29th Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project
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TABLE OF CONTENTS

PART 1: INTRODUCTION
PART 2: DOUBLE JEOPARDY
PART 3: THE CENTER
PART 4: WE THE PEOPLE
FOP Laboratory Team
FOP Clinical Trials Team
PART 5: CLINICAL TRIALS
The Twilight Zone: Benefit, Risk & Hope in Clinical Trials for FOP
Coordinating the Patient’s Journey in FOP Clinical Trials: A Real World Guide
PART 6: TIN SOLDIERS AT PENN
PART 7: EDITOR’S CHOICE – HIGHLIGHTS FROM THE LITERATURE
Social and Clinical Impact of COVID-19 on Patients with FOP
Epidemiology of the Global FOP Community
Prevalence of FOP in the United States: Estimate from Three Treatment Centers and a Patient Organization
While Looking for One, You May Find Another: Tin Soldiers and the Search for Undiagnosed Individuals with FOP
Compartment Syndrome of the Thigh in a Patient with FOP
Patients with AVGR1R206H Mutations Have an Increased Prevalence of Cardiac Conduction Abnormalities on Electrocardiogram in a Natural History Study of FOP
Deterioration of Pulmonary Function: An Early Complication in FOP
BMP Signaling and Skeletal Development in FOP
Dysregulated BMP Signaling Through ACVR1 Impairs Joint Development in FOP
Skeletal Malformations and Developmental Arthropathy in Individuals Who Have FOP
The Developmental Phenotype of the Great Toe in FOP
FOP Mutant ACVR1 Signals by Multiple Modalities in the Developing Zebrafish
FOP Mutant ACVR1 Signals by Multiple Modalities in the Developing Zebrafish
Dynamics of Skeletal Muscle-Resident Stem Cells During Myogenesis in FOP
Activin A Does Not Drive Post-Traumatic Heterotopic Ossification
FOP: A Segmental Progeroid Syndrome
Clearance of Senescent Cells from Injured Muscle Abrogates Heterotopic Ossification in Mouse Models of FOP
Off-On-Off-On Use of Imatinib in Three Children with FOP
Saracatinib Is an Efficacious Clinical Candidate for FOP
An ACVR1R375P Pathogenic Variant in Two Families with Mild FOP
PART 8: THE INTERNATIONAL CLINICAL COUNCIL ON FOP
PART 9: AWARDS & HONORS
Promotions
Teaching Awards
Radiant Hope Foundation Distinguished Clinician-Scientist Award
The College of Physicians of Philadelphia
International Clinical Council on FOP Leadership Position
Co-Recipients of the Henning Anderson Prize of the European Society for Pediatric Endocrinology
2020 Castle Connolly’s Top Doctor
Top Docs in Philadelphia Magazine
PART 10: COMMUNICATIONS
FOP – The Spoken Word
FOP – The Written Word
“What can we do to help?”
PART 11: MANY THANKS TO YOU
PART 12: THE LAST WORD
Preface

The 29th Annual Report (2022-2023) of The FOP Collaborative Research Project describes events and accomplishments of 2020 through 2021. Despite the late publication, we trust that the contents are relevant and informative.

The FOP world has been changing rapidly. Old clinical trials have ended, new ones have started, and more are on the way. All are based on important FOP research developments, old and new, some of which are reported here. What has not changed is the inextinguishable human voice, and the goal of a better life for FOP patients everywhere.

The 30th Annual Report is scheduled for 2024-2025. For now, enjoy the 29th Annual Report and join us as we continue on our journey – our collective and timeless mission to develop better treatments and a cure.

Fred

Frederick Kaplan
Philadelphia
December 2023
When people think of research, they often think of the basic science laboratory. But that’s not always where the journey begins. Not to deny that the laboratory plays a critical role in FOP research – it certainly does. It just doesn’t always begin there. The journey sometimes begins in a busy clinic – at an inconvenient moment – when it is easy to ignore what is right in front of one’s eyes – to make an association, a connection, and most importantly to ask a question.

As the past few years have taught us, we don’t yet know all the answers. More importantly, we don’t yet know all of the questions; at least all the relevant questions. There are clearly big parts of the puzzle that are still missing – if only we knew what they were. We may need to ask better, more probing questions – and it often begins with patients. Listen, observe, then question. As William Osler, a famous 19th-century physician said, “Clinics are laboratories; laboratories of the highest order.” So many of the clues that have led us up to the mountain top – along the BMP pathway to the discovery of the FOP gene and beyond – have come from the clinic – hypotheses based on careful clinical observations – from listening, observing and questioning.

In the popular television game show JEOPARDY, the answers are given first – and from those enigmatic answers, the relevant questions are asked. The contestants supply them. So too with FOP, except FOP is not a game. Most problematic are the answers that go unheard, unobserved and most importantly unquestioned – the patient’s stories, the subtle clues that often lead to important questions – and through the laboratory – to important discoveries.

In the ultra-rare disease world, the Final Jeopardy category is “FOP.” The Final Jeopardy answer is: “Progressiva.” As the host would undoubtedly remind, “Please make sure your answer is in the form of a question. Again, the Final Jeopardy answer is ‘Progressiva.’ You have 30 seconds, good luck.”

Thirty seconds; it seems like a flash. But, for those who are waiting, it is a lifetime. Remember the jingle? Does FOP progress with flare-ups? Does it progress without flare-ups? What is the difference? When does it progress? How does it progress? How does it stop progressing? Why do different people – even identical twins – progress at different rates?

As a father of a little girl with FOP remarked long ago ... and these words echo through the eons, “Doc, I can deal with the FO. It’s the P that is a problem – the Progressiva. What will the Progressiva mean for her?” That is the FINAL JEOPARDY question.

In this 29th Annual Report, we will focus on some of the unquestioned answers – answers that are right in front of us, if we take time to listen, observe and question. Questions that will help us discover the big pieces of the puzzle that are still missing – that could help us plot a better future – and eventually out of Final Jeopardy.
We highlight two big questions in this year’s report – a sort of double jeopardy. One question is a central focus of ongoing work. The other, a new look at an old mystery. Most importantly, each question highlights a notable advance in FOP research – a constant probing into the incompletely explored realms where inquiry may be most revealing. We are confident that both questions will inspire additional avenues of investigation and may identify unanticipated new targets for therapy.

1. What is inflammation, and what role does it play in FOP?

As the physicist, astronomer and philosopher Galileo (1564-1642) famously said, “All truths are easy to understand once they are discovered; the point is to discover them.” And we might add that they are not likely to be discovered if the relevant questions are not asked. What are the relevant questions?

Let us go back – way back – to the second year of medical school when one of us began a course in human pathology. It was more than 50 years ago, but the memory is still vivid. Excited to finally delve into the frailties of the human body, the course, unfortunately, began with a big yawn. The first two weeks were devoted to what seemed like a dull and diffuse topic – inflammation. Not much was known back then. Neither genes nor pathways – only symptoms and signs of swelling, tenderness, pain, fever and redness – the same old stuff that had been around for centuries and the armies of tiny white blood cells that could be seen under the microscope that were responsible for those boring symptoms that were known to just about everyone.

“Okay, boring, boring inflammation. When are we going to get to the good stuff? Like the heart, the brain, the lungs, the kidneys and the bones,” one of us remembers thinking. Well, we might have been too ignorant or naive to realize it at the time, but inflammation WAS the good stuff. It was right in front of our eyes.

Fifty years ago, the study of inflammation and the immune system was in its infancy. Many of the tools needed to discover what a critical and supporting foundation it would become to all of clinical medicine were not yet available. A half century later, and 15 years after the FOP gene discovery, we are finally beginning to grasp the fundamental role of inflammation in the understanding of FOP.

Richard Feynman, a Nobel laureate in physics wrote, “Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry.” Let us begin by examining each small piece of the fabric – and see what we can make of the entire tapestry.

In all affected individuals, FOP is caused by a gain-of-function mutation in ACVR1, a bone morphogenetic protein (BMP) receptor that sends mixed-up signals to make bone outside of the skeleton. Overactive and dysregulated BMP pathway signaling is responsible for the developmental features of FOP such as the great toe malformations, but does not appear sufficient to induce the episodic flare-ups that lead to disabling heterotopic ossification that are a hallmark of the disease.
Flare-ups of FOP strongly implicate an underlying immunological trigger that involves inflammation and the innate immune system, that ancient branch of the immune system that responds immediately to any threat – internal or external. Recent studies show that BMP and Activin, locally produced hormone-like molecules that stimulate mutant ACVR1, also have critical regulatory functions in the immune system. Crosstalk between the bone-forming pathways and the inflammation pathways that regulate tissue maintenance and wound healing reveals important clues.

Critically, the clinical and pathologic features of FOP strongly point to an underlying inflammatory component:

- Episodic disease flare-ups are triggered by soft tissue injury, muscle fatigue, viruses and immunizations.
- Local and systemic activation of flare-ups occur following antigenic re-challenge by intramuscular immunization.
- Ongoing flare-ups are exacerbated by intercurrent immunizations.
- Trauma induced by surgical removal of heterotopic bone leads to new bone formation.
- Sudden and massive soft tissue edema occurs at the clinical onset of many flare-ups.
- Accumulation of neutrophils, lymphocytes, mast cells and macrophages – white blood cells derived from the immune system and circulating in the blood – occurs around the blood vessels in affected skeletal muscle during the earliest phases of flare-ups in FOP patients and in mouse models of FOP.
- Infiltration of neutrophils, lymphocytes, mast cells and macrophages occur between the fascicles of skeletal muscle and invades the fibers of skeletal muscle during the early phases of disease flare-ups in patients and in mouse models of FOP. This is responsible for the swelling and pain of acute flare-ups of FOP.
- Dramatic clinical response to high-dose corticosteroids (like prednisone – a potent anti-inflammatory medicine) is noted in the first 12 to 36 hours following the onset of a flare-up.
- Prophylactic use of high-dose corticosteroids limits the formation of heterotopic bone in a mouse model of FOP.
- Long periods of disease quiescence can occur between flare-ups, reminiscent of the exacerbation-remission cycles of patients who have auto-immune or auto-inflammatory conditions.
- Long periods of disease quiescence occur following immune ablation or immune suppression.
- Immunosuppression blocks heterotopic ossification in FOP mouse models.
- Targeted ablation of macrophages and mast cells impairs heterotopic ossification in mouse models of FOP.
- Increased sensitivity of mutant ACVR1 to auto-inflammatory ligands (BMP4 and Activin A) in mouse models of FOP is observed.

These myriad epidemiologic, clinical, pathological, cellular and molecular features of FOP support that inflammation plays a prominent and provocative role in the pathophysiology of FOP.

In addition to their effect on stimulating heterotopic ossification, native and recombinant BMPs are potent pro-inflammatory proteins. Soon after the BMP genes were identified, investigators showed that BMP4 was a potent chemoattractant to monocytes (circulating precursors to macrophages) in vitro, and likely promoted heterotopic ossification through its profound effects on monocyte recruitment and inflammation. In a recent study from our lab, Convente and colleagues reported that targeted ablation of macrophages and mast cells (commonly known as “bulldozers” of inflammation) dramatically impaired heterotopic ossification in FOP mice.

Inflammatory cells from the blood have been implicated in the heterotopic ossification of FOP. A patient with FOP who had a bone marrow transplant for the treatment of a fatal anemia (unrelated to FOP) was evaluated twenty-five years later to determine whether the clinical course of his FOP had been influenced by bone marrow replacement or immunosuppression, or both. Replacement of bone marrow from a healthy donor cured the aplastic anemia, but was not sufficient to prevent heterotopic ossification. Even healthy transplanted bone marrow could not prevent heterotopic ossification once the immunosuppression was stopped. These findings demonstrated that bone marrow...
transplantation did not cure FOP in the patient and that even a normal bone marrow (immune system) can trigger a flare-up of FOP in a genetically susceptible host.

While the role of inflammation in FOP is compelling, it is also incredibly complex and glaringly incomplete. A central challenge in FOP research is to construct a unified theory that explains both the heterotopic bone formation and the inflammatory features of the condition. It turns out that there is a direct connection between the bone-forming pathway and the inflammatory pathway, and that connection is orchestrated by a protein called ECSIT (evolutionarily conserved signal intermediate in the Toll pathway) that controls critical crosstalk between inflammation and the BMP signaling pathway that regulates bone formation. ECSIT provides an important evolutionary link between these two ancient molecular pathways, and it is hard-wired into our biology. Thus, ECSIT plays a pivotal role in signals that activate both inflammation and the BMP signaling pathways and is hijacked in FOP to exchange molecular messages between them.

It is intriguing to speculate that perhaps all flare-ups, even those that appear spontaneously, are activated by the innate immune system that controls inflammation. Clearly, the innate immune system is constantly active even in the absence of overt injury. The discovery of an innate immune system-BMP signaling network has important implications for understanding the pathophysiology of FOP.

From the wealth of recent data from humans and mice with FOP, we and others hypothesized that the FOP mutation confers a chronic pro-inflammatory state independent of acute flare-ups. Recently, we used a carefully curated set of plasma samples from 40 FOP patients with the classic FOP mutation and 40 age and gender-matched unaffected individuals and identified several FOP-associated and several flare-up-associated biomarkers of FOP that reflect a chronic inflammatory state as well as biomarkers that reflect an acute flare-up related inflammatory phase of disease activity. We found that adiponectin (implicated in hypoxia, inflammation and heterotopic ossification) and tenascin-C (an endogenous activator of innate immune signaling and a substrate for Kallikrein-7) were highly correlated with the FOP mutation while kallikrein-7 was correlated with acute flare-up status. Thus, plasma soluble biomarkers for FOP support a flare-up-related acute inflammatory phase of disease activity superimposed on a genetic background of chronic inflammation.

The finding that tenascin-C, a protein that stimulates the innate immune system, is elevated chronically in individuals with FOP strongly suggests that chronic inflammation is a pathophysiologic signature of FOP. The inflammatory molecules involved in the chronic inflammation of FOP have been elusive, but the findings described here may provide an important clue that can be explored in future studies. This study recently published in The Journal of Bone & Mineral Research by investigators at the University of Pennsylvania and the Mayo Clinic represents the first comprehensive evaluation of plasma biomarkers in classically affected FOP patients and represents a milestone in our understanding of FOP.

And that leads us full circle back to our critically important question: Is it possible to identify a factor that would allow us to interrupt the inflammatory trigger of FOP flare-ups without risking the potential of fatally shutting down the entire innate immune system? Perhaps.

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 substantially reduces the extra bone formation of FOP. This work is revealing a completely unexpected and novel molecular target that may be useful in limiting extra bone
formation and progressive disability in FOP. What wakes up the grizzly bear of FOP? What is responsible for the “P” in Progressiva? Stay tuned.

2. What are temperature gradients and what role do they play in the initiation of FOP lesions?

Progressive heterotopic ossification is a hallmark of FOP. However, this progression is not random. Rather, we noticed that heterotopic ossification in FOP progresses in well-defined patterns that correlate precisely with temperature maps of the human body. FOP is caused by gain-of-function mutations in ACVR1, a BMP receptor. The receptor functions as a trans-membrane enzyme, catalyzing a molecular reaction that results in heterotopic bone formation when it is triggered by a hormone-like molecule such as BMP or Activin A. As with all enzymes, the activity of ACVR1 is temperature-dependent. We hypothesized that connective tissue progenitor cells (CTPCs) in skeletal muscles (cells that orchestrate heterotopic ossification) that express the FOP mutation exhibit a dysregulated temperature response compared to control CTPCs and that the temperature of FOP CTPCs that initiate and sustain heterotopic ossification at various anatomic sites determines, in part, the anatomic distribution of heterotopic ossification in FOP.

We compared BMP pathway signaling in primary CTPCs isolated from FOP patients and unaffected controls at a range of physiologic temperatures and found that BMP pathway signaling and resultant cartilage formation (an obligate precursor to FOP bone formation) were amplified in FOP CTPCs compared to control CTPCs. From these studies, we concluded that the anatomic distribution of heterotopic ossification in FOP may be due, in part, to a dysregulated temperature response in FOP CTPCs that reflects their anatomic location in the human body. While the association of temperature gradients with spatial patterns of heterotopic ossification in FOP does not demonstrate causality, our findings provide an important clue to the anatomic distribution of heterotopic ossification in FOP and unveil a novel therapeutic target that might be exploited for this disabling condition. This work was done in collaboration with Dr. Robert Pignolo and colleagues from the Mayo Clinic and was published in a peer-reviewed paper entitled “Spatial Patterns of Heterotopic Ossification in Fibrodysplasia Ossificans Progressiva Correlate with Anatomic Temperature Gradients” in BONE in 2021.

Let us examine these intriguing observations in some detail. Progressive heterotopic ossification in FOP occurs by an endochondral process and forms in well-defined patterns that are familiar to all of us. For example, the extra bone in FOP tends to form in the trunk before the limbs, the back before the chest, the upper portion of the limbs before the lower portion of the limbs, the head region before the legs, and the upper limbs before the lower limbs. Curiously, there is no obvious basis for this pattern.

Also curiously, surface body temperature in healthy individuals is non-uniform, varying across anatomic regions – higher in the trunk than the limbs, higher in the head than the arms, higher in the back than the trunk, higher in the upper limbs than the lower limbs, higher in the shoulders than the wrists and higher in the hips than the ankles. These patterns, in fact, are identical to those of heterotopic ossification in FOP.

In humans as well as in many mammals, core body temperatures are substantially higher than limb temperatures. Since it is difficult to perform direct measurements of regional body temperature in humans,
surrogate measures such as infrared thermography (body surface temperature heat maps) are often used. Although infrared thermography cannot measure actual muscle temperature, this physiologic imaging modality provides a non-invasive measure of underlying tissue metabolism, blood flow and muscle temperature. Infrared heat maps of the human body show the well-established anatomic patterns described above.

As mentioned above, FOP is caused by gain-of-function mutations in one of the two copies of the ACVR1 gene in every cell. And importantly, the ACVR1 receptor acts like an enzyme and promotes heterotopic ossification when it is activated by a hormone-like molecule such as BMP or Activin A. As with all enzymes, the activity of ACVR1 is expected to be temperature-dependent. Since the baseline activity of ACVR1 is increased in FOP CTPCs compared to those containing wild-type ACVR1, we conjectured that the threshold leading to the formation of HO might be met or exceeded in those anatomic regions in which the CTPCs were at a higher endogenous temperature. To explore the association of regional anatomic temperatures with heterotopic ossification, we undertook thermography in two young children with FOP as well as temperature studies in FOP and control CTPCs.

In summary, we found that regional temperatures in the human body predict anatomic distribution of heterotopic ossification in FOP, that BMP pathway signaling is temperature-sensitive and dramatically amplified in FOP CTPCs compared to control CTPCs and that cartilage formation (a stepping-stone to bone formation in the process of endochondral ossification) is temperature-sensitive and amplified in FOP CTPCs.

Cellular and molecular studies from the laboratory have provided an in-depth understanding of many clinical features of FOP. However, the non-random progression of heterotopic ossification in FOP has followed curious anatomic patterns that have remained an enigma until now. Our study sheds new light on that mystery and outlines a likely role of temperature in the regional patterns of progression of heterotopic ossification in FOP.

The patterns of progression of heterotopic ossification in FOP have been well-known for centuries. However, what was not known was the relationship between patterns of body surface temperatures in FOP and typical early patterns of heterotopic ossification formation in young children before the onset of heterotopic ossification. We showed that (1) the temperature gradients across the human body correspond to the progression of heterotopic ossification in FOP, (2) there is a dysregulated temperature response in FOP CTPCs compared to that of control CTPCs and (3) BMP pathway signaling, and the pre-osseous cartilage formation, is amplified in FOP CTPCs in response to temperature.

Patients and parents often report that elevated body temperature, commonly accompanying suspected viral illnesses, precede the onset of symptomatic flare-ups in core body regions by one to three days. Hence, such rises in temperature might precipitate flare-ups in children in the most vulnerable core regions. However, whether elevated body temperature is a cause or a consequence of a flare-up – or perhaps both – is difficult to ascertain.

Interestingly, mouse models currently used in FOP research do not reproduce the anatomic patterns of heterotopic ossification seen in humans. The conditional mouse models most widely used in FOP research commonly exploit trauma-induced heterotopic ossification rather than spontaneous heterotopic ossification that might best establish anatomic patterns of progression of heterotopic ossification. An FOP mouse model of true spontaneous heterotopic ossification could potentially provide the basis to determine the correspondence of regional differences in the predilection to develop HO. Furthermore, whether CTPCs from different anatomic regions in FOP mice respond to temperature differences could be determined. Thus, our observations, findings and questions foster further investigation into the molecular and cellular basis for the well-established anatomic patterns observed in the clinic.

Notably, recent studies suggest that brown fat (more common in the body core where body temperatures are higher than in the limbs) is involved in heterotopic ossification. It is possible that brown fat metabolism might regulate regional temperature differences at baseline, as well as generate a hypoxic microenvironment that amplifies BMP pathway signaling in FOP lesions. Indeed, cellular metabolism has been shown to be robustly amplified in brown fat cells.

Our study raises intriguing questions and provides insight into the role that temperature plays in the pre-lesional microenvironment in FOP. Also, potential avenues for therapeutic investigation arise. For instance, pharmacologic
manipulation of body temperatures with antipyretics, β-adrenergic blockers, BMP inhibitors or central or peripheral thermoregulatory manipulation, all of which are known to lower core or regional body temperature, could conceivably have beneficial effects, although none have been specifically evaluated in FOP. Brown fat distribution, which also correlates with anatomic temperature gradients, is intensely thermogenic (heat producing) and could plausibly play a role here. Such speculations, in fact, suggest possibilities that might be further explored along with other modalities in the management of FOP. While the association of physiologic body temperatures with anatomic patterns of progression of heterotopic ossification in FOP does not prove causality, temperature can be added to a growing list of microenvironmental factors that likely influence the initiation of FOP lesions and subsequent HO.
Top left to right: Dr. Fred Kaplan greets Joe Hollywood (New Jersey) and his parents Joe & Suzanne Hollywood at Penn; Maria Wray (New York) & Ellie Klein (Ohio) meet for a chat; The Center for Research in FOP & Related Disorders at the University of Pennsylvania. (Seated from left to right): Dr. Eileen Shore, Tzpora Schein, Meiqi Xu, Dr. Fred Kaplan, Dr. Mona Al Mukaddam, Kamlesh (Kay) Rai, Doug Roberts. (Standing from left to right): Bob Caron, Dr. Elisha Tichy, Dr. Salin Chakkalakal, Jenny Tu. Not pictured: Vitali Lounev, Katherine Toder, Deyu Zhang.
The FOP Collaborative Research Project was established in July 1989 and has had a singular mission from the very beginning – to determine the cause of FOP and to use that knowledge to advance the treatment, and a cure, for FOP. During the past 35 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 lives of individuals with FOP.

- The Center for Research in FOP & Related Disorders was established at The University of Pennsylvania in 1996 by a generous grant from the Cali Family & the Ian Cali Fund.
- The Center is led by Drs. Kaplan, Al Mukaddam and Shore – and supported by generous endowments from Mrs. Diane Weiss and The Cali & Weldon families and funded by the IFOPA and many grassroots fundraisers and private donations.
- The Center and The FOP Collaborative Research Project has had more than six contributing principal investigators over the decades including Drs. Frederick Kaplan, Eileen Shore, Michael Zasloff, David Glaser, Robert Pignolo and Mona Al Mukaddam.
- The Center has educated countless scientists and clinicians on FOP and many generations of medical students over the past 25 years.
- The Center has been at the foundation of every major discovery and development in basic and clinical science of FOP in the past three decades – including the discovery of the FOP gene in 2006 – and now for clinical trials.
- The Center and its physicians and scientists have consulted on more than 1,000 FOP patients worldwide.
- The Center and The FOP Collaborative Research Project have issued 29 Annual Reports (including this one) and have published more than 200 seminal papers on FOP & related disorders – leading the world in this effort.
- The Center has been instrumental in the founding and establishment of The International Clinical Council on FOP (ICC).
- The Center has been instrumental in expanding its clinical reach to Children’s Hospital of Philadelphia (CHOP) and Thomas Jefferson University – establishing Philadelphia and Penn as the major hub of FOP research and care worldwide.

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 (pre-clinical 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 several 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 virtually over the past two years during the COVID pandemic for patients and families worldwide
• Co-authored a seminal paper outlining the optimal multidisciplinary care for FOP patients undergoing operative intervention for semi-emergent intercurrent conditions
• Delivered worldwide webinars and seminars on women’s issues in FOP
• Delivered worldwide webinars and seminars on COVID guidelines for individuals with FOP
• Published editorial guidelines on clinical trials for FOP

Clinical Research and Infrastructure Development

• Advanced the mission of The International Clinical Council on FOP
• Edited a major revision – the second in three years – of “The Medical Management of FOP: Current Treatment Considerations” popularly known worldwide as The FOP Clinical Guidelines
• Created and disseminated 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 and curated comprehensive joint survival curves from most of the world’s known population of FOP patients. These joint-specific survival curves are used to facilitate clinical trial design and to determine if potential treatments can modify the predicted trajectory of progressive joint dysfunction and immobility
• Published the baseline findings of the industry-sponsored Longitudinal Natural History Study and worked with collaborators to write the definitive manuscript
• Probed the Penn FOP Cell Repository to identify inflammatory biomarkers for FOP and FOP flare-ups
• Published the first study of curated plasma biomarkers in FOP
• Supported the development and growth of the IFOPA Biobank
• Served on the FOP Biomarker Consortium
• Championed the prospective deposit of data from sponsored clinical trials into the IFOPA FOP Registry Database
• Advocated for the direct deposit and open access of annotated whole genome sequence data from a sponsored clinical trial into the IFOPA 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
• Conducted genetic screening for FOP variants: What are they, who has them and what do they mean for those who have them?
• Identified an extremely mild variant of FOP in two multigenerational families
• Supported the development of in vitro and in vivo models of FOP variants
• Co-authored a seminal paper on the global demographics of the international FOP community
• Co-authored a seminal paper on the demographics of FOP in the United States
• Co-authored a landmark paper on the contribution of senescent cells to FOP lesions, their causative role in heterotopic ossification and the use of senolytic drugs to inhibit the process
• Co-authored the landmark FOP ECG study
• Authored a landmark paper on the role of compartment syndromes in the evolution of FOP flare-ups
• Co-designed, investigated and led the International FOP Burden of Illness Study

**Basic Research (Identification of Therapeutic Targets)**

• Probed the inflammatory triggers of early FOP lesions using novel knock-in FOP mouse models and identified key genetic and molecular targets in the innate immune system that are responsible for the progression of heterotopic ossification in FOP
• Uncovered a likely soluble factor that confers protection against heterotopic ossification in a resilient patient with FOP
• 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 inflammatory triggers of FOP flare-ups in state-of-the-art knock-in mouse models of classic FOP
• Discovered that inflammatory stimuli broadly activate the innate immune system in FOP connective tissue progenitor cells
• Identified the toll-like receptors (TLRs) of the innate immune system that amplify and dampen BMP pathway signaling in connective tissue progenitor cells
• Identified a clandestine connection between the BMP signaling pathway that directs morphogenesis and the innate immune signaling pathway that regulates tissue repair. This clandestine connection is subserved by a single protein called ECSIT (Evolutionarily Conserved Signal Intermediate in the Toll Pathway) that shuttles molecular signals between both pathways and promiscuously allows the formation of heterotopic ossification in FOP

Dr. Fred Kaplan examines a tissue section from the FOP Resilience Project at The FOP Lab at Penn
• Explored the role of the innate immune system in heterotopic ossification of FOP
• Identified a previously unrecognized role for the FOP mutation in muscle repair independent of bone formation
• Determined that a population of tissue-resident muscle stem cells (FAPs) from FOP mice repress the regeneration of muscle following injury
• Discovered the detrimental effect of FOP FAPs on regulating muscle stem cell repair of injured skeletal muscles
• Proposed that therapeutic interventions should consider boosting the muscle-forming potential of regenerating muscles, along with reducing heterotopic bone formation
• Determined that FOP is not only a disease of heterotopic ossification, but also a breakdown of muscle repair and regeneration and provided the foundation for targeting this process in future therapeutic approaches to improve muscle repair
• Contributed to the evaluation of cell senescence and senescence-related cellular reprogramming in early FOP lesions
• Published a series of landmark papers that showed that the BMP type I receptor ACVR1 is a key regulator of joint formation in embryonic development, 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
• Published a landmark study that documents the effects of the classic FOP mutation on the normotopic skeletons of individuals who have FOP and extends beyond malformation of the great toes and includes both morphological abnormalities and severe developmental arthropathy (joint disease)
• Published a landmark study that documents widespread developmental joint disease in FOP mouse models and in patients, as well as early post-natal degenerative joint disease throughout the FOP mouse skeleton and in patients
• 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
• Identified the mutant FOP receptor ACVR1 as a temperature-sensitive enzyme that catalyzes dysregulated BMP pathway signaling and stimulates increased cartilage and bone formation compared to the wild-type receptor at all physiologic temperatures
• Defined stages of heterotopic ossification in tissues in a knock-in mouse model of FOP and identified FOP mutation-induced effects prior to the formation of ectopic cartilage and bone
• Investigated molecular mechanisms by which ultra-rare FOP variants trigger promiscuous BMP signaling and subsequent HO
• 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 genes that modify the BMP pathway in several patients with the FOP mutation who have relatively little HO
• Served as medical and scientific advisors to the ongoing FOP gene therapy program
• Served as medical and scientific advisors to the IFOPA on global research strategies

Translational Research (Pre-Clinical Drug Testing & 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 two highly innovative developmental research projects initiated through the Cali Developmental Research Grants Program
  1. “Molecular Basis of Pathogenic Signaling and High Throughput Testing of FOP Therapies in a Zebrafish Model System” (Dr. Mary Mullins, PhD – The University of Pennsylvania)
  2. “Identifying Alternative Therapeutic Targets and Genetic Interactors in FOP” (Dr. Ed Hsiao, MD, PhD – The University of California, San Francisco)

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

• Continued to investigate the clinical application of a small molecule tyrosine-kinase inhibitor that targets the cellular response to tissue hypoxia and inflammation on a compassionate off-label basis for the management of refractory FOP in children
• Evaluated the utility of imatinib to diminish flare-up symptoms in children with chronic flare-ups of the back in an off-on-off-on compassionate regimen
• Consulted on the study design of five clinical trials in development by five pharmaceutical/biotech companies
• Continued to advise pharmaceutical and biotech companies on the design of clinical trials and the development of novel drugs in clinical trials for children and adults with FOP, based on identified targets
• Contributed to the evaluation of the safety and efficacy of an oral retinoid receptor agonist in inhibiting heterotopic ossification in FOP
• Contributed to the evaluation of the safety and efficacy of an antibody against Activin A in inhibiting heterotopic ossification in FOP
• 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
• Contributed to the evaluation of the natural history of FOP in a longitudinal natural history study
• Continued to nurture the expansion of the FOP Center that includes a pediatric clinical trial site at the Children’s Hospital of Pennsylvania

Education

• Presented lectures and seminars virtually to doctors, scientists, 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
• Supported the global outreach program of Tin Soldiers to identify undiagnosed and unconnected FOP patients in third-world countries
• 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
• Educated physicians, scientists, researchers, and regulators at virtual medical and scientific forums, meetings, and conferences worldwide during the COVID pandemic
• Continued to educate FOP experts worldwide on the use of the CAJIS evaluation for clinical management and clinical trials of FOP patients
• Contributed to the educational exhibits of two FOP skeletons at The Mütter Museum of The College of Physicians of Philadelphia
• Reviewed and Edited the Tin Soldiers Diagnostic Handbook
• Consulted and advised the Tin Soldiers Global Continuing Medical Education Master Series Program

Our work at the FOP 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.

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 can be described in 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, Jianing Xu, and Vitali Lounev. 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.**
   Studies are conducted by research scientist Vitali Lounev to investigate the cellular response to the immunologic, biochemical, and biomechanical microenvironments of early (pre-cartilage/bone) FOP lesions. New therapeutic targets are emerging from this work, and it is possible that one or more targets will become the basis for clinical trials with re-purposed drugs. In addition, Salin Chakkalakal and Doug Roberts are conducting pre-clinical testing of drugs targeting immune cells using FOP mouse models.
3. **Identifying cell and tissue targets in FOP lesions and the skeleton.** These studies are conducted by Vitali Lounev, Salin Chakkalakal, Yue (Jenny) Tu, Tzipora Schein, Aparna Sumanth, and Robert Caron. These studies identify the specific cells and mechanisms that can be targeted to block heterotopic ossification and bone formation.

4. **Developing in vitro and in vivo FOP models for drug “target testing.”** These studies are conducted by research scientists Salin Chakkalakal, Vitali Lounev, Deyu Zhang, Doug Roberts, and Meiqi Xu. These 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 of drug discovery and development – the infrastructure for a cure.

5. **Pre-clinical drug testing** in FOP mouse models is conducted by Vitali Lounev, Deyu Zhang, Doug Roberts, Jeffrey Xi, 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. The answers to these questions will help identify and confirm novel targets for drug discovery and development and eventually decrease the jeopardy of FOP.
The Center for Research in FOP & Related Disorders is only as strong as its people. We are very proud of our team.

**FOP Laboratory Team**

**Robert (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 25 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 Master in Biotechnology degree 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 and providing meaningful opportunities to develop cures. After postdoctoral training in the FOP laboratory, Salin has helped develop animal models for FOP and conducted pre-clinical drug testing to stop heterotopic ossification. When not working in the lab, Salin spends his time with his family – a little daughter and his wife, who also works in the medical field.

**Vitali Lounev, PhD**

Vitali Lounev is from Belarus and received his Master of Science degree in Minsk, Belarus and his PhD degree 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 the 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 Bachelor of Science degree in Biology from De Sales University and his Master of Biotechnology degree from the University of Pennsylvania. Although he is a relatively new addition to the FOP lab, 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 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.

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 pre-clinical drug testing, that use mouse models of FOP.

Meiqi Xu

Meiqi Xu was born and raised in Shanghai, China where she received her Bachelor of Science 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 lab 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 she spent her career at the FOP Center conducting studies on the FOP gene, its mutations, and activity. Meiqi retired in October 2022 after 30 years of dedicated service to the FOP community. In her spare time, Meiqi enjoys traveling so that she can see and understand different countries and people.

We miss those who have left our research group during the recent (and challenging COVID) years but have been joined by new students who are making important contributions to our research. Jianing Xu is a Veterinary student who continues to work with us since starting in 2020, and Yue (Jenny) Tu and Aparna Sumanth are Bioengineering Master’s students who both joined the lab in 2021. Penn undergrad Vicky Wong worked in the lab for a year before graduating in May 2021 (with research honors). Tzipora Schein and Jeffrey Xi are Penn undergrads who joined the lab last summer and continued through the school year. Ann George is a student at the University of the Sciences, Philadelphia College of Pharmacy who worked with us last year through the 2021 Penn Genetics Summer Internship Program.
FOP Clinical Trials Team

Mona Al Mukaddam, MD, MS, CCD

Dr. Mona Al Mukaddam is an Associate Professor in the Departments of Medicine and Orthopaedic Surgery and the Director of the Penn Bone Center in the Division of Endocrinology. She received her Medical Degree from the American University of Beirut in Lebanon and her Master’s Degree in Translational Research from the University of Pennsylvania where she completed her fellowship in endocrinology.

Dr. Al Mukaddam joined the FOP team in 2016 and has been the Principal Investigator on all of the industry-sponsored clinical trials in FOP at The Center for Research in FOP & Related Disorders in the Department of Orthopaedic Surgery.

Dr. Al Mukaddam is a world-renowned expert in FOP. She is a founding member and serves on the executive board of the International Clinical Council (ICC) on FOP which was established to consolidate a global voice for the best practices for clinical care and clinical research in FOP. She is the recipient of The Radiant Hope Foundation Clinician Scientist Award in FOP and is a fellow at the College of Physicians of Philadelphia. She is recognized in Philadelphia Magazine’s annual Top Docs and Castle Connolly’s Top Doctor, and her work has been recognized in The Washington Post.

Her tremendous contribution to the FOP clinical research program at The Center for Research in FOP & Related Disorders has been remarkable. She has successfully conducted several phase-2 and phase-3 clinical trials in FOP, encompassing half of the clinical trial research portfolio within the Department of Orthopaedic Surgery. She has successfully completed an extensive FDA inspection with the following comments from Dawn Lundin (Director of Compliance, Office of Clinical Research at The University of Pennsylvania) “Please know that this was a particularly extensive inspection with inspectors on site for 12 days. Most inspections typically conclude within five days. The inspectors complimented Dr. Mona Al Mukaddam (PI) and Katherine Toder (Chief Research Coordinator) on “immaculate record-keeping” and for having executed the studies well with no concerns impacting data integrity. Please join me in congratulating Dr. Al Mukaddam and Katherine on this positive outcome which demonstrates their unwavering commitment to high-quality patient care and excellence in their research at Penn.”

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. I am proud of the success of the FOP clinical research program and support our solemn commitment to excellence in research and clinical care.”

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 Bachelor of Arts degree 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 program. Katherine goes above and beyond to ensure that our patients are well cared for 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.”

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 41 years and is 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, D.O.

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 the 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 degree from Emory University and Doctor of Osteopathic Medicine from 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 – in both clinical genetics and biochemical genetics – and in pediatrics.

Edna E. Mancilla, MD

Dr. Mancilla is a renowned pediatric endocrinologist at the Perelman School of Medicine and at CHOP and has been leading the clinical trials in FOP at CHOP. Dr. Mancilla has 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 from the University of Chile and worked as a visiting fellow at the 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 nationally and internationally and has published articles in The Journal of Clinical Endocrinology & Metabolism, Endocrinology, Human Mutation and The Lancet.
Michael A. Levine, MD

Michael A. Levine is the Chief Emeritus of the Division of Endocrinology and Diabetes and Director of the Center for Bone Health at CHOP. Dr. Levine holds the Lester Baker Endowed Chair of Pediatrics 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 for Bone and Mineral Research and the Judson Van Wyk Award from the Pediatric Endocrine Society. He has been named “One of America’s Best Doctors” since 2005.

Jennifer Pizza

Jennifer Pizza is a Research Nurse Coordinator at CHOP. Jennifer obtained a nursing degree from Widener University, Chester, Pennsylvania and a Certificate in Clinical Trials Management from 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.

Norma Oliphant

Norma Oliphant is a Clinical Research Coordinator at CHOP. She received her Master of Psychology from the University of Phoenix where she counseled young girls at the Einstein Healthcare Network. Norma has over 30 years of experience in the medical field. She has worked as a Certified Medical Assistant at Thomas Jefferson University Hospital (Hematology) and Einstein Healthcare Network (Pediatrics and Endocrinology). She was a Clinical Research Coordinator in The Cardenza Hemophilia Foundation at Thomas Jefferson University Hospital for eight years. She is dedicated to the well-being of people, both physically and mentally. She is grateful to have the opportunity to be part of the FOP clinical trial team at CHOP.
Clinical trials are our new reality, 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 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.

Our science has made progress possible – the identification of varied targets and the development of different drugs for those targets. The puzzle is not yet complete and major questions remain, but we are headed to a new frontier. During the past 35 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.

Sixteen pharmaceutical and biotech companies 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 35 years ago.

Many from industry say that there is an urgent unmet need for drugs, now made possible by well-defined targets. 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 need to be optimistic, but vigilant.

We have identified the central cause of FOP – the FOP gene, ACVR1. 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 step on our journey to the new frontier is traceable to that reality. But let’s not be blinded by the light of success, by the exuberance of how far we have come. We are not there yet, and the route to get there, is not yet certain.

During the past two years, we have all been besieged with news releases and related publications about FOP clinical trials that have been started, stopped, started, paused, and started again, as well as other clinical trials that have fallen off the radar screen or that have left us with more questions than answers. “Hope,” however, “is alive” as the late Stephanie Snow reminded us. The following piece, adopted from an International Clinical Council essay of the same name and presented as a keynote address at the FOP Family Gathering in November 2021 is offered here in written and illustrated form as a guidepost and a guardrail for a necessary journey that provides cautious hope and that was never promised to be easy.
The Twilight Zone: Benefit, Risk & Hope in Clinical Trials for FOP

This year, I am going to depart from the usual academic formula of laboratory updates and speak to you from the heart. I am speaking as a clinician, a researcher, a principal investigator, the chief author of the ICC editorial on clinical trials, and a long-time friend of the FOP community.

Recent developments in clinical trials for FOP have left us all feeling as if we are in the twilight zone – "that neutral territory somewhere between the real world and fairyland" – as the author Nathaniel Hawthorne described.

On the one hand, we have emerging results from some clinical trials that inspire hope. While on the other hand, the same clinical trials have been paused or stopped due to the emergence of serious adverse events including unexplained deaths or concern for futility. How do we reconcile this? Do we accept it without inquiry as part of the routine of clinical trials? Or do we question its very nature? Clearly, the latter. We not only have every right, but every obligation to question deeply. Only then we truly understand the very essence of clinical trials – that elusive bond between risk and hope.

Some may feel frustrated,
While others may feel relief.
Some may feel despair,
While others may feel hope.
Some may feel disappointed,
While others may feel lucky.
And some may feel confused.
While others may feel enlightened.

It wouldn’t be unusual to feel all these emotions and more as old clinical trials remain in limbo and new clinical trials with new targets close to the cause of FOP continue to emerge.

In reality, this is a critical time to reflect and take stock of where we have been, where we are now, how we got to where we are now, and where we are going as a community.

A notice for a symposium in the journal NATURE recently stated, “Translating cutting-edge technologies into therapies remains a major challenge in biomedical research. The process of transferring promising innovations from the laboratory to the clinic is often tortuous and complex – if not downright frustrating.”

Clinical trials are not a risk-free journey. A lot can go wrong, and it is not for the faint of heart. We are constantly reminded that there are obstacles along the path. But, it is not a journey devoid of hope; quite the opposite, in fact.

There have always been ups and downs; the journey up the mountain isn’t always up. Sometimes there are dips and deep descents, but the trajectory is up – both in understanding FOP and in the pursuit to foster safe and effective medicines.
Clinical trials require a pioneer spirit. A REAL pioneer spirit, and as we know, the arrow doesn’t always strike the right target. That’s where we are. Let’s look at where we have been.

The discovery of the FOP gene signaled hope, heralded the emergence of a new grammar for drug discovery in FOP, and the explosion of interest in the biopharmaceutical world on the well-defined and evolutionarily-conserved bone morphogenetic protein (BMP) signaling pathway.

It signaled “HOPE for Escape from a Prison of Bone,” but also risk.

Like dominoes in descent, the FOP gene discovery enabled the development of genetically correct animal models of FOP which have been instrumental in testing novel therapeutics for druggable targets.

We are very lucky as a community that such an FOP Zoo exists — although the animal models are far from perfect. Flies, fish, chicken, and mice are not human beings — far from it. We need to interpret results from these in vivo studies with great respect and caution. Animal models validated the dysregulated BMP signaling pathway in FOP, the pathophysiology of heterotopic ossification in FOP, and the progenitor cells responsible for heterotopic ossification in FOP. They have given us very important clues, but we must interpret them with humility.

Dramatic basic science discoveries coupled with a comprehensive understanding of the natural history of FOP and methodologies to detect early heterotopic bone formation further fueled the advent of clinical trials for FOP. The grammar of investigational drug discovery rapidly became a babble of promising new approaches that were rapidly cast on the stage of human clinical trials, a dazzling place to be for an ultra-rare condition that had existed in the backwaters of medicine for over three centuries and for which no approved treatment and no discernible hope previously existed.
But beware of good news. As Shakespeare said, “Roses have thorns and silver fountains mud.” While dramatic advances showed that the FOP gene discovery could enable the identification of druggable targets, it also revealed that drug development would likely be constrained by an ancient highly conserved signaling pathway that was redundant and iterative, thus making therapeutic specificity extremely difficult.

While the desired goal of targeting the dysregulated BMP signaling pathway in FOP is clearly the abrogation of heterotopic ossification, the BMP pathway is critically important in the maintenance and repair of nearly every major organ system, thus expanding the risks of collateral side effects of potentially therapeutic drugs.

In addition, there are important logistical considerations and constraints of model systems, not the least of which is that FOP mice are laboratory-raised, pathogen-free genetic clones and are not people with FOP, and thus they do not inherently manifest either the immunological vitality or the genetic variability that underlies both the range of potential efficacy and the range of potential risks that human beings will inevitably display. Thus, while translational studies are essential to enlighten the way forward, they in no way guarantee an unobstructed path.

Potential efficacy and inherent risks – safety risks – need to be weighed, not just at the outset, but continuously throughout every clinical trial. And, it is the sponsor’s responsibility to make those risks clear, transparent and understandable – to investigators and to patients.

Aspirational outcomes of successful treatments may vary from one clinical trial to another based on the mechanism of action of the investigational drug and the pre-determined, primary outcome of a clinical trial which must be stated clearly and unequivocally before a trial begins. You can have course corrections during a clinical trial, but your final destination must remain the same throughout the journey.

Possible long-term benefits of patient involvement in a clinical trial may theoretically include, but are not limited to, decreased flare-ups, decreased heterotopic ossification, preservation of joint mobility, retardation of joint degeneration, liberation of joints ankylosed with heterotopic ossification, pain relief, frequent medical monitoring, increased self-awareness and FOP-awareness, improved quality of life, a pioneer spirit, contribution to a greater good, and contribution to future generations.

It is well-recognized that childhood (NOT adulthood) is the main battlefield for FOP. So, why aren’t there more clinical trials for children? The answer lies not in the realm of potential benefits, but in the realm of potential risks – namely unintended and irreversible harm.

No one wants anyone, especially children, to be harmed in the war against FOP. And, no one wants children to be the victims of friendly fire from untested pharmacologic weapons. If new drugs are effective AND safe for adults, we’ll cautiously move down in age to children. Animal models are not good enough.

We all know what happens if we jump the However, it may be possible to test re-purposed drugs that have already been approved for other conditions, and those efforts are underway.
Individual participation in a clinical trial must be balanced by a thoughtful consideration of potential benefits and risks. Clinical trials are not proven treatments, but rather an opportunity to determine if a potential therapy is effective and if it is safe.

Placebo groups are important; one could argue vital. Everyone wants an effective treatment, but clinical trials are NOT treatments. Safety is always the other side of the coin.

Drugs may seem safe, but any new medication in a properly conducted clinical trial is always circumspect. Even though it is well-vetted, it is not fool proof. There are always risks.

As the Dali Lama said wisely, “Remember, that sometimes NOT getting what you want is a wonderful stroke of luck.” It is a growing sentiment echoed by many FOP patients and parents. In other words, being in a placebo group is not always an unfortunate roll of the dice. It may be a blessing in disguise. Potential efficacy is the shiny side of the coin; potential risk is the flip side.

Potential risks may vary from one clinical trial to another. These are assessed based on pre-clinical toxicology studies, phase I clinical trial results, or knowledge of the mechanisms of action of an investigational drug. However, these assessed risks may not be comprehensive and new risks and safety concerns may be identified when potential therapies are tested in a clinical trial. One can predict where the known risks may lurk so that they can be avoided, but it is not always possible to predict where the hidden risks may be or predictably see over the horizon.

Common categories of risk include the inconvenience of participating in a clinical trial – especially during a pandemic, the uncertainty of knowing whether one is initially randomized to a placebo group or a treatment group, the annoyance of side effects both anticipated and unanticipated, potential allergies to a drug, adverse drug reactions, non-responsiveness to a drug, intolerability of a drug, resistance to possible therapeutic effects, and even possible worsening of FOP despite pre-clinical data that suggest that the drug being tested may be beneficial.

Every drug has side effects, but with investigational drug development for FOP, the spectrum of side effects may not be fully known until the drug is tested in FOP patients, despite extensive pre-clinical toxicology studies.

Even approved and re-purposed drugs may have different side effects in the FOP population than are seen when the same drug is used in other conditions.

Potential risks can often be prevented or minimized, but even with safety nets and firewalls in place, certain risks can elude prompt detection.

And then, there are the “unknown unknowns” that everyone dreads. The unanticipated and unpredictable risks that arise out of nowhere and take everyone by surprise. Often these risks are relatively minor, but sometimes – to the consternation of all – they might be harmful or even fatal, and it may be difficult to sort this out or find a common thread.

Our early foray into FOP clinical trials reminds us what we knew from the very beginning – that clinical trials are NOT proven treatments. They are human experiments guided by the best available knowledge at the time the trial was designed and even modified as the trial progresses.
Theoretical benefit and palpable risk must be spelled out in informed consent. Informed consent is not just a quaint formality or a box to be checked. It is a solemn requirement of the sponsor and investigator, and an ongoing process at every step of the clinical trial journey.

ALWAYS...

1. Read & Re-read Consent Forms
2. Question Everything
3. Follow All Instructions
4. Report Everything

Further, patient safety is hard-wired into all clinical trials in the form of an independent Data Safety Monitoring Board – known as the DSMB.

The DSMB is required for every clinical trial and is comprised of three to six experts in various disciplines related to the study drug and the trial design.

The DSMB monitors occurrences such as unexpected serious adverse events (or SAEs) and can pause or stop a trial – in its tracks – if it detects an unforeseen problem that may be related to an investigational drug.

A DSMB can also stop a clinical trial early, before the trial is supposed to end, if the beneficial effects are so overwhelming as to suggest that continuation of the trial would not be necessary or if it was determined that the investigational drug is futile. Thus, the DSMB and the sponsor or regulatory authorities (such as the FDA) have the jurisdiction to pause or stop a clinical trial for any reason at any time.

And, of course, the trial participant has the absolute right to bail out at any time, for any reason, or for no expressed reason at all.

As one sponsor observed, “There is not an endeavor on the planet that is more highly regulated than clinical trials.”

Clinical trials, as I have said over and over, are NOT treatments; not yet at any rate. Some may be. Some may never be. It is worth remembering. In fact, one must remember that. Clinical trials are NOT treatments.

As patients and families are bombarded by possibilities and choices – by good news and bad – where does that leave you?

For the moment – in the twilight zone – somewhere between an old world of symptomatic management and a brave new world of therapeutic possibilities.

That ultimate gateway of approved drugs is possible only through clinical trials. Patients who embark on that journey are courageous pioneers. As we have said before, the pioneer journey is not without its risks.

Patients and parents must always be aware that there are risks – some known and closely monitored – and some unknown and clearly unexpected – the “unknown unknowns.”

So, how should patients and investigators proceed? Obviously with caution, but NOT paralyzed by fear. Obviously with hope, but also with humility for the unknown.
Novel therapies can emerge only from an FOP community working together. Without clinical trials, there will be no approved treatments and all our efforts will be in vain.

We must advance not just with the power of our collective intellect, but with the intellect of our collective power. As a community, we have the ability to hit the accelerator pedal or the brake, but only if we act together. Otherwise, we will strip the gears of progress and caution as the two are linked. It is futile to move uphill without an accelerator, but foolish to go downhill without a brake. And in clinical trials, there are hills and there are valleys.

We must move forward not just with blind hope, but with a well-informed and clear-sighted caution. Not with a red light or a green light, but with a yellow light – constantly blinking.

We must join ranks, not just with vigor, but with vigilance. This is the necessary tension of our time. It is the only path forward.

So what is the take-home message? There are two. First, and you have seen this before, but it is worth repeating over and over again: Clinical trials are NOT treatments.

They have the potential to become treatments IF – and only IF – they prove efficacious and safe. They must be BOTH.

Each patient (or parent) must weigh the potential benefits, as well as the potential risks, of enrolling in a clinical trial and decide for themselves if it is right for them and, if it is, then which trial is right for them with ongoing informed consent as the guiding light; it is a deeply personal decision.
Second, clinical trials are the only path to an approved treatment. And, it is a difficult path. Make no mistake about it. But, without knowledge, we are left in the dark. We all have an abiding hope and belief that well-designed and meticulously conducted clinical trials will be the path that will lead there.

We are encouraged that so many pharmaceutical and biotech companies are developing novel therapeutics for such a rare and complex disease as FOP, and that they are doing this carefully, responsibly, and at great risk to themselves.

But the pharmaceutical companies are not soothsayers, and they do not have the last word. You do!

Side effects, adverse effects, and even unanticipated effects will inevitably occur. Nobody wants them, but in every case, they will be monitored and investigated by the sponsors and researchers to determine if, and how, they are related to the investigational drug. If questions are not answered to your satisfaction, then do not enroll. And, if you do enroll, you must report everything – Everything.

And, if and when, risks are identified that may be related to the investigational drug, appropriate risk management measures and mitigations will need to be rapidly incorporated into further iterations of the clinical trial in order to ensure ongoing patient safety. And again, question Everything. If questions are not answered to your satisfaction, then make sure you speak up. You are not a hostage. You can leave a trial for any reason, at any time.

Scientists, doctors, patients, clinical research personnel, pharmaceutical companies, and regulatory authorities must and will continue to work together to make clinical trials as safe, transparent, and successful as possible. This vigilance to safety and transparency on everyone’s part will lead us together through the twilight zone.

In summary, clinical trials are painstaking processes that weigh potential benefits to the patient and society against potential harm to the individual enrolled. And they are based on the painstaking laboratory work – on the part of many – that has paved the way.

Clinical trials are a bold step into the future, along a path like no other – a path that is hopeful, but with obstacles, to be sure. But as someone famously said, “Obstacles along the path are not obstacles – they ARE the path.”

Together, we will get there.

That is our hope.
Coordinating the Patient’s Journey in FOP Clinical Trials: A Real-World Guide

by Katherine Toder

[Editors’ Note: Clinical trials are necessary in order to translate the most promising discoveries of the laboratory into the possibility of a treatment for FOP. Every aspect of FOP research – basic or clinical – requires enormous coordination and care. Caring is part of the cure and an essential part of conducting clinical trials. Here, Katherine Toder shares her insights and perspectives in coordinating that real-world journey for each individual who voluntarily participates in a clinical trial.]

I am the research project manager for FOP clinical trials at the University of Pennsylvania and have worked with the FOP community since 2015. I assist in educating clinical staff, pharmaceutical sponsors, and vendors about the specific needs of FOP patients and their families to make participation in clinical trials safer and more comfortable. When I was invited to share some experiences and lessons learned, I wanted to speak to potential study participants as well as the individuals who design the operations of clinical trials. Participating in a clinical trial is an enormous commitment, and my hope is to encourage more conversations that will improve the experience for participants and better prepare researchers for unanticipated operational challenges.

Most patients have developed specialized and unique solutions to their physical needs and activities of daily living. Clinical trials require travel and staying in unfamiliar spaces without the customizations that allow patients to be comfortable. Patients may not even realize the impact being without these necessities of daily living may have until they are away from home as some patients travel infrequently or may not have traveled with their current degree of mobility. Part of my team’s role is to anticipate needs so that a patient’s stay at our clinical trial site can be as safe and comfortable as possible. I will mention just a few of these needs and some of the challenges we have encountered, in addition to resources that make participating in a clinical trial possible and other considerations that routinely arise.

**ADA Accessibility & Hotel Rooms**

One may assume that ADA-accessible spaces will be appropriate and sufficient for patients’ comfort and safety but often they are not, especially for an individual with the unique challenges of FOP. Patients have varying mobility, may be immobilized in different ways, and their caregivers may have their own physical limitations.

Patients may use adaptive and assistive devices and some of these are not portable. Some patients have beds at home that are a specific height or height adjustable. These may not be available even in an ADA-accessible room.

ADA-accessible rooms will usually have a “roll-in” shower option instead of a bathtub, but one patient was unable to get into an ADA-accessible shower because they could not clear a very small ridge around the shower, so they were not able to bathe during their stay. The height of a toilet that each patient needs may vary. Some patients have adjustable toilet seats at home or use portable commodes. I have delivered adjustable toilet seats to hotels so they were available on the patient’s arrival and patients have traveled with portable urinals they and their caregivers are familiar using.

ADA rooms will have grab bars. These may be helpful for some patients who have use of their upper limbs, but for others, these have been superfluous and in one case actually blocked their use of the facilities.

One patient stayed in a particular hotel for multiple visits, but on one occasion was assigned a room where the layout was reversed, and the grab bar next to the toilet was on a side of their body that made it impossible for them to sit down on the toilet. The room had to be changed.

Patients may wish to be on a lower floor of a hotel in the event of an emergency evacuation. Patients transported on
stretchers have expressed feeling self-conscious going through hotel lobbies or around the back of a building while the transportation crew tried to find an elevator that would accommodate the length of their stretcher.

Patients who expressed feeling unsure or unsafe navigating a new city to go out to eat have appreciated hotels that offer room service. I know some patients who have tried an entire room service menu during the course of a trial. Familiarizing patients with apps for takeout and grocery delivery services has also improved their visits to the site.

**Planes, Trains & Automobiles**

Patients travel to their study visits on many different modes of transportation with different benefits, restrictions, and challenges. Patients with more severe progression may not want to travel because of the logistical burden and the attendant discomfort. Our goal is to provide the safest and most comfortable trip to and from the site for those who wish and are eligible to participate.

Patients who fly to our site typically need more space than a standard economy seat has to offer and will require a caregiver seated next to them. All our patients have flown in business- or first-class seats.

Airplane toilets are unpleasant to navigate for any able-bodied person and are sometimes impossible for FOP patients to use. Some patients report that they avoid drinking or eating while traveling in order to avoid public restrooms and airplane restrooms specifically. The study team needs to consider possible dehydration when patients plan to visit and how that will impact scheduling and performing study procedures.

Some patients are unable to board a standard aircraft, for example, those who are locked in a standing position or are experiencing an active flare-up. Some patients may require an air ambulance or they may travel in a ground ambulance if they live close by.

Some patients travel by train. The train was preferred by a patient who could not walk but was able to balance and pivot on the great toe to go from one surface to another. They were not able to travel by plane because they would not be able to maneuver their power chair onto an aircraft and safely transfer to an airplane seat. This limitation meant a twelve-hour travel day from their home to the site and back again.

Some patients may choose to use their own vehicles or use our help to reserve rental cars, ambulances, wheelchair vans, or chauffeured SUVs & sedans. Not all wheelchair vans can accommodate all customized power chairs so gathering chair specifications is important. Additionally, some patients are only able to crouch down into a sedan, while others can only step up or fit into an SUV. Others can only sit in the front or back seats of certain vehicles. Mix-ups have happened when booking rides and resulted in relying on ride-share services such as Uber or Lyft to avoid being stranded at the hospital or hotel.

**Traveling with Wheelchairs & Other Assistive Devices**

Some patients have power chairs or scooters that have been customized to fit their specific needs; others use manual wheelchairs or walkers and some use both. They may also have specialized padding for comfort and to reduce the risk of pressure ulcers.

Despite the customization and comfort, patients are reluctant to travel with their wheelchairs. This equipment is very expensive and is often the key to independence. When patients fly, they must check their chairs and are parted from them until baggage claim. They have seen those chairs handled poorly and damaged, and have experienced difficulty navigating an airport in a manual wheelchair. Drivers who provide ground transportation need to be able to assist with wheelchairs and respectfully accommodate the patient or caregiver’s instructions for handling and storage. I have gone to a hotel to put a wheelchair into the trunk of a car because a driver was not able to do so.

If a patient chooses not to travel with their own chair and instead use a wheelchair at the site, the manual chairs at the hospital may not be able to adjust to the needs of the patient. One patient was able to sit in a manual chair that was offered in one clinic at our hospital, but they could not sit in the standard hospital wheelchair.
Another patient planned to travel by air ambulance because they would be unable to sit in an airplane seat, but their power chair was too heavy and bulky to fit in the air ambulance with them. They were given the option to have the power chair dismantled and shipped to their hotel or the site, but they did not know if they could reassemble the chair themselves or guarantee when the chair would arrive back at the site. They ultimately choose to transport themselves on a multiple-day drive to and from the site.

**Adapting Study Procedures**

Pre-screening measures to assess inclusion and exclusion criteria are important to establish before a patient assumes the burden of traveling to a site for screening.

Pictures and measurements may establish if a patient is able to undergo the required imaging. Patients who know they have chronic challenges with vein access may be ill-suited for a study where there are frequent blood draws, IV placement, or contrast administration.

Patients have concerns about tourniquet use or venipuncture resulting in FOP flare-ups and have specific spots they are comfortable using for venipuncture or blood pressure measurements. Patients are very hesitant to involve limbs with more mobility. A patient should always be involved in the discussion about how to obtain blood and vital signs.

Patients may need Hoyer lifts or careful transfer from their chair or a gurney to a hospital bed or scanner. Transfers can be uncomfortable or painful and require the staff to verbalize a transfer plan, involve an appropriate number of people, and slow down, if needed, to avoid physical trauma and stress.

Some clinical trials collect all or most information on paper while others use electronic platforms for all or some of the documents and questionnaires. Patients may have restrictions on how they write. We have created notes for witnesses when patients could not legibly date a consent form themselves and notes for changing a questionnaire to an interview format when patients could not complete or correct paper forms. Patients may also use specific adaptive devices for questionnaires and forms on electronic platforms that are important to bring to study site visits.

**Specialized Vendors**

Some clinical trials are supported by vendors that are contracted by an institution or industry sponsor. These vendors may help make parts of study participation easier. Some functions vendors have performed are booking concierge travel arrangements including reimbursing costs while traveling, delivering medication held at the correct temperature to a patient’s door, and sending trained clinicians local to the patient to their home to perform some study assessments. It is important for patients to know what personal health information vendors are allowed to collect and keep about them, and to know that working with some of these vendors is optional and not necessary for study participation.

Dedicated travel agents have been invaluable from the perspective of the study team. The time saved by using their established connections has made scheduling visits feasible. The patient can communicate directly with a travel agent to create their preferred itinerary and the travel agencies build a dossier on each patient and record previous preferences and experiences. A dedicated travel agent will also help with last-minute changes that may arise from weather conditions or medical events.

If a patient takes a drug for a clinical trial at home, they may benefit from having re-supplies of the drug sent to their house directly instead of traveling more frequently to the study site to pick up a new supply. This is particularly important when the dose of the drug changes in between study visits and we do not want a patient to be without the study drug for an extended time. Working with dedicated shippers will require a patient or family member to plan to be at home to receive a shipment in an extended window of time, and there may be a lot of telephone calls to confirm a scheduled delivery with the shipping company.
The study team is also supported tremendously by contracted clinicians local to a patient who are trained to perform specific study procedures. This reduces the travel burden a patient takes on to participate in a study and allows some long procedures to be performed at home that are time consuming such as 24-hour pharmacokinetics (PK) testing where multiple blood draws are made over a 24-hour period to see how much of a drug is in the bloodstream. A remote visit can be convenient but it is important to consider that the clinician will be in the home for an extended amount of time and will need to set up lab equipment and other study supplies.

Pets may need to be put in other rooms and items rearranged to make sure that the space the clinician uses is suitable for the study procedures. Patients may request to meet a potential clinician they are working with before a first study visit at their home, so it is a little more comfortable to have a new person suddenly in the house for an extended amount of time. The study team appreciates any feedback about experiences a patient has with a vendor so processes can be evaluated to make them more efficient, and patients do not have people in their homes with whom they are not comfortable working.

**Family Dynamics**

Many FOP patients and family members are actively involved in FOP communities and advocacy groups and share information about their experiences. Most patients I have worked with come to the site with family members. Parents of FOP patients have been heavily involved in their child’s healthcare decisions from a young age and are often the momentum behind the patient’s involvement in clinical trials. Potential patients and their families have had varying expectations, interests, and levels of engagement and enthusiasm.

I have met very excited parents with adult children who were at best ambivalent about involvement in clinical trials. It is important to have direct conversations with the patient who would be involved in a clinical trial to confirm that they understand their participation is voluntary and the decision to enroll is entirely their choice.

Many families have been waiting for treatments for a long time and there are a lot of emotions that go into these discussions. It is important to remember that clinical trials are not treatments; they are experiments, and it is important to emphasize this at every opportunity.

Patients may wish to operate with as much independence as possible but need assistance from family caregivers to successfully complete study procedures. For example, patients may not be able to prepare medications taken at home or complete paperwork without assistance.

It has also been helpful to involve family members for their collective memories of medical history and adverse events. Caregivers can tell you about things that a patient may not be able to see or examine themselves. However, it has been the preference of some patients to cover some sensitive material without family members present. Conversations about mental health and general outlook have been more candid without family members present. Some patients have said they do not want to upset or disappoint their family by admitting that they are not doing well. Additionally, family members have sometimes answered for patients and stated that they have an upbeat attitude and positive outlook when the patient may have expressed otherwise.

Perhaps unsurprisingly, patients may prefer to discuss matters of sexuality and birth control without their parents present. These may be topics that have not been discussed at length at home but are necessary to discuss in detail in a clinical trial because of potential risks. The clinical trial site needs to consider how to involve family members in a way that is the safest for the patient while protecting their privacy and confidentiality.

FOP patients are experts in understanding their bodies. However, it is extremely important for the research team to not make any assumptions about the patient’s knowledge and to explain the rationale for study procedures and confirm the patient’s understanding.
The Person not the Disease

Finally, I want to talk about the privilege of working with individuals with FOP and their families and their extraordinary commitment to clinical trials. I work with a small number of patients with an ultra-rare condition and have the luxury of getting to know each patient and their family very well. Research visits are long and may feel overwhelming, but each patient is like a star supported by an entourage of coordinators, clinicians, and caregivers in orbit around them. Each patient has a unique experience with FOP and each patient has a life outside of their FOP diagnosis.

One cannot assume that FOP patients have unlimited time for study participation, or that their caregivers have unlimited time to support their participation. Patients may be enrolled in school or have jobs that generate the income they need to support themselves and their families. The patients may have children or may be full-time caregivers for others. Their responsibilities to their family or community may restrict open travel. FOP impacts patients across all demographics: one patient’s religion limited their dates of travel and use of electronics which was an important consideration for participating in demanding clinical trials.

I get to spend hours on the phone and in-person with patients and their families. Patients have varied hopes and expectations for study participation. Some patients may not be satisfied with their experience in a study but are afraid to lose access to a medication or to the medical team that may help them despite assurances to the contrary. Some patients talk about the day when they will be able to have surgery to remove extra bones and live a life indistinguishable from their peers. Some patients just want to be able to move a specific joint. Some patients go through horrible flare-ups and incredible physical misery and distress and yet remain optimistic. Some patients do not think that they will personally benefit from clinical research, but feel a commitment and passion to participate, nonetheless. Some are excited to contribute to science and others are hopeful that their involvement and investment in clinical trials will have a meaningful impact on younger patients and future generations. Many remain interested to see what participation opportunities are on the horizon and how they can shape the direction of studies in the future. My team’s job is to remove operational barriers and make participation in clinical trials as safe, accessible and convenient as possible for those who are eligible and wish to participate.
On Thursday evening February 20, 2020, just weeks before the COVID-19 pandemic emerged, The Center for Research in FOP & Related Disorders at Penn hosted the US premiere of the acclaimed feature-length FOP documentary Tin Soldiers. The Rubenstein Auditorium at Penn Medicine was packed with faculty, students, physicians, researchers, administrators, patients, families, filmmakers, producers, directors, journalists, philanthropists, friends, and guests from around the world. The audience was riveted by the 79-minute documentary and by the question-and-answer forum that followed.

The producers iterated that Tin Soldiers was not just a feature documentary on FOP, but the launch of a movement to educate the public and, importantly, healthcare workers worldwide to aid in finding undiagnosed individuals with FOP in remote regions of the world (and maybe even close to home) to:

- End Isolation
- Prevent Harm
- Lessen Misery and Suffering
- Afford Participation in Clinical Trials
- Empower Education
- Build a Global FOP Community

The US premiere of the Tin Soldiers documentary was highlighted in a feature article in The Philadelphia Inquirer by Marie McCullough in March 2020. The article was titled:

“A Crippling Disease called FOP is so Rare, it Usually Goes Undiagnosed. A Documentary May Change That”
McCullough wrote, “The documentary, Tin Soldiers, is taglined ‘More than a film, it’s a call to action.’ The 79-minute movie is the centerpiece of a worldwide education and outreach campaign that aims to find the estimated 4,000 undiagnosed FOP sufferers and connect them to FOP families and experts — the small but mighty group that funded the film.

Amanda Cali of Mountain Lakes, New Jersey, executive producer of the film and a patient advocacy dynamo, said, ‘I remember how isolated I felt 25 years ago when my son was diagnosed. There were only 83 known cases in the world. Now we have about 900 confirmed cases. So, we don’t have even a quarter of the estimated total.’

Ironically, recognizing a potential case is easy — if doctors know what to look for — because patients are born with bent big toes. Dr. Fred Kaplan points out the bunion-like deformities while examining a boy in the movie.

Another irony: The obscure disease is a research hotbed thanks to the 2006 discovery by the FOP laboratory at Penn of the gene mutation that causes it. Now, dozens of universities and drug companies are studying the molecular mechanics of FOP because it has implications for many bone diseases. As the documentary explains, seven potential therapies are in clinical trials for FOP, offering the first hope for more than just symptom relief.

But as Cali is acutely aware, trials need patients — even if their rare disease afflicts just 1 in 1.5 million. About a year ago, Cali pitched the idea of a documentary to Odette Schwegler, a South African journalist and filmmaker who had done a segment on FOP for a TV news magazine.

‘The story of FOP just touched me on another level,’ said Schwegler, who has a history of supporting charities, especially in South Africa’s desperately poor communities.

What started with a plan to film at an FOP meeting grew into a sprawling, four-continent chronicle of resilience and courage. Schwegler’s crew trekked to big cities, small towns, affluent suburbs, and dangerous slums to follow FOP patients, their families, and doctors.

In Allentown, Stacy and David Scoble are shown holding the seventh annual ‘Bingo for a Cure,’ inspired by their 13-year-old son, Joshua, who must use a wheelchair. The event has raised $1 million for research.

In Gugulethu, a township near Cape Town, South Africa, 52-year-old Thozamile Mciki talks about being shunned by neighbors who think he is ‘bewitched,’ about hoping FOP becomes treatable, and about wishing the outhouse weren’t so far from his living quarters. ‘Anyway, I would say I’m lucky to be this age, having FOP,’ he says, smiling.

In Manhattan, Whitney Weldon, 28, zips along in her motorized wheelchair, visiting restaurants to review their food — and accessibility — on social media. ‘FOP is all about adaptation,’ she says.

In family videotapes, Cali’s son Ian is shown through the years, laughing in his highchair, playing softball, and roughhousing with his brother. Now 30 and a computer application developer, he discusses how anxiety about FOP’s unpredictable ‘flare-ups’ can be as disabling as the ossification. ‘I look back on all my major flare-ups. In my head, I had already jumped down the rabbit hole,’ he says. ‘Now, I try to maintain my mental independence more than my physical independence.’

The film premiered in Johannesburg in October and is slated to be screened at film festivals around the world. The co-producers are also getting invitations to showcase it at medical and educational gatherings. The University of Pennsylvania showed it; sites in Australia, Prague, Holland, Kenya and Namibia are upcoming.

Posters, public service announcements, and other pieces of the outreach campaign are now rolling out. A nonprofit, tinsoldiers.org has been created to raise funding and recruit volunteers.

‘The more we get, the more we can do,’ Schwegler said.”
Top to bottom, left to right: Dr. Edna Mancilla & Dr. Staci Kalish at The Penn Premiere of Tin Soldiers; The audience watches in rapt attention at the Penn Premiere of Tin Soldiers; The Power of Penn at the Tin Soldiers premiere. (From left to right): Dr. Jonathan Epstein (Executive Vice Dean of the Perelman School of Medicine, Senior Vice President and Chief Scientific Officer of the University of Pennsylvania Health System), Dr. Fred Kaplan, Dr. Eileen Shore, Mrs. Odette Schwlegler (Producer of Tin Soldiers; South Africa), Mrs. Amanda Cali (Chairperson Emeritus, IFOPA & Executive Producer, Tin Soldiers), Mr. John Cali, Dr. Scott Levin (Chairman, Department of Orthopaedic Surgery) and Mrs. Diane Weiss; Dr. Mona Al Mukaddam (second from left) greets Mrs. Kristi Gonzalez (2020 Chairperson of the Board of the IFOPA), Mrs. Amanda Cali (Chairperson Emeritus, IFOPA & Executive Producer, Tin Soldiers), and Ms. Michelle Davis (Executive Director of the IFOPA) at the premiere of Tin Soldiers, The University of Pennsylvania; Mrs. Suzanne Hollywood (Bridgewater, N.J.) answers questions from the spellbound audience after the premiere of Tin Soldiers at the University of Pennsylvania; The Cali and Helmick Families at the Tin Soldiers premiere at Penn Med (From left to right: Mrs. Allison Funk, Mrs. Amanda Cali (Executive Producer, Tin Soldiers), Mr. Ian Cali, Mr. Jason Cali, Mr. John Cali, Mrs. Melissa Helmick, Ms. Christina Helmick; Mr. Joseph Martucci, Dr. Fred Kaplan, Mr. Ian Cali and Mr. John Cali at the Tin Soldiers premiere at The University of Pennsylvania; Tin Soldiers – Courage, Triumph, Hope; The Premiere at the University of Pennsylvania. (From left to right: Mrs. Odette Schwlegler (Producer of Tin Soldiers; Johannesburg, South Africa), Dr. Mona Al Mukaddam, Dr. Fred Kaplan, Dr. Eileen Shore, Dr. Jonathan Epstein (Executive Vice Dean of the Perelman School of Medicine, Senior Vice President and Chief Scientific Officer of the University of Pennsylvania Health System), and Mrs. Amanda Cali (Chairperson Emeritus – IFOPA & Executive Producer, Tin Soldiers); Dr. Fred Kaplan answers questions from the inquiring audience after the premiere of Tin Soldiers at the University of Pennsylvania.
Research Square, 2021

Social and Clinical Impact of COVID-19 on Patients with FOP

Thousands of articles about COVID were published in 2021, but none were more important for our community than the one by Samuel Kou and colleagues from the University of California, San Francisco (UCSF).

To better understand the impact of COVID-19 on patients with FOP, Kou and colleagues examined the social impact of the pandemic using data from the IFOPA’s FOP Registry. They also identified patients with FOP who were exposed to or contracted the SARS-CoV-2 virus, or who received a COVID-19 vaccine, to investigate if patients with FOP were at increased risks of complications from SARS-CoV2 exposure. Data from 326 individuals in 69 countries were examined in the IFOPA’s FOP Registry. Twenty-six (28.9%) participants 15-years-old and above rated satisfaction with their social activities and relationships as poor in 2020, which was an increase from 18 (18.9%) in 2019, prior to the SARS-CoV-2 outbreak. Similar trends were noted for physical and mental health in the FOP pediatric population. Frequency of physician visits was not changed, but a larger portion of patients reported missing dental visits in 2020 compared with 2019. A second cohort of 32 subjects was tracked after SARS-CoV-2 exposure or vaccination. Ten subjects were positively diagnosed with COVID-19, 15 received a COVID-19 vaccine, and seven had high-risk SARS-CoV-2 exposure but either did not have a confirmed clinical diagnosis or tested negative. Subjects who tested positive for the virus showed no major complications or increased FOP disease activity, though the sample size was very limited. Among the 15 subjects who received a COVID-19 vaccine, using the ICC-issued FOP Guidelines which recommend prophylaxis with ibuprofen or acetaminophen, only one person experienced flare-up activity at the injection site.

Taken together, patients with FOP showed a significant decrease in social activities due to the pandemic which was reflective of the isolation and mobility changes in individuals with FOP. In the limited cohort that Kou and colleagues studied, the majority of the patients with FOP who tested positive for COVID-19 showed no major complications. Although limited in sample size, the majority of patients who received a COVID-19 vaccination and followed guidelines from the FOP International Clinical Council tolerated intramuscular vaccination well. Only one person experienced a flare-up following their injection. Thus, the emergent risks and benefits of COVID-19 vaccination need to be assessed and discussed carefully in order to support informed decisions.

Journal of Rare Disease Research & Treatment, 2020

Epidemiology of the Global FOP Community

During the past several years, there has been a growing concern – fueled by the emergence of regional and local FOP organizations – that the cited prevalence of FOP may not reflect community experience. Moira Liljesthröm (from
Buenos Aires, Argentina) and colleagues undertook a study to determine the emerging global population of FOP patients who were associated with a regional, national, or international FOP organization. The study used the patient membership database of the IFOPA and those of the 16 regional or national FOP organizations in order to assemble a non-redundant worldwide census of patients living with FOP in 2016 who were associated with a pre-identified FOP community.

The total registered population of the global FOP community was 834 individuals (54% females, 46% males), distributed in 67 countries and five continents. The greatest number of individuals known to be living with FOP were in North America (28%), followed by Western Europe (24%), Latin America (19%), Asia-Pacific (16%), Eastern Europe (10%), Oceania (2%), and Africa (1%). The apparent prevalence of confirmed FOP patients varied by several orders of magnitude from approximately 1:2 million in North America and Europe to approximately 1:15 million in Latin America and Africa to nearly 1:110 million in the Asia-Pacific region.

The high variability in apparent prevalence is likely associated with lack of awareness of FOP in under-represented medical communities, delay in achieving the correct FOP diagnosis, lack of supporting regional infrastructure, and inability of individuals with FOP to reach a local FOP organization or the international FOP community. Emerging knowledge of the regional discrepancy in prevalence of FOP can serve as a catalyst for resource allotment; physician, patient education, community outreach, clinical trial recruitment, and global networking to achieve a more globally robust and interconnected FOP community.

Orphanet Journal of Rare Diseases, 2021

Prevalence of FOP in the United States: Estimate from Three Treatment Centers and a Patient Organization

This study aimed to provide a baseline prevalence of FOP in the United States, based on patient contact with one of three leading treatment centers for FOP (University of Pennsylvania, Mayo Clinic, or University of California, San Francisco) and the IFOPA membership database or the IFOPA FOP Registry through July 22, 2020.

Patient records were reviewed, collected, and deduplicated. Three hundred seventy-three unique patients were identified in the United States. Based on survival probability, 279 patients were estimated to be alive on July 22, 2020. An adjusted prevalence of 0.88 per million US residents was calculated using a survival estimate of between 92%-98% and the US Census 2020 estimate of approximately 330 million.

This study suggests that the prevalence of FOP in the United States is higher than the often-cited value of 0.5 per million. Even so, because inclusion in this study was limited to those under clinical care by the authors, IFOPA membership with confirmed clinical diagnosis, and the FOP Registry, the prevalence of FOP in the US may be higher than that identified. Thus, it is imperative that efforts be made to identify and provide expert care for patients with this ultra-rare and significantly debilitating disease.

27th European Paediatric Rheumatology Congress, 2021

While Looking for One, You May Find Another: Tin Soldiers and the Search for Undiagnosed Individuals with FOP

[Editors’ Note: Meeting abstracts are brief summaries of works in progress that are presented to inform and stimulate discussion and interchange between colleagues in disciplines of interest. The abstracts are submitted to professional meetings and conferences, are peer-reviewed, and are presented orally or in poster form. Abstracts often precede publication of detailed, peer-reviewed papers on the subject of interest. There have been more than 30 abstracts on FOP presented at various meetings either in-person or virtually in 2020 & 2021. This is one that caught our attention and was not sponsored by a pharmaceutical or biotechnology company. The abstract was presented by Dr. Christiaan Scott from Cape Town, South Africa at the 27th European Rheumatology Congress.]
“FOP is an ultra-rare condition where heterozygous, gain-of-function missense mutations in the ACVR1 gene result in progressive heterotopic bone formation in ligaments, tendons and muscles and result in severe disability. FOP has an estimated incidence of 0.6-1.3 per million individuals suggesting that currently there are approximately 8,000 patients living with FOP worldwide, however only about 900 patients are currently diagnosed worldwide. The diagnosis of FOP is made clinically by identification of typical malformations of the great toes as well as inflammatory swellings (flare-ups) that result in progressive and episodic ossification of soft connective tissues, often triggered by trauma. Muscle biopsies, though contraindicated, are often performed mistakenly during the course of diagnosis, as FOP is not well known. There is a need to identify people with FOP in order to avoid harmful biopsies and to provide a pathway to care.

*Tin Soldiers* is a global FOP patient search program utilizing a multimedia campaign. The mission of *Tin Soldiers* is to identify every person with FOP who is currently undiagnosed, as well as to deliver education and support to those living with FOP, but not connected to support networks. Once found, all people living with FOP are connected to pathways of care.

*Tin Soldiers* creates multimedia campaigns to create awareness and to educate medical professionals, healthcare workers, the general public, and local communities on FOP. At the heart of the communication program is storytelling of people living with FOP, from a feature-length documentary to public service announcements, animated short films, and an eight-part Global Master Series – all designed to bring attention to FOP in order to find patients and provide a pathway to diagnosis and care.

Since March 2020, *Tin Soldiers* has trained 535 medical professionals, established an African Clinicians Council of ten doctors with the intention of mentoring others across the continent, increased the number of African patients with a diagnosis from 25 patients in December 2020 to 32 in April 2021, connected previously diagnosed (but not connected) patients to a robust support network, and held the first African FOP Family Gathering with clinicians from South Africa and Nigeria.

On the journey, patients with other conditions have been discovered including Juvenile Idiopathic Arthritis (JIA), Progressive Osseous Heteroplasia (POH), and Multiple Osteochondromas (MO). These patients have been diagnosed and connected to both medical care and patient support networks. Another important outcome is the continued education of doctors globally with the introduction of the continuing medical education Master Series in Russia and planned rollouts in Algeria, Nigeria, Kenya, Namibia, Sweden, and Brazil.”

*Journal of Orthopaedic Case Reports, 2020*

**Compartment Syndrome of the Thigh in a Patient with FOP**

Individual case reports are often the least valuable of clinical observations because they are difficult to generalize. Occasionally however, a case report can alter a way of thinking and transform an entire field of medicine by recognizing a feature of a disease that has been overlooked for centuries (such as the great toe malformation in FOP) even though it was right in front of everybody’s eyes, or by unveiling a new mechanism of disease. The case report described here falls squarely into these two categories and presents evidence of a phenomenon so important that it will likely change how we think about and potentially treat flare-ups of FOP.

The severe pain that commonly accompanies limb flare-ups of FOP is often ascribed to compartment syndrome – a potentially disastrous complication in which the circulation and function of skeletal muscle within a closed space is compromised by increased pressure within that space. However, until now there has been no direct evidence of such a phenomenon.

The case report that the authors present documents the story of a 40-year-old woman with classic FOP who came to the emergency department of a local hospital with a several week history of a spontaneous pain and swelling of the...
right thigh unresponsive to prolonged prednisone therapy and narcotic analgesia. Unfortunately, the patient was not recognized as having FOP and underwent invasive measurement of compartmental pressure of the anterior thigh.

The pressure in the swollen compartment of the thigh was 95-110 mm of Mercury (normal compartment pressure is 0-8 mm of Mercury). A fasciotomy of the thigh was performed. A fasciotomy is a surgical procedure where the fascia or thick and unyielding fibrous covering surrounding muscles and nerves (especially in the limbs) is cut to relieve pressure in order to restore the capillary circulation to the muscle and nerves that is compromised because of the swelling. Despite immediate post-operative relief of pain, progressive heterotopic ossification and loss of function of the hip and knee occurred. This unique case documented and confirmed the suspected presence of a severe compartment syndrome during an acute flare-up of FOP and has vital implications for understanding the pathophysiology and care of patients with acute flare-ups of FOP and for the design of emerging clinical trials.

This unique case illustrates conclusively what has long been suspected – that extremely elevated pressures (due to tissue swelling) within a closed compartment of muscles, blood vessels, and nerves can exist in an acute flare-up of FOP. The normal pressure of a tissue compartment is between 0 and 8 mm of Mercury. Capillary blood flow to the compartment becomes compromised and severe pain may develop when tissue pressure inside a compartment increases above 30 mm of Mercury. Muscles and nerves are severely deprived of oxygen when tissue swelling pressures approach resting blood pressure levels; the pressure is simply too high for blood to flow to the muscles within a closed compartment. And we know what happens then – the muscle cells become hypoxic (deprived of oxygen), HIF1-alpha acts like gasoline to stimulate BMP signaling from the mutant FOP receptor, and heterotopic bone forms.

In the FOP patient reported here, the compartment pressure greatly exceeded the threshold for acute compartment syndrome. This is the only case to our knowledge that ever measured the pressure within a compartment of a limb during a flare-up of FOP.

It is difficult to determine the temporal emergence of a compartment syndrome as severe edema may occur throughout the evolution of an FOP flare-up. The early phase of an FOP flare-up, regardless of whether it is induced by trauma or occurred spontaneously (as in our patient), is characterized by increasing pain and by extensive inflammation and swelling. This early phase of a flare-up is often responsive symptomatically to a brief course of high-dose prednisone, but is commonly subject to rebound edema with tapering or cessation of prednisone. The later stages of an FOP flare-up – specifically the transition from the fibrotic to the pre-osseous cartilage stage – are often characterized by obstructive edema best seen on magnetic resonance imaging as the cartilage swells and the lesion increases in volume. In the very late stages of lesion formation, reactive edema may occur at the periphery of a lesion where it abuts against healthy tissue. Thus, soft-tissue swelling and edema may occur throughout all stages of a flare-up, lead to increased compartmental pressure that threatens the viability of the soft tissues (muscles and nerves) within the compartment, precipitate cellular hypoxia (low oxygen due to poor blood flow) of muscle and nerves, amplify the bone morphogenetic protein signaling pathway, and exacerbate the progression of heterotopic ossification.

It is unfortunate that the patient underwent compartmental pressure measurement and fasciotomy as invasive procedures such as these are contraindicated in FOP. However, many important lessons may be learned from this case. While emergency fasciotomy is the treatment of choice for acute compartment syndrome, the diagnosis of FOP is a contraindication to such a therapeutic maneuver, as surgical intervention will inevitably exacerbate the flare-up or be futile.

Importantly, this stunning case suggests that acute compartment syndrome exists during flare-ups of FOP especially in the limbs, and may be more common than previously appreciated. The patient described here had a typical presentation for an acute flare-up involving the hip or thigh. Her clinical picture is consistent with many FOP patients.

The presence of severe swelling and resultant tissue hypoxia in a closed compartment will release inflammatory proteins, stimulate immune receptors, and amplify and exacerbate the formation of heterotopic bone. The recognition
of that principle should propel efforts to study compartment syndrome in FOP in a relevant animal model so that efforts can be developed to intervene non-invasively in an attempt to reduce compartment pressures.

The recognition that extreme compartment pressures may exist during a flare-up of FOP, especially within tight muscle compartments of the limbs, may severely impair the delivery of therapeutic agents to the skeletal muscles within the compartment and thereby jeopardize the potential efficacy of drugs in clinical trials. Thus, chronic therapy with agents under development may be needed in order to prevent the onset of acute flare-ups and resultant compartment syndromes.

Finally, one wonders why flare-ups of the back are accompanied by little pain and no consideration of compartment syndrome. One might speculate that perhaps the fascial compartments of the back are more capacious than those of the limbs and can accommodate the acute swelling of FOP flare-ups at those locations.

In summary, this unique case documents the presence of compartment syndrome during a flare-up of FOP and has important implications for the care of FOP patients with acute flare-ups of FOP and for the design of emerging clinical trials.

Orphanet Journal of Rare Diseases, 2020

Patients with AVCR1R206H Mutations Have an Increased Prevalence of Cardiac Conduction Abnormalities on Electrocardiogram in a Natural History Study of FOP

The rarity of FOP makes it difficult to develop the large datasets needed to understand how the FOP mutation affects non-skeletal tissues such as the heart. To better define potential cardiovascular complications that may be found in patients with FOP, Kou and colleagues examined the baseline and 12-month follow-up electrocardiograms (ECGs) of 114 patients (ages 4-56 years) with classical FOP enrolled in an international Natural History Study (NHS) of FOP.

Cardiac conduction abnormalities were present in 45% of baseline ECGs, with the majority of abnormalities classified as nonspecific intraventricular conduction delay (38%). More specifically, 22% of patients greater than 18 years old had conduction abnormalities, which was significantly higher than a prior published study of a healthy population (5.9%; p<0.00001). Patients with FOP who were under 18 years old also had a high prevalence of asymptomatic cardiac conduction abnormalities (62%). Conduction abnormalities did not correlate with chest wall deformities, scoliosis, pulmonary function test results, or increased Cumulative Analog Joint Involvement Scale (CAJIS) scores.

The study found that patients with FOP may have subclinical cardiac conduction abnormalities manifesting on ECG, independent of heterotopic ossification. The clinical significance of cardiac conduction abnormalities observed in individuals with FOP remains unclear. Although clinically significant heart disease is not typically associated with FOP, and the clinical implications for cardiovascular risk remain unclear, knowledge about ECG and echocardiogram changes is important for clinical care and research trials in patients with FOP. Clinical awareness of the potential for detecting ECG conduction or structural abnormalities may be important, but the investigators did not yet have recommendations for clinical care for patients with FOP.

The investigators concluded that data obtained from the Natural History Study of FOP suggest that cardiac conduction abnormalities are common on ECGs among patients with FOP. Although cardiac conduction abnormalities seen in patients with FOP typically do not require major clinical intervention, these findings are important to consider for future clinical care and treatments. In addition, investigators need to be aware of cardiac conduction abnormalities as a possible subclinical phenotype of FOP, particularly when testing investigational agents. Further studies are needed to understand how the ACVR1 mutation of FOP and the dysregulated BMP signaling pathway affects cardiac function, and how the conduction and structural changes detected affect medical care for patients with FOP.
**Bone Reports, 2021**

**Deterioration of Pulmonary Function: An Early Complication in FOP**

In FOP, heterotopic ossification (HO) first develops in the chest wall before more peripheral sites are affected. As a result, movement of the chest wall is restricted. Because development of HO is progressive, it is likely that pulmonary function deteriorates over time, but longitudinal data on pulmonary function in FOP are missing.

Longitudinal pulmonary function tests (PFTs) from seven FOP patients were evaluated retrospectively by Botman and colleagues from the Netherlands to assess whether there were changes in pulmonary function over time. In addition, HO volume of the chest wall together with its progression as identified by whole-body low-dose CT scans were correlated to PFT data.

Restrictive pulmonary function was found in all but one patient. No significant obstructive pulmonary function was found, nor was there any relationship between the degree of pulmonary function impairment and heterotopic ossification volume of the chest wall. The authors concluded that longitudinal PFTs confirmed restrictive pulmonary function in FOP patients at an early age. However, progression of thoracic heterotopic ossification did not seem to further affect pulmonary function later in life. Importantly, the study did not account for early degeneration of costovertebral joint function, a possible cause of chest wall restriction independent of heterotopic ossification. The authors caution that longer follow-up periods are needed to confirm this finding.

**Developmental Dynamics, 2021**

**BMP Signaling and Skeletal Development in FOP**

**Developmental Biology, 2021**

**Dysregulated BMP Signaling Through ACVR1 Impairs Joint Development in FOP**

**Bone, 2020**

**Skeletal Malformations and Developmental Arthropathy in Individuals Who Have FOP**

**Frontiers in Cell and Developmental Pathology, 2020**

**The Developmental Phenotype of the Great Toe in FOP**

This series of four seminal manuscripts – published over two years by graduate student (now Doctor) Will Towler & colleagues – describes in meticulous detail how the classic ACVR1 mutation of FOP orchestrates embryonic malformation of the great toes, one of the signature features of FOP, and for centuries a mystery. Importantly, Towler & colleagues lay out a blueprint that describes how widespread joint malformations and developmental osteopathy and arthropathy occur throughout the normotopic skeleton of individuals with FOP. This tour-de-force of basic and clinical science was featured in the 28th Annual Report of the FOP Collaborative Research Project.

In a nutshell, while too much bone-forming signal through ACVR1 stimulates HO bone formation after birth, increased ACVR1 signaling inhibits normal joint development during embryogenesis and skeletal formation. Towler & colleagues tell us ‘why and how’ and importantly which joints are at risk. “In measuring the toe,” Victor Hugo said famously, “we estimate the giant.” In probing the ageless mystery of the great toe in FOP, Towler and colleagues found that joint pathology in FOP is far more subtle and widespread than previously thought; findings that have important implications for the symptomatic treatment of evolving arthropathy as well as for the design and evaluation of clinical trials.
eLife, 2020

**FOP Mutant ACVR1 Signals by Multiple Modalities in the Developing Zebrafish**

All cases of FOP are caused by activating mutations in the cell surface receptor ACVR1, which over-activates the BMP signaling pathway. To investigate the mechanism by which mutant ACVR1 enhances BMP pathway signaling, Allen and colleagues used zebrafish embryonic dorsoventral (DV) patterning, a highly sensitive and quantitative assay for BMP pathway signaling. The investigators determined that the FOP mutants ACVR1<sup>R206H</sup> and ACVR1G328R do not require their ligand binding domain to over-activate BMP signaling in DV patterning, consistent with previous reports that ACVR1<sup>R206H</sup> is ‘leaky’ and can signal in the absence of any ligand. However, intact ACVR1<sup>R206H</sup> can respond to both BMP and Activin A ligands. Additionally, BMPR1, a type I BMP receptor normally required for BMP-mediated patterning of the embryo, is dispensable for both ligand-independent signaling pathway activation and ligand-responsive signaling hyperactivation by ACVR1<sup>R206H</sup>. These results demonstrate that signaling activity of FOP-ACVR1 is not constrained by the same receptor/ligand partner requirements as WT-ACVR1. Identification of the molecular mechanisms that regulate the function of BMP receptors and BMP signaling pathway activity provides new opportunities to develop highly specific therapeutic approaches to regain control over FOP ACVR1.

NPJ, Regenerative Medicine, 2022

**Dynamics of Skeletal Muscle-Resident Stem Cells During Myogenesis in FOP**

The replacement of muscle tissue with bone tissue in FOP in response to injury indicates that muscle regeneration that normally repairs injured muscle tissue is severely perturbed. Previous work has examined the origins of heterotopic ossification but the impact of the ACVR1 mutation in FOP on muscle tissue regeneration remains unclear. In this study, Stanley and colleagues from Penn demonstrate that muscle tissue in FOP regenerates poorly after injury.

Utilizing an inducible FOP knock-in mouse, the authors found that two resident stem cell populations from muscle tissue – muscle stem cells (that regenerate injured muscle) and fibro-adipogenic progenitors (FAPs; that interact with muscle stem cells and act as tissue foremen), have similar proliferation rates after injury; however, the differentiation potential of mutant muscle stem cells is compromised. The authors further determined that FAPs from FOP mice unpredictably repress the regeneration of muscle. This occurs because of the improper interaction of muscle stem cells and FAPs during muscle regeneration.

The data from Stanley and colleagues highlight the detrimental effect of FOP FAPs on regulating muscle stem cell repair of injured muscles. Stanley and colleagues propose that therapeutic interventions should consider boosting the muscle forming potential of regenerating muscles, along with reducing heterotopic bone formation. Taken together, Stanley and colleagues document that FOP is not only a disease of heterotopic ossification, but also a breakdown of muscle repair and regeneration and provides the foundation for targeting this process in future therapeutic approaches in order to improve muscle repair.

Bone, 2020

**Activin A Does Not Drive Post-Traumatic Heterotopic Ossification**

Heterotopic ossification (HO) has been extensively studied in its two primary forms: post-traumatic HO typically found in patients who have experienced musculoskeletal or neurologic injury and in FOP, where it is genetically driven. Given that in both forms, HO arises by endochondral ossification, the molecular mechanisms behind both forms of HO are thought to engage similar pathways. In FOP, mutant ACVR1 is responsive to activin A, a locally acting hormone-like molecule. In detailed experiments, Hwang and colleagues showed that activin A was expressed...
in response to injury in both FOP and post-traumatic HO, but by different types of cells. The authors hypothesized that inhibition of activin A would not block the formation of post-traumatic HO. Nonetheless, as activin A was expressed in post-traumatic HO lesions, Hwang and colleagues tested its inhibition and showed that antibodies against activin A in fact do not block post-traumatic HO, while they are very effective at blocking HO in mouse models of FOP, as previously shown. Interestingly, antibodies that block osteogenic BMPs are beneficial at inhibiting post-traumatic HO, though not completely curative. The study by Hwang and colleagues demonstrates that although activin A is a driver of HO in FOP, it plays little if any role in the formation of post-traumatic HO.

Frontiers in Endocrinology, 2020
FOP: A Segmental Progeroid Syndrome

Journal of Bone and Mineral Research, 2021
Clearance of Senescent Cells from Injured Muscle Abrogates Heterotopic Ossification in Mouse Models of FOP

FOP results in a constellation of features, many of which resemble accelerated aging. Characteristics of accelerated aging in FOP include those that are related to dysregulated BMP signaling as well as those that are secondary to early immobilization.

Features of aging that may primarily be associated with mutations in ACVR1 include osteoarthritis, hearing loss, hair thinning, myelination defects, heightened inflammation, menstrual abnormalities, and perhaps kidney stones. Features of aging that may secondarily be related to immobilization from progressive heterotopic ossification include decreased vital capacity, osteoporosis, fractures, muscle wasting, and predisposition to respiratory infections. Some manifestations of accelerated aging may be attributed to both primary and secondary effects of FOP.

At the level of lesion formation in FOP - cellular hypoxia, cell damage, and inflammation may all lead to the accumulation of senescent cells, as in aged tissue. Senescent cells accumulate in wound healing as well as aging, and are cells that can no longer divide but express a potent array of inflammatory factors (including Activin A which potently stimulates FOP lesions) and tissue-reprogramming factors. Production of Activin A, platelet-derived growth factor, metalloproteinases, interleukin 6, and other inflammatory proteins are part of the rich cocktail of factors produced by senescent cells and could conceivably mediate the initial signaling cascade that results in the intense fibroproliferative response as well as the stem cell reprogramming that leads directly to heterotopic ossification. Consideration of FOP as a syndrome of accelerated aging offers a unique perspective into potential mechanisms of normal aging as well as wound healing and may also provide insight for identification of new targets for therapeutic interventions in FOP.

Based on the hypothesis that senescent cells accumulate in early FOP lesions in patients, Pignolo and colleagues demonstrated that muscle injury in mouse models of FOP also results in the accumulation of senescent cells, and that senescence promotes tissue reprogramming toward a cartilage fate in FOP muscle but not wild-type muscle. Importantly, the investigators showed that elimination of senescent cells with senolytic drugs reduces the cocktail of inflammatory proteins (including Activin A) and potent tissue reprogramming factors made by senescent cells and thereby dramatically reduces heterotopic ossification in mouse models of FOP.

Pignolo and colleagues conclude that senescent cells contribute to FOP lesion formation, orchestrate tissue reprogramming from muscle to cartilage and divert a muscle-repair fate to a bone fate. Most importantly, the work of Pignolo and colleagues provides evidence for senolytic drugs as a future therapeutic strategy in FOP.

The potential for a senolytic drug to become part of standard-of-care for FOP seems possible soon, due both to encouraging pre-clinical data and the availability of senolytic drugs as nutraceuticals or repurposed drugs. Potential concerns about side effects and long-term deleterious consequences of senolytic drugs are mitigated by the fact that
they can be administered infrequently, owing to the rapid clearance of senescent cells and the lag time for senescent cells to re-accumulate after clearance. These data suggest a way-forward for a randomized clinical trial with senolytic drugs for FOP.

Bone, 2021

**Off-On-Off-On Use of Imatinib in Three Children with FOP**

The compassionate use of available medications with unproven efficacy is often in conflict with their clinical evaluation in placebo-controlled clinical trials. For ultra-rare diseases where no approved treatments exist, such as FOP, routine clinical trial enrollment for available medications may be difficult to achieve. Therefore, adaptive methods of evaluation are often desirable. Off-on-off-on (O4) approaches offer an opportunity to rapidly assess the potential symptomatic efficacy and tolerability of a medication with a limited number of patients and may aid in the design of more focused clinical trials that are amenable to enrollment.

In this article, Kaplan and colleagues report three children with classic FOP who had recalcitrant flare-ups of the back and who had been treated with an O4 regimen of imatinib. In all three children, fewer flare-ups, decreased swelling and improved function with activities of daily living were reported by the parents and treating physician when the children were “on” imatinib than when they were “off” imatinib.

The median time to improvement on imatinib was 2-3 weeks. The anecdotal O4 experience with imatinib reported by Kaplan and colleagues in three children with FOP who had recalcitrant flare-ups of the back supports the design of a brief placebo-controlled trial to assess the potential efficacy of imatinib in reducing the symptoms in children with refractory flare-ups of FOP. A tool to prospectively measure and quantitate flare-up symptoms has been developed and validated and could be used in such a study.

The authors acknowledge that there is no evidence to support or refute that imatinib has any effect on heterotopic ossification in FOP; this remains an open question. Imatinib was considered repeatedly for compassionate use in three children to abrogate symptoms of flare-ups of the back based on in vitro, in vivo and translational studies of its off-target effects on c-Kit, HIF1-α, Smad1 and PDGFR that are relevant to mast cell recruitment and innate immune activation, hypoxia and inflammation, BMP pathway activation and fibroadipogenic progenitor cells respectively – all relevant to the inflammation that accompanies early FOP flare-ups.

The authors are clear that the most effective pharmacologic interventions to prevent new episodes of heterotopic ossification in FOP; this remains an open question. Imatinib was considered repeatedly for compassionate use in three children to abrogate symptoms of flare-ups of the back based on in vitro, in vivo and translational studies of its off-target effects on c-Kit, HIF1-α, Smad1 and PDGFR that are relevant to mast cell recruitment and innate immune activation, hypoxia and inflammation, BMP pathway activation and fibroadipogenic progenitor cells respectively – all relevant to the inflammation that accompanies early FOP flare-ups.

The best way to determine conclusively if imatinib has potential benefit in the symptomatic management of FOP in children would be in a brief placebo-controlled clinical trial. Too often, clinical studies are focused on formation of heterotopic bone as the most important endpoint of treatment and neglect the misery and suffering that often occurs with FOP flare-ups, especially in young children for whom no other remedies are presently available.
Saracatinib Is an Efficacious Clinical Candidate for FOP

Currently, no effective therapies exist for FOP. From a screen of known biologically active compounds, the authors identified saracatinib, an unapproved and repurposed drug, as a potent inhibitor of ACVR1. In enzymatic and cell-based assays, saracatinib preferentially inhibited ACVR1, compared with other receptors of the BMP signaling pathway. In mouse models, saracatinib was well tolerated and potently inhibited the development of heterotopic ossification, even when administered transiently following soft tissue injury. Together, these data suggest that saracatinib is a promising candidate for repurposing in clinical trials for FOP. Such studies are presently underway.

An ACVR1R375P Pathogenic Variant in Two Families with Mild FOP

The two hallmarks of classic FOP (which comprises ~ 97% of all individuals with FOP) are malformed great toes and progressive heterotopic ossification. Approximately 3% of individuals with FOP have clinically variable presentations (referred to as non-classic FOP) that can be placed broadly into two groups – one with nearly normal or completely normal-looking great toes; the other with severe malformations of the great toes.

To date, all patients with classic FOP have the same activating pathogenic mutation in ACVR1. In contrast, patients with non-classic FOP have gain-of-function pathogenic variants at other positions in the ACVR1 gene. Genotype-phenotype correlations have been noted between some ACVR1 pathogenic variants and the age of onset of heterotopic ossification. The most predictive clinical feature of non-classic FOP, in combination with heterotopic ossification, is the degree of malformation of the great 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. non-classic FOP, the only way to ascertain FOP at a molecular level is by molecular diagnosis through DNA sequence analysis of the ACVR1 gene. Classic FOP is caused by a single pathogenic variant in ACVR1. To date, approximately 15 pathogenic variants in ACVR1 have been identified in individuals with FOP with no more than 10 known affected individuals with any given pathogenic variant.

In this important article, Kaplan and colleagues describe eight members of two families with an ultra-rare ACVR1 pathogenic variant (ACVR1R375P) responsible for very mild non-classic FOP features. Both families include people with the ultra-rare ACVR1R375P variant who exhibit features of FOP while other individuals currently do not express any clinical signs of FOP. One individual is, to our knowledge, the oldest reported patient with a newly diagnosed FOP pathogenic variant, remaining completely asymptomatic until the eighth decade. His son was completely asymptomatic until the sixth decade.

The individuals described in these two unrelated families had either no malformations or mild malformations of the great toes. Additionally, all individuals who developed heterotopic ossification in both families had very late onset heterotopic ossification (range: 14–72 years; median age: 40 years). In comparison, the median age of onset of heterotopic ossification in individuals with classic FOP is about 4 years (range, 2–5 years). Intriguingly, three individuals in Family 1 are 27-30 years old and remain completely asymptomatic but have an ACVR1 pathogenic variant by genetic testing.

Despite the generally mild nature of the ACVR1R375P pathogenic variant, both inter-family and intra-family variability was noted by the authors, possibly indicative of genetic modifiers, differences in environmental factors, or both. At the present time, we cannot determine the relative contributions of the genetic and environmental contributions to the observed phenotypes. The generally mild consequences of the ACVR1R375P variant, both in the developmental joint phenotype and in post-natal heterotopic ossification, raises the possibility that the ACVR1R375P variant may not only go clinically undetected, but be common in the general population. However, this does not seem to be the case as this, and
other mild variants, are rarely represented in large genetic databases.

Despite the milder phenotype, important clinical implications remain for individuals with the ACVR1 R375P pathogenic variant. First, whether an individual has ACVR1 R206H or ACVR1 R375P, they have increased activity of BMP pathway signaling and thus the tendency to form heterotopic bone. Therefore, the clinical precautions for FOP are the same for classic FOP and for those with the ACVR1 R375P variant. Second, the symptomatic management of flare-ups is the same for patients with classic FOP and for those with the ACVR1 R375P variant. Third, whether someone has classic FOP or the ACVR1 R375P variant, the histologic process by which heterotopic bone forms is the same. Fourth, there is tremendous variability in the phenotypic expression of ACVR1 R375P, even within a family as exemplified in both families described by the authors, and this observation has implications for genetic counseling. Fifth, many approaches to block the overactive ACVR1 receptor encoded by the FOP gene should be applicable to the ACVR1 R375P variant as well as to classic FOP caused by ACVR1 R206H. Finally, knowledge of a spectrum of pathogenic variants in ACVR1 and their correlation with the broad range of phenotypic variability in FOP should lead to better treatments for all of those with FOP regardless of whether one has classic FOP or non-classic FOP.

In summary, the ACVR1 R375P pathogenic variant provides a unique perspective in determining the wide range of clinical phenotypes of FOP, informs physical diagnosis, guides genetic counseling, and reveals a molecular basis of phenotypic variability in this ultra-rare condition.
Despite the restrictions of COVID-times, the International Clinical Council grew and thrived in a virtual world over the past three years. The International Clinical Council on FOP (ICC) is an autonomous and independent group of 21 internationally recognized physicians who are clinical experts in FOP from 16 nations (Argentina, Australia, Brazil, Canada, China, France, Germany, India, Italy, Japan, Republic of Korea, Mexico, the Netherlands, 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 was 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 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 Clinical 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 clinical 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.

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Frederick S. Kaplan, MD
Philadelphia, Pennsylvania, USA

Richard Keen, MD, PhD
London, United Kingdom

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).
In 2020-2021, Dr. Robert Pignolo, The Kogod Professor and The Chairman of the Department of Geriatrics at the Mayo Clinic, served as the second President of the ICC. During Dr. Pignolo’s tenure, the ICC accomplished the following:

- Conducted ICC activities virtually in the era of COVID-19, including year-round global ICC committee work
- Published a major revision of the FOP Treatment Guidelines
- Published timely Guidelines on COVID-19 and COVID-19 Vaccinations
- Acted on patient safety and participation in clinical trials
- Published an editorial on clinical trials
- Wrote a review and editorial on gene therapy in FOP
- Established the ICC website (www.iccfop.org)
- Formed the Global Health and Education Task Force
- Created emeritus status for ICC members rotating off the Council
- Recruited a new member from India
- Expanded pharmaceutical/biotech relationships
- Developed working relationships with the IFOPA, the International Presidents’ Council and the Tin Soldiers Initiative
- Developed member participation in the Tin Soldiers Continuing Medical Education (CME) Global Masters Series and other educational activities

Dr. Christiaan Scott has served as the third President of the ICC in 2022 and 2023.
President’s Lifetime Achievement Award to the ICC

[Editors’ Note: The following is an unpublished interview by the IFOPA with Dr. Frederick Kaplan, Founder of the ICC, on the occasion of the Jeannie Peeper Lifetime Achievement Award to the ICC in 2020.]

Can you discuss what your role in the ICC has meant to you personally and professionally?

The ICC is the professional response to that quiet and powerful patient voice – first articulated by Jeannie Peeper that has motivated every step of my lifelong journey in FOP. Patients are the reason, the strength, and the inspiration that allow us all to care, to do research, to work tirelessly for a better future. Every individual with FOP has taught us what every doctor should know and re-learn every day – that diseases are not just physical processes but human experiences. The ICC has been inspired by this voice and enables the worldwide FOP medical community to give back to patients, families, and community our collective wisdom in the best way we know how.

The establishment of the ICC has been a personal dream that has been realized during my nearly 40-year journey with FOP. When Mrs. Amanda Cali, Chairman Emeritus of the IFOPA and mother of Ian Cali, proposed a way forward, the dream became a reality. As U.S. Senator John McCain said so eloquently, “There is nothing more liberating than to fight for a cause larger than yourself, something that encompasses you but is not defined by your existence alone.” And, I may add, there is nothing more powerful than an idea whose time has come. The ICC is an idea whose time has come. The ICC was established out of need – an emerging need to coordinate and consolidate a global voice for the best practices for clinical care and clinical research for people who suffer from FOP. I saw that need emerge in my conversations with FOP patients, with families, as well as with leaders and pioneers in the FOP community like Jeannie Peeper and Jennifer Snow and Amanda Cali. The ICC arose from that extraordinary need. The ICC was established as a worldwide voice for all clinical concerns for individuals with FOP everywhere – a United Nations for the clinical care of those with FOP.

As I wrote in the Preamble of our Constitution, the FOP community has moved from the wastelands of a rare disease to the watershed of clinical trials. The recent seismic activity in FOP basic and clinical research presents exciting challenges for clinicians caring for FOP patients worldwide. Importantly, ongoing clinical care and emerging clinical trials present medical and logistical challenges for individuals with FOP. Additionally, the pharmaceutical biotechnology complex continually seeks expert advice from our ranks on clinical trial development. There was clearly an urgent unmet need to consolidate and coordinate clinical knowledge and advice on clinical care, symptomatic treatment, and clinical trial development into a framework that best serves the needs of the FOP patient community worldwide. The ICC is the answer to that need, and I am proud of its members and its missions.

What outcomes of the ICC’s work do you find most significant for FOP patients and families?

There are tangible outcomes and intangible ones – and then there are dreams. In the tangible category, we have created three products that are highly significant for the FOP patients and families. First, in 2019, under the leadership of Dr. Edward Hsiao, The ICC published a landmark article “Special Considerations for Clinical Trials in FOP” in the British Journal of Pharmacology. This article sets forth a roadmap – a blueprint – of all that should be considered by any investigator or pharmaceutical company sponsor in conducting a clinical trial for FOP patients. Second, in March 2019, the ICC culminated a year-long effort and published major revisions of the widely acclaimed FOP Treatment Guidelines, used by FOP patients and medical professionals worldwide. Each time a revision is done, The ICC works diligently for over a year on this project – a monumental effort on the part of many. Third and finally, The ICC under the leadership of Dr. Mona Al Mukaddam launched an innovative website that is the home for all matters pertinent to the missions of the ICC and the patients it serves. Those are three of the most important tangible accomplishments of the ICC.

In the intangible category, the formation of the ICC has transformed a loose international consortium of medical experts in FOP into a cohesive and powerful council with worldwide reach. A sounding board and firewall for clinical
excellence and clinical care of FOP patients worldwide. In a sense, a “United Nations” for everything clinically relevant to the best interests of the patient. As the world of FOP becomes more vibrant with clinical trials, the ICC also serves as a forum for discussion – both formal and informal among international experts who share the common missions for best practices in clinical research and clinical care. Together as a council and individually as members of the ICC, we continue to provide our best advice – often gratis – to pharmaceutical sponsors on the design and conduct of clinical trials worldwide, and we are a powerful voice for the sharing of non-proprietary data that should belong to the FOP community, not to pharmaceutical and biotechnology companies. The establishment of the ICC and the robust communications among its members has established a vibrant network that affords the stature and ability to reach out to colleagues around the globe each and every day to exchange ideas and gather opinions, consultations and insights that are often life-saving for patients. That vital, yet intangible, reality of a global network of communications among the leading FOP clinicians in the world is truly invaluable and ultimately serves the best interests of the patients and the FOP community more than any tangible edifice ever could.

And finally, there is the dream. Perhaps not everyone shares this dream, but I envision an ICC that is composed of several tiers: of global clinical leaders – a sort of security council of FOP; of national and regional clinical leaders who provide expertise and guidance and organizational leadership on clinical matters for their nations and regions; and local clinical leaders who complete the network – field generals on the battlefield at the local level in large cities, small towns, tiny villages and remote hamlets around the globe bringing compassionate care and the best clinical guidance to those they serve, one patient at a time. And I envision that all three tiers will be bound into a vibrant international council that is connected in a seamless network that spans the globe. That, I believe, is the ICC of the future. That is the dream, and the time to start building it is now.

Please share what it means to you for the ICC to be selected by Jeannie Peeper.

Jeannie Peeper is an extraordinary individual. A true visionary and a dear friend who used a magic loom to first imagine and then create the IFOPA to end the isolation of an ultra-rare disease, to stimulate monumental scientific progress, and to weave together a scattered global community into a single indelible tapestry from the golden thread of committed patients and families. Jeannie did this from a unique vision of empathy, compassion, commitment, and need. We owe our voice, our values, and our vision to Jeannie.

Jeannie has given her life to the FOP community and has endowed my life with purpose and meaning. I will never forget the day that I called Jeannie to tell her the monumental news that the FOP gene had been discovered. The creation of the ICC was a response to the need that emanated from that remarkable discovery and all the promise that it has brought.

The news that the ICC has received the Jeannie Peeper Award – not in reward – but in recognition of what it means to patients, families, and community is an unfathomable tribute from the founder of our global community and a dear lifelong friend of mine. Jeannie’s wisdom continues to inspire us all. The ICC and all of its members are deeply honored by this remarkable tribute.
Promotions

Dr. Mona Al Mukaddam was promoted to Associate Professor of Medicine (Division of Diabetes, Endocrine & Metabolism) and Associate Professor of Orthopaedic Surgery at The Perelman School of Medicine of The University of Pennsylvania.

Dr. Staci Kallish was promoted to Associate Professor of Medicine (Division of Translational Medicine & Human Genetics) and Associate Professor of Pediatrics at The Perelman School of Medicine of The University of Pennsylvania.

Teaching Awards

Dr. Mona Al Mukaddam was awarded the prestigious Edward Rose Faculty Teaching Award of the Hospital of the University of Pennsylvania.

Radiant Hope Foundation Distinguished Clinician-Scientist Award

Dr. Mona Al Mukaddam was awarded the Radiant Hope Foundation Distinguished Clinician-Scientist Award, effective July 1, 2020.

The goals of this meritorious award are to:

1. Facilitate ongoing clinical and research endeavors in FOP not currently supported by other funding sources.
2. Provide protected time for clinical and research endeavors in FOP that would not otherwise be available.
3. Support travel to FOP and related conferences.

The College of Physicians of Philadelphia

Drs. Mona Al Mukaddam & Eileen Shore were elected to and inducted into the oldest and most prestigious College of Physicians in the United States noting their august and lasting contributions to the FOP research and to the FOP community.

International Clinical Council on FOP Leadership Position

Dr. Mona Al Mukaddam was elected as Chair of the Governance & Membership Committee of the International Clinical Council on FOP (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.
Co-Recipients of the Henning Anderson Prize of the European Society for Pediatric Endocrinology

Drs. Mona Al Mukaddam & Fred Kaplan along with their international co-authors received the Henning Anderson Prize for their abstract on the Longitudinal Natural History Study of FOP which was presented by ICC member and co-author Richard Keen of London, UK. at the European Society for Pediatric Endocrinology.

2020 Castle Connolly’s Top Doctor

Dr. Al Mukaddam was named through peer nomination as a Castle Connolly Top Doctor.

Top Docs in Philadelphia Magazine

Dr. Mona Al Mukaddam was selected by her peers as one of leading Endocrinologists by Philadelphia Magazine.
FOP – The Spoken Word

In 2020-2021, lectures on FOP were presented during the COVID-19 pandemic either virtually or in-person (as permitted) at:

- Advances in Mineral Metabolism; Snowmass, Colorado
- American Society for Bone and Mineral Research; San Diego, California
- Ashley’s Cure Fundraiser; New York, New York
- American Association of Clinical Endocrinology
- American Society for Bone & Mineral Research; Montreal, Canada
- Brown University; Providence, Rhode Island
- Children’s Hospital of Philadelphia; Philadelphia, Pennsylvania
- CME Masters Series on FOP; Johannesburg, South Africa
- College of Physicians of Philadelphia; Philadelphia, Pennsylvania
- Cooper Medical Center; Camden, New Jersey
- Dubai International Conference for Medical Sciences; Dubai, The United Arab Emirates
- European Pediatric Rheumatology Congress; Geneva, Switzerland
- FOP Argentina; Buenos Aires, Argentina
- FOP Germany; Valbert, Germany
- Grand Hamdan Award Webinar; Dubai, The United Arab Emirates
- Harvard School of Dental Medicine; Boston, Massachusetts
- Icahn School of Medicine at Mount Sinai; New York, New York
- IFOPA Family Meetings; Kansas City, Missouri
- IFOPA International President’s Council
- IFOPA Webinar on COVID-19
- Ipsen Pharmaceuticals; Paris, France
- Jefferson University; Philadelphia, Pennsylvania
FOP − The Written Word

In 2020-2021, publications from numerous groups on FOP and FOP-related issues appeared in peer-reviewed journals. There were more than 170 papers published on FOP worldwide - a continuing tribute to the broad international interest and awareness of FOP.

As of January 1, 2022, the classic paper in Nature Genetics (April 2006) describing the discovery of the FOP gene has been cited in 1,102 major scientific publications worldwide.

“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. It is even more urgent now during the COVID pandemic as the world’s attention is diverted elsewhere. But FOP is not going away.”

As Kate Griffo and John Glick 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.” We are in great jeopardy of seeing this reality, and the COVID pandemic has made us understand how real this is. Because of the funding lull, we have had to put projects on hold.

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 30 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 needed to 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 three 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, silent auctions, country fairs, benefit concerts at the Metropolitan Opera, raffles, rodeos, sales of holiday cards and embroidered quilts, 5K runs, ice fishing contests, chamber music benefits, Hard Rock concerts, horse-plowing contests, competitive swims, golf tournaments, 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. Please help during this critical time.

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.
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. We 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.

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 the 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:**

- International FOP Association
- National Institutes of Health (The People of the United States of America)
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- Weldon Family Endowment for FOP Research
- Cali-Weldon Professorship of FOP Research
- Radiant Hope Foundation
- Ashley Martucci Fund for FOP Research
- Roemex Fellowship in FOP Research
- Jesse David Hendley Foundation
- Gene Spotlight, Inc.
- Morgan Fund for FOP Research
- Canadian FOP Families & Friends Network
- FOP Australia
- FOPcV (Germany)
- FOP Italia
- FOP Scandinavia
- Cary 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
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 patients’ voices are always the most important voices in the room. This year, those voices are amplified by Kay Rai. We will let her tell you her story.

“My name is Kay Rai; I have worked with Dr. Kaplan and the FOP patients for the past 37 years, since we started seeing FOP patients from all over the world at the University of Pennsylvania. I coordinate the patient visits and interact with them in my capacity as a critical member of the FOP team at the University of Pennsylvania.

Often, I am the initial contact when we receive a request for an FOP evaluation from a doctor, family member or patient. Patients and parents from all over the world often arrive bewildered, distraught, or in shock. They do not know what to do about an emerging clinical dilemma that not many medical professionals really know how to address. So, patients come with many questions hoping to learn more about FOP.

Our goal is to confirm their diagnosis, define their understanding of what FOP involves, and answer their questions as best as we can (in terms of the do’s and don’t’s of FOP, what to do at the onset of a flare-up, what amenities are available for children in all stages of life, what aids are available, and what clinical trials are enrolling or on the horizon). And most importantly, we try to provide reassurance that they are not alone – that there is an FOP community willing to help.

After their visit, patients leave our facility with a much better understanding of FOP, knowing more about what to do in terms of flare-ups, care, schooling, and knowing that they can contact us at any time for answers to their questions and assistance with their needs.

Most people do not understand what FOP is and how it affects the patient and the family. Often, it takes a personal touch – someone who knows and cares.
Over the years, I have had the honor and privilege of meeting many patients with FOP; everyone is memorable, but several stick in my mind.

- A two-year-old little girl with FOP whose family relocated to Philadelphia so she could be near her FOP doctor. She arrived with stiffness in her neck. Slowly her body progressed with the ravages of FOP. She was in a wheelchair in her teens, and sadly passed away in her 20s. We watched her grow as she visited us over the years and remember her vibrant personality. She loved the color purple.

- One of our very first FOP patients was in her 20s. She would arrive for her appointment at the Hospital in her motorized wheelchair with zest and energy; her meticulously self-applied makeup in place despite her physical disability. She would zoom to the cafeteria (within the speed limits of course) or visit a friend in the hospital with one of her paintings that she had completed. She died at the age of 58 and wanted avidly to continue her journey in the afterlife at The Mütter Museum of the College of Physicians of Philadelphia. I feel honored to have helped make her wish come true.

- A three-year-old little boy with severe FOP, growth retardation, cardiac issues, and failure to thrive (to name some of his complex medical issues) had lost both parents. He was initially shy when he came to see us with his older brother (from whom he was inseparable) and his foster parents. Despite his disabilities and the ravages of FOP, this little boy was the happiest, smartest child – full of life, spirit, energy, and love. He didn’t let FOP or his other medical ailments bother him or faze him in any way. One day, one of his doctors asked him what his name was, and he replied, “I am the King of Awesome!” His wit, charm, and free, fun-loving character touched my heart (and many hearts); never to be forgotten. He was in sixth grade and 11 years old when he passed away. It was indeed a true pleasure to meet this unforgettable amazing young man.

We meet many FOP patients who prevail and follow their dreams to become writers, medical professionals, attorneys, IT professionals, businessmen and women, accountants, financial advisors, bankers, journalists, social workers, teachers, farmers, artists, and parents themselves who enjoy life without letting FOP dictate who they are. Quotations from several FOP patients come to mind: “Accentuate the Positive,” said one; “Hope Is Alive,” said another. I admire these amazing people through their courage, strength, and perseverance in dealing with their daily obstacles. I term my experience in meeting patients with FOP, a privilege. I feel honored that I can be able to help them with their needs. Seeing their courage and strength and determination in dealing with life every day is a very humbling experience. I feel honored to know them.