DISCLOSURE

Following the death of my father, I inherited common stock in Regeneron Pharmaceuticals, Inc.
THE CENTER FOR RESEARCH IN FOP & RELATED DISORDERS

26TH
Annual Report of the
Fibrodysplasia Ossificans Progressiva (FOP)
Collaborative Research Project

SUMMER 2017

Penn Medicine
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Here, at The Center for Research in FOP & Related Disorders, our work is broad and comprehensive while focused on seven spheres of FOP activity:

- Clinical care and consultation worldwide
- Clinical research and infrastructure development
- Basic research (identification of therapeutic targets)
- Translational research (preclinical drug testing & biomarker discovery)
- Cali Developmental Research Grants Program
- Clinical trial development and proof-of-principle Investigation in patients
- Education
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26th Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project
During war, targets are identified based on their strategic importance and selected to destroy those targets and minimize collateral damage.
The Target Range: Hope for Escape from a Prison of Bone

Frederick S. Kaplan, M.D.
Center for Research of FOP & Related Disorders

December 2, 2017
IFOPA Family Meeting
San Francisco
are identified through research. *Today’s targets define tomorrow’s therapies.*

Worldwide interest in FOP skyrocketed in the wake of the historic discovery of the FOP gene in 2006 - the first hard target for FOP therapy. The FOP gene discovery launched an industry that catapulted the field to clinical trials. FOP research is now a worldwide enterprise. As of January 1, 2017, there were 24 universities actively engaged in FOP research; 14 in the United States, seven in Europe, and three in Asia. As of January 1, 2017, there were 11 pharmaceutical and biotechnology companies actively developing drugs for FOP based on a multitude of hard targets, and over 30 companies that have expressed interest.

Presently, there are over 20 medical experts in FOP on six continents, 13 active FOP support groups worldwide, and eight sites actively involved in clinical trials for FOP. This has been a remarkable sea change in the past few years that is occurring in a rapidly-evolving area of target discovery and drug development.
ACVR1 (c.617 G>A; R206H)

One misspelled letter in 6 billion
One of the most highly specific disease causing mutations in the human genome
A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva.

Eileen M Shore1,3, Meiqi Xu1,2, George J Feldman1,2, David A Fenstermacher5–6, Tae-Joon Cho7, In Ho Choi7, J Michael Connor8, Patricia Delat2, David L Glaser1,2, Martine LeMerrer10, Rolf Morhart11, John G Rogers12, Roger Smith13, James T Triffitt14, J Andoni Urtizberea15, Michael Zasl dov1,2,16,17, Matthew A Brown14,16,18 & Frederick S Kaplan1,2,19

Bone Disease Gene Finally Found

Biomedical Research

28 April 2006 Vol 312 Science

Published by AAAS

Before dozens of people in an auditorium at the University of Pennsylvania, announcing the biggest discovery of his career, Fred Kaplan fought back tears. His 15-year search for the gene behind a rare and horrifying bone disease had ended, fingerling a single DNA base as the culprit and offering hope to the small number of people afflicted with the often fatal illness. Three days before, Kaplan, an orthopedic surgeon, had privately shared the news that the gene search was over with some members of the International Fibrodysplasia Ossificans Progressiva (FOP) Association. “We were all crying,” he says.

The relentless hunt for the FOP gene had tightly bound Kaplan and a small band of researchers to FOP families from places as far away as the Amazon rainforest, rural Georgia, Bavaria, and South Korea. Thanks to fundraising efforts such as barn dances in Scotland and sales of barbecued chickens in California, these families’ communities have collected about 75% of the money used in FOP research.

In people with FOP—2500 or so are thought to be living with the disease—muscle and connective tissue gradually turn to apparently healthy bone, freezing the neck, spine, hips, and even jaw into place and trapping patients inside a “second skeleton.” The newly discovered gene mutation, described this week online in Nature Genetics, not only has potential therapeutic implications for the currently untreatable disorder, but it may also reveal novel avenues for harnessing the tragic talent

Trapped. Extra bone blankets the torso of this 12-year-old who has a genetic disease in which sufferers grow a “second skeleton.”
Heredity

Dangerous Transformation

When Harry Eastlack was born, his parents noticed that there was something wrong with his big toe. It was slightly deformed. Otherwise, Harry seemed like a healthy and normal baby. And, in most ways he always would be. But gradually, tragically, Harry's family realized that he was one of the very unlucky few suffering from an extremely rare hereditary genetic disorder called fibrodysplasia ossificans progressiva (FOP). From the age of 10, Harry Eastlack's body began to ossify, or turn to stone. By the time he was 39, Harry was able to move only his lips.

< An x-ray of the foot of a child born with FOP shows a malformation of the big toe. This deformity is the first sign of the disease.
Dr. Eileen Shore and research specialist Meiqi Xu, in the FOP research laboratory at the University of Pennsylvania, contributed to the discovery of the FOP gene mutation.

Dr. Frederick Kaplan with a 15-year-old FOP patient in his lab at the University of Pennsylvania School of Medicine. Dr. Kaplan, along with his colleague Dr. Eileen Shore, found what they called the "skeleton key" to FOP when they discovered the gene responsible for FOP in 2006.
Finally, With Genetic Discovery, Hope for Escape From a Prison of Bone

By MICHAEL MASON

Peering into the hollow stump of a redbud tree, Hayden Pheiff, 5, finds a cache of treasured river rocks exactly where he left them.

It’s a luminous afternoon in Mill Valley, Calif., perfect for tossing a few of them back into the creek that runs through this small park. But Hayden’s mother, Megan Pheiff, knows better than to let her son scramble down the steep embankment to the stream.

Hayden can barely bend forward, and he cannot raise his arms much above his shoulders. Once down that slope, he may not be able to get back up. So she lifts him, over loud protests, back onto the walking trail, lingering for a moment over the banch that has begun to form on his back. In Hayden’s body, too, there are pockets of stone.

“It’s upsetting, obviously,” said Ms. Pheiff, 41, a sales representative for a textile company. “The childhood you thought your kid would have isn’t possible. The doctors don’t have a cure, and they can’t tell you what’s...

The skeleton explodes in bodies that eventually become living statues.

MUSCLES TO BONE: Hayden Pheiff, 5, at his home in Mill Valley, Calif., has F.O.P., a rare disease that transforms his soft tissue into bone, as illustrated below in the skeleton.
message inside. Finally, during the ambidextrous end and the fortune was revealed:

The odds of hitting your target go up dramatically when you aim at it.

gene-whisperer discreetly slipped out of the kitchen annual report? One can only imagine.
Clinical Features of FOP
FOP is a Metamorphosis

Perivascular Lymphocytic Infiltration

Intramuscular Lymphocytic Infiltration

Muscle Degradation

Fibro-Proliferation / Angiogenesis

Chondrocyte Condensation

Endochondral Ossification
Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-γ agonists

Kengo Shimono¹⁴, Wei-en Tung¹⁴, Christine Macolino¹, Amber Hsu-Tsai Chi¹, Johanna H Didizian¹⁴, Christina Mundy¹, Roshantha A Chandraratna², Yuji Mishina³, Motomi Enomoto-Iwamoto¹⁴, Maurizio Pacifici¹⁴ & Masahiro Iwamoto¹⁴
FOP: THE METAMORPHOSIS

Embryogenesis

Muscle Destruction

Inflammation

Tissue Progenitor Cells

Chondrogenesis

Osteogenesis

Fibroproliferation
The FOP gene is a powerful target for drug discovery.
Computational Docking of Dorsomorphin to ACVR1 Kinase

- Jay Groppe, 2008
DM- Analogue Partly Inhibits HO in Conditional caAlk2 Mice

Paul Yu et al.
How Does One Build a Second Skeleton?
ACVR1 (R206H)

Inflammation; Hypoxia
Early FOP Lesions
1. **BMT Does NOT Cure FOP**

2. **Even a Normal Immune System Can Trigger FOP in a Genetically Susceptible Host**

3. **Cells that form FOP lesions arise from the affected tissue**

**Activity of FOP**

**IMMUNOSUPPRESSION** (Prednisone/ Methotrexate/ Cyclosporin)
Cellular Contribution to FOP

- Inflammation
- Fibroproliferation
- Mesenchymal Condensation
- Chondrogenesis
- Hypertrophic Cartilage
- Calcified Cartilage
- Osteogenesis
- Bone Remodeling

Cells of Hematopoietic Origin

Cells of Connective Tissue Origin (FAPs)

SKELETAL ANLAGE
Mast Cell Involvement in Fibrodysplasia Ossificans Progressiva

FRANCIS H. GANNON, MD, DAVID GLASER, MD, ROBERT CARON, MS, LESTER D.R. THOMPSON, MD, EILEEN M. SHORE, PHD, AND FREDERICK S. KAPLAN, MD
Significant reduction of HO in immunodeficient Acvr1<sup>cR206H/+</sup> mice

One-way ANOVA with Tukey's multiple comparisons test comparing Acvr1<sup>cR206H/+</sup> versus other cohorts was performed; * p < 0.05, ** p < 0.01, ns = not significant

Convente et al., 2017
Cellular Hypoxia Promotes Heterotopic Ossification by Amplifying BMP Signaling

Haitao Wang,1,2 Carter Lindborg,1,2 Vitali Lounev,1,2 Jung-Hoon Kim,3 Ruth McCarrick-Walmsley,1,2 Mei Qi Xu,1,2 Laura Mangiavini,4 Jay C Groppe,5 Eileen M Shore,1,2,6 Ernestina Schipani,4 Frederick S Kaplan,1,2,3 and Robert J Pignolo1,2,3

HIF-1α THE BAD ALARM

HIF-1α: Imatinib; Apigenin; PX-478
Inhibition of HIF-1α diminishes heterotopic ossification in a FOP mouse model

- Control
- Apigenin
- Imatinib

Bone Volume (mm³)

Percent of Mice Retaining Joint Mobility

n=8  n=9  n=11

14 Day
Mammalian Pathway Targets of Gleevec (mTOG)

- Inflammation: c-KIT, MAPK
- FAP Cells: PDGFRα/Sca1+
- BMP Signaling: SMAD1
- Lesional: HIF1-α, mTOR
Mast cells (cKit)

HIF1-α

BMP signaling
[ACVR1 (R206H)]

Muscle Destruction

FP (PDGFRα)

Tissue Injury

MAPK

Inflammation

Hypoxia

↑HIF1-α

↑↑↑ BMP signaling
[ACVR1 (R206H)]

SMAD1

IMATINIB

OP

CP

Muscle Destruction
Early clinical observations on the use of imatinib mesylate in FOP: A report of seven cases

Frederick S. Kaplan a, *, Jeffrey R. Andolina b, Peter C. Adamson c, David T. Teachey c, Jerry Z. Finklestein d,1, David H. Ebb c, Benjamin Whitehead f, Benjamin Jacobs g, David M. Siegel h, Richard Keen i, Edward Hsiao j, Robert J. Pignolo k, **

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k Department of Medicine, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN 55905, United States
IMATINIB

Day 0

Day 7
The FOP mutation causes postnatal HO by allowing mACVR1 to respond to Activin A.
“We would like to caution, however, that there is a paucity of data implicating Activin A as the driver of HO in FOP patients per se; this is largely due to the inability to safely biopsy patients…We cannot therefore formally exclude the possibility that other ligands play a role in the development of HO in FOP patients.”

Hatsell et.al.  
Science Translational Medicine  
September, 2015
Act 2 for Act A: The Human FOP Story
Dysregulated BMP Signaling and Enhanced Osteogenic Differentiation of Connective Tissue Progenitor Cells From Patients With Fibrodysplasia Ossificans Progressiva (FOP)

Paul C Billings,1,2 Jennifer L Fiori,1,2 Jennifer L Bentwood,1,2 Michael P O’Connell,1,2 Xiangyang Jiao,1,2 Burton Nussbaum,3 Robert J Caron,1,2 Eileen M Shore,1,2,4,5 and Frederick S Kaplan1,2,5,6
Activin A induces BMP pathway signaling in HUMAN FOP SHED cells.
Activin A induction of BMP pathway signaling is inhibited by neutralizing antibody to Activin A
BMP4 and Activin A synergistically induce BMP pathway signaling.
Act A in Human FOP Cells

- Activin A stimulates BMP pathway signaling in primary human FOP cells, consistent with recent reports.

- Both BMP4 and Activin A have a synergistic effect on BMP pathway signaling in WT & FOP cells and thus may co-dependently alter the threshold for HO in FOP.

- Finally, although much can be learned from animal models of FOP, none is fully predictive of the human condition.
POTENTIAL Rxs

- Injury Prevention
- Immunosuppression
- mAbs; Ligand Traps
- mAbs; STIs; siRNA
- Anti-inflammatory drugs
- HIF1-α Inhibitors
- RARγ agonists
- Surgical Removal (Under Cover of Upstream Inhibitors)

TARGETS

- Soft Tissue Injury
- Spontaneous Flare-Up
- BMP4; Activin A
- ACVR1 (R206H)
- Inflammation
- Tissue Hypoxia
- Heterotopic Endochondral Ossification
- Heterotopic Bone
1. Mice are not people.

2. FOP mouse models are just that - “models” for human FOP.

3. It’s easy to cure FOP in mice.

4. Clinical trials in FOP are not treatments for FOP.

5. Clinical trials have risk; patients put themselves at risk to enter clinical trials.

6. Clinical trials are highly regulated.
Pocket Guide to Translational Research & Clinical Trials in FOP

7. Clinical trials are inconvenient.

8. Clinical trials are costly.

9. Even so, clinical trials are the most effective way to determine if a drug is safe and effective in FOP.

10. There are many hard targets and there will likely be many effective medicines for FOP.

11. There are two major models (The Paternalistic Model and The Equanimity Model) for patient guidance on multiple clinical trials.

12. Ultimately, the decision is entirely yours.
Stops Flare-ups
Prevents Flare-ups
Maintains Function
Slows Joint Degeneration
Changes Natural History

Side Effects
Off- target Effects
Allergy
Non-response
Rebound
Resistance
Compliance
Tolerability
Access
Cost
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MUSCLES TO BONE Hayden Pheiff, 5, at his home in Mill Valley, Calif., has F.O.P., a rare disease that transforms his soft tissue into bone, as illustrated below in the skeleton.
“From Hopeless to Hopeful”

-Ian Cali
"We need hope, and if we have hope, we'll be OK."
- Yak Gamboa; Puebla, Mexico
ACKNOWLEDGEMENTS

• The International FOP Association
• Friends and Families of FOP Patients Worldwide
• The Isaac & Rose Nassau Professorship of Orthopaedic Molecular Medicine
• The Ian Cali Endowment
• The Whitney Weldon Endowment
• The Ashley Martucci FOP Research Fund
• The McGuire FOP Research Fund
• The Gary Whyte FOP Research Fund
• FOPe.v.
• FOP Canada
• FOP France
• The Stephen Roach- Whitney Weldon Fellowship
• The Roemex Fellowship
• The People of Santa Maria
• The National Institutes of Health
Highlights from the 10th Annual Joshua’s Future of Promises Bingo for a Cure! Event in Allentown, PA

Top row, left to right: Joshua Scoble (Emmaus, PA) gives an amazing speech at the opening of the event, while his parents, David and Stacy Scoble, look on proudly; Dr. Kaplan and A.J. Gonzales (Bellema, N.J.); Joey Hollywood (Bridgewater, N.J.) and Dr. Kaplan; Middle row, left to right: More than 1,500 supporters play bingo; Right: Dr. Kaplan with (from left to right) A.J. Gonzales (Bellema, N.J.) and Joshua Scoble (Emmaus, PA); Joey Hollywood (Bridgewater, N.J.); Kathy Ford (Somers Point, N.J.); Lindsay Rule (Somers, N.Y.); Jeannette and Lisa Bordeau (Kinnineville, PA); Bottom row, left: Suzanne Hollywood, Mei qi Xu, Amaniad Coll and Dr. Qi Shen.
Above: Whitney Weldon (Manhattan, NY) and Dr. Kaplan at FOP Ashley’s Cure Finding a Cure for FOP Charitable Event in New York City [Photo Courtesy: }