



THE CENTER FOR RESEARCH IN FOP & RELATED DISORDERS

**28<sup>TH</sup>**

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



Penn Medicine

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2020 - 2021

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## Preface

The 28th Annual Report (2020-2021) of The FOP Collaborative Research Project describes events and accomplishments of 2018 through 2019. The report was completed in February 2020, immediately before COVID erupted. The final publication of the report was delayed by unavoidable pandemic-related shutdowns and delays.

The FOP world is very different in the wake of the seismic global pandemic. 2020 was devoid of FOP gatherings, but not the inextinguishable human voice. Virtual meetings became the norm in 2020, and the global FOP research communities persisted and thrived in new and uncharted ways. Despite the unexpected detour, we re-calibrated, re-grouped and re-re-imagined. Laboratory research and clinical studies remained active despite unprecedented diversions. The International Clinical Council (ICC) on FOP issued major new FOP Treatment Guidelines and has been at the forefront of pandemic-related and vaccine-related issues for the FOP community.

The 29th Annual Report is scheduled for 2022. For now, enjoy the 28th Annual Report; catch up on the immediate pre-Covid FOP world, and join us as we continue undaunted on our old journey, our “new normal” and our timeless mission to develop better treatments and a cure.



**Frederick Kaplan**  
Philadelphia  
July 2021

## 1ST CLINICAL MEETING OF FOP POLAND – THE UNIVERSITY OF RZESZÓW — MAY 2018 (RZESZÓW, POLAND)



1. Magdalene Jerierska (Gielczew, Poland) and her mother  
2. At the First Clinical Meeting of FOP Poland 3. Dr. Kaplan with  
Professors Jacek Tabarkiewicz and Gosia Dabrowska of The  
University of Rzeszów

## FREEDOM FROM FOP, BRAZIL & SOUTH AFRICA FAMILY MEETING — AUGUST 2018 (SÃO PAULO, BRAZIL)



1. Dr. Patricia Delai & invited guests at FOP Brazil (São Paulo, Brazil)  
 2. Dr. Vanessa Schaker, (Porto Alegre, Brazil) and colleague Dr.  
 Daniel from Albert Einstein Hospital in São Paulo 3. Jessica Beltramin  
 Lira (São Paulo, Brazil) and her mother Solange 4. Maria Luiza Dias  
 Santos (São Paulo, Brazil) with silly Dr. Kaplan 5. Anesipho Stemmla  
 (Gugulethu Township, Cape Town, South Africa) and her mother  
 Eugenia (to her immediate right) visit the clinic

**IFOPA'S 2018 FOP FAMILY GATHERING — NOVEMBER 2018  
(BALTIMORE, MARYLAND)**



1. Carli & Lori Henrotay (St. Louis, MO) and some canine friends meet with the Ask a Doctor Meeting staff  
 2. Ethan Szumetz (Greencastle, PA) & his parents Tara & Marshall meet with Drs. Kaplan & Pignolo  
 3. Jasmin Floyd (Woodstock, CT) and her mother RoJeanne Doege meet with Kay Rai  
 4. Emma Albee (Seal Cove, ME) greets the doctors at the IFOPA Family Gathering in Baltimore, Maryland (from left: Dr. Mona Al Mukaddam (Penn),  
 Patti Pinkham (Emma's mother), Dr. Eileen Shore (Penn), Dr. Ed Hsiao (UCSF), Emma Albee (seated),  
 Dr. Zvi Grunwald (Jefferson), Dr. Fred Kaplan (Penn) & Dr. Robert Pignolo (Mayo Clinic)

FOP GERMANY ANNUAL FAMILY MEETING — JULY 2019  
(VALBERT, GERMANY)



1. Gilles Keller (Gumbrechtshoffen, France) & Fred Kaplan 2.  
Nadine Grossmann (Berlin, Germany), her mother Grace and  
her brother Patrick

## 4TH INTERNATIONAL FOP RUSSIA MEETING — JULY 2019 (MOSCOW, RUSSIA)

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1. The FOP Clinic Doctors 2. Angelina Popova (Nizhny Novgorod, Russia) displays her wonderful snow scene painting (as seen from her home). With her mother Svetlana and Dr. Kaplan 3. Alexy Lensky (St. Petersburg, Russia) and his parents Olga & Sergey meet with Drs. Kaplan and Morhart 4. Olesya Radushko (Kemerovo, Siberia) meets with Drs. Kaplan & Morhart 5. Elizaveta Kalishnikova (Tyumen City, Russia) entertains the FOP clinic staff with a traditional Russian song



**WORLD PREMIERE OF TIN SOLDIERS, THE JOZI FILM FESTIVAL — OCTOBER 2019  
(JOHANNESBURG, SOUTH AFRICA)**



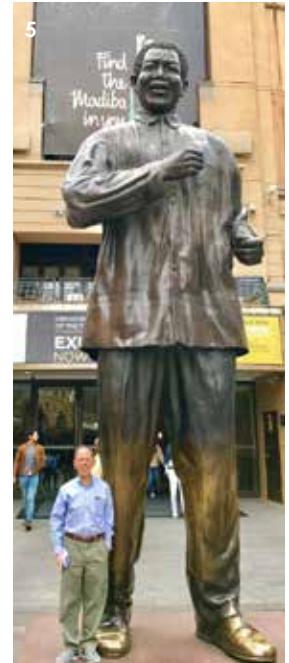
1. Thozi Mciki (Cape Town, South Africa) & Fred Kaplan  
2. Amanda Cali (IFOPA Board Chair 2005 & 2006 and Tin Soldiers Executive Producer) & Fred Kaplan 3. Drs. Christiaan Scott (Cape Town, South Africa), Patricia Delai (São Paulo, Brazil) & Fred Kaplan (Philadelphia, USA) 4. Thozi Mciki and friends 5. Kearabetswe Mofokeng (Johannesburg, South Africa) with Julie Schmidt & Dr. Kaplan 6. Julia Mofokeng, mother of Kearabetswe proudly displays the newspaper featuring her story



## ADDITIONAL PHOTOS FROM THE TIN SOLDIERS GLOBAL FOP PATIENT SEARCH



1. Dr. Fred Kaplan (University of Pennsylvania) & Dr. Ashraf Coovadia (Chairman, Department of Pediatrics at University of the Witwatersrand; Johannesburg, South Africa) 2. Amanda Cali & Dr. Fred Kaplan at Rahima Moosa Women & Children's Hospital; Johannesburg, South Africa 3. Have You Seen a Human Tin Soldier? (from left to right); Odette Schwegler, Producer of Tin Soldiers; Dr. Elizabeth Ho (Johannesburg, South Africa), Dr. Patricia Delai (São Paulo, Brazil), and Dr. Fred Kaplan (Philadelphia, USA) at Rahima Moosa Women & Children's Hospital; Johannesburg, South Africa 4. A meeting of the global outreach program of Tin Soldiers - "The Search for the Undiagnosed;" Johannesburg, South Africa 5. A Truly Great Toe – In the footsteps of giants at Mandela Square; Sandton City, Johannesburg, South Africa



**IFOPA'S 2019 FOP FAMILY GATHERING — NOVEMBER 2019  
(ORLANDO, FLORIDA)**



1. Jeannie Peeper (Winter Springs, FL; President Emeritus & Founder of the IFOPA) meets with the Ask a Doctor Meeting staff 2. "Good Vibes" for Ashley Kurpiel (Peachtree, GA) & Dr. Kaplan 3. Joey Hollywood (Bridgewater, NJ) greets Dr. Kaplan 4. Elle Klein (Grove City, OH) greets Dr. Kaplan 5. Dr. Kaplan displays a wonderful painting of a tropical scene by artist Jack Sholund (Grand Rapids, MN) as Jack's family, Drs. Al Mukaddam and Pignolo all meet at the IFOPA Family Gathering in Orlando, FL 6. Gabby Assouline (Miami, FL) and her mother Sandra (seated) visit with Drs. Patricia Delai (São Paulo, Brazil), Fred Kaplan (Philadelphia, PA, USA) & Alberto Hidalgo-Bravo (Instituto Nacional de Rehabilitacion; Mexico City, Mexico) 7. "Together We Will Cure FOP."

# PART 1

## Introduction



There is a delightful science fiction story about a team of scholars tasked each year with summarizing the world's scientific discoveries into one succinct paragraph, then condensing it into one terse sentence and finally distilling it into a single word. In 2006 that word was "ACVR1" – the FOP gene – and it is the same word today in 2021.

From a scientific perspective, every early discovery in FOP led to the gene discovery, and every discovery in FOP after the gene discovery emanated from it. It was the ship's bell in the fog, the narrowest point of the hourglass, the tipping point of FOP.

But, in order for that discovery to have occurred, a diverse worldwide community had to be established, patients from every racial, ethnic and geographic background had to join hands, a purpose had to be articulated, a dedicated and committed laboratory had to form, a center had to emerge, a spark had to be lit, and a movement had to be inspired; essentially a community had to care – no small miracle. Caring IS part of the cure.

"War has just been declared on FOP," proclaimed an anonymous scientist in a crowded elevator of biologists and physicians at the Children's Hospital of Philadelphia during the First International Symposium on FOP in September 1991. Two symposiums, nine years and one hundred families later, the international community of FOP had come together and was flourishing. The troops had been mobilized and the "war" was on.

ACVR1 is one word. "Community," "Determination" and "Collaboration" are others – all indelible words that define our singular mission – to determine the cause of FOP and to use that knowledge to advance safe and effective treatments and a cure.

Clinical trials are our new world and our new words – and they are beginning to exert their effect on our patience, our imagination and on our lives. Some trials will fail because they lack safety and some because they lack efficacy. Others will succeed – and we hope for many of those – and those that succeed will undoubtedly succeed in different ways, to different degrees, for different individuals, for different ages of life and for different stages of FOP.

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*Captions continued from page 10*

Drs. Marat Chaikoudinov (Brooklyn, NY), Fred Kaplan (Philadelphia, PA), Zvi Grunwald (Philadelphia, PA) and Mr. Fadel Al-Garni (Major-General Air Force [Retired]; Riyadh, Saudi Arabia) 8. Karina Chaikhoudinov (Brooklyn, NY) with Drs. Mona Al Mukaddam, Zvi Grunwald, Marat Chaikhoudinov (Karina's father), Fred Kaplan & Elizabeth Ho (Johannesburg, South Africa) 9. Steve Eichner (Austin, TX) and his wife Nancy (standing, second from right) with Drs. Delai (São Paulo), Pignolo (Rochester, MN), Hidalgo-Bravo (Mexico City) & Hsiao (San Francisco) and Drs. Al Mukaddam & Kaplan (kneeling) 10. The Ask a Doctor Meeting doctors of the IFOPA Family Gathering in Orlando, FL. (from left): Drs. Alberto Hidalgo-Bravo (Mexico City, Mexico), Elizabeth Ho (Johannesburg, South Africa), Zvi Grunwald (Philadelphia, PA, USA), Fred Kaplan (Philadelphia, PA, USA), Robert Pignolo (Rochester, MN, USA), Mona Al Mukaddam (Philadelphia, PA, USA), Edward Hsiao (San Francisco, CA, USA), Xiaobing Yu (San Francisco, CA, USA), & Patricia Delai (São Paulo, Brazil) 11. Claudia Cabrera (Westminster, MA) & her mother Maria Fuentes meet Drs. Ho (Johannesburg), Pignolo (Rochester, MN), Hidalgo-Bravo (Mexico City) and Kaplan (Philadelphia) 12. Anthony Olson (Hulett, WY) and his mother Rosanne (seated) visit with the doctors 13. Allyson Long (Middleburg, FL) and her parents Allan & Trish Long stop by to say hello to the doctors 14. Cade Russell (Brownstown Township, MI) and his parents Ben & Wendy Russell (seated) with the Ask a Doctor Meeting doctors 15. Shane Terry (Sackets Harbor, NY) visits with Dr. Mona Al Mukaddam 16. Drs. Kaplan & Grunwald with Kordylia Kniceley (Cape Coral, FL) 17. Princess Grace Taylor (Adelaide, Australia) holds court with Dr. Kaplan

But there is unlikely to be one treatment and one cure for FOP. What works for one person may not work for – or be tolerated by – another. What works at one stage of FOP progression may not work at another. FOP is a complex disorder. The FOP gene is required to understand FOP, but FOP is much more than the mutated gene that causes it. For example, one has to understand the chemical bonds of hydrogen and oxygen to understand the physical properties of water, but a waterfall is more than the chemical bonds of hydrogen and oxygen. There are emergent properties to self-organizing systems – to life and to problems that affect human beings at every level – and FOP is no different.

Our science has made progress possible – the identification of varied targets and the development of different drugs for those targets. There will be even more unpredictable discoveries ahead. The puzzle is not yet complete, but our destination is certain. We are headed to a new frontier. During the past thirty years, we have moved from the wastelands of a little-known and poorly-understood ultra-rare disease through the watershed of clinical trials to the mainstream of modern medicine.

More than thirty pharmaceutical companies have expressed an interest in FOP – more than thirty! And sixteen are actively developing drugs to reach a wide variety of targets. Hundreds of scientists worldwide are engaged in the development of those drugs at universities, independent laboratories and pharmaceutical companies. Hundreds more are involved in the pipelines for making those drugs a reality. Thousands are employed in basic research, drug development, clinical trials, clinical care, clinical monitoring, regulatory affairs and marketing. Billions of dollars are being spent in the effort – all for a little-known ultra-rare disease that affects fewer than one thousand known individuals in the world – and for whom little, if any, attention was paid 30 years ago. But why?

Many from industry say that there is an urgent unmet need for drugs – now made possible by a well-defined target – ACVR1. Others say that they are touched deeply by the plight of those who live daily with FOP, especially the children. Some even pledge to provide any drug they develop at cost to the FOP community, but let's wait and see.

We have identified the central cause of FOP – the FOP gene. We have mapped the gene, identified downstream pathways, and we have used that knowledge to move toward a deeper understanding of FOP. Every clinical trial and every route on our journey to the new frontier is traceable to that reality.

In a transformative article entitled “*A New Grammar for Drug Discovery*” (*Nature* 437: 491-493, 2005) Fishman and Porter explain, “The choice of a gene product of clinical relevance is the greatest impediment to expanding the pharmaceutical arsenal. The major reason is that targets are of value for drug discovery only if they can be convincingly related to disease.”

Interestingly, among the 15 examples of human diseases mentioned in the article – is FOP. Although the article was published seven months before the FOP gene discovery, every indication from the research at that time suggested that the bone morphogenetic protein (BMP) signaling pathway was intimately involved in FOP. Fishman & Porter explained that signaling pathways in cells provide the “right level” for drug discovery:

“Intracellular molecular signaling pathways provide such a grammar for drug discovery. Those pathways are triggered by extracellular molecules that bind to receptors in the cell membrane, thereby switching on relay systems inside the cell. The upshot is gene activation (as in FOP) that affects a cell’s behavior – its ability to grow or differentiate...The link between disease and signaling pathways is best validated for genetic disorders ... The rationale for extrapolating from rare genetic diseases to common sporadic illness is that nature is conservative: this is a safe bet. And there would be immense immediate benefit in tackling the rare diseases in themselves. Patients with uncommon disorders (such as FOP) are often neglected, their only hope being that medicines designed and marketed to treat common disorders might coincidentally be able to treat theirs. In contrast, in the logic of molecular pathways, such patients would be viewed as key intermediaries in the drug discovery process, providing proof-of-concept. This approach could have a salutary ‘side effect’ – a refocusing of drug-discovery research on neglected diseases (such as FOP).”

So there we have it – an answer to “but, why?” An explanation for the activity we see today in our FOP world – ACVR1, the downstream BMP signaling pathways and the emergence of drug development for FOP. It makes little sense if you don’t understand the powerful influence of the ideas, knowledge and forces behind the motivation. For FOP, ACVR1 and the dysregulated BMP pathway are as powerful as gravity is for understanding the movement of the planets. As Tolstoy explained in the final epilogue of *War & Peace*, “It is true that we do not feel the movement of the Earth, but by admitting its immobility we arrive at absurdity, while admitting its motion (which we do not feel) we arrive at laws.”

Seven months after the prophetic article by Fishman & Porter – the jackpot – the bullseye of the target was discovered – ACVR1 – the gene for FOP – mutated in every individual who has the condition – right at the heart of the BMP signaling pathway – and a potential bonanza for the pharmaceutical industry. The gold rush was on. Just Google “FOP” and almost daily you will see an article flash on your screen “Trends & Insights by Global FOP Drug Markets (2020-2029).”

The first Annual Report on FOP was written nearly 30 years ago in order to document the central hypothesis of FOP research (which is now the central catechism of the disease: the dysregulation of the BMP signaling pathway), to document the earliest fledgling steps of modern FOP research, to encourage reluctant scientists and researchers from around the world to devote their attention – for even a minute – to this scientific dilemma and medical mystery, to educate physicians about the existence of such a rare, illustrative and catastrophic disease, to enlist global collaborators on the urgency of such a journey and to convince a skeptical community that progress could be made. These goals have all been accomplished, and continue to be renewed, and the ultimate mission of using seminal discoveries and unbridled passion to navigate and achieve a better future, is well within reach. As the late Christopher Reeve said, “At first dreams seem impossible, then improbable, then inevitable.



## PART 2 The Center

Since being established in 1989, the FOP Collaborative Research Project has had a singular mission – to determine the cause of FOP and to use that knowledge to advance the treatment and a cure for FOP. During the past thirty years, we have moved from the wastelands of a little-understood rare disease to the watershed of clinical trials. We have identified the genetic cause of FOP and have used that knowledge to spearhead worldwide research efforts to develop therapies that will transform the care and the lives of individuals with FOP.

In partnership with our benefactors, we have expanded the frontiers of drug discovery and development in this rare and disabling condition, dismantled physical and perceptual barriers that have impeded progress, and inspired global research into small molecules, antibodies and gene therapy for FOP. We not only support the FOP dream, we helped create it.

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

- 1** Clinical care and consultation worldwide
- 2** Clinical research and infrastructure development
- 3** Basic research (identification of therapeutic targets)
- 4** Translational research (preclinical drug testing and biomarker discovery)
- 5** Cali Developmental Research Grants Program
- 6** Clinical trial development and proof-of-principle investigation in patients
- 7** Education

The Center for Research in FOP & Related Disorders is unique. It is the world's first comprehensive center for FOP. During the past two years, we achieved tremendous milestones in our FOP program. Our impact is worldwide.

### Clinical Care and Consultation Worldwide

- Guided patients, families and doctors worldwide in their daily battles with FOP
- Directed the world's largest FOP clinic and referral center
- Coordinated medical management of FOP patients worldwide
- Conducted international FOP clinics over the past two years for patients and families in Orlando, Florida; Baltimore, Maryland; Denver, Colorado; Dubai, United Arab Emirates; Johannesburg, Republic of South Africa; Manchester, United Kingdom; Moscow, Russia; Orlando, Florida; Rzeszów, Poland; São Paulo, Brazil; Tokyo, Japan and Valbert, Germany

## Clinical Research and Infrastructure Development

- Served in the growth and governance of The International Clinical Council on FOP
- Edited two major revisions – the first in eleven years – of “The Medical Management of FOP: Current Treatment Considerations” popularly known worldwide as The FOP Treatment Guidelines
- Published the *FOP Cumulative Analogue Joint Involvement Scale (CAJIS)* – a novel, universally accessible and rapidly administered evaluation tool for FOP. CAJIS is now used in the clinical evaluation of FOP patients worldwide and has been incorporated into four ongoing clinical trials on six continents.
- Published comprehensive joint survival curves from most of the world’s known population of FOP patients. These joint-specific survival curves are being used to facilitate clinical trial design and to determine if potential treatments can modify the predicted trajectory of progressive joint dysfunction and immobility.
- Published a major paper on acute unilateral hip pain in FOP describing bone and joint pathology that may confound and inform the evaluation of acute flare-ups
- Published a major paper outlining the prevalence, risk factors, prevention and treatment of kidney stones in patients with FOP
- Published a patient-reported physical function outcome measure for children and adults with FOP
- Published the baseline findings of the sponsored Ipsen (Clementia Pharmaceuticals, Inc) Natural History Study
- Published a study on skeletal and joint formation in FOP patients using data from the Ipsen (Clementia Pharmaceuticals, Inc) Natural History Study
- Expanded the Penn FOP Biobank
- Supported the development of the IFOPA’s FOP Biobank
- Served on the IFOPA’s FOP Biomarker Consortium
- Supported the prospective deposit of data from sponsored clinical trials into the IFOPA’s FOP Registry
- Advocated for the direct deposit and open access of annotated whole-genome sequence data from a sponsored clinical trial into the IFOPA’s FOP Registry medical portal
- Fostered the development of a single, unified international patient registry for FOP by the IFOPA, and owned by the FOP community
- Supported the development and implementation of an international study of dermatological lesions in FOP patients
- Conducted genetic screening for FOP variants: what are they, who has them and what do they mean for those who have them?
- Developed and supported the development of *in vitro* and *in vivo* models of FOP variants
- Co-authored a paper on the baseline features of the IFOPA’s FOP Registry
- Co-authored a seminal paper on the global demographics of the international FOP community

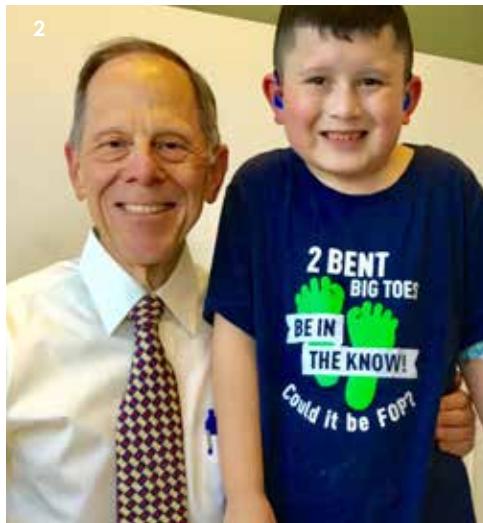


Drs. Mona Al Mukaddam (Philadelphia, PA, USA) and Patricia Delai (São Paulo, Brazil) getting ready for the start (in 2022) of the much-anticipated FOP Dermatology Project

## Basic Research (Identification of Therapeutic Targets)

- Established the BMP type I receptor ACVR1 as a key regulator of joint formation in early development
- Showed that dysregulated BMP signaling, caused by the classic FOP mutation, inhibits joint development in multiple digits of the mouse and induces aberrant endochondral ossification at developing growth plates in the FOP skeleton

- Showed that the effects of the classic FOP mutation on the normotopic skeletons of individuals who have FOP extend beyond malformation of the great toes and include both morphological defects and severe developmental arthropathy (joint disease)
- Documented widespread developmental joint disease in FOP mouse models and in humans
- Documented early post-natal degenerative joint disease throughout the FOP mouse skeleton and in humans
- Established that degenerative joint disease occurring at multiple sites throughout the FOP skeleton starts in adolescence and progresses throughout life. This important clinical feature occurs independently of heterotopic bone formation, indicating a potential role for ACVR1 (the FOP gene) in the development and progression of degenerative joint disease.
- Showed that FOP is a disease of not only progressive heterotopic ossification, but also widespread and extensive developmental joint disease and associated degenerative joint disease. These findings have relevance for understanding the natural history of FOP and for designing and evaluating clinical trials with emerging therapeutics.
- Investigated the molecular mechanisms by which the FOP gene mutation alters the response of cells to their physical environment and showed that FOP cells are predisposed to misinterpret signals from their tissue microenvironment as instructions to form cartilage and bone
- Showed that increased BMP signaling in FOP cells alters the tissue microenvironment, improperly senses that microenvironment and alters the threshold for commitment to bone-forming cell lineages
- Examined the molecular mechanisms of the altered mechanosensing of FOP progenitor cells and established it as a novel target for therapeutic development
- Published that Activin A amplifies dysregulated BMP pathway signaling and induces cartilage and bone differentiation of primary connective tissue progenitor cells in patients with FOP
- Investigated cellular inflammatory triggers of early FOP lesions using novel triple knock-in FOP mouse models and identified key cellular targets in the innate immune system in the progression of FOP
- Defined stages of heterotopic ossification in tissues in a knock-in mouse model of FOP and identified FOP mutation-induced effects prior to formation of ectopic cartilage and bone
- Published a major paper documenting wide variability in the enhancement of BMP pathway signaling in a spectrum of ACVR1 mutations seen in patients with variant FOP
- Investigated molecular mechanisms by which ultra-rare FOP variants trigger promiscuous BMP signaling and subsequent HO
- Investigated the molecular mechanisms by which the innate immune system amplifies inductive BMP pathway signaling in FOP connective tissue progenitor cells
- Investigated molecular mechanisms and innate immunologic triggers of FOP flare-ups in state-of-the-art knock-in mouse models of classic FOP
- Published that inflammatory stimuli broadly activate the innate immune system in FOP connective tissue progenitor cells
- Published that toll-like receptors (TLRs) of the innate immune system amplify BMP pathway signaling
- Published a major paper describing how the innate immune system triggers and amplifies dysregulated BMP pathway signaling in FOP – providing new targets for therapeutic approaches to blocking the induction and amplification of FOP lesions



1. Sophia Forshtay (Fort Lee, NJ) & Fred Kaplan at The Center for Research in FOP & Related Disorders at the University of Pennsylvania 2. Nicholas Santillan (Durham, NC) and Dr. Kaplan at The Center for Research in FOP & Related Disorders at Penn 3. Kyle McWilliams (Victor, IA) and his parents Margie & Curtis McWilliams during a visit to the University of Pennsylvania 4. Justin Henke (Middletown, DE) and his parents Wendy & Kevin Henke visit Penn. 5. Space explorer Bobby Johnson (Warren, PA) visits with Dr. Kaplan at Penn 6. Jordyn Bugarin (Dundalk, MD) visits with Dr. Kaplan at Penn 7. Maria Wray (Pittsford, NY) & A.J. Gonzales (Bellmawr, NJ) meet for lunch and a chat in Philadelphia 8. Janeisha Owens (Plainview, NY) and Dr. Kaplan confer on tunes in Philadelphia



- Continued to expand and develop the FOP SHED Cell Tooth Fairy Program – a limited and precious library of primary connective tissue progenitor cells from FOP patients that is essential for ongoing and future studies in therapeutic target identification and drug discovery in FOP
- Continued collaborative studies to identify modifier genes in several patients with the FOP mutation who have relatively little HO; intense investigation continues on this project
- Uncovered a possible factor that confers protection against heterotopic ossification in a resilient patient with FOP

### **Translational Research (Preclinical Drug Testing and Biomarker Discovery Program)**

- Used FOP mouse models to screen new categories of compounds for efficacy in preventing HO
- Annotated an extensive library of plasma biomarker samples in a large cohort of classically affected FOP patients and non-FOP age and sex-matched controls
- Analyzed and are preparing to publish detailed biomarker analysis on these plasma samples

### **Developmental Research Grants Program**

- Continued to support three highly innovative developmental research projects in the Cali Developmental Research Grants Program:
  1. “Molecular Basis of Pathogenic Signaling and High Throughput Testing of FOP Therapies in a Zebrafish Model system” (Mary Mullins, PhD – The University of Pennsylvania)
  2. “Identifying Alternative Therapeutic Targets and Genetic Intedactors in FOP” (Ed Hsiao, MD, PhD – University of California, San Francisco)
  3. “Novel Allosteric Destabilizers as Therapeutics for FOP” (Jay Groppe, PhD, Texas A&M University)

### **Clinical Trial Development and Proof-of-Principle Investigation in Patients**

- Introduced a small molecule tyrosine-kinase inhibitor that targets the cellular response to tissue hypoxia and inflammation into the clinic on a compassionate off-label basis for the management of refractory FOP in children
- Consulted on the study design of five clinical trials in development by five pharmaceutical and biotech companies
- Advised 30 pharmaceutical and biotech companies on the development of novel drugs for clinical trials in children and adults with FOP, based on identified targets
- Advanced understanding of small molecule inhibitors in physiologic and pathologic chondrogenesis in children – knowledge and approaches that are vital to future clinical trials for FOP
- Cared for patients in two sponsored interventional clinical trials
- Followed patients in the Ipsen (Clementia Pharmaceuticals, Inc) Natural History Study
- Nurtured the expansion of The FOP Center that includes a pediatric clinical trials site at The Children’s Hospital of Pennsylvania

### **Education**

- Co-edited a special edition of **Bone** on heterotopic ossification (published online in 2018 and in print in 2019) and comprising nearly 50 papers on FOP and related disorders of heterotopic ossification
- Presented lectures and seminars to doctors, students, nurses, administrators, regulators, donors and lay communities worldwide on the clinical care, basic research, translational science and clinical trials of FOP and on the mission of the worldwide enterprise



1. Laura Rossano (Cold Spring Harbor, NY) meets (from left) with Dr. Mona Al Mukaddam, Dr. Arupa Ganguly, Katherine Toder, Renee Jurek and Dr. Eileen Shore after lecturing about her experiences with FOP to the first year medical students during their introductory genetics course at the Perelman School of Medicine of the University of Pennsylvania 2. Ian Cali (Mountain Lakes, NJ), his parents Amanda & John Cali, and his friend & energy therapist Mrs. Gloria McCahill meet with Drs. Kaplan & Shore after lecturing about his experiences with FOP to the first year medical students during their introductory genetics course at the Perelman School of Medicine of the University of Pennsylvania 3. Dr. Eileen Shore lectures on latest developments in FOP Research

- Conducted multiple international clinics for FOP patients in five continents
- Articulated a vision for finding undiagnosed patients with FOP in third world countries at the world premiere of *Tin Soldiers* and at public hospitals in Johannesburg, South Africa
- Supported the Tin Soldiers Global FOP Patient Search Program to identify undiagnosed and unconnected FOP patients in third world countries
- Hosted a scientific workshop on “The Immunology of FOP,” sponsored by the IFOPA. This workshop focused on fundamental immunological issues relevant to the progression of FOP.
- Mentored the next generation of physicians and scientists working on FOP in the classroom, clinic and laboratory
- Mentored high school, college, medical and graduate students on research projects to expand vital knowledge and scientific and public awareness of FOP
- Supported the mentorship of summer students in the FOP laboratory
- Taught the principles and practice of FOP research in an Advanced Placement (AP) High School Biology Course
- Educated physicians, scientists, researchers and regulators at medical and scientific forums, meetings and conferences worldwide
- Continued to educate FOP experts worldwide on the use of the CAJIS evaluation for clinical management and clinical trials of FOP patients
- Assisted the unique donation of a precious anatomical gift to The Mütter Museum of The College of Physicians of Philadelphia
- Contributed to the sacred educational exhibit of two FOP skeletons at The Mütter Museum of The College of Physicians of Philadelphia

Our work at The Center is continually evolving as we cross the bridge daily between the clinic and the laboratory and back again in a process that builds knowledge and deep understanding of FOP to help us accomplish our ultimate mission.



Assembled doctors and scientists at the FOP Immunology Workshop at the University of Pennsylvania



Skeletons of Harry Eastlack (left) & Carol Orzel (right). Photo credit: Constance Mensh for The College of Physicians of Philadelphia

The scope of research in the FOP laboratory covers a range of investigations that are focused on identifying and characterizing transformative targets for therapy.

The collaborative activities of the FOP laboratory focus on six major research areas:

**1. Identifying and characterizing central signaling targets in the induction and amplification of FOP lesions.**

These studies are conducted by Meiqi Xu, Salin Chakkalakal, Vitali Lounev, Alexandra Stanley (now Dr. Stanley), Robyn Allen, Will Towler, Kannan Karuppaiah and Niambi Brewer. This vital research enables the development of drugs that target these pathways.

**2. Identifying and characterizing immunologic and microenvironmental targets that amplify FOP flare-ups.**

These studies are conducted by graduate students Niambi Brewer and Alexandra Stanley and research scientist Vitali Lounev. Their projects investigate the cellular response to the immunologic, biochemical and biomechanical microenvironments of early (pre-cartilage/bone) FOP lesions. Stunning new therapeutic targets are emerging from their work, and it is possible that one or more such targets will become the basis for clinical trials with re-purposed drugs.

**3. Identifying cell and tissue targets in FOP lesions.** These studies are conducted by Vitali Lounev, Salin Chakkalakal, Will Towler, Alexandra Stanley and Robert Caron. These studies identify the specific cells and mechanisms that can be targeted to block heterotopic ossification.

**4. Identifying and characterizing developmental targets in FOP that impact joint development and degenerative joint disease.** These studies are conducted by Will Towler and Salin Chakkalakal.

**5. Developing *in vitro* and *in vivo* FOP models for drug “target testing.”** These studies are conducted by post-doctoral fellows Salin Chakkalakal, Robyn Allen and Alexandra Stanley, and by research scientists Vitali Lounev, Deyu Zhang, Doug Roberts and Meiqi Xu. Their projects are centered on developing new resources for FOP research that will be used in multiple other projects as well as used for *in vivo* screening of drug candidates. This work is a vital part of the infrastructure for drug discovery and development – the infrastructure for a cure.

**6. Pre-clinical drug testing** in FOP mouse models is conducted by Vitali Lounev, Deyu Zhang, Doug Roberts and Salin Chakkalakal.

Despite remarkable advances in FOP research over the past several years, we remain far from understanding some of the most basic and fundamental mysteries of FOP:

- What are the inflammatory triggers of FOP flare-ups?
- How does FOP progress in the absence of flare-ups?
- How do the immune system and the lesional tissue microenvironment influence the progression of FOP?
- What is the relationship between the innate immune system and the skeletal progenitor cells that initiate FOP flare-ups?
- What factors confer protection from heterotopic ossification in those few resilient individuals with classic FOP?
- What insights do the ultra-rare genetic variants of FOP (which affect only 2-3% of FOP patients worldwide) teach us about the function of the genetic switch that drives heterotopic ossification in FOP and how do these ultra-rare insights inform the identification of new targets for drug development?

These questions and more continue under intense investigation at The FOP Center, and their answers will help identify and confirm novel targets for drug discovery and development.

# PART 3 We the People



The Center for Research in FOP & Related Disorders is only as strong as its people. We are very proud of our team.



The Center for Research in FOP & Related Disorders at the University of Pennsylvania. (Seated from left): Dr. Mona Al Mukaddam, Dr. Fred Kaplan, Dr. Eileen Shore, Meiqi Xu (Standing from left): Kamlesh (Kay) Rai, Katherine Toder, Renee Jurek, Dr. Kannan Karuppaiah, Doug Roberts, Dr. Vitali Lounev, Dr. Will Towler, Niambi Brewer, Dr. Deyu Zhang, Dr. Salin Chakkalakal, and Bob Caron

## FOP LABORATORY TEAM



### Robyn Allen, PhD

Robyn Allen hails from Maryland where she trained horses and aspired to become a veterinarian. She became interested in research during college while working at the National Institutes of Health (NIH), where she experienced translational medical research in action from animals to humans. As a dual VMD-PhD student in the Developmental, Stem Cell and Regenerative Biology program at Penn, studying FOP with Dr. Mullins and Shore, she has had a wonderful opportunity to apply both her clinical and research training. Her goal is to become an academic researcher in developmental biology and genetics.



### Niambi Brewer

Niambi Brewer is from Bowie, Maryland and received her undergraduate degree in Biology from the University of Maryland. She is a 6th year PhD student in Biomedical Graduate Studies in the Genetics and Epigenetics Graduate Group at Penn with her focus on Genetics and Epigenetics. She greatly enjoys working in the FOP laboratory to discover pathways for treatment of genetic and non-genetic forms of HO. She greatly enjoys her interactions with the FOP patient community. “In my free time, I like to explore Philadelphia and all of the great food!”



### Bob Caron

Bob Caron grew-up in Havertown, Pennsylvania. He attended Widener University and graduated with a degree in science administration with a minor in biology, finance and accounting. Bob has worked in the FOP laboratory for almost 20 years – working on histopathology, informatics and communications, and recently, cell culture. On this journey he hopes to continue to make discoveries that will help improve patients’ lives. When he is not in the FOP laboratory, he enjoys exercising and bodybuilding.



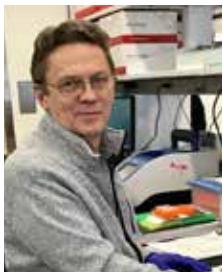
### Salin Chakkalakal, PhD

Salin Chakkalakal is a senior research investigator at the University of Pennsylvania. His academic background began with a Bachelor of Pharmaceutical Sciences degree and a Masters in Biotechnology during his studies at universities in India. He was one of ten research scholars selected internationally to pursue a fully funded PhD program in genetics at the University of Cologne, Germany where he completed doctoral work in medical biochemistry. While working on his doctoral thesis, he began to learn about genetic diseases of cartilage and bone that have no cure and are poorly understood – motivating him to work on FOP provides meaningful opportunities to develop cures. After postdoctoral training in the FOP laboratory, Salin has helped develop animal models for FOP and conducted preclinical drug testing to stop heterotopic ossification. When not working in the lab, Salin spends his time with his family – his little daughter and wife, who also works in the medical field.



### Kannan Karuppaiah, PhD

Kannan Karuppaiah received his PhD in Microbiology from University of Rostock, Germany in 2003. He then came to the US and worked as a post-doctoral scientist in skeletal development with interests in signaling pathways in growth plate and bone development. He is happy to have joined the FOP laboratory at Penn to work on bone diseases. In addition to supporting other ongoing FOP projects in the lab, Kannan is working to identify mechanisms by which GNAS inactivation causes progressive osseous heteroplasia (POH) and to identify drug targets to prevent POH and FOP using mouse genetic models. Prior work has identified common HO mechanisms in POH and FOP, and Kannan will apply what he learns about GNAS signaling mechanisms in HO to FOP.



### Vitali Lounev, PhD

Vitali Lounev is from Belarus and received his MS in Minsk, Belarus and his PhD in Moscow, Russia. He joined the FOP laboratory in 2005 as a post-doctoral fellow. He is interested in and motivated by developing new knowledge in the lab’s ongoing work to improve the lives of people with FOP and to find a cure for FOP. He works on projects to understand mechanisms of FOP and to screen new drugs to prevent HO. Vitali is the current Ashley Martucci Fellow in FOP Research. Additionally, Vitali provides support to FOP patients from Russia with translation and interpretation of information about FOP.



### Doug Roberts

Doug Roberts grew up in Dallas, Pennsylvania, and was interested in the biological sciences at a young age. He earned his BS in Biology from DeSales University and his Master of Biotechnology from the University of Pennsylvania. Although he is a new addition to the FOP laboratory, Doug has worked in the bone field for over 20 years. “I consider myself blessed. Doing work that directly affects patients has been invigorating, and I’m thrilled that I can lend my talents to this defeating this disorder.” Doug is actively engaged in pre-clinical drug testing and biomarker studies, mouse and laboratory management and coordinates shipping and receiving of patient samples. In his spare time, he volunteers with the Boy Scouts of America and his church.



### Alexandra Stanley, PhD

Alexandra Stanley (“Lexy”) grew up in San Diego, California. She attended the University of California, San Diego and earned a BS degree in Human Biology. As a student in the Developmental, Stem Cell and Regenerative Biology graduate program at Penn, she joined the FOP laboratory motivated by research that focused on therapies to treat genetic disease. “My favorite part about the lab is meeting patients and being reminded why we do the work we do.” When she’s not in lab, she’s playing with her dog, kickboxing or wine tasting. Lexy is now a post-doctoral scholar at the University of California, San Diego working on exercise-mediated glucose uptake in aging and diabetes.



### Will Towler, PhD

Will Towler is from Greenville, South Carolina and graduated from Furman University in 2011. He is a post-doctoral researcher who recently received his PhD in Developmental, Stem Cell and Regenerative Biology at Penn. His thesis project and continuing research focus on the big toe mystery of FOP – what it is, how it happens and what it can tell us about FOP. “I joined the FOP laboratory because I love figuring out the puzzle of how the body takes the shape it does and how changing that process in one context – like the great toe – can affect the rest of the body.” When not in the lab, Will pursues his hobbies of tabletop gaming, mixology and martial arts.



### Deyu Zhang

Deyu Zhang grew up in Beijing and graduated from Nanjing University, China. He has worked in the FOP lab for more than 17 years. He provides valuable expertise and support for all projects in the laboratory, including preclinical drug testing, that use mouse models of FOP.



### Meiqi Xu

Meiqi Xu was born and raised in Shanghai, China where she received her BS degree. She worked in the Chinese Academy of Sciences on drug discovery before coming to the United States. “When the FOP lab was starting, I was the first person hired to work in the FOP laboratory with Dr. Kaplan and Dr. Shore; we have worked together for more than 25 years.” She was the first person in the world to see the FOP mutation in the ACVR1 gene, and continues to conduct studies on the FOP gene, its mutations and activity. In her spare time, Meiqi enjoys traveling so that she can see and understand different countries and people.

## FOP CLINICAL TRIALS TEAM

### Mona Al Mukaddam, MD, MS



In October 2016, Mona Al Mukaddam, MD, MS, an endocrinologist at the Perelman School of Medicine, assumed the role of principal investigator of ongoing clinical trials in FOP at The Center for Research in FOP & Related Disorders at Penn. Since then, Mona has attended the IFOPA Drug Development Forum in Boston, Massachusetts in October 2016; Sardinia, Italy in October 2017 and Orlando, Florida in November 2019.

Dr. Al Mukaddam's involvement with clinical research and care of people living with FOP has soared and continues to grow. She has also attended several Family Gatherings and Ask a Doctor Meetings and has served on a medical expert panel to address common FOP-related health questions.

Dr. Al Mukaddam is an active member of the International Clinical Council on FOP (ICC). She is the chairperson of the Communications Committee of the ICC and led the effort to create the website ICCFOP.org. She is also a member of the Governance & Membership Committee of the ICC and was voted Chairperson-elect of this committee. In addition, she serves on the executive panel of the ICC and became Secretary-Treasurer in November 2020.

Dr. Al Mukaddam states, "It's remarkable to witness the advances in research that have led to a significant increase in the knowledge and care for people living with FOP.

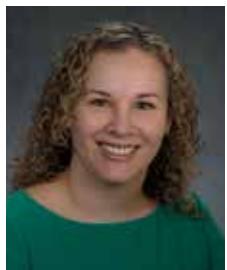
However, I also recognize that there is so much that can be done today to help our FOP patients and families. Everyone has an important and crucial role in providing education, knowledge and care for our FOP patients and their families. I am very thankful for my dedicated team that has allowed us to provide assistance and care to our FOP patients' daily needs while advancing research."



### Kamlesh (Kay) Rai

Kay Rai is a clinical research assistant at the University of Pennsylvania's Perelman School of Medicine's Department of Orthopaedic Surgery. Kay has worked with Dr. Kaplan for 39 years and is a key to starting this clinical team. Kay is Indian-born and was raised in Scotland before moving to the US in her early twenties.

Kay started working with Dr. Kaplan in 1981, the day he became an attending at the University of Pennsylvania. She has met most of the FOP patients and families who have come to the University of Pennsylvania since the FOP program was started in 1989. She coordinates new patients' visits, obtains clinical information, schedules appointments and assists in any of the needs of the FOP community that may come her way. Kay always does that with a smile and kind demeanor. In her spare time, Kay enjoys music, art, books, gardening and meeting people and most of all spending time with her grandchildren. Kay notes, "I have found our journey with FOP to be an extremely rewarding experience. I am very humbled and honored and feel privileged to have worked with the wonderful FOP community over the years."



### Staci Kallish, DO

Dr. Kallish is a medical geneticist at the Perelman School of Medicine at the University of Pennsylvania. She is the President of the Board of Directors of the National Tay-Sachs and Allied Diseases Association and a member of the Society of Inherited Metabolic Disorders and American College of Medical Genetics and Genomics. Her clinical expertise in rare genetic diseases is an extremely valuable addition to our team. Dr. Kallish received her Bachelor of Science at Emory

University and Doctor of Osteopathic Medicine at the University of Medicine and Dentistry of New Jersey. She completed her pediatric residency at Cooper University Hospital and a fellowship in medical genetics at Children's Hospital of Philadelphia. Dr. Kallish is board-certified in medical genetics – both clinical and biochemical genetics – and in pediatrics.



### **Edna Mancilla, MD**

Dr. Mancilla is a renowned pediatric endocrinologist at the Perelman School of Medicine and the Children's Hospital of Philadelphia (CHOP) and has been leading the clinical trials in FOP at CHOP. Dr. Mancilla has the research and clinical expertise in metabolic bone health in children and has performed research on the effects of retinoic acid on the growth plate. Dr. Mancilla received her medical degree at the University of Chile, worked as a visiting fellow at National Institutes of Health in the laboratory of Cell Biology and Genetics. Dr. Mancilla completed her residency in pediatrics at NYU Bellevue Hospital Center and Georgetown University Hospital. She completed a fellowship in pediatric endocrinology at Children's Hospital of Pittsburgh and the National Institutes of Health. Dr. Mancilla practiced in Chile from 1998 till 2009, when she moved to the United States and was appointed to the faculty at CHOP. She has lectured both nationally and internationally and has published articles in **The Journal of Clinical Endocrinology & Metabolism, Endocrinology, Human Mutation** and **The Lancet**.



### **Michael Levine, MD**

Michael Levine is Chairman-Emeritus of the Division of Endocrinology and Diabetes and Director of the Center for Bone Health at The Children's Hospital of Philadelphia. Dr. Levine holds the Lester Baker Endowed Chair and is Professor Emeritus of Pediatrics and Medicine at the University of Pennsylvania Perelman School of Medicine. Dr. Levine has an active laboratory that focuses on the genetic basis of endocrine signaling abnormalities. His laboratory studies the basis of altered hormone action that affects growth and development. He has identified the molecular basis of several inherited disorders of mineral metabolism, including familial hypoparathyroidism, pseudohypoparathyroidism and McCune-Albright Syndrome. Dr. Levine has published over 400 manuscripts, reviews and chapters and is a former Associate Editor of the **Journal of Clinical Endocrinology and Metabolism**. He is an active member of numerous renowned professional societies and serves as a member of the Board of Directors of the Pediatric Endocrine Society. He is the recipient of numerous prestigious awards including the Frederic C. Bartter Award from the American Society of Bone and Mineral Research and has been named “One of America’s Best Doctors” since 2005.



### **Katherine Toder**

Katherine Toder is a Research Project Manager in the University of Pennsylvania's Perelman School of Medicine's Department of Orthopaedic Surgery. Katherine moved to Philadelphia from Zimbabwe in 2004 and has enjoyed exploring the city's diverse art and restaurant scene ever since. She studied psychology and sociology at the University of Pennsylvania and started exploring different types of research after graduating with a BA in psychology in 2008. She is currently enrolled in the Masters in Regulatory Affairs Program at Penn. Her research background includes suicide risk assessment and prevention, the dissemination of cognitive behavioral therapy and the epidemiology of various reproductive cancers. She has been a

member of the FOP clinical research team since 2015 and has been the project manager of the clinical research team since 2017. Katherine's knowledge, dedication and meticulous work ethic are instrumental for the success of our clinical trials. Katherine goes above and beyond to ensure that our patients are well taken care of in every detail. She is frequently asked for advice on places and restaurants in Philadelphia. Katherine notes: "I feel privileged to meet so many inspiring FOP patients and their caregivers, families and advocates through my involvement in these groundbreaking projects."



### **Renee Jurek**

Renee Jurek is a Clinical Research Coordinator at the Perelman School of Medicine at the University of Pennsylvania. Renee grew up in Michigan and received her bachelor's degree in Athletic Training from the University of Michigan in 2015. She moved to Philadelphia soon after graduation from Michigan and began working at Penn. She has recently become a student again, starting coursework for a Masters in Regulatory Affairs at Penn in the summer of 2019. In her free time, Renee plays in various recreational sports leagues around the city, including kickball and Ultimate Frisbee. Renee is a vital member of our team. She quietly and meticulously coordinates and orchestrates many aspects of the clinical trials with amazing attention to detail and with superb memory. Renee notes: "The past four years working on the FOP trials have been incredible. I have learned so much and feel very grateful to work with such an amazing team and group of patients. This is a very exciting time in FOP research and I am looking forward to seeing where it leads."



### **Jennifer Pizza, RN, BSN**

Jennifer Pizza is a Research Nurse Coordinator at the Children's Hospital of Philadelphia (CHOP). Jennifer obtained a nursing degree at Widener University, Chester, Pennsylvania and a Certificate in Clinical Trials Management at the University of Delaware, Wilmington, Delaware. She has enjoyed working as a registered nurse in different pediatric settings such as The Chester County Hospital, West Chester, Pennsylvania; A.I. Dupont Hospital for Children, Wilmington, Delaware and Bayada Nursing Home Care, Malvern, Pennsylvania.

Jennifer has been a Research Nurse Coordinator at CHOP since 2006, initially in the Division of Cardiothoracic Surgery, joining the Division of Endocrinology in 2014. During her time in Endocrinology she has worked on various projects relating to thyroid, bone and calcium disorders. She is extremely devoted to research and pediatric care and is very excited about the opportunity to work on the FOP clinical trials team.



### **NaDea Mak, MPH, CIP, CCRP**

NaDea Mak is Clinical Research Coordinator at the Children's Hospital of Philadelphia (CHOP). NaDea received her Masters of Public Health in 2014 from Drexel University, with a concentration in health management and policy. She then worked at CHOP as Coordinator in a Community Asthma Prevention Program. From there, she became an Institutional Review Board (IRB) Project Coordinator in the Human Subjects Protection Program at Drexel University. NaDea has experience in research compliance with expertise in both biomedical research and social behavioral research. She is very excited to participate in our FOP clinical trials and help in the care of children with FOP. Her experience in biomedical and behavioral research makes a great contribution to our program.

# PART 4 Notable Advances in FOP Research in 2019



In 2019, we made great strides in understanding foundational aspects of FOP. Our progress is highlighted here in Notable Advances in FOP Research in 2019. We chose two projects to feature this year. Each was a central focus of committed and inspired graduate students and spanned several years of diligent work. Each project culminated in important publications, as well as a doctoral degree, for the students involved. Most importantly, each of these projects represents a notable advance in FOP research. We anticipate that these studies will inspire more work in these areas of FOP research and will be crucial to identifying additional robust targets for therapy.

## 1. BY MEASURING THE TOE, WE ESTIMATE THE GIANT

It's almost a refrain: "I get the flare-ups and the heterotopic ossification, but what's the story with the toes?" Graduate Student Will Towler (now O. Will Towler, PhD) decided to find out. In his own words, he will tell you, and what a story it is! It took several years to decipher and its long-term implications for FOP are vast. As the novelist Victor Hugo stated in *The Hunchback of Notre Dame*, "By measuring the toe, we estimate the giant."

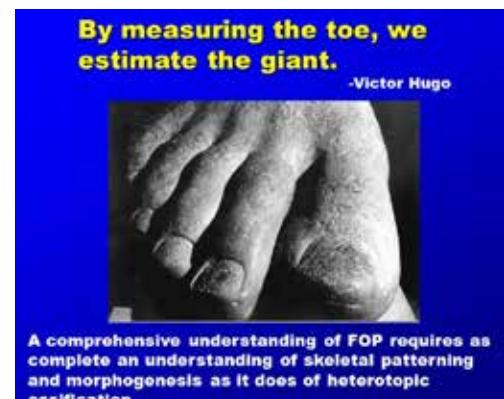
The most significant clinical consequence of FOP is the progressive formation of heterotopic bone. However, ACVR1 is widely expressed in most tissues, and increased signaling activity by the mutated ACVR1 receptor in FOP is expected to impact the development and function of these tissues as well. The clearest example of this can be seen in the great toe.

The goal of this project was to better define the consequences of the FOP mutation on joint and skeletal development by using mouse models of FOP.

To investigate the role of the classic FOP mutation in malformation of the joints, we used a genetic mouse model of FOP developed in our laboratory in which the ACVR1<sup>R206H</sup> mutation is specifically expressed in cells of the developing skeletal elements of the limbs. These mice not only form heterotopic ossification after birth as occurs in human FOP, but also recapitulate the characteristic FOP great toe malformation and provide an *in vivo* model to investigate the role of ACVR1 and downstream BMP pathway signaling in skeletal development. Using these mice, we investigated the effect of the common activating FOP mutation in ACVR1 on site-specific joint development, focusing on the digits.

My colleagues and I found that:

- ACVR1 is a key regulator of joint formation in early development.
- Dysregulated bone morphogenetic protein (BMP) signaling caused by the FOP mutation inhibits joint development in multiple digits of the mouse and induces aberrant bone formation at developing growth plates.



"By Measuring the Toe, We Estimate the Giant"

- The FOP mutation dysregulates temporal-spatial BMP signaling during embryonic formation of the skeleton and severely affects the formation of many joints – some more than others.
- The FOP mutation leads to delayed and disrupted joint formation and alters the development of cartilage and bone at sites of joint formation.

These findings demonstrate a critical role for ACVR1-mediated BMP signaling in the regulation of joint formation, show a direct link between failure to restrict BMP signaling at the exact sites where joints form, and implicate impaired joint development as the cause of toe malformations in FOP.

The development of joints occurs via changes in morphology of pre-cartilage connective tissue that separates skeletal elements into distinct bones. While BMP signaling is needed to form the bones, BMP activity must be kept out of the area where the joints will form. Down-regulation of the BMP signaling pathway in joint progenitor cells is absolutely critical for the normal initiation and progression of joint formation. Such tight regulation does not occur in FOP. Thus, while BMP signaling is necessary for the formation of bones, dysregulation of that pathway – as in FOP – prevents the normal formation of the joints. My colleagues and I have determined that while the great toe is the most severely affected, other joints of the developing skeleton are also altered.

Our studies in FOP mice provide new insight into the molecular regulation of joint development by the FOP mutation. Dysregulation of the ACVR1-BMP pathway impairs skeletal patterning by delaying and disrupting joint formation. Our data reinforce the importance of BMP pathway restriction during the critical developmental process of joint formation and have long-term implications for the health of many joints into adulthood in FOP patients.

The extensive data from the mouse studies and the scattered reports over many years that described additional bone and joint abnormalities in individuals with FOP supported a complementary study of the skeleton in a large cohort of FOP patients that Dr. Kaplan, Dr. Shore, and I conducted. Thus, what we learned at the bench was immediately translated to the bedside. The findings are described in a paper that my colleagues and I published recently in the journal **Bone**, entitled: “*Skeletal Malformations and Developmental Arthropathy in Individuals Who Have Fibrodysplasia Ossificans Progressiva*.”

So, how could we best build on the lessons we learned from the FOP mice? To reiterate, the studies in the FOP mice revealed that the joint malformations caused by ACVR1 mutation were *not* isolated to the great toe – we found them in multiple joints such as the hips and knees as well. Although the mouse studies examined developing and young stages, we knew from the orthopaedics literature that events affecting early joint formation can have big impacts later in life. Accordingly, we analyzed baseline whole body computed tomographic (CT) scans of 113 individuals with classic clinical features of FOP and the classic ACVR1<sup>R206H</sup> mutation (61 males, 52 females; ages: 4–56 years) who were enrolled in a non-interventional natural history study. We analyzed the baseline CT scans for skeletal malformations, atypical bone and joint structure, developmental joint disease, and associated degenerative joint disease. Individuals were evaluated in three age groups: 4–13, 14–25, and 26–56 years old, based on historical models of FOP disease progression.

Importantly, we found widespread evidence of developmental joint disease throughout the entire FOP skeleton in all age groups. Asymmetric narrowing and subchondral sclerosis, classic findings of degenerative arthritis, were present throughout the joints of the skeleton and bone spurs were common in the hips and knees in all age groups of individuals who have FOP. The costovertebral joints (where the ribs join the spine and are critically important for chest expansion and breathing), intervertebral facet joints (where the spinal joints move allowing us to bend), and proximal tibio-fibular joints (necessary for movement and stability of the knee) frequently showed partial or total intra-articular fusion – independent of any heterotopic bone formation – particularly after age 13. We found that the hip joints of individuals with FOP are frequently

malformed. We also found evidence of extremely early degenerative joint disease after age 13, particularly in the spine, sacro-iliac joints, and lower limbs, at frequencies that greatly exceed those found in the general population.

The study found that fusions of the vertebral facet joints, costo-vertebral joints, and proximal tibio-fibular joints of people with FOP are extremely common. Although the mechanism is undetermined, the specific sites of intra-articular joint fusion are nonetheless extremely important in understanding the clinical effect of FOP progression on people with FOP. Costo-vertebral joints (where the ribs join the spine) were fused in almost half of all subjects, which may lead to rapidly progressive scoliosis, restrictive chest wall disease and restricted breathing, all occurring independently of HO formation. In some subjects, facet joints of the thoracic and lumbar vertebra were fully fused, and the pattern of joint fusion suggested possible ossification of the associated tendons and ligaments.

Thus, the effects of the ACVR1 mutation on the joints of individuals who have FOP extend far beyond malformation of the great toes and include both structural skeletal defects and severe developmental joint disease. Associated degenerative joint disease occurring at multiple sites starts in adolescence and progresses throughout life. These findings appear to be uncoupled from heterotopic bone formation, indicating a potential role for ACVR1 in the development and progression of degenerative joint disease independently of the extra bone formation. This finding may also have important implications for those millions of individuals suffering from more common forms of degenerative joint disease (or wear-and-tear arthritis).

The current study in FOP patients not only validates widespread structural changes at sites of joint formation, but also confirms that signs of degenerative joint disease become more frequent with age in the FOP population, verifying both the hypothesis of inhibited joint formation and that of dramatically decreased joint health in adulthood.

Thus, FOP is a disease of not only progressive heterotopic ossification, but also widespread, extensive and severe developmental joint disease and accelerated degenerative joint disease. These findings have relevance for understanding the natural history of FOP and for designing and evaluating the outcome of clinical trials for HO with emerging therapeutics.

Finally, it will be critically important to assess whether the long-term fate of joints in those with FOP is affected by drugs that inhibit overactive BMP signaling from the mutant ACVR1 receptor – or whether the damage has already occurred during embryonic development, pre-determining the subsequent fate of the abnormally-formed joints in individuals with FOP. If the latter turns out to be the case, treatment options for preserving and restoring joint function will be investigated to further improve the health and well-being of those with FOP.

## 2. MECHANICAL FACTORS MATTER

FOP Postdoctoral Fellow Julia Haupt, PhD and graduate student Alexandra Stanley (now Alexandra Stanley, PhD) embarked on a project to determine how physical (biomechanical) properties of tissues influence FOP stem cells and how FOP stem cells affect physical tissue properties. Here is their story.

Two papers – the first in the journal **Molecular Biology of the Cell** (“*ACVR1<sup>R206H</sup> FOP Mutation Alters Mechanosensing and Tissue Stiffness During Heterotopic Ossification*”) and the second in the **Journal of Bone & Mineral Research** (“*Elevated BMP and Mechanical Signaling Through YAP1/RhoA Poises FOP Mesenchymal Progenitors for Osteogenesis*”) document the opening of a new frontier in FOP biology and the identification of a new molecular target for therapy.

As Drs. Haupt, Stanley and colleagues explain:

Biomechanical signals from the tissue microenvironment and cellular responses to these physical signals, such as stiffness and rigidity, are important determinants of cell differentiation and are modulated by BMP signaling.

We used a FOP mouse model of injury-induced HO to examine the early lesional tissue that occurs in a flare-up preceding heterotopic bone. We unexpectedly identified pathologic stiffening of the tissue at this early pre-bone phase of the FOP lesion. Additional assays showed that cells with the classic FOP mutation inappropriately sense their tissue environment, responding to soft surfaces similarly to wild-type cells on stiff surfaces - and identical to cells undergoing differentiation to form bone. The data support that increased BMP signaling in FOP cells alters the tissue microenvironment in a fundamental way that results in misinterpretation of mechanical stimuli and dysregulation of biomechanical signaling pathways, lowering the threshold for forming heterotopic bone.

The authors showed that the FOP mutation stimulated increased activation of RhoA and YAP1, biomechanical protein switches that increased mechanosignaling in the FOP cells. The authors also showed that FOP cells are poised for differentiation into bone, expressing increased levels of cartilage and bone markers compared with control cells even when those cells are in a soft environment that does not normally promote cartilage and bone formation.

These studies support that aberrant mechanical signals caused by increased BMP pathway signaling in FOP cells lead to misinterpretation of the cellular microenvironment and a heightened sensitivity to biomechanical cues that causes FOP progenitor cells to form cartilage and bone. Importantly, these studies provide the first direct experimental evidence that FOP progression may be influenced by the tissue microenvironment.

Understanding the mechanism by which FOP progenitor cells are directed to cartilage and bone formation by improper mechanosignaling may have relevance in identifying novel treatment approaches for FOP. Such treatment strategies to prevent HO formation in FOP patients, and potentially more common non-hereditary forms of HO, may reside in the regulation of mechanotransduction pathways during tissue repair and may combine inhibitors of mechanosignaling and BMP signaling pathways.

# PART 5 Targets, Drugs & Approaches to Stop FOP



The discovery of the FOP gene in 2006 was a transformative event in the history of FOP, and immediately revealed at least four targetable approaches to treatment and/or prevention. These include:

1. Diminishing the activity of the mutant receptor (ACVR1/ALK2) that causes increased BMP pathway signaling through inhibitory monoclonal antibodies, ligand traps, signal transduction inhibitors (STIs), or inhibitory RNA
2. Inhibiting the inflammatory triggers of FOP flare-ups
3. Directing FOP stem cells away from cartilage or bone to alternate cell fates
4. Blocking the body's response to signals within the tissue microenvironment, such as hypoxia, that amplify dysregulated BMP signaling and promote the formation of FOP lesions

A contemporary view of hard targets for FOP treatments places the mutated ACVR1 receptor at the center of the storm. As Fishman and Porter remind us, the identification of a gene product “is the greatest impediment to expanding the pharmaceutical arsenal.” Impediment? No longer! Identification of the FOP gene as a druggable target and its essential role in the BMP signaling pathway has provided the “pipeline” for drug discovery.

## “PIPELINE” DRUGS

### **Activin A Antibodies**

Two major studies described the role of Activin A (Act A) in the pathogenesis of heterotopic ossification (HO) in FOP. Investigators showed that mutant ACVR1 unexpectedly sensitized FOP cells to Act A, a ligand (hormone-like protein) that has been shown to inhibit BMP signaling. Importantly, they showed that antibodies that block Act A abolished HO in mouse models of FOP. The authors cautioned about the paucity of data implicating Activin A as a driver of HO in FOP patients, largely due to the inability to safely acquire relevant human tissues and cells for testing.

The use of primary connective tissue progenitor cells [CTPCs; also known as stem cells from human exfoliated deciduous teeth (SHED) cells] from FOP patients provided an extraordinary opportunity to examine the proposed molecular pathophysiology of the disease in an *in vitro* system directly relevant to the human condition. Importantly, these cells are obtained innocuously from FOP patients (these are the good “tooth fairy cells” that you have kindly donated) and are not transfected with viral agents that could alter the immune response to BMP pathway signaling in FOP.

Studies published in 2018 from The Center for Research in FOP & Related Disorders show unequivocally that Act A stimulates BMP signaling and enhances cartilage and bone differentiation in CTPCs from FOP patients and controls (but much more in cells from FOP patients), a finding relevant to the primary pathology of FOP in humans. Importantly, our study shows that endogenous and exogenous Act A has a stimulatory effect on BMP pathway signaling in human FOP CTPCs, consistent with recent reports.

In summary, the unexpected discovery of Act A in the pathogenesis of FOP identifies a therapeutic target for FOP and excavates a foundation for clinical development in FOP patients. The preliminary results of the clinical trial of the Regeneron-sponsored Phase II clinical trial to investigate the safety and efficacy of garetsomab (REGN2477), an anti-Activin A Antibody, in 44 adults with FOP are being evaluated. Details of the trial can be found on [clinicaltrials.gov/fop](https://clinicaltrials.gov/fop).

### Rapamycin

Although Activin A (Act A) in FOP causes heterotopic ossification (HO), the underlying mechanism is unknown. Writing in **The Journal of Clinical Investigation** (“*Activin A enhances mTOR signaling to promote aberrant chondrogenesis in FOP*”), Hino, Ikeya and colleagues from Kyoto University in Japan identified mTOR signaling (a molecular pathway involved in tissue injury and repair) as a critical pathway for the increased chondrogenesis of connective tissue cells derived from FOP-induced pluripotent stem cells. Two different HO mouse models, including an FOP mouse model, revealed critical roles for mTOR signaling *in vivo*. By using the mTOR inhibitor rapamycin, a drug used to prevent the rejection of transplanted organs, the investigators were able to inhibit heterotopic ossification in the FOP mice. These results uncovered an Act A - ACVR1/mTOR axis in FOP pathogenesis and identified the widely used and approved drug rapamycin as an inhibitor of this pathway.

As a result of this work, a clinical trial with rapamycin is underway in Japan. The one-year trial has enrolled approximately 20 individuals (ages 6-59) with FOP across four sites in Japan – Kyoto, Kyushu, Nagoya and Tokyo. The results are pending.

### Palovarotene

In FOP, heterotopic bone forms by a mechanism called endochondral ossification. In other words, through an obligate cartilage scaffold. This is how most bones of the skeleton grow and how fractures heal – by forming a cartilage template and then transforming into bone.

Palovarotene, a drug now in Phase III clinical trials for FOP, selectively targets cartilage formation. Details of the trial can be found on [clinicaltrials.gov/fop](https://clinicaltrials.gov/fop). Pacifici and Iwamoto showed in 2011 that palovarotene inhibited HO in mice genetically engineered to form heterotopic bone. Chakkalakal, Pacifici, Shore and colleagues showed in 2016 that palovarotene inhibited both spontaneous and trauma-induced HO in FOP mice. If the cartilage scaffold can be inhibited, bone formation will be inhibited.

Palovarotene activates the turn-off signal for cartilage formation. Palovarotene does not directly target ACVR1, the mutated BMP pathway receptor encoded by the FOP mutation, nor does it stop flare-ups, but targets molecules interacting with BMP signaling pathways in pre-cartilage cells that are directly downstream of ACVR1. The clinical trial is ongoing.

### Imatinib

In 2018, Kaplan, Pignolo and colleagues reported in **Bone** (“*Early Clinical Observations on the Use of Imatinib in FOP: A Report of Seven Cases*”) a combined case experience with off-label use of imatinib in seven children with relentless flare-ups and rapid symptomatic progression of FOP. Prior to publication, a reviewer wrote:

*“When treating patients with a very rare disease, reporting cases of off-label use of medications is extremely important. This paper presents very helpful information regarding the age of the patients taking the medication, presentation at time of starting imatinib, duration of treatment, side effects and rationale for stopping medications. Additionally, it provides compelling preclinical data on the possible utility of imatinib and very useful information regarding the safety and tolerability of the drug.”*

The full paper is available by contacting Dr. Kaplan at [Frederick.Kaplan@pennmedicine.upenn.edu](mailto:Frederick.Kaplan@pennmedicine.upenn.edu). Here, we present a brief summary:

Research studies have identified multiple potential targets for therapy in FOP, and novel drug candidates are being developed for testing in clinical trials. A complementary approach seeks to identify approved drugs that could be re-purposed for off-label use against defined targets in FOP. Imatinib is one such drug.

Imatinib is a tyrosine kinase inhibitor originally developed for use in patients with chronic myeloid leukemia (CML). Imatinib is a safe, well-tolerated medication that has been used in thousands of adults and children with CML. Importantly, imatinib has the desirable effect of down-regulating multiple targets relevant to the pathophysiology of FOP. Preclinical studies demonstrated that imatinib decreases HIF1- $\alpha$ /inflammation activity, decreases mutant ACVR1 activity in hypoxic FOP stem cells, and is effective in reducing HO in a mouse model of FOP.

In addition to targeting HIF1- $\alpha$ , imatinib may have the added benefit of impacting other targets including c-Kit (an essential gene for mast cell generation and mast cell activity) which plays a major role in FOP lesion formation, PDGFR $\alpha$  (expressed by the FOP lesional fibroproliferative cells), and multiple MAP kinases involved in inflammation. Imatinib also has potential beneficial effects in lymphocytes, macrophages and mast cells by dampening multiple signaling pathways implicated in the pathophysiology of FOP lesions. Notably, imatinib is effective in the treatment of systemic mast cell disease and inhibits multiple inflammatory proteins implicated in the formation of heterotopic ossification. Thus, imatinib has potential impact on major therapeutic targets of FOP although it was not designed for that.

Based on compelling biologic rationale, strong preclinical data, and a favorable safety profile, imatinib was prescribed on an off-label basis in seven children with continuous FOP flare-ups, predominantly in the axial regions, and which were not responsive to standard-of-care regimens. All seven children failed to demonstrate any durable symptomatic response to the standard medications used to manage symptoms of FOP such as corticosteroids, non-steroidal anti-inflammatory agents, cromolyn, or intravenous bisphosphonates. All seven children were referred to a pediatric hematologist-oncologist or a pediatric rheumatologist for consideration of imatinib therapy after detailed consultation with the parents on the relative risks and benefits of off-label use of imatinib for FOP. Parents were informed that imatinib use was on an off-label basis and was not part of a clinical research study. The parents were also informed that progress would be monitored clinically and that radiographs would not be performed routinely.

Anecdotal reports in these cases document that the medication was well-tolerated with an overall reported decrease in the intensity of flare-ups in the six children who took the medication. Moreover, the parents of all six children who were able to take imatinib on a daily basis noted subjective decreases in flare-up intensity after several weeks of use.

Clinical trials for rare diseases commonly focus on one target and one potential therapeutic at a time. However, the exigencies of clinical care in a real-world setting require flexibility in managing symptomatic disease, especially when no other alternatives are available. Approved medicines for one condition may have potential off-target effects for another and thereby be suitable for off-label use on a compassionate basis. Early anecdotal experience with such medications may suggest useful parameters for monitoring meaningful endpoints in future clinical trials.

As a result of our experience in these seven children, we strongly feel that imatinib should be evaluated in a controlled clinical trial in the pediatric FOP population who are experiencing relentless axial flare-ups and for whom few, if any, tangible treatment opportunities presently exist. These early clinical observations support the implementation of imaginative – perhaps N of one – clinical trials in children with uncontrolled FOP flare-ups to determine if imatinib may ameliorate symptoms or alter the natural history of this debilitating and life-threatening disease. Alternatively, imatinib may be used by physicians on an off-label basis to manage symptoms in children with uncontrolled FOP.

### **Blocking Antibodies against ACVR1**

Mutant ACVR1 demonstrates leaky BMP pathway signaling and ligand hyper-responsiveness, providing a rationale for using blocking antibodies to ACVR1 in the prevention and treatment of FOP. Therapeutic monoclonal antibodies specific for ACVR1 are under development by at least two pharmaceutical companies.

### **Signal Transduction Inhibitors (STIs)**

STIs are the bullseye of all targets for FOP. As a class, these orally available small molecules block the “mouth” of the FOP receptor, thus preventing it from transmitting its misdirected message to make more bone. STIs are important molecular tools for studying the BMP signaling pathway in FOP and have great potential for development into powerful therapeutic drugs for FOP. Selective STIs for FOP will inhibit ACVR1 rather than closely associated receptors and are concurrently being developed by at least five pharmaceutical or biotechnology companies. Broad-spectrum STIs that target ACVR1 are also being repurposed for clinical trials.

### **Allosteric Inhibitors**

On a variation of the STI theme, known as allosteric inhibition, Dr. Jay Groppe from Texas A&M College of Dentistry and Dr. Alex Bullock from Oxford University have recently highlighted alternative approaches to silence the mutant FOP receptor that has promise for future drug development. Instead of targeting the mouth of ACVR1 that is nearly identical among related receptors, the allosteric approach capitalizes on the unique aspects of ACVR1 (compared to other BMP receptors) to present novel targets.

# PART 6 The Broken Faucet



There are now at least 16 drugs in research or development for FOP. Nine have entered clinical trials and more will come. There is a dizzying array of approaches being discovered and developed to combat FOP. Is there any way to make sense of all this? The answer is “yes.” All the approaches start with the ACVR1 gene mutation that causes FOP and the BMP signaling pathway that ACVR1 signals through. Thus, it is helpful to put all of these drugs and approaches into a simple framework as they are all part of the BMP signaling pathway to which ACVR1, the FOP gene, belongs. As Fishman & Porter explained, “The signaling pathway in cells provides the right level for such analysis.”

Let's begin with a simple metaphor – an example we can all picture. Imagine that the ACVR1 protein is a faucet – a water faucet – made by the ACVR1 gene (the genetic blueprint for making the ACVR1 receptor protein) in the ACVR1 factory. Individuals who do not have FOP have two “normal” faucets manufactured by the two gene copies that each of us has for ACVR1. In the human genome, most genes are present as two copies, or alleles. *[Picture 1]*

However, individuals with FOP have one normal ACVR1 gene (blueprint) and one damaged ACVR1\* gene (blueprint) so that half of the faucets made in the FOP factory are “normal” and half are damaged. *[Picture 2]*

In cells, the ACVR1 gene (blueprint) is translated to produce the ACVR1 protein that does the functional work of ACVR1. If the blueprint is damaged, then the resulting faucet will not work correctly. In those who do not have FOP, the “normal” faucet will be “off” when there is no signal to make bone, and “on” when there is a signal (BMPs; the hand that turns on the faucet). When the ACVR1 faucet is turned on by the BMPs, water comes out. The water is the signal (pSmad1/5) for making bone. *[Picture 3]*

In FOP, the damaged faucet is leaky when it should be “off,” but gushes with water when it is turned on with BMPs (the hand that turns on the faucet). *[Picture 4]*



Left to Right: Picture 1; Picture 2; Picture 3; Picture 4

Thus, the damaged (mutant) ACVR1 faucet leaks water at rest and gushes with water when turned on, as depicted here.  
 [Picture 5]

A detailed “scientific” depiction of the damaged FOP faucet [ACVR1<sup>R206H</sup>] and the downstream pathway is shown in the next figure. [Picture 6]

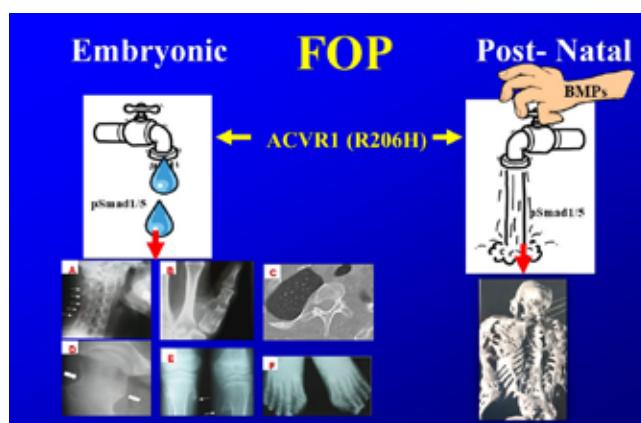
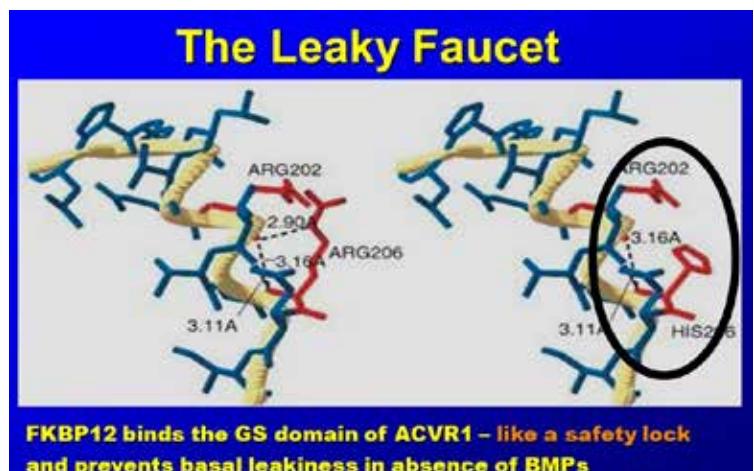
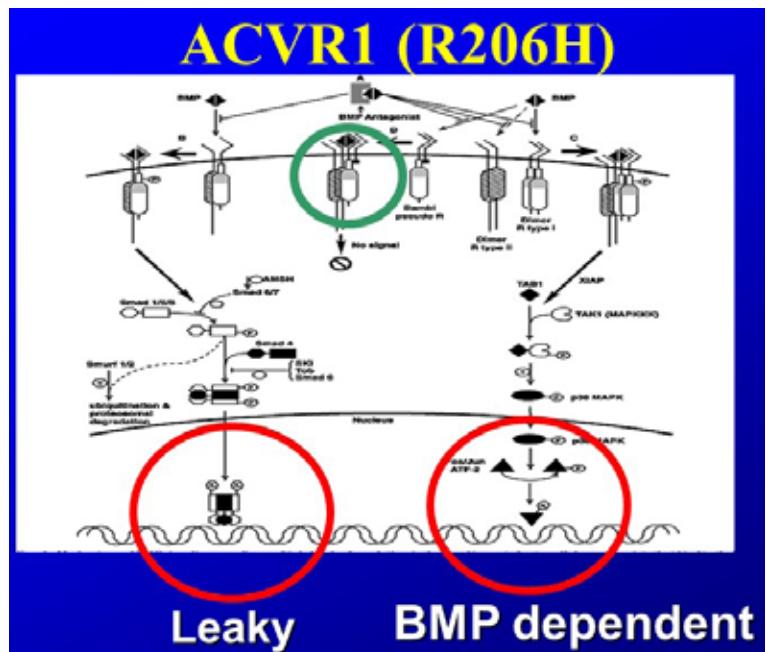
The exact place in the ACVR1 protein molecule where the FOP faucet is damaged is shown in the next figure. The normal faucet should have an “ARG” at position 206. The damaged FOP faucet has a “HIS” instead (circled area). This substitution causes the faucet to malfunction (leaky when “off”; gushing water when “on”).  
 [Picture 7]

So, now we have some background understanding about the normal faucet and about the FOP faucet. Let’s move on.

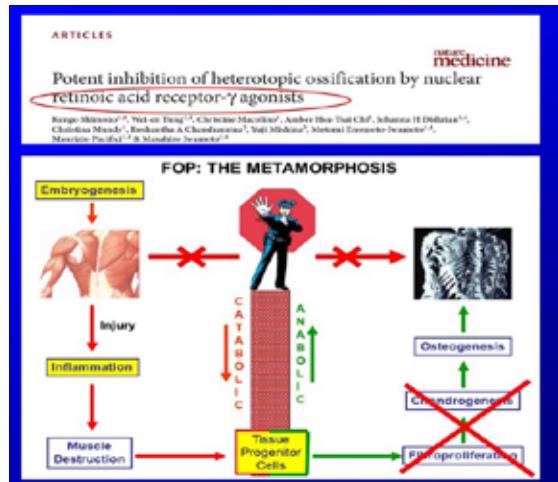
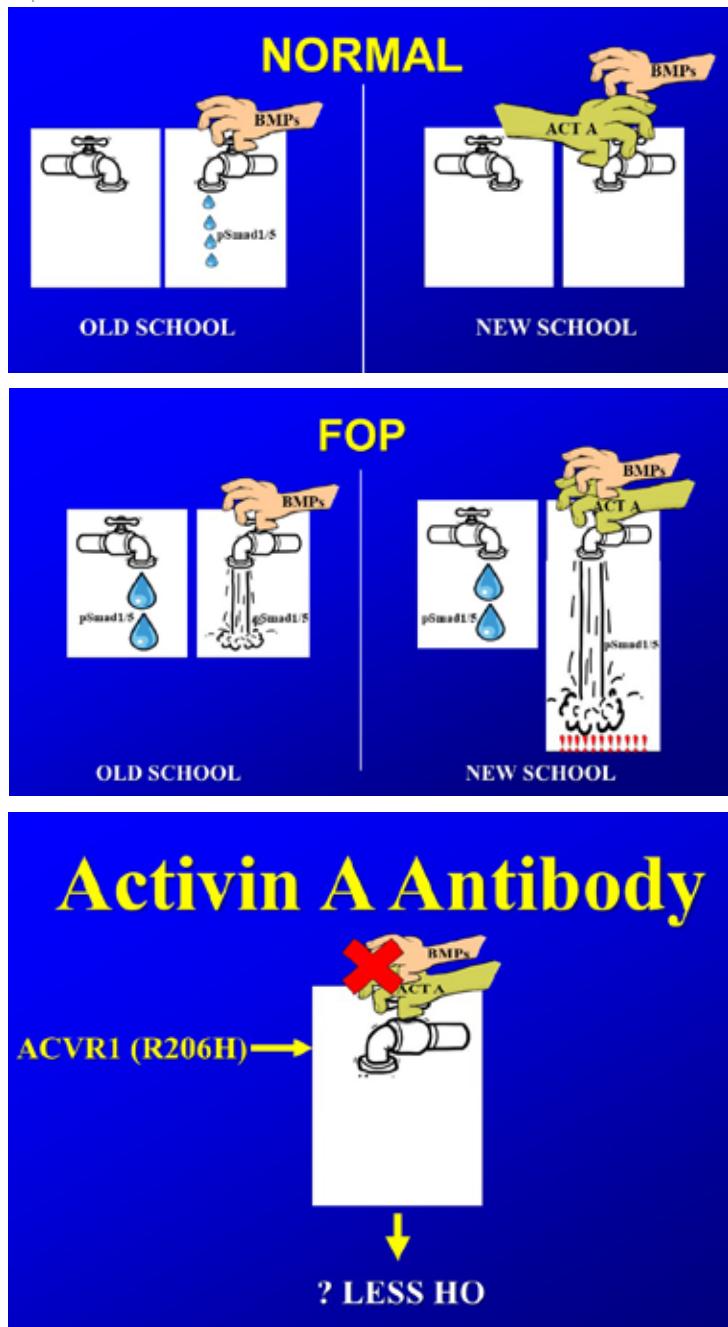
The damage done by the FOP faucet can be divided into two phases – a stage before birth (embryonic) and a stage after birth (postnatal). The stage before birth occurs when the skeletal bones and joints are forming in the womb. This stage is responsible for the bone and joint malformations (explained in an earlier section of this report) and most noticeable in the short, malformed great toes, but also involving many other bones and joints such as the spine, ribs, hips, knees and thumbs, to name a few. Data from multiple experiments in many laboratories throughout the world strongly suggest that the “leaky” FOP faucet is responsible for this “before birth” or embryonic stage of FOP. Data from multiple experiments in many laboratories throughout the world strongly suggest that the heterotopic bone after birth is due to the “gushing” faucet.  
 [Picture 8]

In 2015, scientists from Regeneron Pharmaceuticals and scientists from Kyoto University in Japan discovered something

Top to Bottom: Picture 5; Picture 6; Picture 7; Picture 8



Top to Bottom: Picture 9; Picture 10; Picture 11; Picture 12



interesting and unexpected. While the “old school” idea was that BMPs turn on the normal faucet, the scientists discovered the “new school” idea that Activin A, another hormone-like molecule, actively “turned off” the normal faucet. [Picture 9]

What is even more amazing is what they discovered about the FOP faucet. To review, the “old school” idea was that the FOP faucet was chronically “leaky” when it should be off and gushing with water (signal for making more bone) when “turned on” by BMPs. This is true. But, while Activin A “turns off” the normal faucet, it activates the FOP faucet by turning it on – causing the water to gush or explode out of the broken FOP faucet – greatly amplifying the effect of the BMPs and stimulating the formation of flare-ups and heterotopic bone. [Picture 10]

The scientists showed that Activin A caused heterotopic bone, when implanted into the muscle of an FOP mouse, but did not cause heterotopic bone when implanted into the muscle of a normal mouse. Importantly, an antibody against Activin A prevented the formation of heterotopic bone in the FOP mouse. The Activin A antibody is a protein that “grabs” the hand of Activin A that turns on the FOP faucet and prevents the water from gushing out or exploding from the broken FOP faucet. [Picture 11]

In a different approach to blocking the formation of heterotopic bone, Maurizio Pacifici and his colleagues at Children’s Hospital of Philadelphia discovered that drugs, such as palovarotene, inhibit heterotopic ossification (HO) in mouse models of BMP- and ACVR1-induced HO by blocking cell differentiation to cartilage. Chakkalakal and colleagues showed that palovarotene blocked HO in genetically accurate mouse models of FOP.

[Picture 12]

Palovarotene inhibits the process of HO far downstream of the ACVR1 receptor by essentially acting as an umbrella to block the water – the signal for making bone. It does not stop the gusher/explosion of water that initiates the flare-up or the flare-up itself [Picture 13]

The FOP gene mutation [ACVR1<sup>R206H</sup>] – the damaged blueprint that is used by “the factory” to make the broken faucet – does not turn a normal faucet into a gushing faucet. It makes a “leaky” faucet. Something else turns a “leaky” faucet into a gushing/exploding faucet. What does that? [Picture 14]

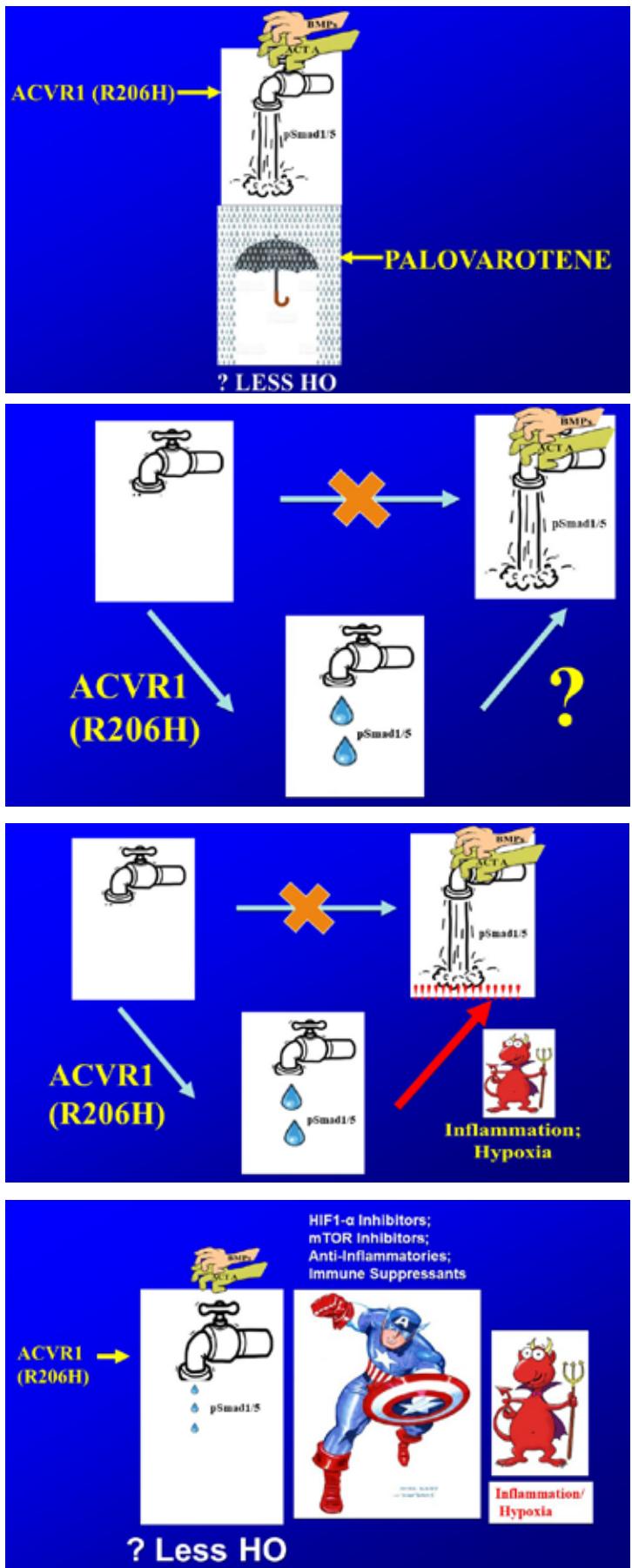
Careful clinical observations and many experiments from laboratories worldwide identify that “devil” of a stimulus as inflammation and tissue hypoxia (low oxygen). [Picture 15]

Many approaches such as the use of HIF1- $\alpha$  inhibitors, mTOR inhibitors; anti-inflammatory drugs and immune suppressants such as rapamycin are being investigated for their ability to prevent “the devil” of inflammation & hypoxia from stimulating BMPs and Activin A to turn on the broken FOP faucet. [Picture 16]

Several years ago, a major discovery was made by David Goldhamer and colleagues from the University of Connecticut. They discovered that progenitor cells (identified as muscle interstitial cells and now called fibroadipogenic progenitor cells or FAP cells) that live in-between the muscle bundles exhibit BMP and Activin A responsive bone-forming activity and appear to be responsible for at least a portion of the unwanted bone formation of FOP.

On the surface of these FAP cells, and many other cells of the body, there are faucets very similar to ACVR1 – faucets that are “turned on” and “turned off” to

Top to Bottom: Picture 13; Picture 14; Picture 15; Picture 16



Top to Bottom: Picture 17; Picture 18; Picture 19

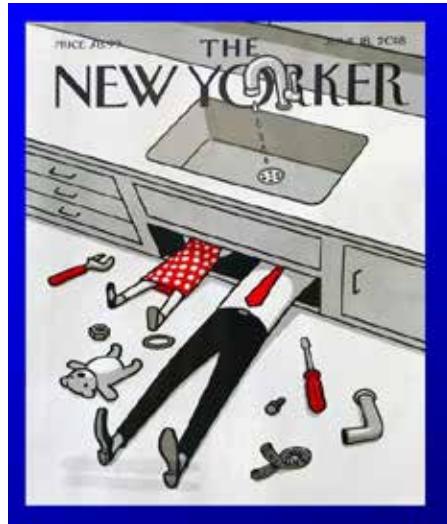
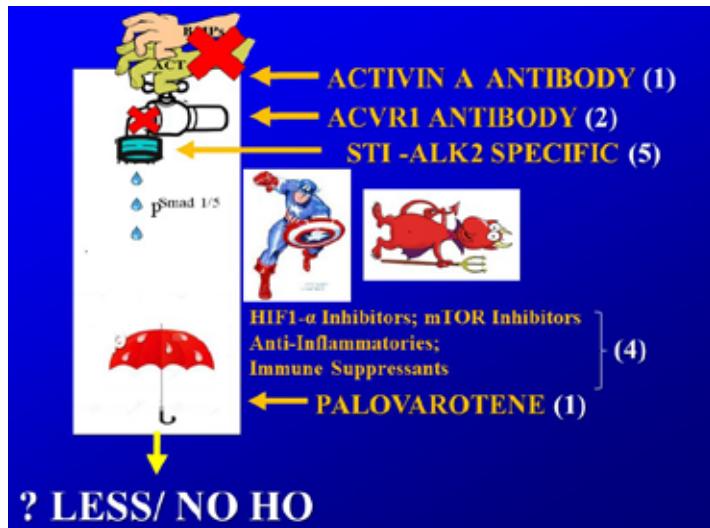
control a number of cell functions – such as in the toilet, shower, and bathtub, for example. It is critically important that a drug that blocks ACVR1 (the FOP faucet) does not block the other similar faucets. It may be beneficial to block the broken FOP faucet, but not the similar “look-alike” faucets that are used in the toilet, shower and bathtub since these have important functions that need to continue to work.

First-generation signal transduction inhibitors (STIs), small molecules that directly blocked the ACVR1 faucet, also blocked all the other faucets. It took many scientists in many laboratories, many years, and many millions of dollars to develop highly selective inhibitors that directly block the ACVR1 faucet, but none of the “look-alike” faucets. [Picture 17]

There are at least five pharmaceutical companies actively developing inhibitors that are specific for the ACVR1 faucet. Three of the five compounds developed by these pharmaceutical companies have entered phase I clinical trials in healthy volunteers. These selective inhibitors are all like small plugs that fit into the ACVR1 faucet and prevent the water from coming out, but still allow the other faucets to work. None are specific only for the damaged FOP faucet – and in the context of FOP will block the normal ACVR1 faucet as well as the FOP ACVR1 faucet – but some show a small selectivity for blocking the FOP faucet. By blocking the ACVR1 faucet, these small molecule “plugs” (to be taken orally) are designed to slow/stop the gushing/explosive waterflow (BMP signaling pathway) that leads to flare-ups, lesions, and HO (unwanted bone). [Picture 18]

Studies show that the small molecule “plugs” (signal transduction inhibitors) should also block the damaged ACVR1 faucets that cause FOP variants. [Picture 19]





Top Row, Left: Picture 20; Right: Picture 21;  
Bottom Row, Left: Picture 22; Right: Picture 23



The above picture summarizes all the different approaches to blocking the “leaky” FOP pathway. Some of these approaches are “upstream” of the damaged faucet – like Activin A antibody. Some are “on-stream” – like antibodies that block the damaged faucet itself and small molecule “plugs.” Other approaches are “side-stream” – like the anti-inflammatories, hypoxia blockers and immune suppressants that block the ability of the inflammatory “devil” from activating the process that unleashes the BMPs and Activin A. And finally, there are downstream approaches like palovarotene that act as an umbrella to prevent the BMP pathway signal (gushing water) from forming bone. [Picture 20]

There will be other approaches – imaginative, creative, and novel – and some are already under development. A few include: destabilization of the receptor so that the faucet “self-destructs” and closes off the pipeline the minute that water (signal to form bone) runs through the receptor/faucet; small inhibitory RNA that “grabs the damaged faucet” off the assembly line as soon as it is made (two papers already published on that); and the ultimate – CRISPR-Cas9-like gene editing targeted specifically to the cells that form HO – so that the damaged faucet isn’t even made in these cells. Stay tuned! [Picture 21]

Just weeks after the FOP gene discovery, **The New York Times** ran a hopeful story with the headline “*Finally, With Genetic Discovery, Hope for Escape from a Prison of Bone.*” [Picture 22]

Just recently, **The Philadelphia Inquirer** ran an even more hopeful story with the headline “*Drug therapies in sight for bone-forming disease.*” [Picture 23]

But, there will be BuMPs along the BMP pathway. Not every drug will work or be safe and effective enough to be approved. We need drugs that will stop flare-ups, prevent flare-ups and HO, maintain function, slow joint degeneration, and ultimately change the natural history of FOP from – as the Developmental Biologist Brigid Hogan described – “a horrible nightmare disease” into something not more than an inconvenience.



Top Row: Picture 24; Bottom Row:  
 Picture 25; Picture 26



But, let's be clear. Some drugs will have dangerous or intolerable side effects, off-target effects, elicit allergic reactions, exhibit rebound or resistance. Some drugs will work best for adults; others may be effective in children. There will be non-responders even to the most powerful drugs. There will be compliance and tolerability issues as well as access to therapy and the dreaded "cost." No one drug will fit all, and no one individual is likely to get by for a lifetime with just one "magic drug" – there's not just one way to disable the FOP faucet. *[Picture 24]*

But, as Ian Cali said, "With the FOP gene discovery, we went from hopeless to hopeful." *[Picture 25]*

And, as Yak Gamboa, a young man from Puebla, Mexico said, "We need hope, and if we have hope, we'll be OK." *[Picture 26]*

Hope is a powerful medicine.



## PART 7 Editor's Choice – Highlights from the Literature

BONE, 2018

### A Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP

Assessment of functional mobility in FOP is essential to support clinical trials of investigational agents. Of necessity, a simple, rapidly-administered, cumulative analogue joint involvement scale (CAJIS) for FOP was developed by Drs. Kaplan, Al Mukaddam and Pignolo based on assessments in 144 individuals worldwide with classic FOP. CAJIS scores correlated with patient age, activities of daily living, and ambulatory status, with excellent inter-rater variability. The CAJIS score provides an extremely accurate and reproducible snapshot of total body and regional impaired mobility burden in FOP that correlates with age and functional status.

In fact, CAJIS score is not linked with flare-up frequency only. The reasons for this are that the CAJIS is a measure of global joint dysfunction due to all causes (e.g. HO due to flare-ups, non-flare-up progression of HO, accelerated arthritis, impingement of a joint due to osteochondromas, joint dysplasias, or intra-articular synovial osteochondromatosis).

The CAJIS is not meant to replace detailed range-of-motion assessment for any particular joint. Rather, it is designed to enable a rapid assessment of total body mobility burden in any clinical setting. The central value of the CAJIS score for FOP is that it is a rapid, comprehensive, cumulative analogue assessment of joint involvement that is independent of the rate, timing, order, or position of progressive disease activity.

Evaluation of the average change in cross-sectional total CAJIS score over time estimates that the score increases by about 0.5 units per year across all ages. This suggests that the CAJIS should be assessed at least every two years to detect an increase in the CAJIS score of one. However, younger patients can be expected to accumulate joint dysfunction more quickly than older patients, and so an annual assessment of CAJIS may be more appropriate. Presently, CAJIS evaluations have been incorporated into the design of three ongoing clinical trials ([clinicaltrials.gov/fop](https://clinicaltrials.gov/fop)).

In conclusion, CAJIS is a simple, rapidly administered, clinical assessment of joint function. As of 2019, CAJIS is being used worldwide and is the standard assessment for clinical staging of FOP. CAJIS scores correlate with patient age, ambulatory, and ADL status with excellent inter-rater variability. The CAJIS evaluation can be performed rapidly in any clinical setting.

**BONE, 2018****[*18F*] NaF PET/CT Scan as an Early Marker of HO in FOP****BONE, 2019*****Evolution of Heterotopic Bone in FOP: An [*18F*] NaF PET/CT Study***

Two papers by Botman and colleagues from Amsterdam document that [*18F*] NaF PET/CT scans are a sensitive method for detecting new bone formation in FOP. [*18F*] NaF PET/CT scans are able to detect early flare-ups of FOP as well as totally asymptomatic disease activity. But, exactly what that activity means in the clinical context of FOP progression is presently unknown. Some of the activity on [*18F*] NaF PET/CT scans may represent new lesions while some may represent residual activity of pre-existing lesions. Correlation with contemporaneous CT scans may add specificity. This new imaging modality has been incorporated into an ongoing clinical trial and at the very least establishes [*18F*] NaF PET/CT scanning as a sensitive method of detecting ossification in FOP.

**ORPHANET JOURNAL OF RARE DISEASES, 2019*****Natural History of FOP: Cross-sectional Analysis of Annotated Baseline Phenotypes***

This prospective natural history study by Pignolo and colleagues describes the baseline, cross-sectional disease phenotype of 114 individuals with FOP.

All subjects underwent protocol-specified baseline assessments to determine their disease status. Cross-sectional analyses were performed in which functional evaluations (Cumulative Analogue Joint Involvement Scale [CAJIS] and the FOP-Physical Function Questionnaire [FOP-PFQ]), as well as the burden of HO as measured by low-dose whole-body CT, were assessed.

Findings from 114 subjects (age range 4 to 56 years) were evaluated. While subject age was significantly correlated with increased CAJIS and FOP-PFQ scores, the estimated mean increases per year were small (0.47 units and 1.2%, respectively). There was also a significant correlation between baseline age and HO volume, with an estimated mean increase of nearly 26,000 cubic millimeters per year. There were also highly significant correlations between the objective assessment of HO volume and clinical assessments of CAJIS and FOP-PFQ.

Based on the cross-sectional analysis of the baseline data, functional and physical disability as assessed by CAJIS and the FOP-PFQ increased over time. Although longitudinal data are not yet available, the cross-sectional analyses suggest that CAJIS and FOP-PFQ are not sensitive to detect substantial progression over a 1- to 2-year period. Future evaluation of longitudinal data will test this hypothesis.

The statistically significant correlations between HO volume (as measured by CT scan) and the functional endpoints, and the estimated average annual increase in total HO volume, suggest that the formation of new HO will be measurable over the relative short-term course of a clinical trial, and represents an endpoint that is clinically meaningful to patients.

The baseline data in this natural history study are representative of the worldwide FOP population. This study contributes to the understanding of FOP by characterizing the cross-sectional changes in physical and functional impairment over the course of the disease and by documenting the importance of HO as a substantial cause of morbidity in individuals who have FOP. Importantly, this baseline study provides a rationale for the selection of whole-body low dose CT scan as a clinically meaningful outcome measure and radiologic biomarker for HO progression and treatment effects over a one to two-year period of a clinical trial.

***Longitudinal Evaluation of Pain, Flare-up and Emotional Health in FOP:  
Analysis of the International FOP Registry***

The principal pathological feature of FOP is the transition of skeletal muscle, tendons, ligaments, and fascia into cartilage and bone. This heterotopic ossification (HO) is often preceded by painful soft tissue swellings, or flare-ups, that may last several months. For many individuals, experiencing a flare-up may represent a worsening of their condition and contribute to feelings of anxiety or suppressed effect, both of which are well-recognized to exacerbate pain perception. To date, much remains unknown regarding the dynamics of pain and emotional health in FOP during flare-up and also quiescent, non-flare-up disease phases.

In order to elucidate the occurrence and effect of pain in FOP, Peng and colleagues from Children's Hospital of Boston analyzed Patient-Reported Outcomes Measurement Information System-based questionnaires completed by 99 patients participating in the international FOP Registry over a 30-month period. Although moderate to severe pain ( $\geq 4$ , 0 to 10 pain scale) was commonly associated with flare-ups (56% to 67%), surprisingly, 30% to 55% of patients experienced similar pain levels during non-flare-up states. In those patients reporting pain levels of  $\geq 4$ , 45% to 74% of patients reported experiencing anxiety, depression, or irritability, with 36% to 48% reporting emotional problems during no to mild pain states. Furthermore, independent of the flare-up status, the severity of pain in FOP patients was found to be significantly anti-correlated with emotional health, physical health, and overall quality of life. These findings strongly suggest the need for an improved understanding of pain and emotional health in FOP patients during flare-ups as well as during quiescent periods.

**NATURE COMMUNICATIONS, 2018*****Activin-dependent Signaling in Fibroadipogenic Progenitors Causes FOP***

In this important paper, John Lees-Shepard and colleagues from the University of Connecticut show that Tie2<sup>+</sup> fibroadipogenic progenitors (FAPs) that reside in muscle tissue but are not muscle progenitors are a major cell-of-origin of HO in a mouse model of classic FOP. Targeted expression of the classic FOP mutation to Tie2<sup>+</sup> cells recapitulate the full spectrum of HO observed in FOP patients. FAPs expressing the classic FOP mutation, but not wild-type FAPs, activate bone-forming signaling in response to Activin ligands. Conditional loss of the wild-type copy of the FOP gene in the FOP mice dramatically exacerbates Tie2<sup>+</sup> cell-directed HO, suggesting that mutant and wild-type ACVR1 receptor complexes compete for Activin ligands or type II BMP receptor binding partners. Finally, systemic inhibition of Activin A blocks HO and restores wild-type-like behavior to transplanted FOP FAPs. Understanding the cells that drive HO may facilitate the development of cell-specific therapeutic approaches to inhibit HO in FOP.

**JCI INSIGHT, 2018*****NF-κB/MAPK Activation Underlies ACVR1-mediated Inflammation in Human Heterotopic Ossification***

Although BMP signaling and inflammation pathways are known contributors to abnormal bone formation in FOP, how these pathways interact remains unclear.

Barruet and colleagues from the University of California, San Francisco examined this potential link in patients with FOP. FOP patients show exquisite sensitivity to trauma, suggesting that BMP pathway activation may alter immune responses. Primary blood, monocyte, and macrophage samples from control and FOP subjects were studied.

FOP subjects at baseline without clinically-evident heterotopic ossification (HO) showed an increase in multiple

inflammatory serum proteins. Primary FOP monocytes treated with an activator of the innate immune system showed abnormal secretion of inflammatory proteins as well as prolonged activation of the NF- $\kappa$ B pathway, a key inflammatory pathway. FOP macrophages derived from primary monocytes also showed similar findings. Thus, abnormal ACVR1 pathway activity in FOP caused a proinflammatory state. These findings suggest that chronic anti-inflammatory treatment may be useful for suppressing heterotopic ossification.

## NEURON, 2017

### ***Fibrinogen Activates BMP Signaling in Oligodendrocyte Progenitor Cells and Inhibits Remyelination After Vascular Damage***

## ACTA NEUROPATHOLOGICA, 2018

### ***Activin Receptors Regulate the Oligodendrocyte Lineage in Health and Disease***

## ENEURO, 2019

### ***Inhibiting BMP4 Type I Receptor Signaling Promotes Remyelination by Potentiating Oligodendrocyte Differentiation***

## INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 2019

### ***Myelination in Multiple Sclerosis Lesions is Associated with Regulation of BMP4 and its Antagonist Noggin***

Four papers from Australia, Germany, the United Kingdom, and the United States published over the past two years document that activation of the BMP signaling pathway is detrimental to the repair of nerve damage in the central nervous system. Importantly, inactivation of the BMP signaling pathway in oligodendrocytes, the cells responsible for the insulation (myelination) of the central neurons, dramatically improves the repair of the central nervous system following damage. These findings have vital significance for the treatment of multiple sclerosis. Importantly, the papers and the corroborated findings also have importance for FOP.

The BMP pathway is over-activated in inflammatory lesions of the skeletal muscles and brain. FOP is characterized by over-activity of the BMP signaling pathway due to the activating mutation of ACVR1. Neurologic problems are common in FOP and FOP mice and many individuals who have FOP have widespread incidental demyelinating lesions of the central nervous system of unknown clinical significance. FOP and multiple sclerosis share the common clinical feature of inflammatory flare-ups fueled by an over-active BMP pathway.

Targeting the BMP signaling pathway, as in some of the clinical trials currently being conducted or anticipated, may be a therapeutic strategy not only to inhibit heterotopic ossification in FOP, but also to promote the regenerative potential of central nervous system progenitors which displays features of remyelination failure. It will thus be important to monitor neurological changes with agents that inhibit the BMP signaling pathway that also cross the blood-brain barrier.

## VETERINARY PATHOLOGY, 2019

### *Identification of the Identical Human Mutation in ACVR1 in Two Cats with FOP*

A paper from Casal and colleagues from the University of Pennsylvania document two domestic shorthair cats, a female and a male, that presented with progressive lameness and digital deformities at four and six months of age. Stiffness and swelling of the distal thoracic spine joints and pelvic limb joints progressed to involve hip and shoulder joints, resulting in reduced mobility. Radiographs in both cats revealed deposits of heterotopic bone that spanned multiple axial and appendicular joints. All findings supported the diagnosis of FOP. In both cats, molecular analyses revealed the same heterozygous mutation in the Activin A receptor type I (ACVR1) gene that causes FOP in humans. Several reports of heterotopic ossification in cats exist, but this is the first one to identify clinical FOP in two cats with the identical mutation that occurs in >95% of humans with FOP.

## ADDITIONAL HIGHLIGHTS FROM THE FOP 2018-2019 LITERATURE:

### JOURNAL OF BONE AND MINERAL RESEARCH, 2018

#### (SELECTED FOR ISSUE COVER IMAGE)

*Depletion of mast cells and macrophages impairs heterotopic ossification in an ACVR1<sup>R206H</sup> mouse model of fibrodysplasia ossificans progressiva*

### BONE, 2018

*Variable signaling activity by FOP ACVR1 mutations*

### BONE, 2018

*Variant BMP receptor mutations causing fibrodysplasia ossificans progressiva (FOP) in humans show BMP ligand-independent receptor activation in zebrafish*

### BONE, 2018

*Activin A amplifies dysregulated BMP signaling and induces chondro-osseous differentiation of primary connective tissue progenitor cells in patients with fibrodysplasia ossificans progressiva (FOP)*

# PART 8 Programs at The Center



## THE “ARC” MICE

A new and improved conditional FOP mouse model has been developed at The Center for Research in FOP and Related Disorders and we have used it successfully in 2019 in multiple experiments and approaches. We have developed assays for heterotopic ossification (HO) induction and have conducted pre-clinical drug testing in these mice. The new FOP mouse model has the classic FOP mutation knocked in to the endogenous ACVR1 locus which means that the mutation is under the control of the endogenous (“natural”) FOP promoter. Additionally, the mutant copy of the gene is inactive until turned on, and this activation can be done generally in all cells of the mouse, or in specifically targeted cell types or tissues at any time during the life of the mouse. Importantly, a fluorescent reporter gene has been engineered into the mutant gene to allow investigators to determine in exactly which cells the mutant gene has been activated.

These new mice exhibit all of the features of the currently available mouse models – and more! These new mice will be available for collaborative research by contacting Dr. Eileen Shore at [shore@pennmedicine.upenn.edu](mailto:shore@pennmedicine.upenn.edu). This work was made possible by a grant from an anonymous and generous donor from Caldwell, New Jersey. The donor, unrelated to, but inspired by, the dedication of Angelo R. Cali (Ian Cali’s grandfather) to FOP research, asked that the mice be designated as the “ARC mice.”

## THE “TOOTH FERRY” PROGRAM AT THE FOP LAB: SHEDDING LIGHT ON FOP

The participation of so many patients and families who contribute blood/DNA samples to advance FOP research has been invaluable and is enormously appreciated. These samples were critical for discovering the FOP gene and for identifying the specific DNA sequence changes that occur in classic and variant forms of FOP. Although much FOP research is more rapidly and effectively conducted using mouse models of FOP, FOP patient cells and tissues will always be essential in order to confirm that the information that we learn from mice holds true in human cells.

We relied on blood samples from patients for many years since blood can be safely obtained without risk of triggering an FOP flare-up. However, blood cells provide limited information about FOP lesion formation. Fortunately, recent advances have identified additional types of human cells and tissues that can be obtained safely and are vitally important to our work. One of these cell types is “SHED cells.”

**SHED** stands for Stem cells from **H**uman **E**xfoliated **D**eciduous teeth – a long name that describes the stem-like progenitor cells that are inside primary or baby teeth. When a baby tooth falls out naturally, we can recover the cells from inside the tooth. We have used baby teeth from FOP patients to show that these cells can be grown in our lab and treated in special ways to form cartilage and bone cells, providing us with an informative system to examine how the FOP mutation affects the differentiation potential of cells involved in an FOP lesion.

A few years ago, The FOP Center started a “Tooth Ferry” program to encourage families to send FOP baby teeth to us so that cells from these teeth could be used for FOP research. These cells have already given us bountiful

information about the effects of the FOP mutation on cartilage and bone cell formation. SHED cells were used in our studies to down-regulate the mutant (damaged) copy of the FOP gene by siRNA and are being used in our ongoing studies on the effects of microenvironment factors on FOP flare-ups and lesion formation. Thus, SHED cells continue to be extremely vital for many of our laboratory experiments. Because the cells have a limited lifespan and since multiple samples from a person are very informative, we continually need additional “donations” to continue to conduct our studies with SHED cells.

Anyone with a child who is losing teeth can participate in “The Tooth Ferry” Program. When your child loses a tooth or needs to have one pulled at the dentist’s office, you can send it to us in a pre-assembled kit that we will provide to you. Teeth from siblings and non-family members are also welcome for comparison. In addition to baby teeth, we are also happy to receive wisdom and other permanent teeth from people with FOP. Permanent teeth also contain stem cells and we are currently investigating their use and applicability in FOP research.

There is a brief window of opportunity for receiving the teeth with still-healthy cells, so we have developed specific instructions for their handling and shipping. If you decide to participate, we will send you a kit including all of the necessary return packaging (for several teeth), return FedEx labels, our contact information, a tooth diagram to fill out and return, and a copy of instructions. We are also providing information about the program on the IFOPA website, however it is very important that you contact us before sending a tooth. If teeth arrive by surprise at the lab, we may not be able to prepare them optimally.

The “Tooth Ferry” kit is very simple to use. This is an IFOPA-supported program and there is no cost to you. In addition to being used by our lab, SHED cells that we derive in our lab will be shared with the IFOPA Biobank upon request by the donor. If you have children with teeth still to lose or are being pulled, please contact Bob Caron by email at [rearon@pennmedicine.upenn.edu](mailto:rearon@pennmedicine.upenn.edu) and a “Tooth Ferry Kit” will be on its way to you soon!

## FOP VARIANTS:

### WHAT ARE THEY, WHO HAS THEM & WHAT DO THEY MEAN FOR YOU?

When we started seeing FOP patients at The FOP Center, nearly 35 years ago, it quickly became obvious that everyone shared two features: malformed big toes and progressive heterotopic ossification (HO). These were clearly two characteristic clinical features and they define classic FOP.

As we saw more patients, we recognized variability in the toe malformations that individuals had, as well as differences in the timing and rate of progression of the FOP extra bone formation. For example, some had short, bent big toes; others had short, straight big toes; others still had long big toes and some were of normal length. But everyone had a toe malformation – most commonly caused by a missing or malformed joint in the big toe that was readily detected on physical examination, x-rays, or both. Likewise, we noted variability in the rate of progression of the FOP HO – some progressed very rapidly while others progressed very slowly, and still others progressed at a more even pace. Much like other traits in any population of people, FOP showed a natural variation that defined the limits of the norm.

Occasionally though, we would see someone who had a feature of FOP that was WAY outside of the “normal” range – even for FOPers. Such outlier features most often were noted by the appearance of the big toes. Among these individuals, we began to recognize two groups:

- One group had nearly normal or completely normal-looking big toes
- The other group had extremely severe toe malformations that involved other digits in the feet and the hands.

In the more “severe” group, we observed additional developmental abnormalities in other organ systems. We refer to these two groups of outliers as “FOP variants” – some mild, some severe.

Approximately 97% of individuals that we have seen with FOP had “classic FOP,” and approximately 3% of individuals were “FOP variants.” About half the patients with FOP variants (1.5%) showed mild clinical variation and about half the patients (1.5%) had a severe variation. Again, these observations were based on clinical evaluation and preceded the discovery of the FOP gene.

After we discovered the FOP gene, we examined the DNA sequence of the FOP gene in all patients who we had seen. Remarkably, nearly every single patient who was diagnosed as having “classic FOP,” regardless of where they were on the spectrum of HO disease severity, shared the same exact FOP mutation: the identical misspelled genetic letter in the FOP gene [ACVR1 c.617G>A; R206H].

As remarkably, every patient who we had identified clinically as being an “FOP variant” had a misspelled DNA letter in the same ACVR1 gene that was different from ACVR1 c.617G>A (R206H).

In other words, those with “classic FOP” as the clinical diagnosis had the same “classic mutation” in the FOP gene [ACVR1 c.617G>A; R206H], while everyone clinically diagnosed as an “FOP variant” had a “variant mutation” in the FOP gene.

While many will ask, “Is the bone formation process less severe in the less severe variants and more severe in the more severe variants?” The answer is: “Sometimes, but not necessarily.” Some of the patients with mild toe variants have a later onset and a milder course of HO and some of the patients with severe toe variants have an earlier onset and more severe course of HO. But there is wide variability – just as there is in the onset and severity of HO in the patients with “classic FOP,” even among identical twins with classic FOP. The most important defining feature of the “FOP variants” is the malformation of the big toes – either far less severe or far more severe than the patients with “classic FOP.”

Although the clinical assessment is extremely important in assigning a clinical status of “classic FOP” vs. “FOP variant,” the only way to be sure of the exact type of FOP at a molecular level is by genetic testing and DNA sequence analysis of the FOP gene. To be clear, the absolute defining factor in whether someone has “classic FOP” or an “FOP variant” is the exact genetic sequence of the ACVR1 (FOP) gene. If someone has the commonly shared ACVR1 c.617G>A; R206H mutation, then they have “classic FOP.” If they have a variant genetic mutation in the ACVR1 gene, then they have an “FOP variant.” So far, there are approximately 20 identified ACVR1 gene variants in the FOP gene. Some of these gene variants are found in a few individuals, others have been identified in only a single person.

The evaluation of the FOP gene (ACVR1) by DNA sequencing can be conducted in a genetics laboratory through a DNA sample obtained from a blood sample. The analysis can be arranged by your physician. Confirmation of the FOP type by genetic testing (referred to as “genotyping”) is required for enrollment into all clinical studies and is important for proper clinical and genetic counseling.

Keep in mind that FOP variants are much rarer than classic FOP. Since some of the ACVR1 variants have so far been found in only one or two affected individuals in the world, it is difficult to make predictions about the course of FOP over time. With other variants, there may be five or ten affected individuals in the world, so we know a little bit more about the course that FOP may take over time.

So, what does this all mean for someone who has an FOP variant?

**First**, we have less knowledge and therefore less certainty about the FOP variants than we do about classic FOP; but we and other scientists are beginning to learn more about how the ACVR1 variant mutations affect cell functions and how they are similar to and different from the classic ACVR1 mutation. The exact location and characteristic of the mutation in the ACVR1 gene (i.e. the blueprint for the ACVR1 protein; classic vs. variant) informs the structural biologists with whom we work and collaborate to better understand the damaged workings of ACVR1 in FOP. That insight is critical to developing structural models and approaches to inactivating the damaged and overactive switch that leads to disabling HO in all forms of FOP.

**Second**, despite whether someone has “classic FOP” or an “FOP variant,” all have over-activity of the bone-forming pathway and thus the tendency to form heterotopic bone.

**Third**, whether someone has “classic FOP” or an “FOP variant,” the process by which they form heterotopic bone after birth is the same.

**Fourth**, the general precautions for FOP are the same for patients with classic FOP and FOP variants.

**Fifth**, the symptomatic management of flare-ups is the same for patients with classic FOP and FOP variants.

**Sixth**, some of the approaches to develop medications for FOP are mutation-specific while others (so far, most) target the broad process of HO common to both.

**Seventh**, approaches to specifically block the overactive ACVR1 receptor (encoded by the FOP gene) should be applicable to FOP variants as well as classic FOP.

**Eighth**, new clinical trials will likely be limited at first to patients who have classic FOP – and then later, if successful and applicable, to those with FOP variants – based primarily on regulatory requirements.

**Ninth**, every measure and pressure is being exerted to open up applicable clinical trials to patients with FOP variants as quickly and humanly possible. This is being done right now.

**Tenth**, and finally, all patients with FOP – classic and variant FOP – are part of our small but powerful worldwide FOP community. There is a common thread that unites us. We must stay together, speak with one voice, and learn from each other. Knowledge is powerful and will lead to better treatments and a cure for all of those with FOP regardless of whether one has “classic FOP” or an “FOP variant.” We are all in this fight for a cure, and we must band together to win this battle and triumph over FOP.

## THE CALI DEVELOPMENTAL GRANTS PROGRAM

In 1997, the Cali Family, in consultation with Dr. William N. Kelley, MD, then Dean of the University of Pennsylvania School of Medicine, established The Center for Research in FOP & Related Disorders at the University of Pennsylvania. This was and still remains the only such center of its kind in the world. Simultaneously, the Cali Family inaugurated the vanguard Extramural Developmental Grants Program which is administered by The Center. The mission of the Developmental Grants Program is to foster collaborative research between The Center and other research laboratories of excellence at Penn, and at other universities in the United States and around the globe. The program has been in place for over 20 years and has had vast outreach to the relevant basic and translational science community worldwide.

The Cali Developmental Grants Program is proudly one of the crown jewels of the FOP research world. Over the past 20+ years, the Cali Developmental Grants Program has awarded 53 grants of \$50,000 each for total support of \$2.65 million. This innovative program has expanded horizons in FOP research well beyond the physical boundaries of the FOP laboratory at Penn into a true worldwide co-laboratory.

Research partners include other laboratories within the University of Pennsylvania as well as other universities and institutions including Baylor; Brown; Harvard; Northwestern; Texas A&M; Vanderbilt; University of California, San Francisco; Children's Hospital of Philadelphia; The Mayo Clinic; and the Max Planck Institute for Molecular Biology in Germany.

The Cali Family Fund and Developmental Grants Program has funded work that led to the discovery of new therapeutic targets for FOP and to the development of kinase inhibitors, antibodies, extracellular traps, cellular pathway inhibitors, and inhibitory RNA for critical proof-of-principle studies in FOP.

Importantly, more than 80 percent of the scientists and researchers who participated or were represented at the 2014-2019 IFOPA Drug Development Forums have been direct or indirect beneficiaries of a Cali Developmental Research Grant from The Center for Research in FOP & Related Disorders.

Over the past two years, the Cali Developmental Grants Program continued to support three highly innovative research projects:

1. **“Molecular Basis of Pathogenic Signaling and High Throughput Testing of FOP Therapies in a Zebrafish Model System”** is directed by Dr. Mary Mullins from the University of Pennsylvania.
2. **“Identifying Alternative Therapeutic Targets and Genetic Interactors in FOP”** is directed by Dr. Edward Hsiao of the University of California, San Francisco.
3. **“Novel Allosteric Destabilizers as Therapeutics for FOP”** is directed by Dr. Jay Groppe of Texas A&M University College of Dentistry.

## ASHLEY MARTUCCI FOP RESEARCH FUND

Established in 2015, the Ashley Martucci FOP Research Fund supports FOP research at the University of Pennsylvania's Center for Research in FOP & Related Disorders, as well as The Ashley Martucci Fellowship.

- **Basic Research.** The scientific effort supported by the Ashley Martucci Research Fund seeks to identify novel therapeutic targets for FOP by investigating inflammatory and immunologic triggers for forming heterotopic bone.

Recently, much attention has been focused on a healthy, mobile, resilient adult (Patient-R) who has the classic FOP mutation (and the classic malformed toes), but almost none of the extra bone forming features of FOP. This unprecedented and totally unexpected protection from the ravages of FOP led to the hypothesis that Patient-R lacks an inflammatory trigger that is necessary for the extra bone formation – sort of like an atom bomb that is inert because it is lacking a fuse. Biomarker analysis and genetic studies in Patient-R have in fact revealed significantly decreased blood levels of an inflammatory protein that is a possible cause of Patient-R's resilience to flare-ups and extra bone formation. Based on these analyses, we have begun extensive studies in FOP mice that so far suggest that even partial inhibition of this inflammatory protein by genetic or pharmacologic means (through readily available drugs) substantially reduces the extra bone formation of FOP. This work is revealing a completely unexpected and novel molecular target that may be useful in preventing extra bone formation and progressive disability in FOP.

- **The Ashley Martucci Fellowship.** Scientist Vitali Lounev, PhD, is the current Ashley Martucci Fellowship awardee and is actively investigating novel inflammatory and immunological triggers of heterotopic bone formation in FOP as outlined above. The Ashley Martucci Fellowship has previously supported scientists Michael Convente, PhD, and Haitao Wang, PhD, whose work has already identified two novel immunologic targets that are critical for the evolution of FOP – tissue hypoxia and mast cells. As a result of their published work, currently available drugs are being used to target these pathways in FOP.

Generous donations from the FOP Ashley's Cure fundraisers are being used to support this exciting, ongoing research at the University of Pennsylvania's Center for Research in FOP & Related Disorders.

# PART 9 FOP - The Spoken Word



In 2018-2019, major lectures on FOP were presented at:

- Advances in Mineral Metabolism; Snowmass, Colorado
- American Association of Anatomists; San Diego, California
- American Society for Bone & Mineral Research; Montreal, Canada & Orlando, Florida
- American University of Beirut; Beirut, Lebanon
- BMP Signaling in Cancer Conference; Oxford University, United Kingdom
- Charlotte Maxeke Academic Hospital (Formerly Johannesburg General Hospital); Johannesburg, Republic of South Africa
- Chris Hani Baragwanath Hospital; Soweto Township, Johannesburg, Republic of South Africa
- College of Physicians of Philadelphia; Philadelphia, Pennsylvania
- Dubai International Conference for Medical Sciences; Dubai, United Arab Emirates
- European Calcified Tissue Society; Valencia, Spain
- FOP Brazil & Africa; São Paulo, Brazil
- FOP France; Toulouse, France
- FOP Germany; Valbert, Germany
- FOP Stichting Nederland; Haarlem, The Netherlands
- FOP Poland; Rzeszów, Poland
- FOP Russia; Moscow, Russia
- FOP Friends®; Manchester, United Kingdom
- Gordon Research Conference on Bones & Teeth; Galveston, Texas
- Highland Park High School; Highland Park, New Jersey
- IBM Watson Headquarters; New York, New York
- IFOPA 2019 Drug Development Forum; Orlando, Florida
- IFOPA 2018 Family Gathering; Baltimore, Maryland



Top: Dr. Mona Al Mukaddam (center; Philadelphia, USA) meets with Dr. Tae-Joon Cho (Seoul, South Korea) and Moira Liljesthrom (Buenos Aires, Argentina) at the IFOPA FOP Drug Development Forum (Orlando, Florida); Bottom: Drs. Fred Kaplan & Michael Zasloff at the IFOPA Drug Development Forum in Orlando, Florida



Left: At the 12th International BMP Conference in Tokyo, Japan; Right: Dr. Eileen Shore (University of Pennsylvania) meets with Dr. Hari Reddi (University of California – Davis) at the 12th International BMP Conference (Tokyo, Japan)

- IFOPA 2019 FOP Family Gathering; Orlando, Florida
- International BMP Conference, University of Tokyo; Tokyo, Japan
- Keystone Meeting on Cellular Plasticity; Keystone, Colorado
- Molecular Pharmacology Conference/Cancer and Bone Society; Oxford University, United Kingdom
- Quinnipiac University; Hamden, Connecticut
- Rahima Moosa Mother & Child Hospital; Johannesburg, Republic of South Africa
- Rare Bone Disease Alliance; Montreal, Canada
- Sanford-Burnham Rare Disease Day Symposium; La Jolla, California
- Society of Developmental Biology; Boston, Massachusetts
- TGF-Beta Super-Family Signaling in Development & Disease FASEB Conference; West Palm Beach, Florida
- University of Arkansas for Medical Sciences; Little Rock, Arkansas
- University of Michigan, Ann Arbor, Michigan
- University of Pennsylvania; Philadelphia, Pennsylvania
- University of Rzeszów; Rzeszów, Poland
- University of São Paulo; São Paulo, Brazil
- University of Witwatersrand; Johannesburg, Republic of South Africa
- Washington University; St. Louis, Missouri
- Wellcome Genome Center; Hinxton, United Kingdom

We would like to acknowledge the extraordinary medical, scientific, and patient meetings in 2018-2019 that we were honored to attend and in which we were honored to participate in – Ann Arbor, Michigan; Baltimore, Maryland; Dubai, United Arab Emirates; Haarlem, The Netherlands; Johannesburg, Republic of South Africa; Manchester, United Kingdom; Moscow, Russia; Orlando, Florida; Rzeszów, Poland; São Paulo, Brazil; Tokyo, Japan; Toulouse, France, and Valbert, Germany. These meetings were a wonderful opportunity to meet with scientists, researchers, physicians, students, and patients from around the world.

In 2018-2019, highlights of FOP research were presented at local, regional, national, and international FOP family meetings and gatherings in:

- Allentown, Pennsylvania
- Ann Arbor, Michigan
- Baltimore, Maryland
- Beirut, Lebanon
- Blackwood, New Jersey
- Castle Rock, Colorado
- Denver, Colorado
- Dubai, United Arab Emirates
- Haarlem, The Netherlands
- Johannesburg, Republic of South Africa
- Manchester, United Kingdom
- Moscow, Russia
- New York, New York
- Orlando, Florida
- Philadelphia, Pennsylvania
- Rzeszów, Poland
- São Paulo, Brazil
- Tokyo, Japan
- Toulouse, France
- Valbert, Germany



Top: Joshua Scoble (Emmaus, PA) visits Dr. Kaplan in Philadelphia; Bottom: Addie Black (Denver, CO), Liam Rump (Littleton, CO), Caleb Burgess (Castle Rock, CO), and Danielle Coyne (Littleton, CO) with Dr. Kaplan at "Finding a Cure for FOP - Bombers for Bones – Home Run Derby" (Castle Rock, Colorado)

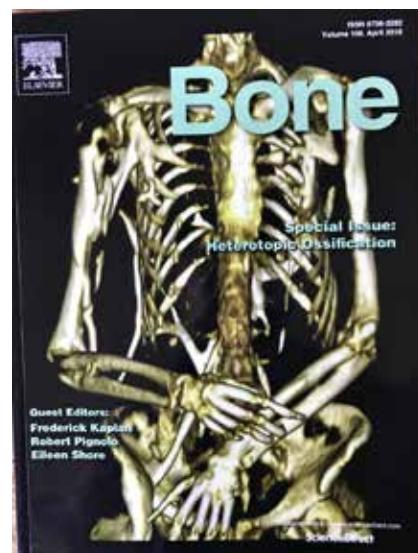
## PART 10 FOP - The Written Word

In 2018-2019, publications from numerous groups on FOP and FOP-related issues appeared in peer-reviewed journals.

There were nearly 200 papers published on FOP worldwide, the most in a two-year period – and a tribute to the newfound and broad international interest and awareness of the disease.

Forty-eight papers on FOP were published in the special issue of **Bone** (on heterotopic ossification) in 2018-2019.

As of January 1, 2020, the classic paper in **Nature Genetics** (April 2006) describing the discovery of the FOP gene has been cited in 898 major scientific publications worldwide.



Cover of BONE – Special Issue on Heterotopic Ossification; April, 2018.



## PART 11

### The International Clinical Council on FOP

The International Clinical Council on FOP (The ICC) is an autonomous and independent group of 21 internationally recognized physicians who are clinical experts in FOP from 14 nations (Argentina, Australia, Brazil, Canada, China, France, Germany, Italy, the Netherlands, Japan, Republic of Korea, South Africa, the United Kingdom, and the United States) and six continents (North America, South America, Europe, Africa, Asia, and Australia). The ICC was established to coordinate and consolidate a global voice for the best practices for clinical care and clinical research for people who suffer from FOP. The Council was officially established and its Constitution unanimously ratified on June 21, 2017.

The ICC independently establishes its rules, committees, and criteria for membership and meets at least twice annually, either in-person and/or by teleconference. The ICC looks forward to a very proactive agenda. Formal announcements, updates and activities will be presented at relevant meetings and on the ICC website.



The International Clinical Council on FOP meets in Baltimore, Maryland. Back Row, from left: Drs. Mona Al Mukaddam (Philadelphia, PA, USA), Coen Netelenbos (Amsterdam, The Netherlands), Zvi Grunwald (Philadelphia, PA, USA), Clive Friedman (London, Ontario, Canada), Marelise Eekhoff (Amsterdam, The Netherlands), Rolf Morhart (Garmisch-Partenkirchen, Germany), Christiaan Scott (Cape Town, South Africa). Front Row, from left: Drs. Robert Pignolo (Rochester, MN, USA), Maja DiRocco (Genoa, Italy), Robert Diecidue (Philadelphia, PA, USA), Edward Hsiao (San Francisco, CA, USA), Fred Kaplan (Philadelphia, PA, USA), Carmen De Cunto (Buenos Aires, Argentina), Richard Keen (London, England, UK), Genevieve Baujat (Paris, France) and Patricia Delai (São Paulo, Brazil). Not Pictured: Drs. Matthew Brown (London, England [formerly Brisbane, Australia]), Tae-Joon Cho (Seoul, Republic of Korea), Nobuhiko Haga (Tokyo, Japan), Michael Zasloff (Philadelphia, PA, USA), Keqin Zhang (Shanghai, China)

## The Mission of The ICC is:

1. **To educate** on best practices for the care of individuals with FOP
2. **To advise** on the design and conduct of interventional trials in FOP patients
3. **To publish** from time-to-time the FOP Treatment Guidelines
4. **To advocate** for a robust infrastructure for data sharing and collaboration on vital and emerging matters of clinical concern to the FOP community
5. **To identify** less explored areas of FOP patient care and issues that may drive insight into research
6. **To share** valuable clinical experiences from the care of patients with classic and variant FOP
7. **To better** understand the variable phenotype of FOP and the systemic nature of FOP pathology

## The ICC has five standing committees that meet regularly in person and by teleconference:

### » Governance & Membership Committee

Function: To establish the ICC governing rules, membership terms, auditing processes, bylaws

### » Ethics Committee

Function: To guard the health and safety of FOP patients by supporting transparency and compliance with Good Clinical Practices

### » Communications & Relations Committee

Function: To provide the external communications to the public

### » Publications Committee

Function: To revise and publish the FOP Treatment Guidelines and provide the resource for all materials published on behalf of the ICC

### » Clinical Trials Committee

Function: To provide guidelines for clinical trials in support of safe and transformative treatments for FOP



*The Publications Committee of the ICC and other members of the ICC meet at the FOP Family Gathering in Orlando, FL. (Seated from left): Drs. Carmen De Cunto (Argentina), Patricia Delai (Brazil), Robert Pignolo (USA), Genevieve Baujat (France). (Standing from left): Christiaan Scott (South Africa), Fred Kaplan (USA), Marelise Eekhoff (The Netherlands) & Rolf Morhart (Germany)*

## THE MEMBERS OF THE ICC ARE:

**Mona M. Al Mukaddam, MD, MS**

Philadelphia, PA, USA

**Genevieve Baujat, MD**

Paris, France

**Matthew Brown,**

**MBBS, MD, FRACP, FAHMS, FAA (Emeritus)**

London, England (formerly Brisbane, Australia)

**Tae-Joon Cho, MD**

Seoul, Republic of Korea

**Carmen L. De Cunto, MD**

Buenos Aires, Argentina

**Patricia L. R. Delai, MD**

São Paulo, Brazil

**Robert Diecidue, MD**

Philadelphia, PA, USA

**Maja Di Rocco, MD**

Genoa, Italy

**E. Marelise W. Eekhoff, MD, PhD**

Amsterdam, The Netherlands

**Clive Friedman, DDS**

London, Ontario, Canada

**Zvi Grunwald, MD**

Philadelphia, PA, USA

**Nobuhiko Haga, MD**

Tokyo, Japan

**Edward Hsiao, MD, PhD**

San Francisco, CA, USA

**Frederick S. Kaplan, MD**

Philadelphia, PA, USA

**Richard Keen, MD, PhD**

London, United Kingdom

**Rolf Morhart, MD**

Garmisch-Partenkirchen, Germany

**J. Coen Netelenbos, MD, PhD**

Amsterdam, The Netherlands

**Robert J. Pignolo, MD, PhD**

Rochester, MN, USA

**Christiaan Scott, MBChB**

Cape Town, South Africa

**Michael Zasloff, MD, PhD**

Washington, DC, USA

**Keqin Zhang, MD, PhD**

Shanghai, China

In 2019, the ICC published a landmark article “*Special Considerations for Clinical Trials in FOP*” in the **British Journal of Pharmacology** with the following abstract.

“*Clinical trials for orphan diseases are critical for developing effective therapies. One such condition, FOP is characterized by progressive heterotopic ossification (HO) that leads to severe disability. Individuals with FOP are extremely sensitive to even minor traumatic events. There has been substantial recent interest in clinical trials for novel and urgently-needed treatments for FOP. The International Clinical Council on FOP (ICC) was established in 2017 to provide consolidated and coordinated advice on the best practices for clinical care and clinical research for individuals who suffer from FOP. The Clinical Trials Committee of the ICC developed a focused list of key considerations that encompass the specific and unique needs of the FOP community - considerations that are endorsed by the entire ICC. These considerations complement established protocols for developing and executing robust clinical trials by providing a foundation for helping to ensure the safety of subjects with FOP in clinical research trials.*”

In March, 2019, the ICC published a major revision of the widely-used and acclaimed **FOP Treatment Guidelines**.

The following letter accompanied that release:

*"Dear Members of the FOP Community,*

*On behalf of The International Clinical Council on FOP (ICC), its 21 members and five consultants, we are pleased to introduce the 2019 edition of*

## **THE MEDICAL MANAGEMENT OF FOP: CURRENT TREATMENT CONSIDERATIONS**

*(Commonly known as The FOP Treatment Guidelines)*

*The ICC has been working diligently on this document for over a year which represents a monumental effort on the part of many. This report contains fifteen new sections that we hope you will find useful as well as completely updated sections that you found useful in the past.*

*You will notice the new **Executive Summary of Key Practice Points**. It is conservative, informative and balanced – and supported by the detailed exposition of the larger report.*

*We emphasize that this document reflects the authors' experience and opinions on the various topics and classes of symptom-modifying medications, and is meant only as a guide to this area of therapeutics for an ultra-rare condition for which evidence-based information is limited.*

*Although there are common physical features shared by every person who has FOP, there are physiological differences among individuals that may alter the potential benefits or risks of any medication or class of medications discussed here. The decision to use or withhold a particular medication must ultimately rest with an individual patient and his or her physician.*

*With ongoing clinical trials and additional ones on the horizon, we anticipate that this document will be updated annually – more frequently if needed.*

*We sincerely hope that this revised edition of the FOP Treatment Guidelines will be useful and relevant to FOP patients, families, physicians, dentists, medical personnel and caregivers worldwide.*

*Sincerely,*

*Frederick S. Kaplan, MD; The University of Pennsylvania, Philadelphia, PA*

*Robert J. Pignolo, MD, PhD; The Mayo Clinic, Rochester, MN*

*Corresponding Editors*



# PART 12 Awards & Honors

## The Grand Hamdan International Award for Medicine

In 2018, Dr. Kaplan received the Grand Hamdan International Award for Medicine. Jamal Al Saleh, MD, Chairman of the Award Committee noted, “The Hamdan Award honors those who have made a substantial impact on others in the field of humanitarian services, medical services and research.”

The award was presented at a ceremony in the Dubai International Convention Center on December 12, 2018, by Sheikh Hamdan bin Rashid al Maktoum, Ruler of Dubai and Patron of the Award. The Award noted that “Professor Kaplan’s and colleagues’ investigations of the rare diseases FOP and POH (progressive osseous heteroplasia) have uncovered mechanisms so pathogenically fundamental to tissue metamorphosis that they have challenged existing dogma far outside the usual realm of musculoskeletal medicine. For example, they challenged the existing dogma that calcific aortic stenosis was caused by a ‘senile degenerative’ process and discovered that aortic stenosis is caused by an inflammatory process that triggers re-activation of the developmental process of skeletal formation – work that led to the discovery of heterotopic bone formation in atherosclerosis – with therapeutic implications for millions.”

Upon receiving the award, Kaplan commented “I am enormously honored and humbled to have been selected to receive The Grand Hamdan International Award for Medical Sciences in the field of Musculoskeletal Medicine. I fervently hope that the research that my colleagues and I have done over the past 30 years will pave the way to relieve the tremendous suffering of those with the rare and catastrophic disorders FOP and POH as well as more common disorders of extra-skeletal bone formation.”

In a letter sent to the Board of the IFOPA and the Khaleej Times in Dubai, Kaplan noted: “The Grand Hamdan International Award in Medicine, which is intended to recognize ‘dedication to alleviating human suffering through research and standard services’, comes with a substantial monetary prize that I would like to donate to the IFOPA as a gift in memory of my beloved parents, Harold and Elaine Kaplan....In that spirit – and in the spirit of the Award – I would like to donate the prize money to the IFOPA to establish in perpetuity – The Harold & Elaine Kaplan Quality of L.I.F.E. Awards.”



Left to Right: Dr. Kaplan receives The Grand Hamdan Award for Medicine from Sheikh Hamdan (Dubai, The United Arab Emirates); Dr. Kaplan is presented the certificate of The Grand Hamdan Award (Dubai, The United Arab Emirates); Drs. Fred Kaplan, Tina Bales Kaplan & former FOP fellow and orthopaedic surgeon Nader Hebele (Cleveland Clinic - Abu Dhabi, The United Arab Emirates) at The Grand Hamdan Award Ceremony (Dubai, The United Arab Emirates)

## Honorary Degree from Quinnipiac University

On May 18, 2018, Dr. Kaplan received an Honorary Doctor of Humane Letters degree at the Frank H. Netter MD School of Medicine Commencement at Quinnipiac University in Hamden, Connecticut.

The IFOPA noted, “Dr. Kaplan was recognized for his pioneering work in heterotopic ossification and skeletal metamorphosis, as well as the co-discovery of the gene mutation causing FOP and for his work as the co-director of The Center for Research in FOP and Related Disorders.”

Dr. Kaplan also delivered the commencement address. In the University’s invitation they noted, ‘Dr. Kaplan’s dedication to his patients and the genetic research he and Dr. Eileen Shore have undertaken is an inspiration to Quinnipiac’s graduates as they embark on their medical careers and specialties.’”



*Dr. Fred Kaplan receives an Honorary Doctorate of Humane Letters from Quinnipiac University at the graduation ceremony of The Frank H. Netter School of Medicine in Hamden, CT (from left: President John J. Lahey, Dr. Kaplan and Provost Mark A. Thompson)*

## Fellow of the American Academy for Bone & Mineral Research

Dr. Eileen Shore was elected to fellowship in the American Society for Bone & Mineral Research (ASBMR) in the inaugural class of 2018. This highly prestigious honor is bestowed on only a select few of the members of the ASBMR who have contributed to substantial and seminal discoveries and landmark publications in the field of bone and mineral research.

## International Clinical Council on FOP Leadership Position

In November 2019, Dr. Mona Al Mukaddam was elected Secretary-Treasurer Elect of the International Clinical Council on FOP (The ICC), a prestigious international council that represents the clinical interests of the FOP patients worldwide. Dr. Al Mukaddam will serve in this leadership position from 2022-2024.

## Top Docs in Philadelphia Magazine

In 2019, Dr. Mona Al Mukaddam was selected by her peers as one of the leading endocrinologists by Philadelphia Magazine.

## PhD Degrees Awarded

Three graduate students mentored by Professor Eileen Shore successfully defended their theses, graduated from Penn’s Biomedical Graduate Studies Cell & Molecular Biology Program, and were granted PhD degrees from the University of Pennsylvania in 2019 for their extraordinary work in FOP research:

» **Alexandra Stanley** for her work on “Aberrant Muscle Tissue Repair by Mutant FOP Progenitor Cells & Dysregulated Mechanotransduction by Mutant ACVR1 in FOP”

» **Robyn Allen** for her work on “Signaling of the FOP Mutant BMP Receptors in the Developing Zebrafish”

» **Oscar W. Towler** for his work on “Regulation of Joint Development by Mutant ACVR1 in FOP”



*Drs. Eileen Shore & Will Towler at the celebration following Dr. Towler's PhD thesis defense at the University of Pennsylvania*

## Graduate Student Awards

**September 2019:** Niambi Brewer & Robyn Allen received Endocrine Fellows Foundation Awards to attend the 13th EFF/ASBMR Fellows Forum on Metabolic Bone Diseases.

**November 2018:** Robyn Allen & Niambi Brewer received poster and presentation awards at the Penn Center for Musculoskeletal Disorders Annual Symposium.

**October 2018:** Niambi Brewer won First Place for her poster at The Genetics and Epigenetics Program at the Penn Cellular & Molecular Biology Graduate Group Symposium.

**September 2018:** Graduate Student Niambi Brewer won a distinguished ASBMR Young Investigator Award for her work which was selected for an oral presentation at the annual meeting of the ASBMR in Montreal, Canada.

**September 2018:** Graduate Students Alexandra Stanley & Niambi Brewer won Rare Bone Disease Alliance Young Investigator Awards at The Rare Bone Disease Alliance Conference in Montreal, Canada.

**May 2018:** Robyn Allen won the “Best Oral Presentation Award” at the University of Pennsylvania Cell & Developmental Biology Retreat for her presentation; “Novel BMP-Smad 1/5 Signaling Interactions in a Zebrafish Model of FOP.”

**2018-2020:** Niambi Brewer was awarded the distinguished “NIH Ruth Kirschstein-NSRA Postdoctoral F31 Award” for her project: “Regulation of Cell Fate Decisions in Heterotopic Ossification.”

# PART 13 “What Can We Do to Help?”



Patients, families, friends, even casual visitors to The Center for Research in FOP & Related Disorders often ask:

“What can we do to help?” The answer is simple. “Anything you can.”

As Kate Griffo and John Click at the University of Pennsylvania’s Perelman School of Medicine said, “In philanthropy, as in medicine, even brief inaction can do harm. A hiatus in research funding may mean that a promising treatment or a new line of inquiry may come to an untimely and devastating end. A break in efforts could halt progress toward finding a treatment that could relieve suffering or save lives.”

Research is laborious, time-consuming, often frustrating, and costly, and is filled with false starts, blind alleys, glimmers of hope, and the fog of frustration, but so too is the FOP we are trying to cure. Formidable enemies require formidable opponents, and teamwork requires resources. When seminal discoveries are made and ignorance is extinguished, the fog lifts, and the summits and the paths between them become clear. When knowledge advances, it illuminates the next horizon. It is a powerful beacon that changes the world like nothing else can. The feeling of accomplishment for all who contribute to this endeavor lights a fire of personal fulfillment and brings knowledge that they have contributed something important and enduring for other human beings for generations to come.

When modern FOP research began 29 years ago in a small laboratory at the University of Pennsylvania, there was little knowledge about this terrible disease, and little hope outside an infinitesimally small circle of believers who knew in their heart that something could be done to change it. Hope prevailed - hope fueled by the faith and commitment of a dedicated and persistent few who year after year funded studies to create and sustain a team devoted to make a difference. Over the years, that team has grown and expanded, and its reach now extends around the world.

Through a sustained effort at The Center for Research in FOP & Related Disorders, research is eradicating the stifling ignorance that was prevalent just two decades ago. Barrier after barrier has fallen and achievable goals are in reach. FOP research holds real promise of preventing, treating, and curing FOP. It is no longer an imaginary dream. We need your help now more than ever to make this a reality.

The often-heard comment, “Call us when you have a treatment or a cure,” is an option, but not one that will help us find a cure. Everyone has a stake in this effort. We need your help in getting there: Bingo, bake sales, swimming events, Burns’ Suppers, barn dances, Santa Maria-style chicken barbeques and spaghetti dinners, garage sales and silent auctions; country fairs and benefit concerts at the Metropolitan Opera; raffles and rodeos, sales of holiday cards and embroidered quilts, 5K runs and ice fishing contests; chamber music benefits and Hard Rock concerts; horse-plowing contests and competitive swims; golf tournaments and bowling parties; wine tasting events and lemonade stands on busy street corners.

No idea or endeavor is too small or too outlandish to help. Every second counts. Please help cure FOP.

You may feel free to contact us directly or through our colleague at Penn Medicine Development, Allyse Orsini, at 215-746-3008 or [aorsini@upenn.edu](mailto:aorsini@upenn.edu).



# PART 14 Many Thanks to You

The members of The Center for Research in FOP & Related Disorders at the University of Pennsylvania and at collaborating laboratories around the world are extremely proud to be a part of this mission, and are enormously grateful to all of those who support this vital research effort to find better treatments and a cure.

Much has been accomplished, thanks in large part to the many benefactors and partners who have supported our work. The Center for Research in FOP & Related Disorders identified the genetic cause of FOP in 2006 and used that knowledge to spearhead worldwide research efforts to develop therapies that will transform the care of individuals with FOP. In 2014, clinical trials for FOP began – a major step forward. Now, as a comprehensive center, we manage and coordinate care for FOP patients – not only at Penn, but globally – and also engage in vital clinical, basic science, and translational research that can change the course of this rare and debilitating condition. We are vitally committed to education; we want to ensure that the next generation of physicians and scientists is as passionate about FOP research as we are.

Despite the progress we have made, there are still many unanswered questions and more monumental discoveries on the horizon that will improve treatment and quality of life, and bring us closer to ultimately finding a cure. Our work is broad and focuses on several areas of major activity, including clinical care and consultation worldwide, clinical research and infrastructure development, basic research to identify therapeutic targets, translational research for preclinical drug testing and biomarker discovery, clinical trial development, and education.

The generous support of our benefactors has led to new therapeutic targets for FOP, new drug discoveries, and a rich research pipeline with diverse approaches to treatment of FOP. Our lifelong goal is to propel the development of therapies and eventually a cure for children and adults with FOP. We envision the day when FOP patients no longer hear the words “no treatment, no cure.”

## We acknowledge the generous support of:

- » The International FOP Association
- » The National Institutes of Health (the people of the United States of America)
- » The Penn Center for Musculoskeletal Disorders (PCMD)
- » The Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine
- » The Cali Family Endowment for FOP Research
- » The Weldon Family Endowment for FOP Research
- » The Cali-Weldon Professorship of FOP Research
- » The Ashley Martucci Fund for FOP Research
- » The Roemex Fellowship in FOP Research

- » The Jesse David Hendley Foundation
- » Gene Spotlight, Inc.
- » The Morgan Fund for FOP Research
- » Canadian FOP Network
- » FOP Australia
- » FOPeV (Germany)
- » FOP Italia
- » Svenska FOP-föreningen (members from Denmark, Finland, Norway and Sweden)
- » Gary Whyte
- » Michael & Donna Gordon
- » The people of Santa Maria, California
- » A generous and anonymous donor from Caldwell, New Jersey
- » And the many individuals, families, friends, and communities throughout the world who contribute generously and tirelessly to the FOP effort



Emma Albee (Seal Cove, ME)

## PART 15 The Last Word

The last word belongs not to the donors and benefactors, not to the physicians, scientists, researchers, journalists, or historians – but to the patients – who struggle valiantly and who look to us for a better way.

The patient’s voice is always the most important voice in the room. This was never more obvious than at the IFOPA Drug Development Forum in Orlando, Florida in November 2019 where Emma Albee delivered the opening address. The last word belongs to her:

“I live on Mount Desert Island, off the coast of Maine. My family has lived there for many generations. It is a beautiful place, cold, but beautiful.

I have a younger sister, Sarah, and we had a “normal” active and busy childhood. Favorite family pastimes included hiking mountains and camping with family and friends. I live in the woods and my family built our own house.

Great memories include boat rides to the Cranberry Islands for the summer fair, lobstering with my cousin Johnny, helping my friend on her farm when the baby goats were born, sledding in the snow, and riding my bike as fast as I could, skidding around corners and crashing in the woods.

When I was 9 years old and playing softball in little league, I developed a limp that just would not go away. X-rays showed a small bone, and I was referred to an orthopaedic doctor. Meanwhile, I was playing on a playground with my sister and fell on the monkey bars, slamming the back of my neck on a bar. When I arrived at the orthopaedic doctor’s office, the swelling in my neck had spread to my back and shoulders. They moved quickly to do a biopsy that evening. Their only thoughts were cancer. We went home for the weekend, and were told to call for the report on Monday. Another doctor stepped in and encouraged more research. The biopsy just did not fit in the cancer diagnosis. Her research led her to the FOP diagnosis, and she got us connected with Dr. Kaplan and the IFOPA.

I do not remember much about that summer, except for having to lie on the couch instead of doing my normal summer stuff. My mother tells me that time was a blur for her - very overwhelming, but she does remember a few things. Talking to Jeannie Peeper and hearing her say that FOPers all seem to have a strong will and determination - and happy lives.

Watching that initial flare-up spread throughout my back, shoulders, neck, chin, chest, and belly with intense swelling, itchiness, tenderness, and pain - there was no medication or treatment we could use. We tried anything we could think of - compresses, smoothies with supplements, some extremely gross soy drinks. It was really hard to just sit back and watch FOP take over my body.

That winter, after a New Year’s Eve pool party with friends, my elbows locked up. Later that year, during fourth grade, I began to walk bent-over, and realized that FOP had spread to my right hip. We had so hoped that the hips would not be affected for years, but that was not the case.

We got advice from two different doctors. One local doctor pushed traction to straighten the hip muscles/joint. The other understood that FOP would take its course. My mother tells of the unimaginable decision she had -

to essentially decide if I was going to live the rest of my life in a sitting position or a standing one. From that day, my right hip froze and I could walk only short distances in a bent position with assistance.

My life changed a lot after this succession of flare-ups. I could no longer play sports, could not stay at friend's houses, gave-up my violin and clarinet. I spent a lot of time at home, with pain, for years. It seemed FOP and doctors had taken over my life and family's life.

When this initial FOP flare-up subsided, after a couple of years, I seemed to get my spirit and strength back, and my family and I adapted to our new life. We decided that FOP would have to become just a small part of who I was. We couldn't do anything to treat it anyways.

FOP stayed quiet for four years. It snuck back up on me in the tenth grade, and my left hip and knee flared for a year. I lost more mobility and am in my wheelchair pretty much all day. I have lost lots of choices in my life, but have found my way to being happy.

I participated in Show Choir in high school. My wheelchair was choreographed into three productions - Rent, Moulin Rouge, and Shout! Two of those years, the shows won "Best in the State of Maine," and best choreography. Being part of those shows was thrilling, and also hard work and stressful. Once, my wheelchair stalled on stage during a dance duet.

I was the scorekeeper for softball teams through middle school, high school, and college. I love softball, and became an important part of the team. Umpires were always glad to see me there, since I kept good books and paid attention.

I attended college at the University of New England, which is about three and a half hours away from my home. I lived in a dorm on campus all four years. I was extremely busy with classes and labs, plus managing all the people I hired to help me. My mother came and helped me every few weeks so I could catch up on sleep and coursework. The first semester of my senior year, I did an internship at the Jackson Laboratory in bioinformatics. It was great to be a part of lab group. I received my Bachelors of Science in Medical Biology. I have always loved biology.

After graduation, I had a hard time finding a job. After two years, I was hired at Acadia National Park. I digitize and upload documents related to science in Acadia. I also manage research permits and help communicate this work to other scientists and the public. I work half-time and have a flexible schedule. During the coldest, snowiest months, I am able to work from home, which is a perk in Maine. I love my job and find it very interesting to be involved with climate change research and the changes to the world around me.

Most of my spare time is spent making cards. I create, through stamping and water coloring, birthday cards, holiday cards, and cards with mermaids. I sell these cards at shops and craft fairs, and enjoy people who share this passion.

I have told you about some things that have made me who I am. A lot of people have helped me along the way, and I am very grateful for their help and support.

Again, I live in Maine. I believe I am the only FOPer in Maine. The only time I see fellow FOPers is at events put on by the IFOPA. I have made many great friends in this group and, sadly, have lost some of those friends.

I have been asked what joints I would like to have surgery on to get the mobility back. That is hard to answer. It had been so long that I do not remember being able to hug, to comb my hair, to walk or run. I do not spend time missing those things anymore. But, I would give anything to keep the mobility I still have. I just need one person to push and turn me for transfers. If I lose more movement in my knees or wrists, I will need more help to use the bathroom, to get up from bed... I probably would not be able to go on trips like this. I may not be able to stay at home. I want to keep working - I love my job. And I want to be able to make my cards.

Again, I so want to keep the mobility I have, and that hope is real. Thank you to all of you who care, who work so hard, and who make that hope real."



