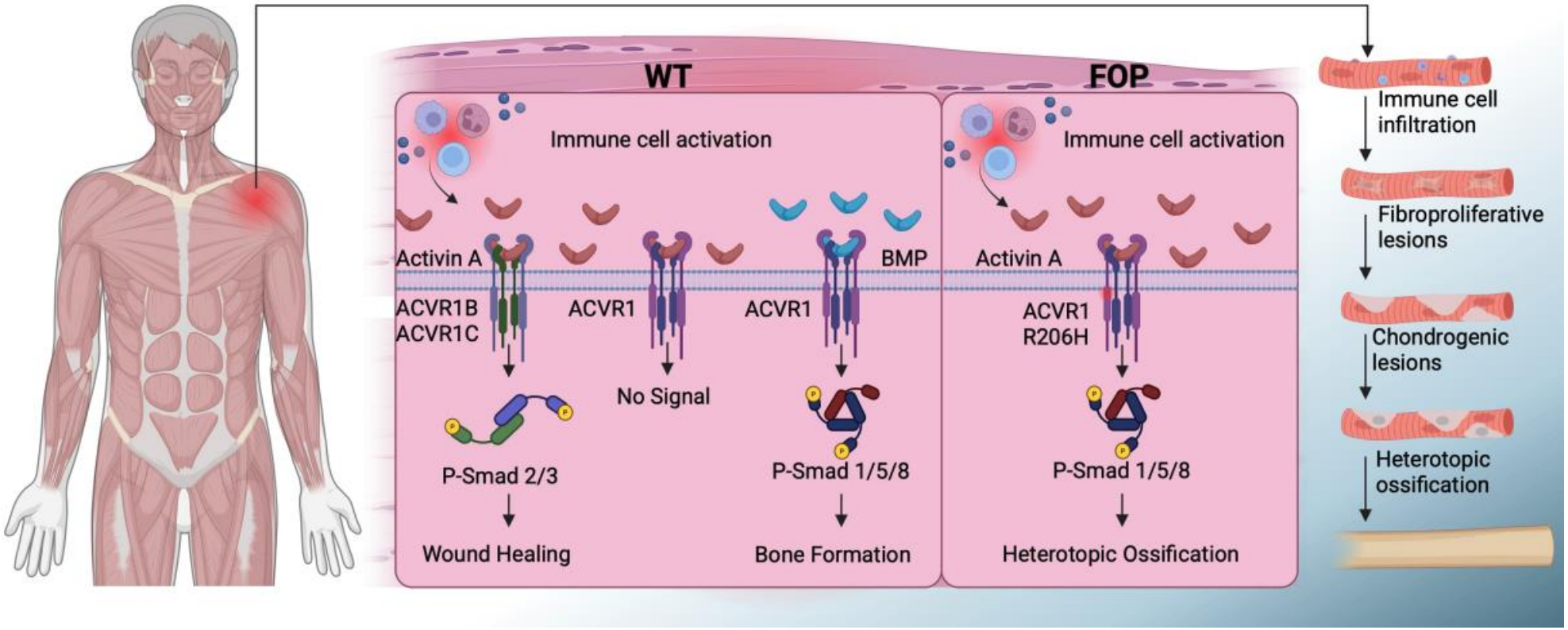
The Evolving Therapy Landscape for FOP

Mark Hamilton, PhD
Director of Research
International FOP Association

Mutant ACVR disrupts normal developmental signals & cell responses



- ACVR1 normally controls wound healing and bone formation in response to different Bone Morphogenic Proteins (BMPs)
- Activin A controls signals from ACVR1/ALK2; The interaction of Activin A with ACVR1 normally turns-off ACVR/ALK2.
- However, the ACVR1 mutations seen in FOP cause Activin A to now turn-on ACVR1/ALK2 promoting the formation of bone

FOP Clinical Trail Landscape

* Trial includes paediatric subjects

Trial	NCT No.	Drug	Drug Class	Enrollment	Ph 1	Ph 2	Ph 3	Current Status
MOVE PIVOINE (ext)	03312634 05027802	Palovarotene (IPSEN)	RARγ activator	N = 107				APPROVED Canada, Russia, USA, UAE, Australia
NEW: FOPal	06089616	Palovarotene (IPSEN)	RARγ activator	N = 100	Long-term Safety and Effectiveness of Palovarotene in Individuals With FOP			RECRUITING OBSERVATIONAL REGISTRY
OPTIMA	05394116	Garetosmab (REGENERON)	anti-Activin A Antibody	N = 63				PHASE 3 BLA FILED: FDA & EMA
NEW: Paediatric study	TBD	Garetosmab (REGENERON)	anti-Activin A Antibody	N = TBD	Estimated start 2026			NOT YET OPEN* ADOLESCENT/PAEDIATRIC
STOPFOP	04307953	Saracatinib (ASTRAZENECA)	ALK2(+) Kinase Inhibitor	N = 17				PHASE 2 ACTIVE
FALKON	05039515	Fidrisertib (IPSEN)	ALK2-selective kinase inhibitor	N = 113				Phase 2 TERMINATED
PROGRESS	05090891	Zilurgisertib (INCYTE)	ALK2-selective kinase inhibitor	N = 98				PHASE 2* ACTIVE
ANDECAL	06508021	Andecaliximab (ASHIBIO)	Anti-MMP9 antibody	N = 92				PHASE 2/3* ACTIVE
IL-1 inhibitor (off-label use)	06724562	Canakinumab or Anakinra (UCSF)	Anti-IL-1β antibody	N = 11	'Exploratory/observational': To inform potential for a Phase 1 study			RECRUITING*

What do we know about the the most advanced FOP drugs?

Drug	Drug Class	Dosing Route	Dose levels tested	Activity/Efficacy	Notes & Side-Effects
Palovarotene (IPSEN) APPROVED Canada, Russia, USA & Australia	RARγ activator	Oral (PO)	• 5mg daily • Upon signs of flare-up, then 20mg daily for 28 days, and then 10mg daily for 56 days	60% reduction in annualized new bone growth	• 35.8% subjects <14 years of age experience complete or partial closure of bone growth plates (premature physeal closure/PPC) • Palovarotene is not recommended for girls under 8 years of age and boys under 10 years age
Garetosmab (REGENERON) Under FDA & EMA review	anti-Activin A Antibody	Intravenous (IV)	• 3mg/kg or 10mg/kg body weight every 28 days	>90% reduction in new bone growth at 56 weeks (Regeneron reported)	• Increase in skin and soft tissue infections • No serious bleeding events reported (Regeneron reported)

- **MOVE trial:** Data collected from the Clementia Pharmaceuticals FOP Natural History Study (NHS: NCT02322255; 2014-2020) was used as the reference/comparator dataset to evaluate the clinical activity of Palovarotene:
  - Primary outcome measures: Annualized new bone growth (HO)
  - NHS enrollment N = 114 subjects
    - 39/97 subjects who participated in the NHS also participated in MOVE: These subjects had a 54% reduction in annual new bone growth compared with standard-of-care (SoC) treatment
- **OPTIMA Trial:** Placebo-controlled with cross-over to treatment for patients receiving placebo after 56 weeks. Extension phase to 84 weeks.
  - Primary outcomes measure: Number of new HO lesions and safety/SAEs

What might a better FOP drug look like?

Palovarotene

- Moderate activity in reducing new bone growth (reported ~60%)
- Long-term efficacy is unknown – requires further study
- Long-term safety is unknown – requires further study
- Equal benefit for all patients? – requires further study
- Not recommended for younger subjects.

Garetosmab

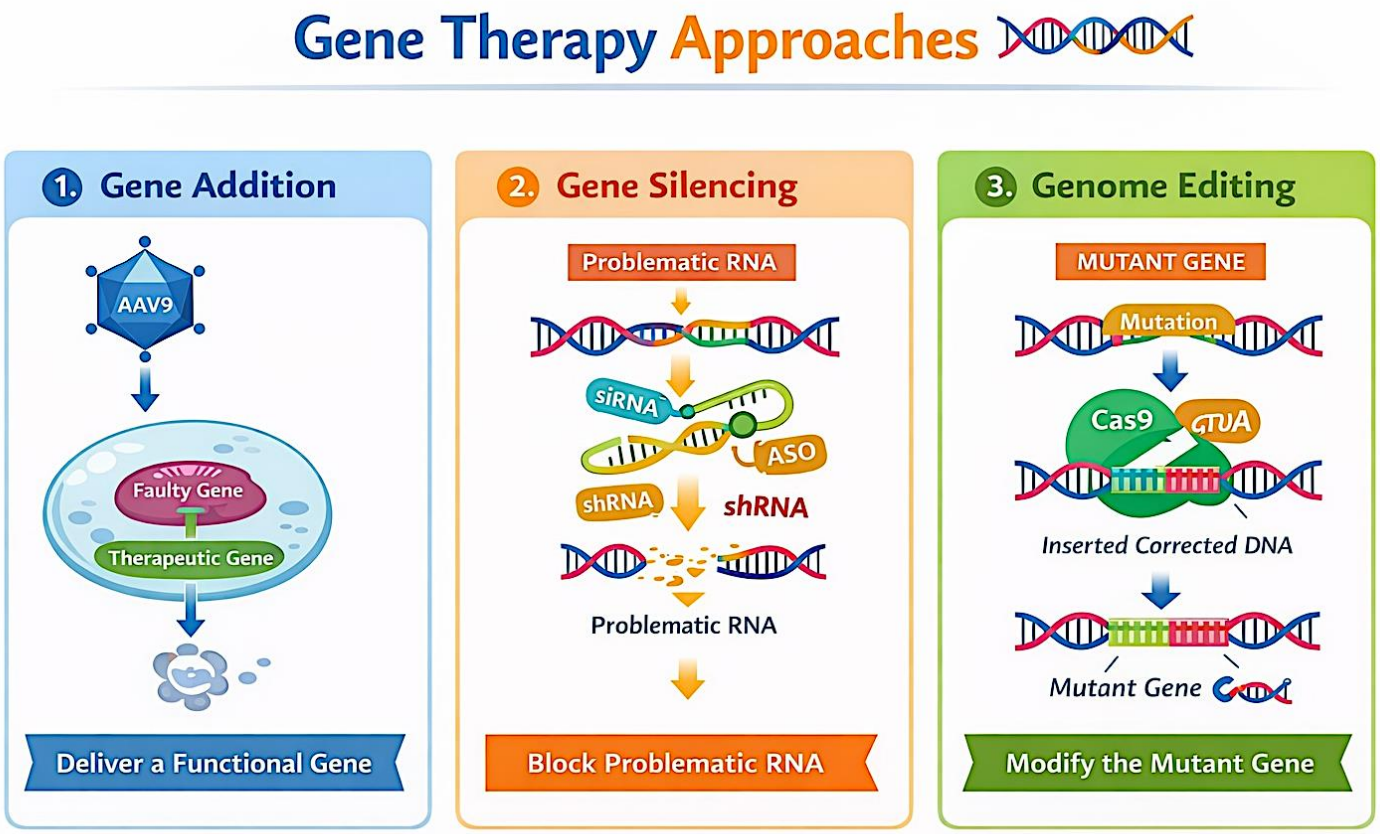
- Highly effective in reducing new bone growth (reported >90%)
- Long-term efficacy is unknown – requires further study
- Long-term safety is unknown – requires further study
- Equal benefit for all patients? – requires further study
- Not yet studied in subjects <18 years

If approved, Garetosmab would be the benchmark for other FOP drugs

What would a better FOP drug look like? Things to consider:

- Similar or better efficacy/activity compared with the best approved treatment – improvements in other symptoms
- Improved safety profile – less toxicity/fewer side-effects and more manageable (avoid drug holidays/discontinuations)
- Safe and effective in adult and pediatric subjects
- Dosing Schedule: ≳ Monthly >> Weekly >> Daily
- Dosing Route: Oral (po) >> Subcutaneous (sc) >> Intravenous (iv)
- **SELECTIVITY – specific inhibition of mutant ACVR1/ALK2 activity.** Sparing of the normal, ACVR1/ALK2 activity and the restoration of normal ACVR1/ALK2 functioning
- **No FOP drugs under development are selective for mutant ACVR1/ALK2 – they are designed to block all ALK2 activity. This blockade of all ALK2 activity may become a problem in the long-term.**

Genetic Therapy for FOP



Fix: Loss-of-function mutations | Fix: Gain-of-function mutations | Fix: Gain-of-function mutations

Gene therapy describes a number of different therapeutic approaches designed to correct a mutated, disease-causing gene at the DNA level:

- Adding a functionally active copy of a gene
- Silencing a mutated gene
- Replacing the mutated part of a gene (exon or base sequence) with a normal version
- Replacing a mutated gene with a normal gene (gene size limitation)

The specific genetic therapy approach may be dictated by the type and location of the gene defect to be fixed

Genetic Therapy for FOP – AAV9 application in FOP

Adenovirus Associated Virus 9 (AAV9) is used to package and deliver different types of genetic therapy to cells

Why deliver therapy using a virus (AAV9)?

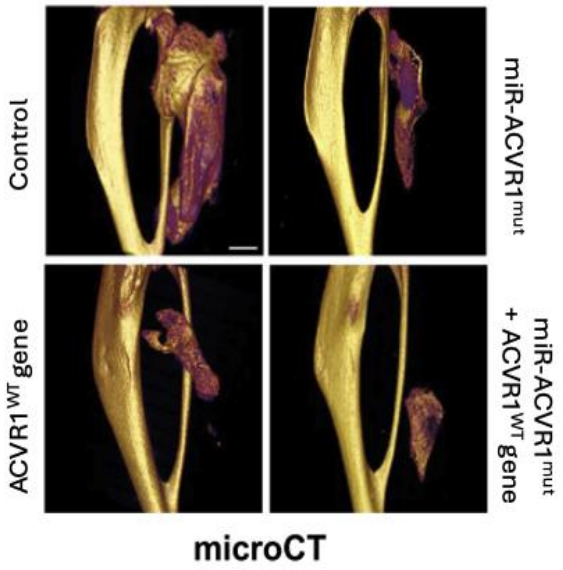
- Systemic – able to infect multiple tissues including muscle and the nervous system
- AAV9 infected cells can express the delivered gene (therapy) for a long time (e.g., possibly years)
- Is less less likely to induce an immune response than other virus delivery systems
- AAV9 is also considered non-integrating – the delivered gene therapy is much less likely to be integrated into your DNA (genome) possibly disrupting other genes and causing new, possibly pathogenic, mutations
    - DNA packaged into AAV9 remains 'outside' your chromosomes (episomal DNA)

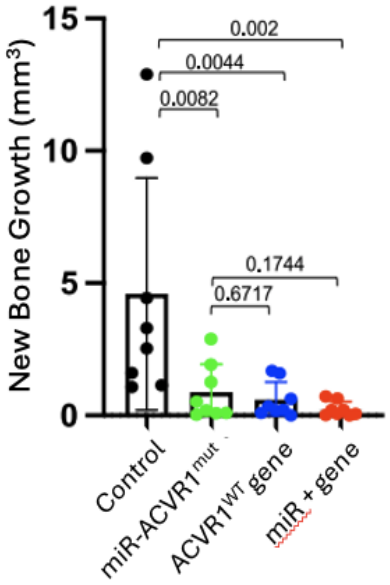
- Feasibility: Zolgensma is an approved AAV9-based drug - delivers the SMN gene to treat spinal muscular atrophy

- However, AAV9 is limited by the size of the gene that can be packaged in the virus
    - Limitation on what genes can be used
    - Therefore, any gene that is being delivered by AAV9 has to be quite small (~1600 nucleotides) or has to be engineered to fit; e.g., reduced to only the coding parts (exons) or truncated to smaller fragment with the desired function

Genetic Therapy for FOP – AAV9 application in FOP

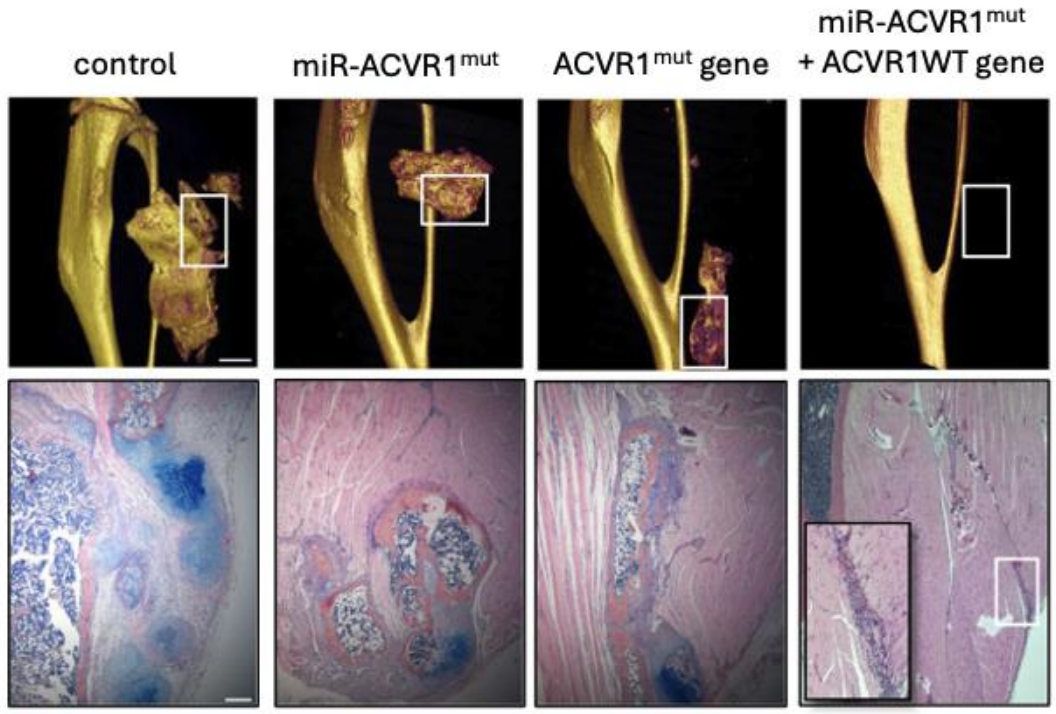
AAV9-delivered FOP genetic therapies block new bone growth in the mouse FOP model





- control: negative control treatment
- miR-ACVR1$^{mut:}$ Interfering RNA (amiR-RH6) against mutated ACVR1(R206H)
- ACVR1^{WT} gene: optimized normal ACVR1 gene
- miR + gene: miR-ACVR1^{mut} + ACVR1^{WT} gene

Injection of AAV9 gene therapy **at birth** prevents HO bone growth in the mouse FOP model (juvenile mice)



- Top: New bone growth (detected by microCT)
- Bottom: Alcian blue staining for chondrogenic analgen, the precursor of endochondral bone (4 weeks post-injury)

Yang, et al., (2022) Nat.Comms (Univ. Massachusetts RNA Therapy Institute)

AAV9 Gene Therapy - Status

- **Goal:** Replace the mutated ACVR1 gene with a normal ACVR1 gene in all affected cells ⇢ ⇢ ⇢ **CURE**
- Current AAV9 gene therapies do not replace a bad gene – they only deliver a working copy of a gene to cells

- Gene Replacement Therapy**:**
  - Replace the whole mutated gene (or the mutated region) where it resides on the chromosome (gene locus)
  - This is still mostly experimental and technically very challenging:
    - Requires efficient delivery - can be further refined to deliver to specific cells
    - Difficult to scale for whole body disorders – possibly resolved via targeting to specific cells (e.g., FAPs)

- Current and Future Technical Challenges:
  - Need for precise targeting of the normal gene (or gene editing machinery) to the exact gene locus to be replaced or repaired (CRISPR technology):
    - Repair process is inefficient
  - Safety and predictable repair outcomes
  - Unintended off-target editing or mis-integration of the replacement gene or gene fragment in the wrong chromosome or locus would likely have serious effect on an individual's health

Currently, there are no gene/genetic therapy trials for FOP

What genetic therapy might be the nearest to clnical development?

Selective Targeting of Mutated ACVR1(ALK2)

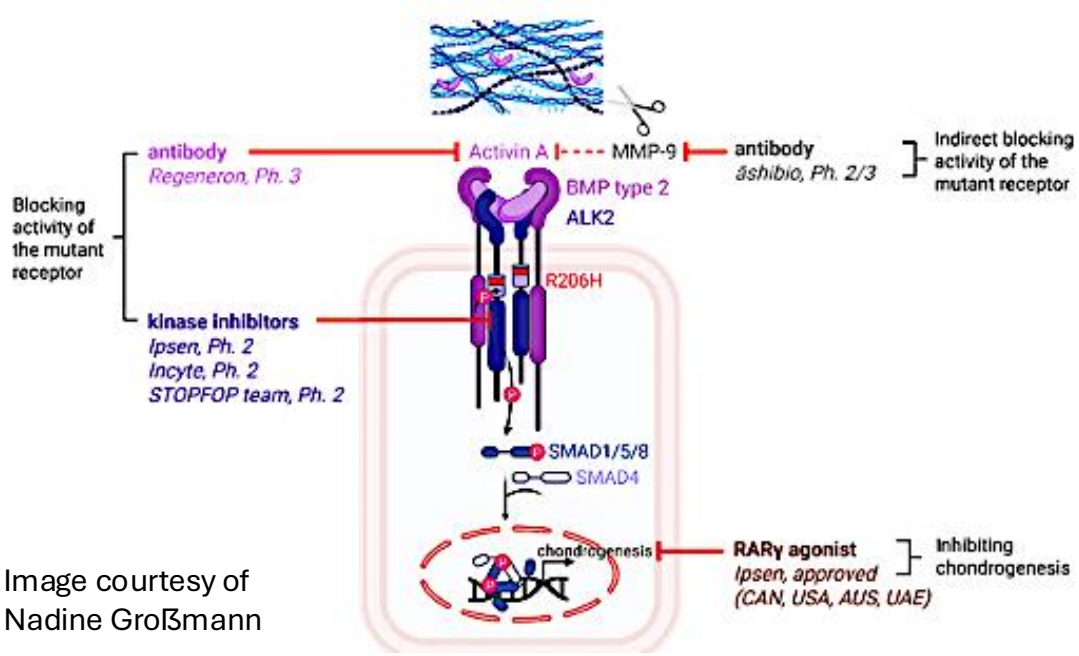


Image courtesy of
Nadine Großmann

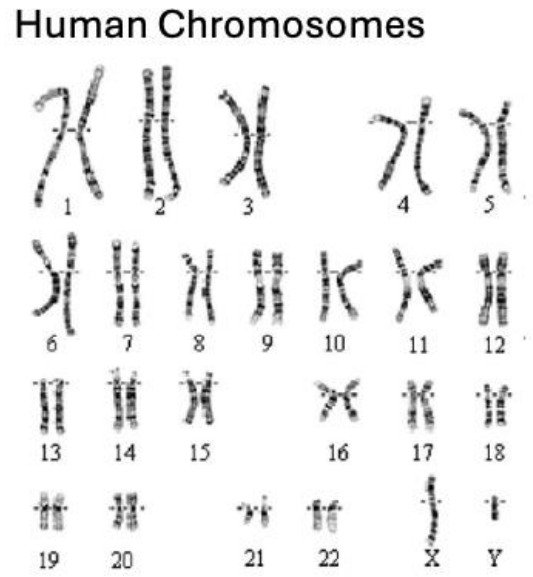
- **Selectivity:** Drugs currently under development block both mutated and normal/wild-type (wt) ACVR1/ALK2
- ACVR1/ALK2 is expressed in multiple tissues, not just FAP cells:
  - Skeletogenesis/bone formation
  - Soft tissue homeostasis (chondrogenesis)
  - Nerve cell development
  - Immune cell function/immunity
  - Iron homeostasis and erythropoiesis (control of anaemia)
  - Angiogenesis (growth of blood vessels/vascular development)
- Blocking both mutated and wt ACVR1/ALK2 can affect the normal function of ACVR1/ALK2 in other cells and tissues
- Current drugs for FOP do not selectively block the mutated ACVR1/ALK2 only
- The lack of selectivity for mutated ACVR1 may have detrimental effects on patients (e.g., long-term safety issues)

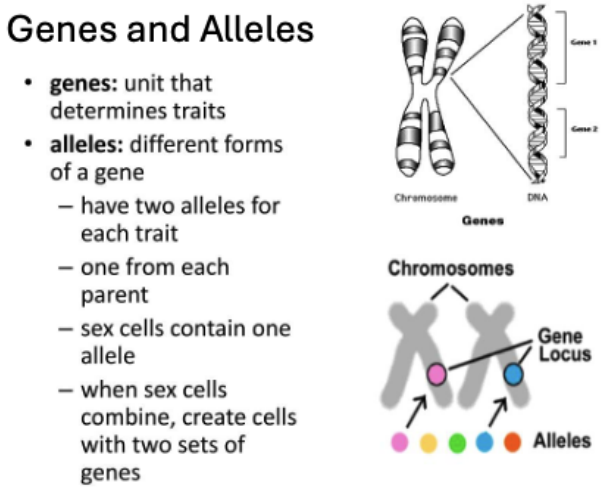
*Excluding Palovarotene, a transcription factor modulator, whose exact Mechanism of Acton (MOA) is less clear, but inhibits chondrogenesis

Genes and Alleles

- Our genetic traits and characteristics are determined by our DNA (genome)
- Our genome is organized on 46 chromosomes.
  - 23 chromosomes from our mother (Chr 1-22 + Chr X)
  - 23 chromosome from our father (Chr 1-22 + Chr X or Chr Y)
- Our chromosomes contain 2 copies of every gene (except males (XY)
- These different copies of the same gene are called alleles
- In FOP, mutation of an ACVR1 allele occurs *de novo* (in either the egg or sperm cell) or very early during embryogenic development
  - Most common, 'classic' R206H mutation is usually a c.617G>A in the DNA sequence of ACVR1
- Mutation of one ACVR1 gene (allele) results in the presence of a normal (wild-type) ACVR1 allele and a mutated ACVR1 (FOP) allele in every cell

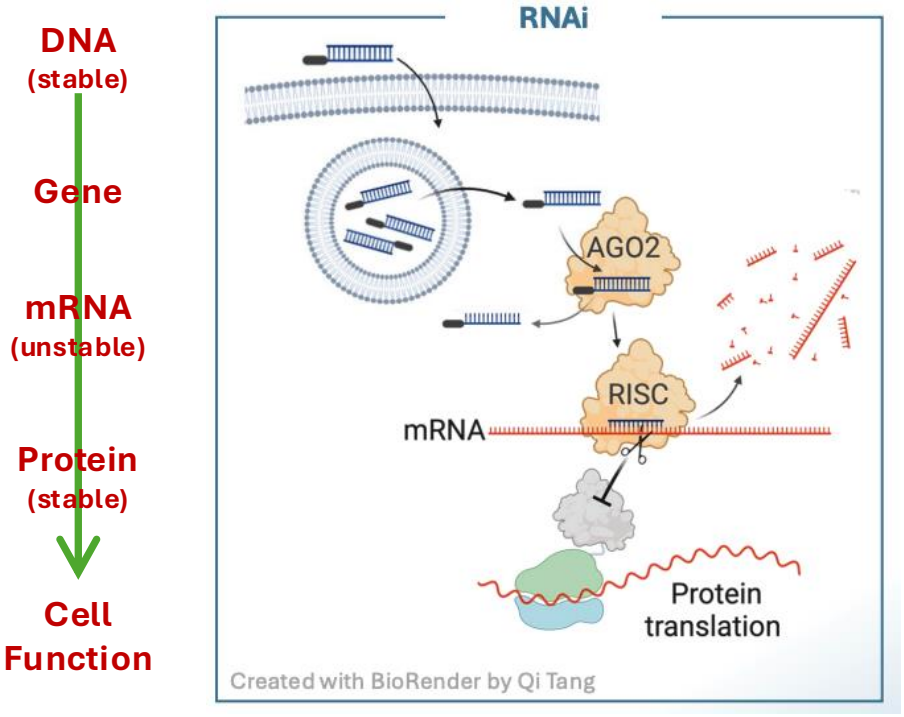
- **The development of drugs that specifically block the expression or activity of the mutated ACVR1 allele could restore normal ACVR1 activity and function**





RNAi Drugs – Targeting the FOP mutated ACVR1

Interfering RNA drugs block gene expression by targeting mRNA for degradation



- RNAi drugs take advantage of a natural, evolutionary conserved biological process that regulates messenger RNA (mRNA) stability.
- RNAi blocks protein expression by interfering with the translation of mRNA to protein for the targeted gene.
- RNAi drugs are chemically modified ribonucleic acid (RNA) molecules (20-30 RNA molecules long):
  - Stable/do not degrade quickly after being administered - can be detected weeks-to-months after administration
  - Retained within cells for long periods of time – long acting
  - Can be targeted to specific tissues.
- RNAi drugs can be designed to specifically target a gene (mRNA) of interest → → → selective degradation of the targeted mRNA (e.g., mRNA that codes for the mutated ACVR1/ALK2)

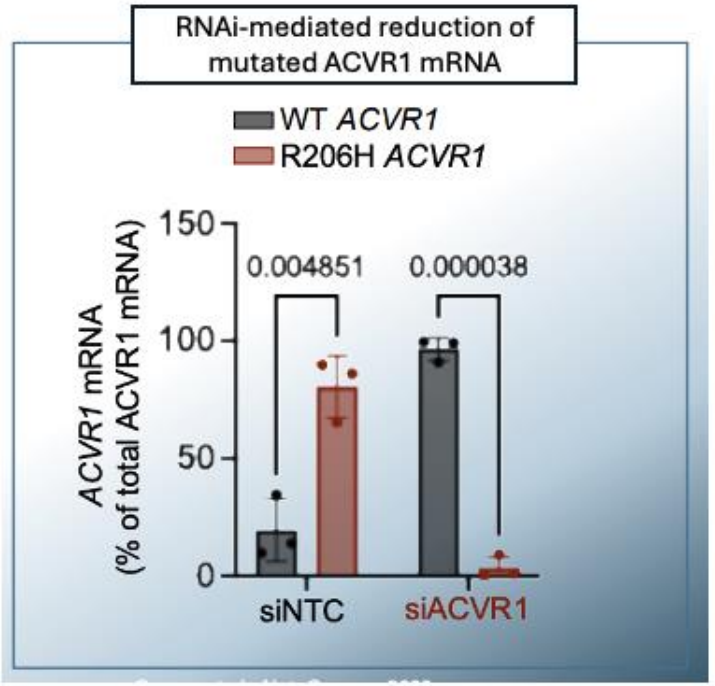
Genetic Therapy for FOP – Selective Targeting of Mutated ACVR1

RNAi allows for the selective targeting of mutated alleles, sparing the normal, wild-type ACVR1 allele

- Selective targeting of the mutated ACVR1 gene by a RNAi drug results in the the normal ACVR1^{WT} becoming the dominant ACVR1 in cells
- This targeted loss/degradation of the mutant ACVR1 mRNA will subsequently lead to the loss of mutated ALK2 protein in cells
- Normal ACVR1^{WT} mRNA and normal AKL2 protein will continue to be expressed in cells, restoring normal ACVR1/ALK2 activity and function

Note: The following slides discuss the activity of RNAi-based drugs that are specific for the ACVR1 c.617G>A mutation (codes for the 'classic' R206H mutation

- Other ACVR1/ALK2 FOP mutations would require unique RNAi-based drugs to selectively target those specific mutations



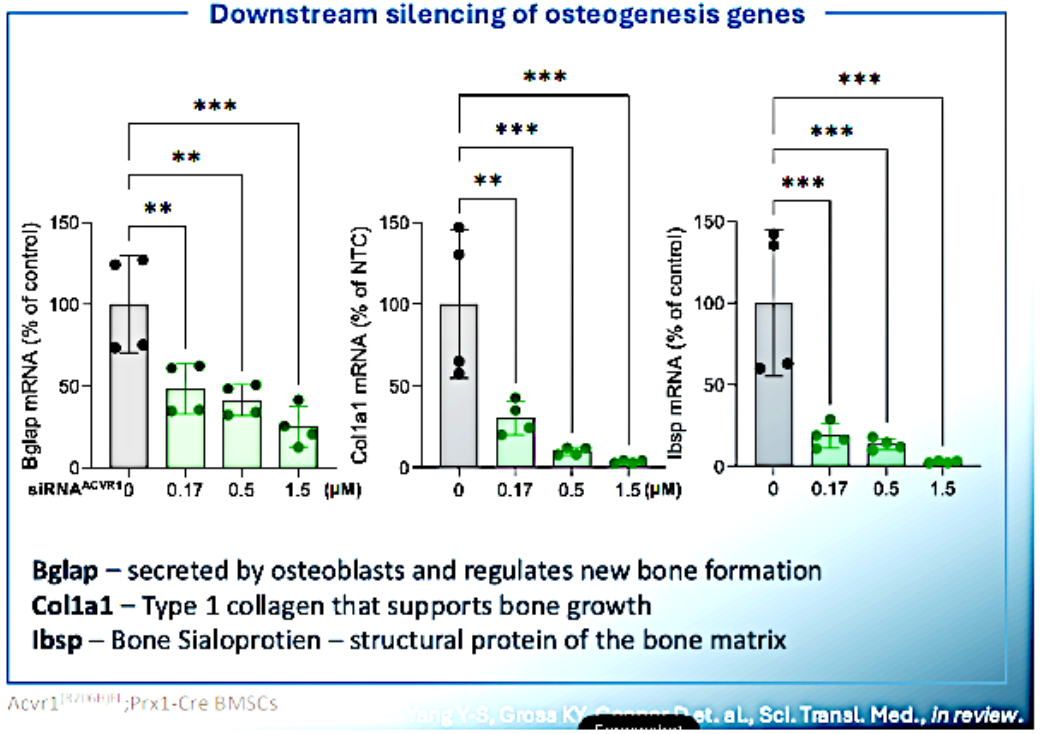
siNTC: non-targeted RNAi control
siACVR1ACVR1^{mut}-selective RNAi

Univ. Massachusetts RNA Therapy Institute

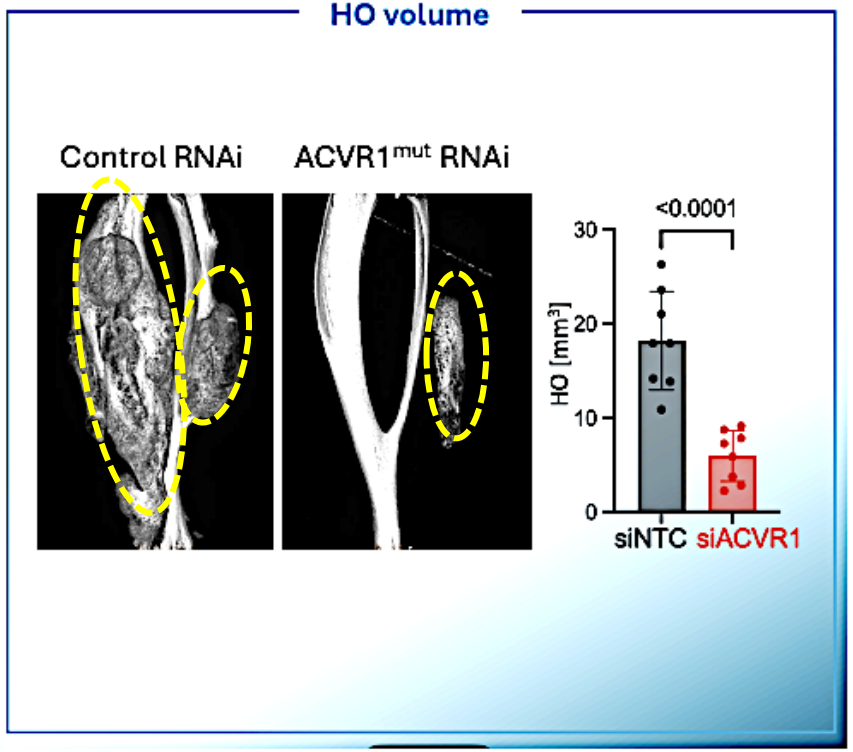
Genetic Therapy for FOP – Targeting Mutated ACVR1

Selective targeting of the FOP mutated ACVR1 allele by a RNAi drug inhibits the expression of genes involved in the development of bone and new bone growth in the mouse FOP pinch model

Loss of mutant ACVR1 expression also reduces the expression of genes associated with bone growth



Mutant ACVR1 RNAi drug inhibits HO formation in the FOP pinch mouse model

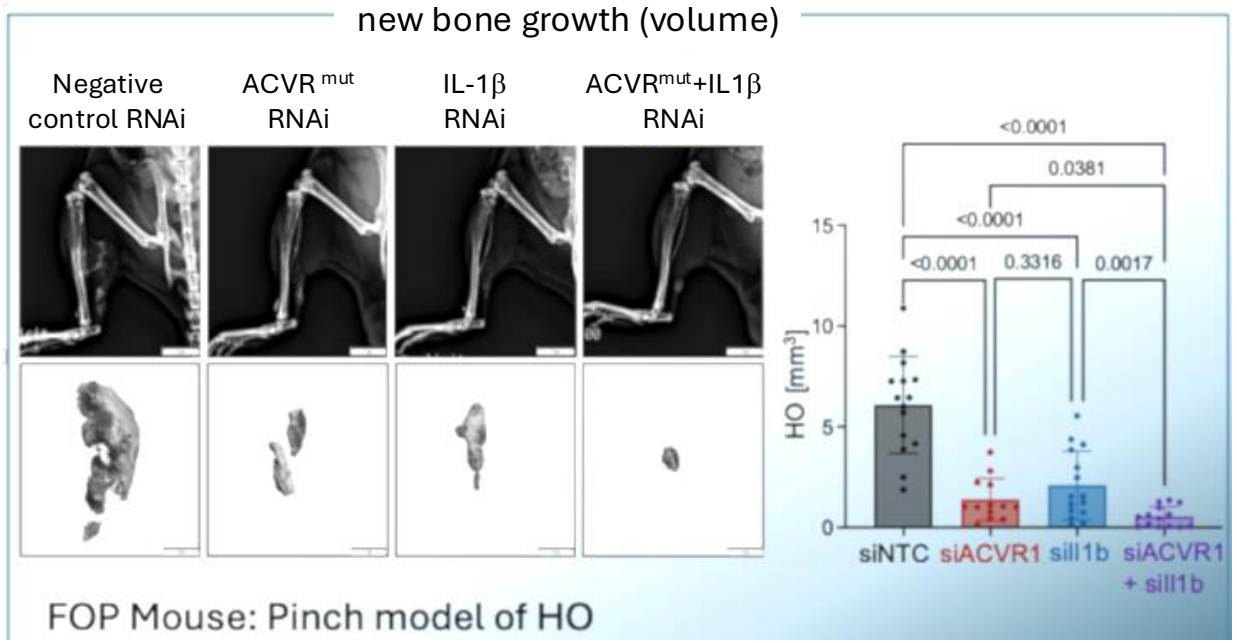


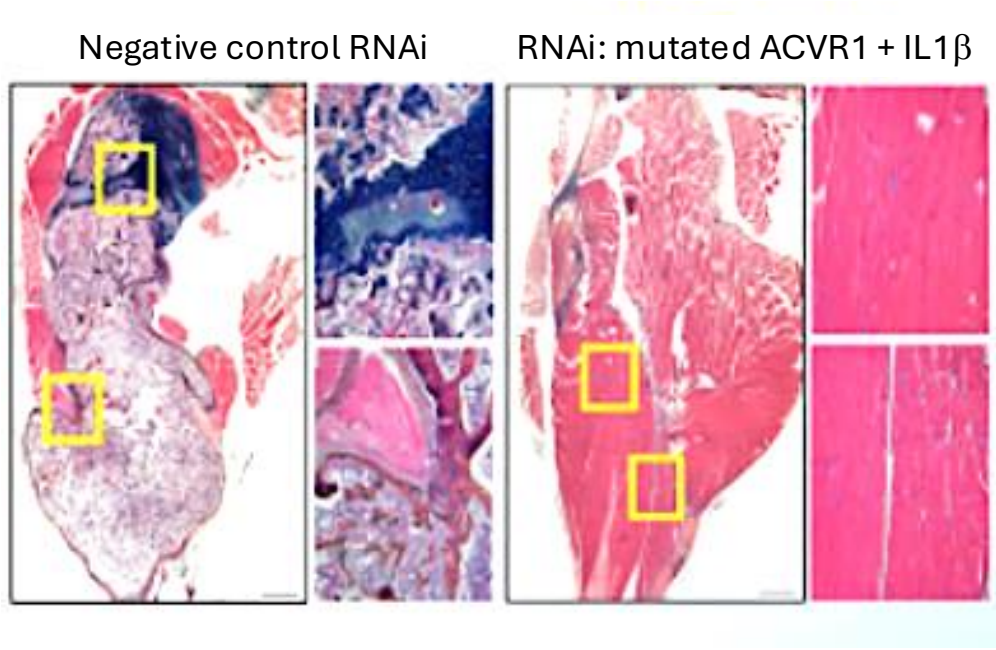
Yang, Gross, Cooper et al., Univ. Massachusetts RNA Therapy Institute (manuscript under review)

Genetic Therapy for FOP – Rational RNAi Drug Combinations

Blocking >1 of the biological events that drive FOP at multiple may have a greater effect than targeting ACVR1 only :

- e.g., Targeting inflammation associated with flare-up and new bone growth in FOP (re: IL-1 trial NCT06724562)





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RNAi Therapy for FOP – Current Status

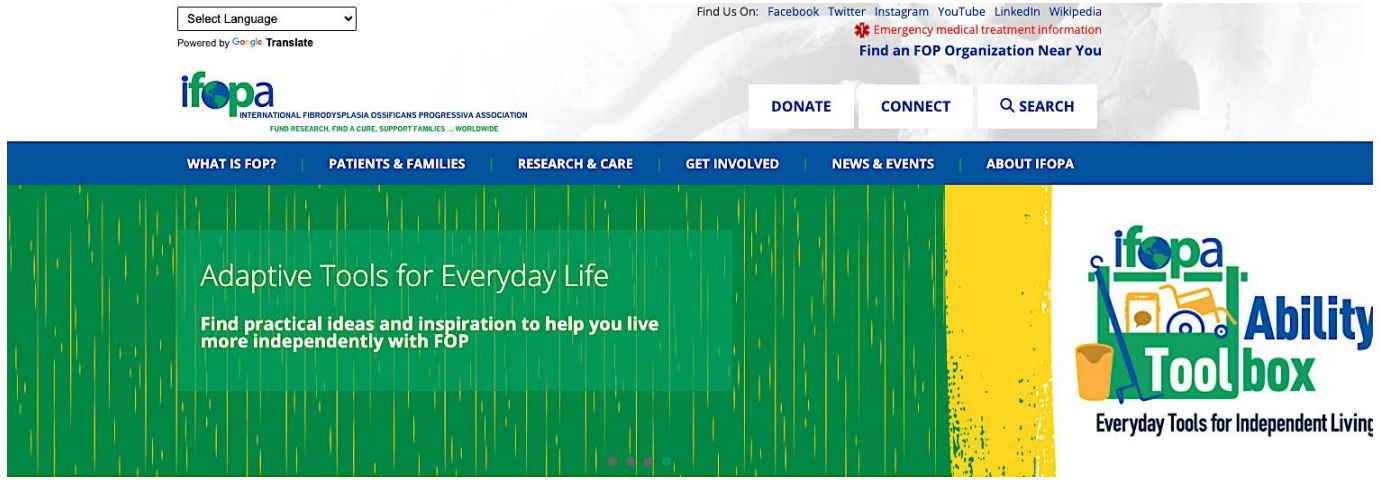
- **Currently, no RNAi drugs have advanced into clinical trials for FOP**
- Several RNA-based drugs have been clinically approved, demonstrating that (some) approaches in genetic therapy are feasible

Drug	Product Name	Indication	Target
Givosiran	Givlaari®	Acute hepatic porphyria (AHP)	ALAS1 mRNA
Inclisiran	Leqvio®	Hypercholesterolemia (high LDL cholesterol)	PCSK9 mRNA
Vutrisiran	Amvuttra®	Hereditary transthyretin-mediated amyloidosis (hATTR)	TTR mRNA
Patisiran	Onpattro®	Hereditary transthyretin-mediated amyloidosis (hATTR)	TTRm RNA
Nedosiran	Rivfloza®	Primary hyperoxaluria (PH1 and related types)	LDHA mRNA
Lumasiran	Oclumo®	Primary hyperoxaluria type 1 (PH1)	HAO1 mRNA

mRNA-based drugs are designed to deliver a nucleotide template (mRNA)to cells that codes for a functional protein

- Univ. Massachusetts is seeking to advance their ACVR1(R206H) RNAi drug for a clinical trial

IFOPA Resources for Patients and Researchers (www.ifopa.org)



- Data from >350 individuals with FOP
- 10 years of data
- Data refresh every 6 months

FOP Registry

FOP Biobank

- Research samples
- Blood, iPSCs from >50 individuals with FOP
- FOP mouse models

Research Grants (ACT for FOP)

FOP DRUG DEVELOPMENT FORUM · August 27-30, 2026 · Toronto · ifopa

Acknowledgements & Thank You

National FOP Organizations, individuals living with FOP, their families and caregivers

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RNA Therapeutics Institute

Alterman Lab
Shim Lab

ifopa staff

INTERNATIONAL FIBRODYSPLASIA OSSIFICANS PROGRESSIVA ASSOCIATION

FUND RESEARCH, FIND A CURE, SUPPORT FAMILIES ... WORLDWIDE

Backup slides

Gene Therapy Pipeline

Disease area	Examples	Editing type	Knock-in maturity/Stage
Cardiac	PRKAG2 syndrome	Allele disruption	🟡 Early
Muscle	DMD, LGMD	Exon skipping/deletion	🔴 Very early
CNS	ALS, Huntington's	Knockdown/excision	🔴 Very early
Eye	Retinitis pigmentosa	Local editing	🟡 Emerging
Liver/systemic	Metabolic diseases	HDR possible	🟡–🟢 (vector-dependent)