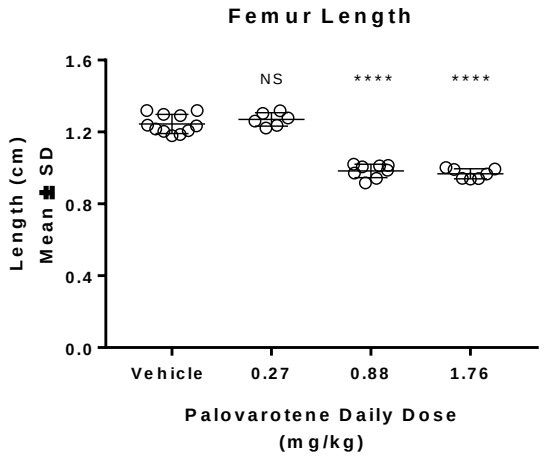
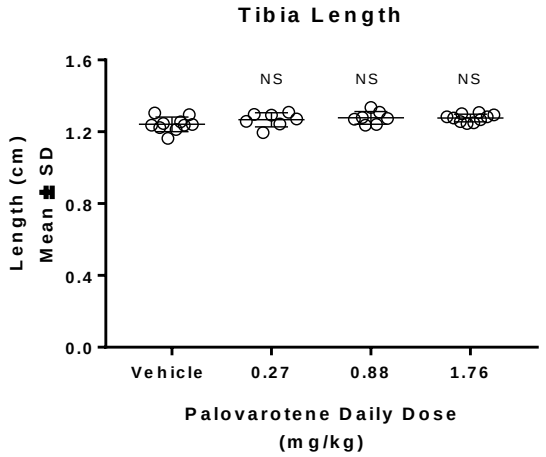
Palovarotene effect on long bone development is age and dose dependent

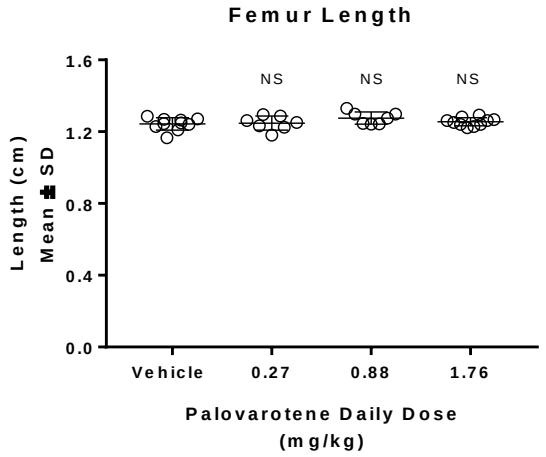
P14-P42





P21-P42





Ordinary one-way ANOVA followed by Tukey's multiple comparisons test
NS, not significant; ****, p<.0001

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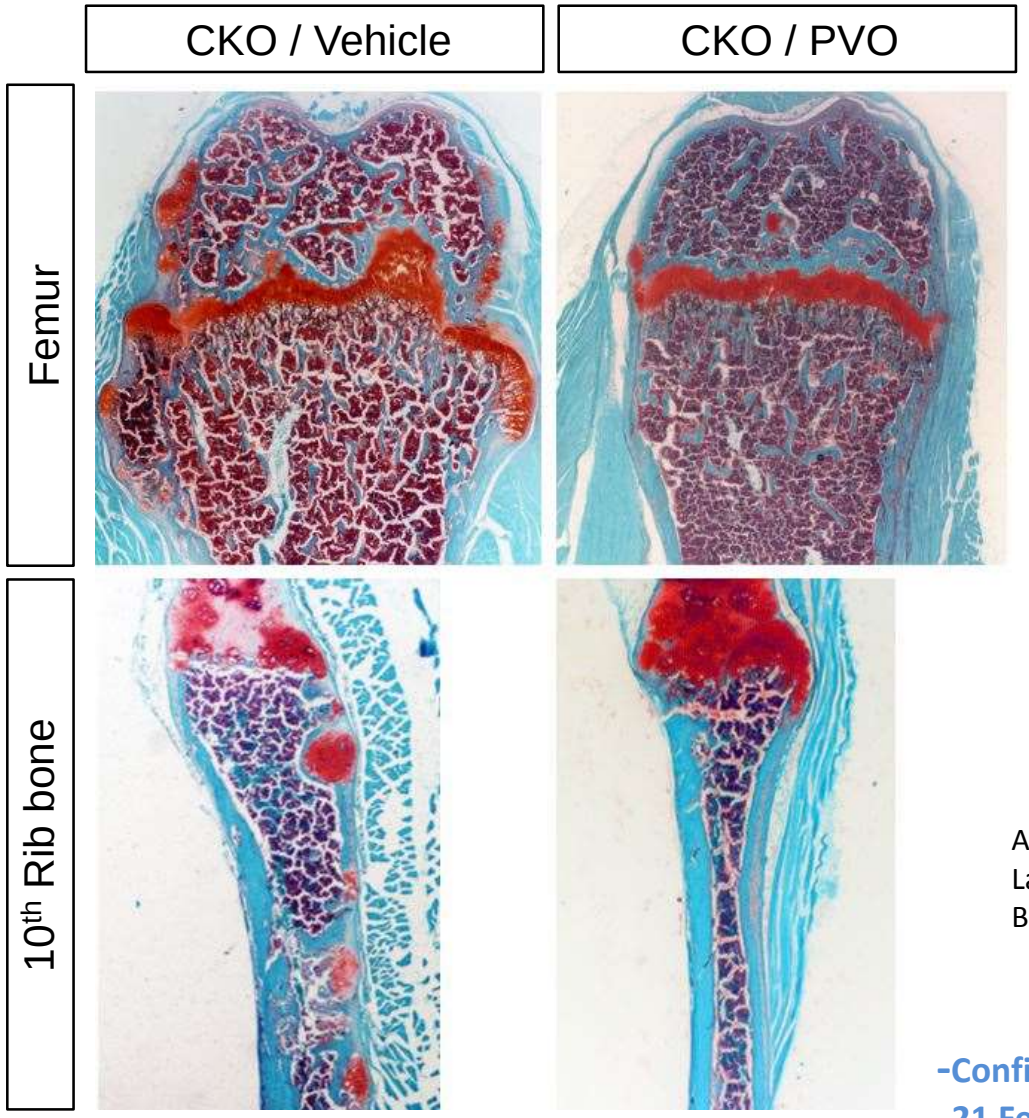
PVO restores growth plate architecture in Fsp1-Ext1^{CKO} mice (cohort P21-P42)



Adapted from Inubushi et al., 2017
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Age and dose selection minimizes risk to growth while optimizing efficacy in children

- Daily treatment of palovarotene reduces OC formation in a dose dependent and age dependent manner
- There is a therapeutic window (timing of treatment and dose) such that bone growth is preserved while maintaining efficacy in suppressing OC formation
- Lower age of 2 years based on juvenile toxicology data
- Doses selected (2.5 mg and 5 mg) are predicted to have exposures below the highest non-severely toxic dose (skeletal effects are mild and reversible at this dose)
- These doses approximate the low and mid doses used in the Fsp1-EXT1 experiments
- Chronic dosing at 5 mg for 2 years was well tolerated in COPD patients
- Safety monitoring for growth and bone health incorporated into study

Palovarotene Program

Sincere Gratitude