THE CENTER FOR RESEARCH IN FOP & RELATED DISORDERS

30TH Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project

Penn Medicine

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2024–2025

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Preface

The 30th Annual Report (2024-2025) of the FOP Collaborative Research Project describes events and accomplishments of 2022 through 2024.

Reflecting on the Annual Reports and on the history of FOP, there are moments that have made a remarkable difference. The discovery of the FOP gene was one such moment; the discovery from patient-R is another. You can read about it here.

The FOP world has been changing rapidly. Old discoveries have new meanings, and new discoveries are being made constantly. Old clinical trials have ended, new ones have started, and more are on the way. All are based on important FOP research developments, many 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.

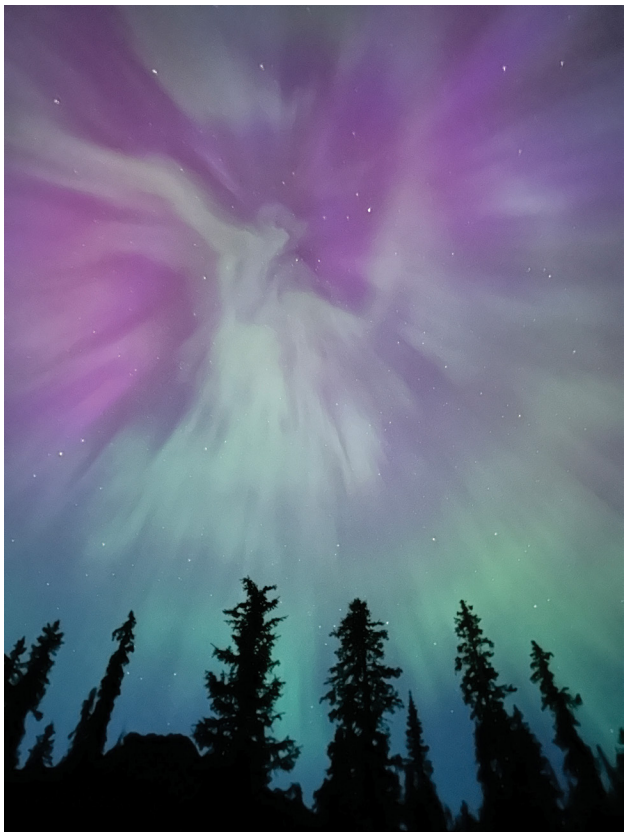
Enjoy the historic 30th Annual Report and join us as we continue our journey—our collective and timeless mission to develop better treatments and a cure for FOP.

Frederick Kaplan
Philadelphia
February 2025

PART 1 Introduction

While walking to a cabin in a remote region of northern Canada, late one moonless night last September, one of us was on the lookout for a grizzly bear, sighted by other hikers. In a moment of distraction, perhaps a noise from the woods, he gazed at the starlit sky and saw a cloud moving back and forth, as if it was dancing. Maybe he was hallucinating, imagining? He switched off his headlamp, reached for his camera, and snapped a picture of the strange phenomenon. Then, he continued on the way, aware that there might be a hungry grizzly nearby. Later, in the cabin, he opened the camera, glanced at the picture, and was awestruck. "That's funny," he murmured to his wife. "I had been on the lookout for a grizzly" (which he did not want to see or encounter). What he saw instead was unexpected, magical, pure serendipity—it was the Aurora.

When least expected, a faint light illuminates something never before seen—a light that seemingly comes out of nowhere or a Rosetta stone that allows one to decipher the undecipherable. Such rare moments are likely accompanied by hushed comments: "That's strange" or "That doesn't quite make sense," or "Is that really true?"



Aurora, Lake O'Hara; British Columbia, Canada

Sound like science fiction? It's not science fiction at all. In fact, such rare moments are in the realm of revelation, an unspoken but real world seldom seen or acknowledged by scientists—and often the driving force behind it. If recognized and pursued, such moments may herald breakthroughs in science and, yes in medicine—including the all too real world of FOP.

In his marvelous book, ***HAPPY ACCIDENTS: Serendipity in Modern Medical Breakthroughs***, Morton A. Meyers, MD, describes what happens "when scientists find what they're **NOT** looking for," when accidental discoveries lead to major medical breakthroughs. "Discovery requires serendipity," he says, "But serendipity is not a chance event alone. It is a process in which a chance event is seized upon by a person who chooses to pay attention to the event, unravel its mystery, and find a proper application for it."

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Meyers goes on to say, "Most of the important breakthroughs in modern medicine... have often been the work of lone researchers or small close-knit teams operating with modest resources and funding and have depended crucially on luck and accident. While serendipity is essential to discovery, it is nothing without the human beings who know the opportunity when they see one... Discoveries are surprises. You can't plan surprises, but you can certainly create an environment in which they are apt to happen and are likely to be recognized and pursued when they do." In our world of FOP, surprises come infrequently, serendipity, rarely.

This 30th Annual Report focuses on a surprise that occurred in the FOP clinic that led to a truly serendipitous discovery—a discovery that may alter the direction of FOP research. But first, a little background.

PART 2 Inflammation and FOP: A Critical Key

In all affected individuals, FOP is caused by a gain-of-function mutation in ACVR1, a bone morphogenetic protein (BMP) receptor that sends a dysregulated signal to make bone outside of the skeleton in soft connective tissue like muscles, tendons, ligaments, and fascia (connective tissue that connects groups of muscles). 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 (HO) that are a hallmark of the disease.

Flare-ups of FOP strongly implicate an underlying inflammatory trigger—that ancient branch of the immune system that responds immediately to any threat internal or external. In fact, inflammatory cells have long been implicated in the heterotopic ossification of FOP. While the role of inflammation in FOP is compelling, it is also incredibly complex and glaringly incomplete.

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.

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

In order to answer that question, we would like to tell you a story—a rather unexpected and astonishing story. We are confident that the story will inspire novel avenues of investigation in FOP precisely because it identifies a new and unanticipated target for therapy. Don Hewett, the producer of the award winning documentary series ***60 Minutes*** was once asked to describe his inspiration. "It's simple," he said. "I can answer that in four words: **Tell me a story.**"

PART 3 The Story— The Power of One

"Clinics are laboratories—laboratories of the highest order."
William Osler, MD (1849–1919)

"We study those who are sick, but if we're trying to develop therapies for prevention, maybe we should study those who don't get sick—those who stay well."
Stephen Friend, MD, Pediatric Oncologist

"If you don't allow for surprises, you won't learn something new."
Avi Loeb, Astrophysicist, Harvard University

"One person can make a difference."
Raoul Wallenberg, Swedish Architect and Businessman

Meet a Superhero of the Resilient—Andrew Davis. From left: Dr. Mona Al Mukaddam, Mrs. Lorna Davis, Andrew Davis, Dr. Fred Kaplan, and Dr. Bob Pignolo.

When people think of research, they often think of the basic science laboratory. But that's not where this journey begins. In this story, the journey begins in a busy clinic—at an inconvenient moment—when it is easy to ignore what is right in front of one's eyes. In this story, the journey begins with perplexity and doubt, and most importantly, with a question. It is a story about something expected that does **NOT** happen—a story of a scientific mystery that begins in the clinic, moves to the laboratory and returns to the clinic in a new and different form.

The story begins when one of us (FSK) met a gentleman who we will describe as patient-R (R stands for Resilient) when he was 21 years old. Patient-R had normal growth and development, had the usual childhood immunizations, played sports in his youth and had been healthy all his life. However,

patient-R developed a swelling on the side of his neck when he was 20 years old and saw a local doctor. The local doctor suspected that the swelling might be an enlarged lymph node and sent patient-R to a surgeon for a biopsy.

When the biopsy report returned, it was clear that the swelling was not a lymph node, but rather a benign fibrous lesion. The following year, when the swelling recurred, the local doctor referred patient-R to a geneticist for further testing. The geneticist examined patient-R and noted that his great toes were short, bent and missing a joint (which patient-R and his parents confirmed had been present since birth). The geneticist astutely suspected FOP on the basis of the great toe malformation and the history of the swelling in the neck, and he ordered a genetic test. The result of the genetic test indicated that in fact patient-R had the classic mutation in ACVR1 that causes FOP and is present in everyone who has classic FOP.

The curious thing was that patient-R was nearly 21 years old by then and had no serious adverse effects of FOP other than the one flare-up and the great toe malformation. The diagnosis of FOP came as a shock to patient-R, who had otherwise been well and lived a normal life. Patient-R was referred to the Center for Research in FOP and Related Disorders at the Perelman School of Medicine of the University of Pennsylvania (Penn Medicine) for further evaluation.

On his arrival, patient-R was walking around the waiting room. There was substantial doubt that he had FOP, mainly because of the preserved mobility at the age of 21. Most patients with FOP are immobilized by the time they are 21 years of age. When patient-R was examined, it was abundantly clear that his great toes were short and missing a joint—a signature of FOP. Amazingly, patient-R had normal range of motion except for some stiffness in his neck resulting from joints at the back of the neck that had not formed properly, a congenital feature that is seen in nearly all individuals with FOP. The genetic diagnosis of classic FOP was questioned and re-confirmed. Patient-R was cautioned to avoid those things that might aggravate FOP and was advised to be in contact if he had any flare-ups or concerns. Then, he went on his way.

Patient-R was seen five years later in the FOP clinic at Penn Medicine and had remained well without any flare-up activity or loss of mobility in the interim. His chart contains a copy of an email sent to a colleague following that visit:

> "I saw a 26-year-old man last Thursday who has the classic FOP mutation and classic malformed great toes but essentially normal range of motion. He has a few tiny "nubbins" of heterotopic bone but almost nothing. He is one of the most interesting FOP patients I have ever seen. Clearly, the mutant gene was expressed during embryonic development because his toes and thumbs are lacking joints, but SOMETHING is protecting him post-natally without making him sick. If we could figure this out, we would have a substantial treatment. He is a gift staring us in the face."

Patient-R was seen in the FOP clinic at Penn Medicine several times thereafter and he remained well. By this time, he was in his late 20's. I introduced patient-R to my colleague, Dr. Robert Pignolo (then, at Penn; now, the Robert & Arlene Kogod Professor of Geriatric Medicine at the Mayo Clinic). Together, we had seen nearly 1,000 individuals with FOP in our careers, but no one like patient-R who was so unaffected with heterotopic bone at his age of nearly 30 years. We pondered the observation that patient-R had the usual congenital features of FOP (short great toes, fusions of cervical vertebrae from failure to form normal facet joints), but almost none of the post-natal features of heterotopic bone formation that we expect to see in someone who has the classic FOP mutation.

At the time, patient-R was very interested in an industry-sponsored natural history study that we were doing at Penn Medicine in individuals with FOP, and he voluntarily enrolled. As part of that study, we measured how much heterotopic bone he had formed in his life. We were shocked to find that patient-R had nearly 90% less heterotopic bone than other individuals of the same age who had the exact same FOP mutation.

We discussed this unique observation and concluded that the FOP gene must have been active in patient-R during embryogenesis when the skeleton and joints were forming but fell nearly silent after birth. We knew that the FOP mutation was necessary for the developmental features of classic FOP that patient-R had, as in all individuals who have

the classic FOP mutation, but suspected that, at least in this patient, the mutation alone may not be sufficient to induce the inflammation that leads to disabling postnatal HO.

We believed that something must be protecting patient-R from the ravages of heterotopic bone formation in FOP despite the fact that he had the classic FOP mutation that relegated nearly everyone to a wheelchair by his age. After much discussion, we formulated a hypothesis that patient-R lacked a sufficient inflammatory trigger for heterotopic bone formation, much like a bomb that lacked a fuse.

For many years, we had been collecting blood samples from FOP patients for genetic testing and had saved those blood samples. We compared the plasma (the liquid part of blood) of patient-R to other individuals who had classic FOP as well as to individuals who did not have FOP to see if patient-R had an inflammatory signature that was different from other individuals. Again, we were greatly surprised at what we found. Of all the inflammatory proteins that we analyzed, patient-R had one protein that was dramatically different from all other FOP patients and controls. That inflammatory protein was **Matrix Metalloproteinase-9 (MMP-9)**. We conducted additional laboratory studies and discovered that patient-R not only had **lower levels** of MMP-9 but also had **decreased activity** of MMP-9.

So, what is MMP-9? First, it is a protein, and a particular type of protein called an enzyme, that does many things. Think of it like a pair of scissors that chops up tissue debris after an injury so that the local environment is conducive for rebuilding. MMP-9 also activates repair molecules that are waiting outside of cells to be activated after an injury, and it recruits progenitor cells that orchestrate tissue regeneration. If it is defective, perhaps it doesn't do those things or doesn't do those things as well as it normally does. And perhaps it is necessary for MMP-9 to do those things to form heterotopic bone.

At that point however, we had no idea why patient-R made less MMP-9 or why the protein that he made was less active. In order to answer those questions, we analyzed all of patient-R's genes—not just the FOP gene. We found quite amazingly that he had a mutation in **both** copies of the gene that encodes the MMP-9 protein. He got one of the mutant MMP-9 genes from his mother and the other mutant MMP-9 gene from his father. Importantly, both parents were well.

One of the mutations that patient-R had in MMP-9 was thought to slightly alter the level of the MMP-9 protein, but the other mutation—which is very rare (about one in 1,000 in the general population)— was thought to produce an MMP-9 protein that was substantially less abundant and also substantially less active. We conducted detailed experiments to verify those predictions—and they were confirmed. So, that answered one question: Why did patient-R have low levels and low activity of MMP-9? Because the MMP-9 gene encoded a damaged MMP-9 protein. But we still did not know the answer to the more important question: Did patient-R's low level **and** low activity of MMP-9 have **anything** to do with protecting him from forming heterotopic bone?

In order to answer that question, we continued our journey in the laboratory. First, we obtained mice that were genetically deficient in MMP-9. In other words, the mice made no MMP-9 at all because both copies of the gene that encodes MMP-9 in those mice were inactivated. These mice were what we call "genetic knockouts" of MMP-9. Interestingly, these mice had some minor abnormalities of their skeletons at birth, which self-corrected after a few weeks and then were completely healthy. Then, we mated the MMP-9 knockout mice with the FOP mice that had the classic FOP mutation (the same exact FOP mutation as patient-R). After several rounds of selective mating, the offspring had the FOP mutation but no MMP-9. Then we performed the critical experiment. We tried to induce heterotopic ossification (HO) in these mice. To our absolute amazement, they did not form any heterotopic bone, but remarkably regenerated their muscles following an injury, while the FOP mice that had normal amounts of MMP-9 formed heterotopic bone following an injury. We were amazed.

We then asked the question, "What if, instead of no MMP-9, we had FOP mice with **half** the amount of MMP-9 (more like patient-R). Would they also be protected from forming heterotopic bone following an injury? So, we performed that exact experiment. And again, to our amazement, the FOP mice with half the amount of MMP-9 also

failed to form heterotopic bone. In other words, **we did not have to eliminate MMP-9 completely to prevent heterotopic ossification in the FOP mice; we only needed to decrease it by half**. We knew from the work of others that MMP-9 was needed to form a normal skeleton. But what the results of this experiment indicated was that a lot more MMP-9 was needed to form the second skeleton of FOP than the normal skeleton, and if the amount of MMP-9 was decreased by half, the threshold for forming that second skeleton was not achieved—at least in mice!

We were astonished by these results and asked ourselves, "Could this be true?" We also asked ourselves, "Is there another way to prove this?" We wondered whether there were any commonly available and inexpensive medications that could lower the MMP-9 levels and provide protection from HO in the absence of an MMP-9 mutation.

We discovered, to our great surprise, during a quick Google search that the tetracycline class of medications are inhibitors of MMP-9 independently of their antibiotic properties. Importantly, tetracyclines confer protection to a number of inflammatory conditions in which MMP-9 has a pathogenic role including periodontal disease, acne, aortic aneurisms, and muscular dystrophy. So, we treated FOP mice with minocycline (a commonly used derivative of tetracycline). And again, to our amazement, FOP mice that were treated with minocycline formed negligible heterotopic bone following an injury while FOP mice that were not treated with minocycline formed massive amounts of heterotopic bone.

Because pharmacologic activity of tetracyclines may not work exclusively through MMP-9 blockade and may have other off-target effects that are relevant to HO in FOP, we investigated whether a monoclonal antibody that specifically blocked MMP-9 might be effective in reducing HO. We obtained such an antibody from colleagues at a pharmaceutical company and showed, in fact, that it inhibited HO in FOP mice.

At this point, we had proof-of-concept that lowering MMP-9 levels and activity by four different methods inhibited HO following injury in FOP—genetically (in patient-R and in the knockout and knockdown mice), pharmacologically (with minocycline), or biologically (with a monoclonal antibody against MMP-9).

We then asked, "By what mechanisms does MMP-9 deficiency confer resilience in FOP? In order to answer that question, we conducted a series of experiments that showed that MMP-9 blockade protects against HO in FOP in at least several different ways. We know that the four cardinal requirements for FOP-like heterotopic bone formation are an inflammatory trigger, an inductive signal, a receptive progenitor cell, and a conducive microenvironment. Our studies, as well as an abundance of published scientific literature on MMP-9, strongly suggested that MMP-9 functions in all four domains in FOP.

The mutation in ACVR1 that causes FOP can be viewed as the architect of FOP. But the incredible and unexpected story of patient-R and the FOP mice opens an entirely new frontier in clinical and basic research in FOP and most importantly in the possible prevention of HO in FOP. This story strongly suggests that MMP-9 acts like a general contractor that assembles the critical components to build the second skeleton of FOP.

It is important to remember that many of the confirmatory studies in this journey were conducted in FOP mice, and that **mice are not people**. Nevertheless, we must also remember that these clues came directly from patient-R.

So, what does this story mean for individuals with FOP? In one word it means **hope**.

As a direct result of this work, there is now a clinical trial with a monoclonal antibody against MMP-9, and hopefully soon (if funds allow) a clinical trial with tetracyclines or other available and inexpensive medications that inhibit MMP-9. Gene therapy in the form of inhibitory RNA against MMP-9 is eventually possible, and such proof-of-concept studies in mice are underway by our colleagues. It is also possible that other available and affordable medications that block MMP-9 will emerge to treat HO in FOP.

MMP-9 inhibition will not likely replace inhibition of ACVR1 as a treatment for FOP but will likely supplement it. Importantly, MMP-9 inhibition provides a novel and unexpected target for therapy in FOP thanks to patient-R. MMP-9

inhibition of HO will likely play an important role in future therapies for FOP as well as in more common forms of HO such as in hip replacements, brain and spinal cord injuries, burns, and massive trauma such as battlefield wounds.

From a laboratory research perspective, it will be important to know exactly how MMP-9 deficiency inhibits HO and which stages of FOP lesion formation it affects. Much exciting work remains to be done.

From a clinical perspective, patient-R is now 36 years old and remains active and well. He has some mild stiffness in his neck and in one hip—not from heterotopic bone but from FOP-related arthritis in those joints. Given the relatively small number of individuals with FOP worldwide as well as the extreme rarity of the MMP-9 variant that patient-R has, it is unlikely that others with FOP will have the same protective variant. However, other resilient patients will likely emerge and additional factors conferring resilience will likely be discovered. Moreover, we hope that this story will stimulate others to investigate the role of MMP-9 not just in FOP but in other more common forms of HO.

Drs. Fred Kaplan, Vitali Lounev, and Bob Pignolo during a working session at Penn on the Patient-R/MMP-9 manuscript.

Finally, it is worth remembering that this story emerged from the recognition of something expected that did NOT happen and the question "Why?" Importantly, it illustrates how the systematic study of a single individual, patient-R, with one of the world's rarest and disabling conditions, unveiled unexpected clues to the formation of the second skeleton of FOP. That unexpected journey of discovery from a single patient in the clinics, to the laboratory, and back to the clinics will hopefully lead to novel treatment strategies that are gateways to a new and exciting frontier in the war against FOP.

This plain language summary is based on the original scientific manuscript:

Lounev V, Groppe JC, Brewer N, Wentworth KL, Smith V, Xu M, Schomburg L, Bhargava P, Al Mukaddam M, Hsiao EC, Shore EM, Pignolo RJ, Kaplan FS. Matrix Metalloproteinase-9 Deficiency Confers Resilience in Fibrodysplasia Ossificans Progressiva in a Man and Mice. Journal of Bone & Mineral Research 39:382-398, 2024

This work was supported primarily by the Ashley Martucci FOP Research Fund at the University of Pennsylvania and by the Radiant Hope Foundation. We thank the Center for Research in FOP and Related Disorders at the University of Pennsylvania; the Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine at the University of Pennsylvania (to FSK); the Cali-Weldon Professorship of FOP Research at the University of Pennsylvania (to EMS); the Ian Cali Distinguished Clinician-Scientist at the University of Pennsylvania (to MAM); the Robert and Arlene Kogod Professorship in Geriatric Medicine at the Mayo Clinic (to RJP); the Gordon Family; an anonymous donor from Caldwell, New Jersey USA; and an anonymous donor from Australia.

Importantly, we profoundly thank patient-R and his family for their magnificent devotion and commitment to participate in this work for the benefit of the FOP community worldwide.

Postscript: "Actionable Insights"

Marc Wein, MD and Yingzi Yang, PhD of Harvard University co-authored an editorial that accompanied the published article on patient-R in the ***Journal of Bone & Mineral Research***:

Wein MN, Yang Y. Actionable Disease Insights from Bedside-to-Bench Investigation in Fibrodysplasia Ossificans Progressiva. Journal of Bone & Mineral Research 39:375-376, 2024

Wein and Yang state:

> "The current study by Lounev and colleagues is particularly exciting as a remarkable example of bedside to bench research...The findings indicate that careful clinical observation of a single patient can uncover new mechanistic insights into FOP pathogenesis.
>
> MMP-9 now emerges as a candidate therapeutic target in FOP, and perhaps in other forms of HO...The description of the critical role for MMP-9 in FOP pathogenesis in this study represents a major advance in the field.
>
> Pharmacologic MMP-9 inhibition may be a useful strategy to prevent lesion growth in MMP-9 "wild type" FOP patients. Whether tetracycline-based antibiotics, which can block MMP-9 activity at multiple levels, might affect HO in FOP patients, thus emerges as a readily testable therapeutic hypothesis...Complementary development of more specific and potent MMP-9 inhibitors also represents an exciting possibility...
>
> Finally, this work beautifully illustrates the concept that genetic modifiers exert an important influence on the natural history of 'monogenic' skeletal diseases. Thus, this work underscores the critical importance of asking simple questions informed from our patients during 'bedside-to-bench" research to gain new insights in rare bone diseases."

PART 4 Therapeutic Targets and Clinical Trials in FOP

The ultimate goal of FOP research is the development of treatments that will prevent, halt, or even reverse the progression of the condition. The prevention and treatment of HO in FOP, as in any of the more common forms of HO, will ultimately be based on at least one of four approaches: disrupting the inductive signaling pathways, suppressing the inflammatory triggers (see previous sections), altering the relevant osteoprogenitor cells in the target tissues, and/or modifying the tissue environment so that it is less conducive to heterotopic bone formation.

The identification of the mutation that causes FOP, and all the discoveries that have flowed from it, provides robust pharmaceutical targets and rational points of intervention in critical signaling pathways.

Clinical trials are our new reality, and they are beginning to exert their effect on our imagination, and on our lives. Some trials may 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.

This is an extremely dynamic time in FOP clinical trials, and it promises to get even more dynamic in the near future as clinical trial eligibility opens up to children. There was a time when we wondered if there would be enough patients to fill clinical trials. There is a now a question whether there are enough clinical trials for patients who want to participate in them.

One drug has been approved regionally, and as many as six are being tested internationally. Many of the drugs in clinical trials have different targets and several different drugs being tested have the same target. Some ongoing trials are closed to enrollment; others are closed in various age ranges. Others yet are evolving and, depending on safety profiles, may open up to younger age groups. And, of course, there are those research breakthroughs, like the one earlier described in this report, that unveil new targets previously undreamed of.

Thirteen 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 nearly four decades ago.

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 the journey to a new frontier is traceable to that reality.

In May 2024, ***SCIENCE*** magazine, one of the world's leading science journals, published a news article specifically about FOP written by the journalist Mitch Leslie. In the article, "*Drug Development Blossoms for Rare, Fatal Bone Disease,*" Leslie writes:

> "Rare Diseases often get the cold shoulder from drug developers, and FOP, an infamous genetic condition that makes bone sprout where it shouldn't, is one of the rarest…Yet at least 13 companies are chasing therapies for FOP, and all this effort has started to pay off. Researchers suggest one reason drug developers have focused on FOP is the cruelty of the disease, which is triggered by a mutation in a gene crucial to bone growth… 'Not that long ago it wasn't even clear the disease was genetic,' says Eileen Shore, a geneticist and cell biologist at UPenn, which is the epicenter for studies of the disease. 'We couldn't get pharma (companies) interested,' she recalls. But when she, Kaplan, and their colleagues identified the faulty gene behind FOP in 2006, 'that changed everything,' Shore says."

Leslie quotes Marc Wein, an endocrinologist from Massachusetts General Hospital and Harvard Medical School, **"The surge in drug development is encouraging for patients with FOP and should also be heartening for patients with other rare illnesses who should think, if they can do it for FOP, they can do it for my disease."**

Indeed, it is being done for FOP. Recent scientific reports on two major FOP clinical trials—the phase 3 palovarotene trial and the phase 2 garetosmab clinical trial—are summarized below:

Palovarotene

In a publication in ***The Journal of Bone & Mineral Research***, palovarotene, an RARγ receptor agonist, was reported to reduce new heterotopic ossification (HO) in an open-label, phase 3 clinical trial. The open-label, phase 3 MOVE trial assessed efficacy and safety of palovarotene in patients with FOP. Findings were compared with FOP Natural History Study (NHS) participants untreated beyond standard of care. The primary endpoint was change in new HO volume by low-dose whole-body computed tomography (CT). Twelve-month interim analyses met futility criteria. However, 18-month post hoc analyses showed 99.4% probability of a reduction in new HO with palovarotene versus NHS participants. New HO volume was 60% lower in MOVE versus the NHS. However, palovarotene had no impact on flare-up occurrence or symptoms. All palovarotene-treated patients reported adverse events; 97.0% reported retinoid-associated adverse events; 29% reported serious adverse events including premature closure of the growth plates (36.8%) in patients who were younger than 14 years old. Results also showed decreased vertebral bone mineral density, content, and strength, and increased vertebral fracture risk in palovarotene-treated patients. Thus, palovarotene showed evidence for modest efficacy of reducing new HO in FOP, but no impact on flare-up frequency or symptoms and high risk of pre-mature growth plate closure in skeletally immature patients.

Palovarotene was approved for FOP by Health Canada on January 24, 2022; the US Food & Drug Administration (FDA) on August 16, 2023; and the Australian Therapeutic Drug Administration on November 30, 2023, for use in boys older than 10 years of age and girls older than 8 years of age when 90% of their height has been achieved, based on national averages. With the approval in Canada, the United Arab Emirates (UAE) also issued a provisional approval.

Garetosmab

In a publication in ***Nature Medicine***, intravenous garetosmab, an inhibitor of activin A, was reported to reduce heterotopic ossification and flare-ups in adults with FOP in a small multi-center, randomized, double-blind, placebo-controlled phase 2 trial.

Patients were randomized to garetosmab or placebo. In this portion of the trial, there was a trend for garetosmab to decrease HO versus placebo (24.6%), primarily driven by near complete prevention of new lesions. Flare-ups were significantly reduced. For placebo patients transitioning to garetosmab in the second portion of the trial (where everyone received garetosmab), no patients developed new HO lesions. Garetosmab was associated with more adverse events than placebo: mild recurrent nose bleeds, loss of eyebrows, and skin/soft tissue infections. However, five deaths

(5/44; 11.4%) occurred in the second portion of the trial or the open-label extension. The deaths were associated with baseline disease severity in some, preexisting comorbidities in others and occurred following 8-16 doses (median: 15) of garetosmab. Thus, although garetosmab reduced flare-ups and prevented new HO lesions in FOP patients, there was an unexpectedly high number of deaths for a small study. Although these were considered by the site investigators unlikely to be related to garetosmab, causality could not be ruled out.

In November 2022, the phase 3 OPTIMA trial opened to further test garetosmab and the number of new HO lesions developed by trial participants and to monitor the incidence and severity of treatment-emergent adverse events of special interest (AESIs).

PART 5 The FOP Center

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 36 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 and 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, Radiant Hope Foundation, the Ashley Martucci Research Fund, and by many grass-root fundraisers and private philanthropies.
- The Center and the FOP Collaborative Research Project have had 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 six continents on FOP and generations of medical students over the past 30 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 FOP Collaborative Research Project have issued 30 Annual Reports (including this one) and have published more than 250 seminal papers on FOP and 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 at home in expanding its clinical reach to Children's Hospital of Philadelphia and 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 six spheres of FOP activity:

- Clinical care and consultation worldwide
- Clinical research and infrastructure development
- Basic research (identification of therapeutic targets)
- Translational research (preclinical drug testing and biomarker discovery)
- Clinical trial development and proof-of-principle investigation in patients
- 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 in person and virtually 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 the FOP Clinical Guidelines for individuals with FOP
- Published guidelines on the care of patients in clinical trials for FOP

Clinical Research and Infrastructure Development

- Supported the design, execution, and analysis of major FOP clinical trials worldwide
- Edited a major revision—the third in six years—of "The Medical Management of FOP: Current Treatment Considerations," popularly known worldwide as The FOP Clinical Guidelines
- Showed the power of one patient to reveal a clinical picture that unveils critical molecular mechanisms of disease that identify novel treatment strategies. As we stated at the beginning of this Annual Report, basic discoveries sometimes begin in the clinic—often from a simple observation that is recognized as potentially important. The observation in patient-R led to a multiple year journey that is a focus of this report and an example of the vital inter-relationship between the FOP clinic and the FOP laboratory.
- 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 six 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 ICC Tissue Procurement Task Force
- Served on the ICC Joint Remobilization Task Force
- Fostered the development of a single unified international patient registry for FOP by the IFOPA (and owned by the FOP community)
- Championed the prospective deposit of data from sponsored clinical trials into the IFOPA's FOP Registry
- Advocated for the direct deposit and open access of annotated whole genome sequence data from a sponsored clinical trial into the IFOPA's FOP Registry medical portal
- Conducted genetic screening for FOP variants: What are they, who has them, and what do they mean for those who have them?
- 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
- Authored 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
- Hypothesized that a unique, resilient patient with FOP (patient-R) lacked a sufficient inflammatory trigger for HO
- Showed that patient-R had a reduction in both the amount and activity of a key inflammatory protein, matrix metalloproteinase-9 (MMP-9)
- Confirmed through a large-scale, unbiased genome-wide data analysis that patient-R harbored mutations in both copies (one copy from his mother and one copy from his father) of the MMP-9 gene
- Showed that inflammatory macrophages that were programmed with patient-R's MMP-9 mutations made less abundant and less active MMP-9
- Identified MMP-9 as a key inflammatory protein that was defective in patient-R
- Made a colony of FOP mice that were completely deficient in MMP-9 as well as a colony of FOP mice that have half the levels of MMP-9
- Conducted ground-breaking proof-of-concept experiments that showed that inhibition of MMP-9 by genetic, pharmacologic or biologic means prevented trauma-induced FOP and orchestrated regeneration of injured skeletal muscle in FOP mice
- Identified key molecular mechanisms by which MMP-9 affected the extracellular -matrix in early FOP lesions
- Identified the critical time course by which MMP-9 acts in FOP lesion formation

- Demonstrated that the lack of MMP-9 sequestered key osteogenic molecules like Activin A in the extracellular matrix and made them inaccessible for HO
- Showed the power of one patient to reveal critical molecular mechanisms of disease that unveil novel treatment strategies
- Identified MMP-9 as a critical inflammatory trigger of FOP lesions
- Led the initiation of a novel clinical trial to test the hypothesis that deficiency of MMP-9 can inhibit or prevent HO in patients with FOP
- Investigated the molecular mechanisms by which the innate immune system amplifies inductive BMP pathway signaling in FOP connective tissue progenitor cells
- 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
- Explored 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
- Documented 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
- Published a series of landmark papers that showed that ACVR1 is a key regulator of joint formation in embryonic development
- Published a landmark study that documents the effects of the classic FOP mutation on the normotopic skeletons of individuals who have FOP extends beyond malformation of the great toes and includes both morphological abnormalities and severe developmental arthropathy (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
- Determined the molecular mechanisms of assembly of the ACVR1 receptor complex on the cell membrane and its broad implication for dysregulated BMP pathway signaling in FOP
- Explored novel digitalized methods of quantifying changes in histologic sections from individuals with FOP as well as mouse models
- Explored age-related changes in FOP lesion formation in FOP mouse models that recapitulate age-related changes seen in individuals with FOP
- Investigated molecular mechanisms by which ultra-rare FOP variants trigger promiscuous BMP signaling and subsequent HO
- Served as medical and scientific advisors to the ongoing FOP gene therapy program

Translational Research (Preclinical Drug Testing & Biomarker Discovery Program)

- Conducted ground-breaking proof-of-concept experiments that showed that inhibition of MMP-9 by genetic, pharmacologic or biologic means prevented or decreased trauma-induced FOP and orchestrated regeneration of injured skeletal muscle in FOP mice
- Demonstrated that the FOP mutation modifies the physical properties of the tissue environment where HO will form by increasing its stiffness and dysregulating mechano-signaling pathways to redirected fate towards cartilage and bone. Blocking biomechanical signaling can prevent this aberrant cell differentiation, identifying a new therapeutic strategy for 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

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

- Determined that most fractures treated non-operatively in individuals with FOP heal with a paucity of flare-ups, heterotopic ossification, or loss of mobility
- Established treatment guidelines for the care of fractures in individuals with FOP
- Investigated 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 six clinical trials in current development by five pharmaceutical/biotech companies
- Cared for patients in five sponsored interventional clinical trials
- 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
- Contributed to the publication of an article on the amelioration of flare-ups in a clinical trial with a monoclonal antibody against Activin A
- 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
- 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 trials site at the Children's Hospital of Pennsylvania

The Children's Hospital of Philadelphia (CHOP) FOP Clinical Trials Team. From left: Annie Hayden, Dr. Srushti Desai, and Dr. Edna Mancilla

Education

- Presented lectures and seminars in-person and 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 FOP 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 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
- Continued to educate undergraduate students, medical students, residents, post-graduate fellows, physicians, scientists, clinical trial caretakers, patients, family members, pharmaceutical executives, and regulators about the tangible lessons of FOP as demonstrated by the legacies of Harry Eastlack and Carol Orzel 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
- Edited a special issue of the scientific journal Biomolecules on FOP
- Wrote, edited, and published the 3rd edition of The FOP Guidelines

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 treatment and cure of FOP.

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 five major research areas:

1. **Identifying and characterizing central signaling targets in the induction and amplification of FOP lesions**
2. **Identifying and characterizing inflammatory and microenvironmental targets that initiate and amplify FOP flare-ups**
3. **Identifying cell and tissue targets in FOP lesions**
4. **Developing in vitro and in vivo FOP models for drug "target testing"**
5. **Pre-clinical drug testing in FOP mouse models**

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

- Why does FOP progress in the absence of flare-ups?
- Why do some flare-ups resolve spontaneously?
- How does the lesional microenvironment influence the progression of FOP?
- What is the communication between inflammatory cells and skeletal progenitor cells in the first minutes and hours of a flare-up?
- 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 and will help identify and confirm novel targets for drug discovery and development and eventually decrease the misery of FOP.

PART 6 We the People

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

FOP Laboratory Team

Vitali Lounev

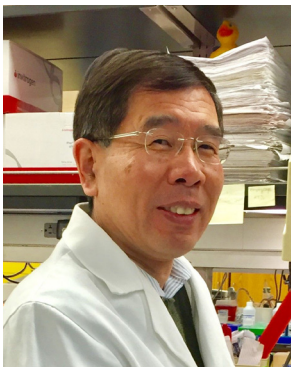
Vitali Lounev, PhD

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 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 DeSales University and his Master of Biotechnology degree from the University of Pennsylvania. Doug has been a part of the FOP lab since 2019 and has worked in the bone field for over 25 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 sings in his church choir and works on his fantasy novels.

Doug Roberts



Dr. Deyu Zhang

Deyu Zhang

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

Loreilys Mejias Rivera

Loreilys Mejías Rivera

Loreilys Mejías Rivera is originally from Cidra, Puerto Rico, and obtained her Bachelor's degree in Cellular and Molecular Biology with a minor in Human Rights from the University of Puerto Rico Rio Piedras Campus. During her undergraduate studies, she became interested in pursuing biomedical research and was selected to be a RISE scholar, performing bone research to investigate the use of biomaterials for bone tissue regeneration. After her summer research experience at Brown University solidified her interest in studying genetics and epigenetics, she applied and was accepted into the Cell and Molecular Biology Genetics and Epigenetics PhD program at the University of Pennsylvania. Loreilys joined the FOP lab in 2022 and began her thesis work in 2023. Her thesis focuses on uncovering how HO progenitor cells undergo aberrant chondro-osteogenic differentiation in FOP. Loreilys actively mentors other graduate, undergraduate, and high school students in the FOP lab, teaching them dry and wet lab techniques as they provide support for ongoing lab research projects. In her free time, she enjoys going out to dance salsa, climbing, and doing outdoor activities when it's not freezing outside.

We are fortunate to have many students who join us to learn about lab research and FOP, and who make important contributions to our research program. Jianing Xu started working with us in 2020 as a Penn Vet student and continues to work with us during her residency training. Nadine Großmann, a graduate student at the Freie University in Berlin, Germany, added to her thesis studies by spending a year in our lab (2023) to conduct an FOP project. Combined degree (MD-PhD) student Diana Rentoria worked with us for a semester lab research rotation (2023). Tzipora Schein and Jeffrey Xi are Penn undergrads who joined the lab in summer 2021 and continued working with us until graduating in 2024. Two Penn undergrads are in the lab now: Nava Schein began working with us in summer 2023 and Diego Ocaranza Nunez joined us in spring 2024. Philadelphia high school students Celine Adomakoh (2022), Moyo Ojediran (2023), Fatoumata Diarra (2024) joined the lab through the Penn Med Outreach, Education, and Research (OER) summer research internship program.

Lastly, but certainly not least, Meiqi Xu is enjoying her retirement but still works in the lab from time to time to conduct ACVR1 gene sequencing studies.

FOP Clinical Trials Team

Dr. Mona Al Mukaddam

Mona Al Mukaddam, MD

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 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 that 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 and has successfully completed an extensive FDA inspection with 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 (Project Manager) on 'immaculate record keeping' and for having executed the studies well with no concerns impacting data integrity. Please join me in congratulating Dr. Mona 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 care for our FOP patient's 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."

Staci Kallish, D.O.

Dr. Staci Kallish

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

Katherine Toder

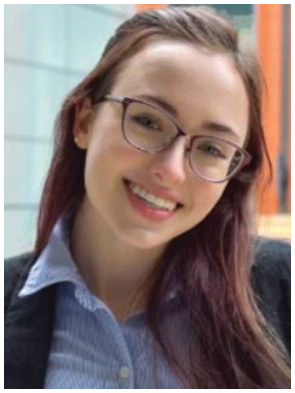
Katherine Toder

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 of in every detail. She is frequently asked for advice on places and restaurants in Philadelphia. Katherine notes, "I feel privileged to meet so many inspiring FOP patients and their caregivers, families, and advocates through my involvement in these groundbreaking projects."

Nathalie Richter

Nathalie Richter is a Clinical Research Coordinator at the Center for Research in FOP & Related Disorders. She joined the FOP clinical research team in 2023 after moving to Philadelphia earlier that year. She grew up in Michigan and graduated from the University of Michigan in 2021 with a Bachelor's degree in Biopsychology, Cognition, and Neuroscience. Nathalie had past experience in clinical research analyzing CT scans of patients who had been in automobile accidents, but this experience was cut short by the COVID-19 pandemic. She was therefore thrilled to return to the world of clinical research as a member of the FOP clinical research team. Nathalie intends to pursue further education in psychology and has enjoyed approaching FOP research through a psychology lens. She hopes to advocate for the psychological well-being of the FOP community and the larger rare disease community later in her career. She is extremely grateful for the opportunity to get to know so many wonderful people through this research.



Nathalie Richter

> "I think the resilience of our patients is truly inspiring to me. I never expected to emerge from conversations with our patients with a renewed motivation to accomplish things in my own life and work as hard as so many of them do. But every time they talk to me about the things they're achieving personally and professionally, I am encouraged to attack the things I want to get done with the same voraciousness that our patients have displayed in overcoming their mobility restrictions. Each patient is an inspiration in completely different ways, and I feel so honored to know each one them as well as I do!"

Raissat Abdallah

Raissat Abdallah

Raissat Abdallah is a Clinical Research Coordinator in the Center for Research in FOP & Related Disorders at the University of Pennsylvania Perelman School of Medicine. She was born in the Comoros Islands and is amongst the first generation of Comorian- Americans to be educated in the United States, obtaining Bachelor of Science in Health Professions and pursuing a Master of Business Administration in Health Systems Management. She joined the FOP clinical trials research team in early 2023 after working in Sanofi's Clinical Study Unit supporting immunology & inflammation, neurology, oncology, rare disease and rare blood studies. She notes, "It has been an honor to work with the FOP community for the last two years. Their optimism and resilience inspires me every single day."

Sarah Vanasse

Sarah Vanasse

Sarah Vanasse is a Clinical Research Coordinator in the Center for Research in FOP & Related Disorders at the University of Pennsylvania Perelman School of Medicine. Sarah graduated from Case Western Reserve University with a Bachelor of Science in Nursing and practiced as a registered nurse for several years. She joined the FOP team in 2023 to learn more about the world of research and rare diseases. Sarah has been excited to be a part of the research team and grateful for the opportunity to work with the FOP patients and their families.

Kamlesh (Kay) Rai

Kamlesh (Kay) Rai

Kay Rai is a clinical research assistant at the Center for Research in FOP & Related Disorders the University of Pennsylvania's Perelman School of Medicine's Department of Orthopaedic Surgery. Kay has worked with Dr. Kaplan for 44 years and is a key to starting this amazing 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 School of Medicine. 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."

Edna E. Mancilla, MD

Dr. Edna Mancilla

Dr. Mancilla is a pediatric endocrinologist at the Perelman School of Medicine and at CHOP and has been leading the clinical trials in FOP at CHOP since 2017. Dr. Mancilla has research and clinical expertise in metabolic bone health in children and has performed research on the growth plate. Dr. Mancilla received her medical degree from the University of Chile, 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***. Dr. Mancilla states, "It has been a privilege to lead the FOP clinical trials at CHOP and learn from the children and their families. It has been very exciting and humbling to walk the path from the development of the trials to drug approval with such courageous and inspiring children, their families, community, and medical teams."

Dr. Michael Levine

Michael A. Levine, MD

Michael A. Levine is 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 the 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 served 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.

Srushti Desai, MD

Dr. Srushti Desai

Srushti Desai is a Clinical Research Coordinator III at Children's Hospital of Philadelphia. She is a medical doctor from India and holds a master's degree in Medical Genetics from Tulane University. After completing her master's degree, she pursued a clinical research fellowship at Tulane where she worked on studies investigating the transmission of diseases like RSV, SARS-CoV-2, and influenza from mother to baby during pregnancy, leading to publications and scientific presentations. Her work spans principal investigator, NIH, and industry-funded pediatric clinical trials. She has been working on the clinical trials for FOP with our team for over two years. Having experience in both patient care and clinical research, Srushti deeply values how research drives advances in medicine. She finds it especially meaningful to connect with FOP patients and their families, drawing inspiration from their resilience. Outside of work, she enjoys painting, calligraphy, playing sports, and spending time with her cat and family.

Annie Hayden

Annie Hayden

Annie Hayden is a Clinical Research Nurse Coordinator at the Children's Hospital of Philadelphia. She studied nursing at the University of Pittsburgh, graduating with a Bachelor's of Science in Nursing in 2020. Annie began working at CHOP as an inpatient nurse and then transitioned to outpatient research by working with the Center for Human Phenomics Sciences' (CHPS) Nursing Core. As a part of CHPS, she worked with various study teams at CHOP administering investigational medications, completing bloodwork, and assisting with study procedures. Annie then joined the FOP clinical trial team in 2024. She finds this work to be very rewarding and has greatly enjoyed meeting the FOP families and learning about the wonderful FOP community. In her spare time Annie enjoys reading, traveling, and exploring the city of Philadelphia.

PART 7 Coordinating the Patient's Journey in FOP Clinical Trials: A Real World Guide

The FOP Adult Clinical Trials Team at Penn. From left: Kay Rai, Katherine Toder, Sarah Vanasse, Raissat Abdallah, Dr. Mona Al Mukaddam, Nathalie Richter, Dr. Staci Kallish, and Dr. Fred Kaplan.

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. This section has been so valuable in the past to patients and their families that it has been updated and revised by the author.]

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. I am hugely appreciative of the enormous commitment required to participate in a clinical trial and am pleased to provide some experiences and lessons learned to prepare others if they plan to participate in or design future studies.

Most patients have developed specialized and unique solutions to their physical and emotional 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 that being without these necessities of daily living may have until they are away from home, and some patients travel infrequently or may not have travelled with their current degree of mobility. Part of our 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. We learn from patients at every visit and welcome opportunities to improve.

ADA Accessibility and Hotel Rooms

Think about all the things that make a home comfortable and safe. Some of these things may be surfaces at specific heights, bars to help with mobility, grip or padding on some surfaces and clear and unimpeded paths to move around. During travel, one may have some portable items that bring the comfort and safety of home, but challenges may arise. One may assume that ADA accessible spaces will be appropriate and sufficient but often they are not, especially for an individual with FOP with distinct needs. 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. Many patients have needed to be lifted on and off a hotel bed by their caregiver. Patients have also found hotel beds uncomfortable without the adjustments and padding they have set up in their bedrooms at home.

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.

ADA rooms will also 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.

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. 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.

Aside from an individual room, we consider the layout of a building when reviewing hotel options. 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 the city to go out to eat have appreciated hotels that offer room service or have explored food delivery options. 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. Some clinical trials will cover the cost of accommodations, travel, and meals for research visits. Sites for clinical trials may be in expensive cities and visits may last multiple days at a time. It is important for a patient and the study team to review the process involved and discuss any upfront costs a patient may incur that are later reimbursed, including temporary holds on their personal bank cards, and what costs cannot be reimbursed.

Planes, Trains, Automobiles

Participating in a clinical trial may be the first time some patients have flown in an airplane, while others have passports full of stamps from travelling the world. 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 travelling 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. 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, SUVs and sedans with drivers. Not all wheelchair vans can accommodate all customized power chairs so gathering chair specifications, particularly the height of the chair, 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.

It is important to prepare for possible challenges while travelling. One patient was denied boarding an aircraft because their power chair was deemed too large for the cargo hold, despite earlier assurances from the airline during the booking that they could be accommodated. The patient needed to re-book their travel on an alternative airline. 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. Every patient should keep the contact information of the study team programmed into their phones and a copy of their itinerary accessible during their trip, in addition to any emergency travel numbers provided to them as part of their bookings.

Traveling with Wheelchairs and Other Assistive Devices

Consider the flow of an average day and all the tools used throughout to make activities possible. 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. In addition to supporting their movement from place to place, they may use a variety of tools for activities such as dressing, bathing, toileting, and eating.

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. Labeling the chair, keeping important information about the chair on a phone so it is available for airport staff, removing any protruding and detachable parts and taking them to the seat inside the plane, and photographing the chair before travel to file a claim if any damage occurs are some precautions. Drivers who provide ground transportation need to be able to assist with wheelchairs and respectfully accommodate the patient or caregivers' 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 that.

If a patient chooses not to travel with their own chair and 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 re-assemble 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.

A patient should speak with the study team about what a study visit day looks like at their site. Think about all the tools that are needed to do daily tasks while travelling in addition to any of the tasks required in the research study. There may be tests that are done in different buildings and some walking may be required to go from place to place in a hospital or clinic. A patient who uses a wheelchair sometimes at home could certainly bring a cane or other assistive device, but in our experience a visit can be tiring, and it is good to have a wheelchair as an option.

Adapting Study Procedures

There are specific tests and procedures a patient will need to agree to and be able to do to safely participate in a clinical trial. 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 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. Despite our best efforts with pre-screening questions over the phone or video calls, there are times when we have not been able to know for certain if a patient could fit into a scanner or would have the required test outcome to be eligible to participate in a clinical trial. We have brought patients to our site with a lot of hope to conduct the procedures completely and safely so they would have the option to move forward with participating if they were confirmed to be eligible.

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. All study staff will receive appropriate training on completing procedures, and we have the best outcomes when patients share with the study team what has been successful before, any concerns, and everyone takes the time to discuss and agree on a plan that is clear and safe.

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. A patient may prefer to travel with a caregiver who is familiar with how to lift and transfer them.

Some study procedures such as receiving different types of imaging can require laying on a hard surface for an extended period or transferring on and off of a surface with a curved or uneven ledge. The hospital should be able to offer some padding, but we have found that the foam wedges and thin hospital blankets & pillows are not sufficient for some situations. Some patients have travelled to their appointments with a rolled-up foam mattress topper or similar padding and pillows to ease transfers and long periods of time on an uncomfortable surface.

Patients may have restrictions on how they write and complete paper and electronic forms. 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 they could not complete or correct paper forms. Patients may also use specific adaptive devices for questionnaires and forms on electronic platforms.

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 travelling, 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 travelling 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. We have yet to encounter a perfect delivery system. A shipment may go through the hands of a few contractors with a company and processing or holding in an outside facility. A patient can expect a large delivery window and anticipate delays, similar to receiving a package from other commercial delivery services.

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 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 is it 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 re-arranged 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 home with whom they are not comfortable working.

Patients and Their Families Work Together with the Study Team

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, interest, and level 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. An important part of participation in a clinical trial is discussing a consent form that contains important information about the study, including potential risks, and what it means to participate in this kind of research. A patient should take the time to review the consent form with any caregivers and family members, so everyone understands the time commitment and responsibilities that a patient has as a research participant. The study team should continuously review these requirements and responsibilities to avoid misunderstandings whenever possible.

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 trials, 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 and self-administer medications at home or may require assistance with completing and maintaining daily paper or electronic diaries.

It has also been helpful to involve family members for their collective memories of medical history and adverse events. Caregivers can report on 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 or other caregivers 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 associated with the experimental medication. 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 body. 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. Similarly, the patient may have worked with an FOP study doctor for many years—sometimes since they were infants—to help manage their FOP symptoms before the patient became a participant in a clinical trial. The experience of participating in research will feel different and have more responsibilities than the experience of a regular clinical patient. The study team can help support a patient to have the safest experience in a clinical trial when the patient continuously communicates any changes to their health as soon as possible and is responsive when the study team reaches out with questions and important updates.

The Person Not the Disease

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. It is interesting to learn the unique journey a patient has with FOP and rewarding to hear about the life that each patient has outside of their experience with FOP.

Finally, FOP impacts patients in all demographics. 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 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. The study team will do their best to reduce the burden of participation, and we appreciate when patients bring challenges to our attention that may not have been considered when study protocols were created so we can find ways to increase access to clinical trials for more patients.

My team spends 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 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 emotional 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.

Finally, our job is to make participation in clinical trials as safe, accessible, convenient and possible for those who are eligible and wish to participate. I remain continuously appreciative of the opportunity to work with the FOP community and my study team in the middle of a rapidly evolving time for this incredible group of people.

PART 8 Editors' Choice—Highlights From the Literature

Genetic Medicine, 2022

The Natural History of FOP: A Prospective, Global 36-Month Study

Comprehensive natural history studies are essential in understanding rare conditions. ***The Natural History of FOP: A Prospective, Global 36-Month Study*** will forever be an icon of collaborative scholarship in the FOP community. In this comprehensive sponsored study, the investigators followed the progression of classic FOP in 114 individuals (male and female, from 4 years of age to 56 years of age) receiving standard-of-care treatment for up to 3 years and showed the debilitating effect and progressive nature of FOP cross-sectionally and longitudinally. The study's most important finding was the accelerated progression of FOP during childhood and early adulthood. The methods were comprehensive and sound—and the results definitive and profound. This important study will facilitate the incorporation of meaningful endpoints in the development of new therapeutics and provide meticulously documented insight into the episodic and progressive nature of the disease. Most importantly, through the magnanimous participation of individuals with FOP of all ages, it ensures a continuing legacy for future generations. The study is unlikely ever to be replicated or repeated.

Clinical Orthopaedics and Related Research, 2023

Most Fractures Treated Nonoperatively in Individuals With FOP Heal With a Paucity of Flare-ups, Heterotopic Ossification, and Loss of Mobility

An important case series drawn from the practices of physician–authors worldwide identified 36 patients with FOP from January 2001 through February 2021 (who were cared for or were referred from five continents and 14 countries) with 48 fractures that were treated nonoperatively.

The most common cause of fractures in individuals with FOP was falls, followed by motor vehicle collisions, direct trauma, and forceful manipulation. Early in life, alteration of gait mechanics secondary to heterotopic ossification (HO) appeared to be a major contributor to falls and fractures, while later in life a major cause was transfers to or from a bed or chair.

The authors found that most fractures treated nonoperatively in individuals with FOP healed promptly, with few flare-ups or HO and with preservation of mobility, a finding that underscored the importance of nonoperative treatment of most fractures in individuals with FOP.

What is responsible for the relative lack of flare-ups and HO after closed treatment of fractures in patients with FOP? Although the report was retrospective and not designed to answer the question of mechanisms, several possibilities can

be considered. There might have been insufficient soft tissue trauma to incite flare-ups and HO, even in the context of FOP. However, such a possibility seemed unlikely because even minor soft tissue trauma can incite flare-ups that leads to HO. It is also possible that some fractures occurred at anatomic sites that are less likely to form flare-ups or HO or at ages when flare-ups and HO were less likely to occur, although the reasons for that discrepancy remain obscure. A brief course of oral prednisone was administered to most patients, as recommended in the FOP Guidelines. Despite the brief course of prednisone, most fractures healed promptly, as one might expect in FOP. It is possible but unlikely that prednisone prevented HO in more than 90% of the fractures because corticosteroids inhibit HO in only 14% of individuals without fracture. Finally, the widespread occurrence of HO associated with fractures in neurologically injured patients along with the general absence of HO after fractures in neurologically intact individuals raises the intriguing possibility that fractures may inhibit HO through an intact neurologic mechanism, even in FOP. These hypotheses require detailed testing with closed fractures in neurologically intact and injured FOP mouse models.

Regardless of the reasons that flare-ups and HO rarely occur after nonoperative treatment of fractures in individuals with FOP, patients with FOP should avoid surgery unless absolutely necessary. Surgery is only rarely considered in those with FOP because of the high risks of complications from intubation, anesthetic management, soft tissue trauma from the operative procedure, triggering of flare-ups and HO and subsequent loss of mobility. However, there are rare situations in the care of patients with FOP where operative treatment of fractures may be the treatment of choice—such as unstable spinal fractures with pending neurologic catastrophe, or unstable appendicular fractures where pain control with nonoperative management fails. However, if surgical intervention is needed, the most minimally invasive approach should be used and an expert in FOP anesthesiology must be consulted.

Bioanalysis, 2022

Bioanalysis of INCB000928 in Human Saliva: Nonspecific Binding and Inhomogeneous Concentration

European Journal of Drug Metabolism and Pharmacokinetics, 2024

Pharmacokinetics of Zilurgisertib With and Without Food from Single and Multiple Ascending Dose Phase 1 Studies in Healthy Adults

Saliva is an attractive alternative to blood for drug monitoring in clinical trials as it is completely non-invasive. This is extremely beneficial for FOP patients as blood draws can be challenging due to soft tissue damage susceptibility that can cause heterotopic ossification, and for whom tourniquet time and blood draws must be minimized.

The authors report the development of a bioanalytical method for quantifying zilurgisertib (INCB000928; an oral, highly selective ACVR1 inhibitor) in human saliva. Testing of saliva showed that zilurgisertib was amenable to once-daily dosing that can be administered without regard to food. This revolutionary monitoring advance has been incorporated into the PROGRESS clinical trial that is testing zilurgisertib (INCB000928) for efficacy and safety in FOP.

Expert Opinion on Pharmacotherapy, 2025

Palovarotene in FOP: Review and Perspective

This article is a scholarly review and perspective by members of the International Clinical Council on FOP (ICC). The conclusion of the article states that the post hoc analyses of the phase 3 MOVE clinical trial for palovarotene in FOP showed that palovarotene may have modest benefits for the inhibition of new heterotopic ossification in FOP but no benefit for the prevention of flare-ups. In addition, a number of concerns have complicated the worldwide approval of palovarotene and led to concerns about its use in clinical practice. While the long-term risks of treatment with palovarotene remain unknown, the regional approval of palovarotene in the United States, Australia and Canada (but not in Europe) marks a milestone for the FOP community at the very beginning of a new era of clinical trials.

Biomolecules, 2024

[18F] NaF PET/CT as a Marker for FOP: From Molecular Mechanisms to Clinical Applications in Bone Disorders

Bone, 2024

Comparison of PET/CT Versus CT Only in the Assessment of New Heterotopic Ossification Bone Lesions in Patients With FOP

In a comprehensive review, Zwama and colleagues from the Netherlands discuss [18F]NaF as a marker for bone formation in FOP and specifically address the applicability of [18F]NaF PET/CT imaging as a monitoring modality in FOP clinical trials.

In contrast, Trotter and colleagues from a pharmaceutical company discuss a post hoc analysis comparing the performance of two imaging modalities for the detection and volumetric measurement of new HO lesions in the phase 2 LUMINA-1 clinical trial of garetosmab. The investigators report moderate agreement between PET/CT and CT-only in the detection and characterization of new HO lesions. The authors conclude that CT-only imaging therefore is a viable option for the assessment of therapies on new HO in patients with FOP and that PET scans were not necessary.

Pain, 2022

An ACVR1 Activating Mutation Causes Neuropathic Pain and Sensory Neuron Hyperexcitability in Humans

Although patients with FOP can harbor incidentally discovered pathological lesions in the peripheral and central nervous system, their etiology and clinical significance, if any, are unclear. Additionally, it remains unknown whether mutant ACVR1 dysfunction as seen in FOP has direct contribution to debilitating pain reported in FOP.

In that light, Yu and colleagues from the University of California, San Francisco identified a novel neuropathic pain syndrome in patients with FOP. Quantitative sensory testing revealed that patients with FOP have hypersensitivity to heat and mechanical pain. Although there was no effect of mutant ACVR1 on differentiation and maturation of pain-sensitive nerve cells derived from FOP induced pluripotent stem cells, electrophysiology analyses of FOP sensory nerve cells displayed hyperexcitability, a hallmark of neuropathic pain. Thus, activated ACVR1 signaling can modulate pain processing in humans and may represent a potential target for pain management with available medications in FOP.

Pediatric Rheumatology Online Journal, 2023

Successful Experience of Tofacitinib Treatment in Patients With FOP

Rheumatology, 2024

Long Term use of Interleukin-1 Inhibitors Reduce Flare Activity in Patients With FOP

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

Recently, there has been growing interest in a number of off-label medications that may have benefits for managing FOP. These include imatinib, tofacitinib, anakinra and canakinumab. Many of these medications modulate the immune system which is a trigger for FOP flare-ups as discussed earlier in this report. At the present time, no clinical trials have been reported and the published results are mostly anecdotal. In addition, these medications do not have results for blocking HO.

During this past year, investigators from Moscow hypothesized that a class of medications called JAK-kinase inhibitors may be able control active FOP flare-ups due to blocking multiple inflammatory signaling pathways. The authors reported their anecdotal observations on the safety and efficacy of tofacitinib in 13 patients with FOP who were refractory to standard-of-care treatment. The authors concluded that tofacitinib was well-tolerated and may decrease FOP flares. Clearly, further studies of the therapeutic potential of JAK-kinase inhibitors in FOP patients are needed. Of note, JAK-kinase inhibitors can lead to kidney and liver toxicity. There is great concern about tofacitinib leading to an increased risk of deep vein thromboses or pulmonary emboli, as well as certain types of cancer, heart-related events, and death. The Food and Drug Administration has issued a black box warning detailing these concerns.

At this time, the use of off-label medications is recommended only for patients with severe, refractory flare-ups that have not responded to standard-of-care therapies, and in which there are no additional contraindications or medication interactions. The ICC has published a statement on the use of off-label medications for the management of FOP. These can be found on the ICC website (iccfop.org) and in the recent FOP Guidelines.

Expert Review of Pharmacoeconomics & Outcomes Research, 2022

The Impact of FOP on Patients and Their Family Members: Results from an International Burden of Illness Survey

An international burden of illness survey was conducted assessing the physical, quality of life, and economic impacts of FOP on patients and family members.

Patient associations in 15 countries invited their members to participate; individuals with FOP and their family members were eligible. The survey was available online, in 11 languages. Participants responded to assessments measuring joint function, quality of life, healthcare service and living adaptation utilization, out-of-pocket costs, employment, and travel.

The sponsored survey received more than 450 responses from around the world. For patients, decreased joint function was associated with reduced quality of life, and greater reliance on living adaptations.

Nearly half of primary caregivers experienced a mild to moderate impact on their health or psychological wellbeing. Most primary caregivers and patients who were at least 18 years of age reported that FOP impacted their career decisions.

Data from the survey will improve understanding of the impact of FOP on patients and family members, which is vital for identifying unmet needs, optimizing care, and improving support for the FOP community worldwide.

Orphanet Journal of Rare Diseases, 2022

Current Challenges and Opportunities in the Care of Patients with FOP: An International, Multi-Stakeholder Perspective

Assiduous attention to the unmet needs of the FOP patient community is crucial in preventing potential iatrogenic harm and optimize care for individuals with FOP.

To gather international expert opinion and real-world experience on the key challenges for individuals with FOP and their families, highlight critical gaps in care, communication, and research, and provide recommendations for improvement, an international group of expert clinicians, patients and patient advocates, caregivers and representatives from the international FOP community participated in a virtual meeting to discuss the key unmet needs of individuals with FOP.

Individuals with FOP often face the frustration of long diagnostic journeys, the burden of self-advocacy and the navigation of novel care pathways. Globally, patients with FOP are also confronted with inequities in access to diagnosis and specialist care, and consequently, unequal access to registries, clinical trials, and essential support from patient associations.

Organizations such as the IFOPA, the ICC, and national FOP organizations work to provide information, facilitate access to expert clinical guidance, nurture patient empowerment, fund FOP research and/or foster meaningful collaborations with the research community.

The nonprofit Tin Soldiers Global FOP Patient Search Program aims to identify and provide a pathway to diagnosis and care for individuals with FOP, particularly in underserved communities. Such global initiatives and the increasingly widespread use of telemedicine offer opportunities to improve vital access to care and research.

This multi-stakeholder perspective highlights some of the unmet needs of individuals with FOP and their families. Although regional and international organizations play an important role in improving the quality of life of those they reach in the global FOP community, fundamental issues remain around raising awareness of FOP among healthcare professionals, identifying individuals with FOP, reducing time to diagnosis, and ensuring access to best practice in care, support, and clinical research.

Science Translational Medicine, 2024

An ALK2 Inhibitor, BLU-782, Prevents Heterotopic Ossification in a Mouse Model of FOP

In this report, Davis and colleagues describe the discovery of BLU-782 (also known as fidrisertib, IPN60130), a small-molecule ALK2 inhibitor developed for the treatment of FOP. A small-molecule library was screened to identify potent ALK2 binding compounds. BLU-782 preferentially bound to ALK2R206H with high affinity, inhibiting signaling from ALK2R206H and other rare FOP variants in cells in vitro without affecting signaling of closely related receptors.

In vivo efficacy of BLU-782 was demonstrated using an FOP mouse model, where oral dosing reduced edema and prevented the cartilage scaffold and HO. BLU-782 treatment preserved the normal muscle-healing response in FOP mice. Delayed dosing revealed a short two-day window after injury when BLU-782 treatment prevented HO in FOP mice. Together, these data suggest that BLU-782 may be a candidate for prevention of HO in FOP. Importantly, BLU-782 (fidrisertib, IPN60130) is presently in the phase 2 FALKON clinical trial for FOP.

Biomedicines, 2024

Cellular and Molecular Mechanisms of Heterotopic Ossification in FOP

In this comprehensive review, Loreilys Mejias Rivera and colleagues review aberrant *ACVR1*^{R206H} signaling in FOP and the cells that give rise to HO in FOP. FOP mouse models and lineage tracing analyses have been used to provide strong evidence for tissue-resident mesenchymal cells as cellular contributors to HO. The authors assess how the underlying mutation in FOP disrupts muscle-specific dynamics during rest and repair, with a focus on muscle-resident connective tissue cells known as fibro-adipogenic progenitors (FAPs). Current research points to FAPs as prominent HO progenitor cells, with *ACVR1*^{R206H} FAPs not only aberrantly differentiating into cartilage and bone lineages but creating a permissive environment for bone formation at the expense of muscle regeneration. The authors discuss the emerging role of *ACVR1*^{R206H} FAPs in muscle regeneration and the future therapeutic targeting of these cells to reduce HO formation in FOP.

EMBO Molecular Medicine, 2024

BMP-9 Mediates Fibroproliferation in FOP in Through TGF-β Signaling

In this study, Zhao and colleagues explore the mechanisms underlying flare-ups in FOP. They found that bone morphogenetic protein (BMP)-9 enhanced the proliferation of FOP derived connective tissue cells by abnormal activation of the transforming growth factor (TGF)-β signaling pathway. In FOP mice, elevated BMP-9 levels correlated with elevated TGF-β signaling while systemic BMP-9 neutralization and knockout mitigated flare-ups and HO. The investigators concluded that BMP-9 induces fibroproliferation by aberrantly stimulating TGF-β signaling and initiating flare-ups. Although this study provides novel insights into the development of FOP therapies, BMP-9 neutralization may be difficult to achieve in the clinic as BMP-9 has many other critical functions such as regulating the formation of blood vessels throughout the body.

Journal of Clinical Investigation, 2022

Anti-ACVR1 Antibodies Exacerbate Heterotopic Ossification in FOP by Activating FOP-Mutant ACVR1

Journal of Clinical Investigation, 2022

An Anti-ACVR1 Antibody Exacerbates Heterotopic Ossification by Fibroadipogenic Progenitors in FOP Mice

Nature Communications, 2022

A Blocking Monoclonal Antibody Reveals Dimerization of Intracellular Domains of ALK2 Associated with Genetic Disorders

In contemporaneous publications in the ***Journal of Clinical Investigation***, two groups, one headed by Aykul and colleagues and the other by Lees-Shepard and colleagues independently surmised that anti-ACVR1 antibodies that block activation of ACVR1 should also inhibit HO in FOP. Therefore, they generated anti-ACVR1 monoclonal antibodies that block ACVR1's activation. Surprisingly and paradoxically, these anti-ACVR1 antibodies profoundly stimulated injury-induced HO. This phenomenon was restricted to FOP-mutant ACVR1 and resulted from anti-ACVR1 antibody-mediated dimerization of mutant ACVR1. Thus, in both studies, the antibodies drove injury-induced HO in the absence of activin A, indicating that they had receptor agonist activity. As expected, wild-type ACVR1 was inhibited by anti-ACVR1 antibodies. These results raise serious safety and efficacy concerns for the use of bivalent anti-ACVR1 antibodies to treat patients with FOP.

In a completely independent study published in ***Nature Communications***, and in contrast to the two groups mentioned above, Katagiri and colleagues identified a blocking antibody that inhibited ALK2 signaling *in vitro* and *in vivo*. The findings presented in their study suggest that their antibody induces a unique dimer of the ALK2 extracellular domain in a back-to-back orientation on the cell membrane that is different from the antibodies to ALK2 described above. Katagiri and colleagues suggest that a human derivative of their antibody might be useful as a therapeutic drug for blocking HO in FOP. Such an antibody has entered a phase I trial with healthy volunteers in Japan.

Nature Communications, 2018

Activin-Dependent Signaling in Fibroadipogenic Progenitors Causes FOP

Journal of Bone and Mineral Research, 2022

Overexpression of Wild-Type ACVR1 in FOP Mice Rescues Perinatal Lethality and Inhibits Heterotopic Ossification

Nature Communications, 2022

Suppression of Heterotopic Ossification in FOP Using AAV Gene Delivery

Biomolecules, 2023

AAV-Mediated Targeting of the Activin A-ACVR1^{R206H} Signaling in FOP

Journal of Bone and Mineral Research, 2024

Matrix Metalloproteinase-9 Deficiency Confers Resilience in FOP in a Man and Mice

Human Gene Therapy, 2022

Gene Therapy for FOP: Feasibility and Obstacles

The discovery of the FOP gene (ACVR1) in 2006 unveiled the foundation for gene therapy as a plausible therapeutic strategy for FOP.

A paper published in 2018 in ***Nature Communications*** by Lees-Shepard and colleagues showed conclusively that the FOP mutation transformed ACVR1 from a brake into an accelerator. People with FOP have one normal copy

of ACVR1 and one damaged copy (the same with mice that have FOP). If a muscle in an FOP mouse is injured, the mouse will form heterotopic bone just as one would expect in FOP. But, if the normal copy of ACVR1 gene is removed so that the mouse has only a damaged copy of the gene, the mouse will form an extraordinary amount of heterotopic bone. Thus, the normal copy of ACVR1 acts like a brake on extra bone formation.

In an article published in the ***Journal of Bone and Mineral Research***, Yamamoto and colleagues suggest that the balance of normal and mutant ACVR1 dictates disease severity in FOP. They tested this model by producing FOP mice that overexpress the normal copy of ACVR1. Injury-induced HO was completely blocked in FOP mice when multiple copies of the normal receptor were expressed in the FOP muscle.

Using this approach in two proof-of-concept gene therapy studies published in ***Nature Communications*** and ***Biomolecules***, Yang and colleagues used recombinant adeno-associated virus-9 (AAV9) to deliver therapeutic genes to FOP mice. By suppressing the mutant ACVR1 gene by using normal copies of ACVR1 to dilute the abnormal copy, Yang and colleagues showed that gene therapy decreased trauma induced as well as spontaneous HO in the FOP mice. The findings of Yang and colleagues provided in vivo evidence that AAV-based gene therapy by diluting mutant ACVR1 with multiple copies of normal ACVR1 is a promising option for the prevention of HO in FOP. However, the authors are aware that as theoretically appealing as gene therapy may be for FOP, there are several important limitations that need to be considered before gene therapy is a viable option in patients who have FOP:

1. Mouse models of FOP may not recapitulate the full spectrum of FOP phenotypes seen in patients with FOP.
2. While AAV treatment appears effective in preventing both spontaneous and traumatic HO in FOP mice, the potential for systemic toxicities and effects on non-bone cells remains a vital consideration.
3. Since immunological triggers are known to pose a high risk for HO induction in FOP patients, any consideration of AAV gene therapy must be scrupulously approached.
4. Long-term durability and safety of therapeutic gene expression are of paramount importance in considering gene therapy or gene editing for potential use in FOP patients where lifelong HO suppression will be necessary.
5. Finally, future investigation for AAV biodistribution, toxicity, and dose-ranging in large animals is required before any consideration can be given to applying AAV gene therapy to individuals who have FOP.

Lounev and colleagues propose an intriguing alternative to gene therapy in their article on MMP-9 inhibition in the ***Journal of Bone and Mineral Research*** (discussed earlier in this Annual Report). Findings that bone marrow-derived MMP-9 deficient cells migrate to repair sites after murine soft tissue injury and are associated with decreased fibroproliferation suggests that targeted ex vivo gene knockdown of MMP-9 in autologous hematopoietic stem cells (cells that produce the body's inflammatory cells) by ex vivo gene editing methods rather than by in vivo gene therapy may be a tantalizing therapeutic possibility to explore in FOP pre-clinical studies. Such studies are ongoing.

Biomolecules, 2024

Molecular Developmental Biology of Fibrodysplasia Ossificans Progressiva: Measuring the Giant by Its Toe

In this comprehensive review, Towler and colleagues detail what is known about the molecular mechanisms of developmental features in FOP and the early role of ACVR1 in skeletal patterning and growth, as well as highlight how understanding of these processes may serve to advance patient care, assessments of patient outcomes.

FOP is recognizable by effects of the causative mutation on skeletal development even before HO manifests, specifically in the malformation of the great toes. This signature skeletal feature is the most highly recognized sign of FOP but is only one among several skeletal abnormalities associated with FOP. Individuals with FOP may present clinically with joint malformation and early joint fusion independently of HO, particularly in the neck and chest wall, as

well as characteristic facial features and a litany of less common, non-skeletal symptoms, all stemming from missense mutations in the *ACVR1* gene.

In the same way that studying the genetic cause of HO has advanced our understanding of HO initiation and progression, insight into the roles of ACVR1 signaling during tissue development, particularly in the joints of the musculoskeletal system, may be critically important in the assessment of functional outcomes throughout life. This knowledge will dramatically affect clinical trial design and evaluation.

Trends in Molecular Medicine, 2024

FOP Emerges from Obscurity

"How could the drops of water know themselves to be a river? Yet the river flows on."

-Antoine de Saint-Exupery, *The Wisdom of the Sands*

In this article, Kaplan, Shore, and Pignolo illustrate how pathogenic variants in ACVR1 emerge as the cause of FOP clinical features. Emergent properties are those properties of a complex system that are different from the individual components that comprise the system. A simple example is a waterfall that has additional properties that a single water molecule does not have. A complex example is consciousness that emerges from networks of nerve cells that has properties that individual nerve cells do not have. In other words, the whole is more than the sum of its parts.

In biology, the organization of molecules into complex signaling networks gives rise to emergent properties that are critical for understanding a disease like FOP. The pathogenic variants in ACVR1 that cause FOP dramatically alter the normal physiologic functions of the ACVR1 protein, and thus dysregulate the BMP signaling pathway and interacting signaling pathways in cells, tissues, organs and organ systems in development and post-natal life. The emergent properties that arise affect a wide spectrum of systems including inflammation, innate immunity, hypoxia sensing, wound healing, aging, temperature and mechanical thresholds, pain sensitivity, skeletal growth, diarthrodial joint patterning, joint function and fate, and HO to name a few. The understanding of such emergent properties can advance the understanding of phenotypes (clinical features) and provide important clues to possible prevention of disease as well as insight into therapeutic intervention.

PART 9 The International Clinical Council on FOP

Dr. Kaplan talks about the ICC at an IFOPA Drug Development Forum.

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, Mexico, the Netherlands, Republic of Korea, South Africa, the United Kingdom, and the United States) and six continents (North America, South America, Europe, Africa, Asia, and Australia). The ICC was established to coordinate and consolidate a global voice for the best practices for clinical care and clinical research for people who suffer from FOP. The Council was officially established, and its Constitution unanimously ratified on June 21, 2017.

The ICC independently establishes its rules, committees, and criteria for membership and meets at least twice annually, either in person and/or by teleconference. The ICC looks forward to a very proactive agenda. Formal announcements, updates, and activities are 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

The members of the ICC are:

Mona Al Mukaddam, MD
Philadelphia, PA, USA

Genevieve Baujat, MD
Paris, France

Alberto Hidalgo-Bravo, MD, PhD
Mexico City, Mexico

Matthew Brown, MBBS, MD, FRACP, FAHMS, FAA*
London, England (formerly, Brisbane, Australia)

Tae-Joon Cho, MD
Seoul, Republic of Korea

Carmen L. De Cunto, MD
Buenos Aires, Argentina

Patricia L. R. Delai, MD
São Paulo, Brazil

Robert Diecidue, MD
Philadelphia, PA

Maja Di Rocco, MD*
Genoa, Italy

E. Marelise W. Eekhoff, MD, PhD
Amsterdam, The Netherlands

Clive Friedman, DDS
London, Ontario, Canada

Zvi Grunwald, MD
Philadelphia, PA, USA

Continued on page 46

**Emeritus*

Nobuhiko Haga, MD
Tokyo, Japan

Edward Hsiao, MD, PhD
San Francisco, CA, USA

Frederick S. Kaplan, MD
Philadelphia, PA, USA

Richard Keen, MD, PhD
London, United Kingdom

Vrisha Madhuri, MD
Vellore, India

Rolf Morhart, MD
Garmisch-Partenkirchen, Germany

J. Coen Netelenbos, MD, PhD
Amsterdam, The Netherlands

Robert J. Pignolo, MD, PhD
Rochester, MN, USA

Christiaan Scott, MBChB
Cape Town, South Africa

Michael Zasloff, MD, PhD
Washington, DC, USA

Keqin Zhang, MD, PhD
Shanghai, China

** Emeritus*

From 2022–2024, the ICC accomplished the following:

- Published a major revision of the FOP Treatment Guidelines
- Conducted, in partnership with the IFOPA, a major international webinar on the use of the FOP Treatment Guidelines
- Published timely guidelines on COVID-19 and COVID-19 vaccinations
- Completed a major research study on the treatment of fractures in FOP
- Published guidelines on the management of fractures in FOP
- Published a major review and editorial on gene therapy in FOP
- Guided patient safety and participation in clinical trials
- Revised the ICC website (iccfop.org)
- Presented at major international and family meetings
- Convened the Global Health and Education Task Force
- Convened the Biobank Task Force
- Convened the Surgical Resection of Heterotopic Ossification Task Force
- Created emeritus status and consulting status for ICC Members rotating off the Council
- Created an associate track membership for the ICC
- Recruited a new ICC member from Mexico
- Expanded pharmaceutical/biotech relationships
- Continued working relationships with the IFOPA, the International Presidents' Council and Tin Soldiers
- Continued member participation in the Tin Soldiers Continuing Medical Education (CME) Global Masters Series and other educational activities

In July, 2024 the ICC published a major revision of the widely-used and acclaimed FOP Treatment Guidelines. Almost every section of the FOP Treatment Guidelines has been updated. The major changes or entirely new sections include:

- The Executive Summary of Key Practice Points
- The Developmental Biology of the Great Toe Malformation in FOP
- Off-Label Use of Potent Medications for Managing Inflammation in FOP
- Clinical Trial Results
- Immunizations
- COVID
- Developmental Arthropathy & Degenerative Joint Disease in FOP
- Ingrown Toenails in FOP
- Fractures in FOP
- Nutrition, Calcium & Vitamin D Guidelines in FOP
- Preventive Oral Health Issues in FOP
- Extraction of Wisdom Teeth
- Swallowing and FOP
- Women's Health in FOP
- Gastrointestinal Issues in FOP
- Pregnancy Issues in FOP
- Impact of FOP on Patients and Families
- Unmet Needs in FOP
- Classes of Medications
- Emergency Guidelines
- Disclosures
- Author's Contact Information
- Targets & Potential Treatments in FOP

The following letter accompanied the release of ***The FOP Treatment Guidelines***:

> Dear Members of the FOP Community,
>
> On behalf of the International Clinical Council on FOP (ICC) and its 21 members, two emeritus members, and six consultants, we are pleased to introduce the 2024 edition of
>
> **THE MEDICAL MANAGEMENT OF FOP: CURRENT TREATMENT CONSIDERATIONS**
> (Commonly known as **The FOP Treatment Guidelines**)
>
> The ICC has worked assiduously on this document which represents a monumental effort on the part of many. This report contains many new sections that we hope you will find useful, as well as completely updated sections that you found useful in the past. You will notice the **Executive Summary of Key Practice Points** (Section II). It is conservative, informative, and balanced–supported by the detailed exposition of the larger report.

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

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

With an approved medication in the US, Canada, Australia and ongoing clinical trials throughout the world and additional ones on the horizon, we anticipate that this document will be updated frequently.

We sincerely hope that this 3rd edition of **The FOP Treatment Guidelines** will be useful and relevant to FOP patients, families, physicians, dentists, medical personnel and caregivers worldwide.

Sincerely,

Frederick S. Kaplan, MD; University of Pennsylvania, Philadelphia, PA
Robert J. Pignolo, MD, PhD; Mayo Clinic, Rochester, MN
Corresponding Editors

PART 10 Awards & Honors

Dr. Eileen Shore, PhD, is the Recipient of the 2024 Lawrence G. Raisz Award of the American Society for Bone & Mineral Research (ASBMR)

The *Lawrence G. Raisz Award* recognizes an ASBMR member for outstanding achievements in preclinical and translational research (cellular or in animals).

Lawrence G. Raisz, MD, was a preeminent leader, researcher, mentor, teacher, and clinician in the field of bone and mineral metabolism for 50 years. Dr. Raisz was a founding member of ASBMR, its second President and the first Editor-in-Chief of the ***Journal of Bone and Mineral Research***. As a researcher, teacher, and clinician, Dr. Raisz epitomized the ideals of the physician-scientist.

On the announcement of the award, the IFOPA posted this congratulatory message:

> **UPenn's Dr. Eileen Shore Receives Prestigious Award from ASBMR**
>
> Congratulations to Eileen Shore, PhD for receiving the 2024 Lawrence G. Raisz Award from the American Society of Bone & Mineral Research (ASBMR).
>
> Dr. Shore is the Cali/Weldon Professor at the Perelman School of Medicine at the University of Pennsylvania in the Department of Orthopaedic Surgery and the Center for Research in FOP & Related Disorders and a member of Graduate Groups in Cell and Molecular Biology and in Bioengineering.
>
> She received her PhD in Cell and Molecular Biology from the University of Pennsylvania and postdoctoral training at the Fox Chase Cancer Center in Philadelphia. Throughout her career, her work has focused on explaining the causes and mechanisms of rare genetic disorders of heterotopic ossification in order to identify therapeutic strategies for these conditions.

Dr. Shore wins the esteemed Lawrence G. Raisz Award of the ASBMR in Toronto, Canada.

Upon receiving this distinguished award, Dr. Shore remarked,

> "It is a special honor to receive this award named for Larry Raisz–a person I admired greatly and knew for much too short a time. My research has been, and continues to be, an enriching part of my life–not only the joy of discovery, but also personal enrichment through knowing patients and their families, and through colleagues, friendships, and experiences gained through ASBMR.
>
> Among so many colleagues to thank, special thanks to Suzanne Jan de Beur, Mike Econs, and Maurizio Pacifici for their nomination and longtime support, and appreciation to Fred Kaplan and Mike Zasloff for introducing me to the rare bone field. I am especially thankful for all of the students, post-docs, and others who have worked together with me over many years. The advances I am recognized for through this award could only have been achieved together with you."

Meiqi Xu Is the Recipient of the Lifetime Achievement Award of the Division of Molecular Orthopaedic Medicine at the University of Pennsylvania

Meiqi Xu with Drs. Kaplan and Shore at Meiqi's retirement luncheon at The White Dog Café in Philadelphia.

The *Lifetime Achievement Award of the Division of Molecular Orthopaedic Medicine* at the University of Pennsylvania was awarded to Meiqi Xu in recognition of her exemplary contributions to science and medicine and her distinguished service to the FOP and progressive osseous heteroplasia (POH) communities throughout her professional career. Meiqi is the first and only recipient of this distinguished award.

On presenting this award at her retirement, Dr. Shore and Kaplan noted:

> "Meiqi, Thank you so much for working for us for 30 years! We could not have achieved the success in our work without so many important contributions from you–highlighted by your work identifying the mutation causing FOP and by all of the students and postdocs who have had success because of your work with them. I think I'd hoped that there would never be a time when you would leave the lab, although I knew that it was bound to happen eventually, but you'll always be a member of our lab family and so will never truly leave us. (Shore)
>
> Meiqi, Eileen said it so beautifully. I think you know how much you mean to us, to so many generations of researchers who you have guided, and to the entire FOP community–patients and families worldwide. You have been a vital part of FOP history and an indelible part of our hearts and souls. We love you dearly. (Kaplan)"

The IFOPA posted this remarkable tribute on Meiqi's retirement:

> Congratulations to researcher Meiqi Xu, who is credited with discovering the FOP gene, on a brilliant career!
>
> After graduating from university and working her first job at the Institute of Materia Medica, Chinese Academy of Sciences, research specialist Meiqi Xu moved to the United States.
>
> "I was eager to find answers to save patients' lives," she explained. "I dreamt of making important contributions to medical research and began my journey with FOP in early 1995."

Meiqi became the first full-time researcher to join Drs. Eileen Shore and Fred Kaplan at the FOP Laboratory at the University of Pennsylvania. She worked to determine the region of the genome that carried the FOP gene, and it was her responsibility to examine a series of candidate genes for DNA sequencing.

"She was the perfect partner for the work," said Dr. Shore. "Smart, thorough, dedicated. I knew if there was a gene mutation to be found, Meiqi would find it!"

Dr. Shore was proven right. In August 2005, Meiqi identified the FOP gene mutation. "After the discovery, I was proud and overjoyed," recalled Meiqi. "At the same time, we realized that we had to shift our priorities to researching effective drugs and treatments." In addition to working to uncover effective therapies, Meiqi also identified FOP variant mutations and conducted DNA sequencing analyses to confirm a clinical diagnosis of FOP in hundreds of people.

It was hard work, explained Dr. Shore. But Meiqi had all the motivation she needed to keep pushing for answers.

"Meeting people with FOP, many of whom were children, became my biggest source of inspiration to find the cause of and cure for FOP," she said."

Meiqi devoted 30 years to doing just that, before retiring in October 2022. After decades of research, testing and progress, she is optimistic about the future for those with FOP.

"Research is not easy, but I believe our efforts will lead to a cure," she said. "Together we have overcome many difficulties and cheered for the great achievements. I look forward to seeing the FOP lab make meaningful strides in the years to come."

Dr. Shore credits Meiqi with much of the lab's past success and potential.

"Meiqi has been devoted to doing as much as she possibly could to support FOP families and work toward an effective treatment and cure," Shore said. "And she has been a teacher and mentor to dozens of students in the FOP lab, sharing her scientific knowledge and providing support and encouragement. "Her work provides a strong foundation for much of the ongoing work in our lab, including pre-clinical drug testing."

Although Meiqi was reluctant to leave the lab after so many years, she is looking forward to retirement with her husband. "Now, we have time for more gardening and traveling, which we both love to do. We hope to build our growing backyard garden and to explore the world," she said. Amid the hobbies and adventures, progress toward treatments and cure—and the people it affects—will remain top of mind for Meiqi.

"Even though I am retired, I will always stay connected with the FOP lab and community to help in any way I can!" she insists. "The IFOPA is a big family that will always have a special place in my heart, no matter where I am."

The IFOPA is grateful to Meiqi for her many contributions to FOP research and her dedication to people living with FOP around the world. We wish you all the best in your much-deserved retirement!

Recognition of Dedicated Service

On his retirement from the FOP Laboratory, Bob Caron was recognized with gratitude for three decades of dedicated service to the FOP and POH communities.

Bob Caron at his retirement—with gratitude for three decades of dedicated service to the FOP and POH communities.

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 worked in the FOP laboratory for 30 years—working on histopathology, informatics and communications, and recently, cell culture. He was proud to contribute to discoveries that improve patients' lives.

The Edward Rose Faculty Teaching Award

Dr. Mona Al Mukaddam was awarded the prestigious *Edward Rose Faculty Teaching Award* of the Hospital of the University of Pennsylvania for the remarkable second time.

Radiant Hope Foundation Distinguished Clinician-Scientist Award

Dr. Mona Al Mukaddam was awarded the *Radiant Hope Foundation Distinguished Clinician-Scientist Award.*

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

Top Docs in Philadelphia Magazine

Dr. Mona Al Mukaddam was once again selected by her peers as one of leading Endocrinologists by ***Philadelphia Magazine***.

Master of Regulatory Affairs

Katherine Toder earned a Master of Regulatory Affairs degree from the University of Pennsylvania in May, 2024. Katherine accomplished this magnificent achievement while simultaneously fulfilling her demanding role as Clinical Care Coordinator for all FOP clinical trials at Penn.

This demanding degree program in regulatory affairs offered by the Perelman School of Medicine's Institute for Translational Medicine and Therapeutics is designed to produce highly trained and sophisticated practice professionals adept in the skills necessary to maximize compliance and minimize risk in the development of FDA regulated products.

The Jeannie Peeper President's Lifetime Achievement Award of the IFOPA

On the announcement of the award, the IFOPA posted this article:

> **The 2022 Jeannie Peeper President's Lifetime Achievement Award**
>
> The IFOPA is honored to present Dr. Fred Kaplan with this year's Jeannie Peeper Lifetime Achievement award. For many, it's difficult to imagine a time when Dr. Fred Kaplan wasn't the expert on FOP. But of course, he had to start somewhere. He learned about FOP as a medical student in the 1970's. But it wasn't until 1988 that Dr. Kaplan met the patient who would change his life.
>
> "I was introduced to a two-year-old child with FOP. That singular event altered the course of my career," he recalled. "I could see in real-time, not just what FOP had done, but what it was doing to a little child. From that day forward, I was committed to asking questions and finding answers."
>
> Dr. Kaplan was determined, not only to understand the science of FOP, but also the human experience behind it. For more than three decades, he has built lasting connections within the FOP community to better people's lives in countless ways.
>
> "The first FOP event I attended was an informal family gathering in Florida in 1991. That's when

I met Jeannie!" he said. "I interacted with the families. We shared stories and bonded. It was truly an amazing experience that had a profound effect on me." Ever since, Dr. Kaplan has created countless memories with patients and families from around the world. "The stories weave an incredible tapestry of my personal journey and our shared journey as a community," he said. That decades-long journey has transformed the FOP research landscape and quality of life for those touched by the condition.

'An international powerhouse'

With help from others, including his mentor Dr. Michael Zasloff, Dr. Kaplan and his colleague Dr. Eileen Shore have realized remarkable progress on a global scale.

"During the past 34 years, we have moved from the wastelands of a little understood rare disease to the watershed of clinical trials," said Dr. Kaplan. "We have identified the genetic cause of FOP and have used that knowledge to spearhead worldwide research to develop therapies that will transform the lives of individuals with FOP."

Dr. Kaplan is encouraged by these "dazzling" discoveries, as he describes them. He explained that they have expanded the frontiers of drug discovery and development and inspired research into small molecules, antibodies and gene therapy. "And while all this was happening, the research and tiny FOP patient communities grew into an international powerhouse fueled by a common goal," he explained.

'The engine that drives all we do'

Shortly after his first informal gathering all those years ago, Dr. Kaplan and Dr. Zasloff organized the first International FOP Scientific and Clinical Symposium in Philadelphia where attendees "declared war on FOP."

Since then, Dr. Kaplan explained, there have been many symposiums, forums, fundraisers and family gathering, each helping to unite the community, ignite change and continue the war on FOP. "It feels like a family—all marching in the same direction—all powerful and inspiring," he said.

Although researchers and clinicians have shepherded promising discoveries, Dr. Kaplan credits the special patient community with the unprecedented developments realized in a relatively short amount of time. "Patients and families are the engine that drives all that we do and all that we want to accomplish," he said. "FOP has gone global and has a very real presence on the world stage, but it is still a village in the best sense—I never want that to be lost."

'The wheels have been set in motion, and it will happen'

Dr. Kaplan's scientific contributions to unlocking FOP cannot be overstated. Nor can the personal impact he's had on so many. His tireless work has fueled life-changing progress and his generosity of time, comforted and uplifted families.

For these contributions, the IFOPA is honored to present Dr. Kaplan with this year's Jeannie Peeper Lifetime Achievement award. Upon learning about it, Dr. Kaplan described the honor as an "unfathomable tribute from an extraordinary individual." "Ever since I met Jeannie in 1991, she had the quiet and powerful voice that has motivated every step of my lifelong journey with FOP," he said. "She had the incredible vision to establish the IFOPA to end isolation and to realize that a problem as rare and complex as FOP had to be approached through research."

Research, Dr. Kaplan explained, that few believed in early on. "Other doctors laughed at us, saying we'd never figure it out," he recalled. "But Jeannie did not laugh. She understood what we were trying to do." Years later, Dr. Kaplan has not let up on his dream of finding a cure.

"Patients are the reason, the strength and the inspiration to work for a better future," he said. "A cure for FOP was a distant dream long ago. It's closer now. The wheels have been set in motion, and it will happen."

Dr. Kaplan stresses, that dream would not be in such close reach without support from Mrs. Diane Weiss, who established the Isaac & Rose Nassau Professorship of Orthopedic Molecular Medicine, the position Dr. Kaplan holds today at the University of Pennsylvania. Additionally, support from the Cali, Weldon, Snow, Scoble, Martucci, Bogard, and Whyte families, among many others, has been crucial.

Dr. Kaplan's insistence that it has been the work of many—from patients and families to mentors and colleagues—speaks to the power of the FOP community; a power he hopes endures. "There is a danger in losing our village mentality if we don't hear and listen to one another," he said. "We all—clinicians, scientists, researchers, patients and families—are united by a common bond: to make life better for those who have FOP."

The IFOPA is deeply grateful for the profound and life-changing impact Dr. Kaplan has made on the FOP community. His compassionate leadership, dedication and tenacity have inspired hope and optimism and created real change. Thank you, Dr. Kaplan, and congratulations on an extraordinary journey that is still unfolding.

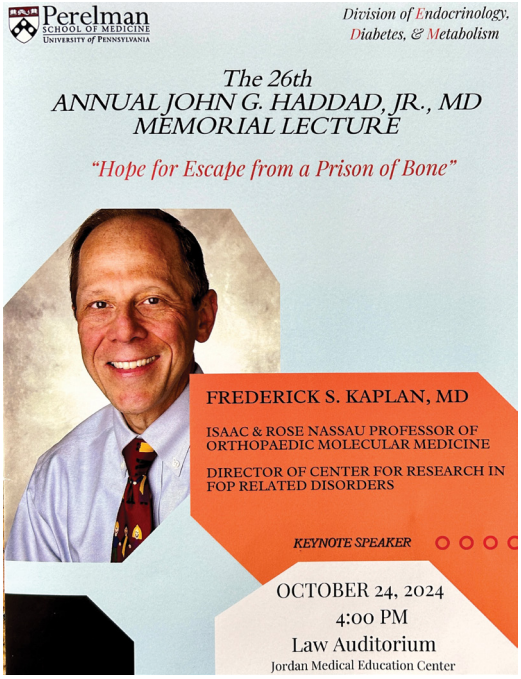
We're #1. For more than 20 years, Gary Whyte, a friend of the FOP Community, has worked diligently to advance the cause of FOP. Among his many charitable deeds is the organization and sponsorship of an Annual Comedy Night Fundraiser that single-handedly endowed the FOP Laboratory at Penn with specially needed scientific equipment—equipment that was used in the discovery of the FOP gene and beyond. Gary and his son Eric visited the Center for Research in FOP & Related Disorders at Penn for a special event of gratitude. From left: Allyse Orsini (Penn Development), Doug Roberts, Eric Whyte, Gary Whyte, Meiqi Xu, Loreilys Mejias Rivera, Aparna Sumanth, Jeffrey Xi, Dr. Eileen Shore, and Tzipora Schein.

The John G. Haddad, Jr., MD Memorial Lecture

For 25 years, Dr. Fred Kaplan opened the John Haddad Memorial Lecture with a personal tribute to his friend and mentor John Haddad, Professor of Medicine, Orthopaedic Surgery, and Chief of the Division of Endocrinology at the University of Pennsylvania, a master clinician and scholar in metabolic bone diseases and a world-renowned research scientist in the field of vitamin-D metabolism.

This year, the surprise invitation from the committee read:

> "Dear Fred,
>
> It is our absolute honor to invite you to give the 26th Annual John G. Haddad Jr., MD Memorial Lecture at the University of Pennsylvania. Your lifetime achievements and discoveries reinvented how we care for patients with rare diseases worldwide, the gene discovery fueled research and therapeutic discovery in FOP leading to the first FDA approved drug. Your curiosity about the resilient patient leading to our understanding of the role of MMP-9 in FOP is truly groundbreaking. The lecture committee enthusiastically extends the invitation to you this year for your superb work. We hope you are able to accept this invitation."



The 26th Annual John G. Haddad, Jr., M.D. Memorial Lecture

The lecture entitled "Hope for Escape from a Prison of Bone," highlighted the discoveries of the FOP Center made by Dr. Eileen Shore, Dr. Michael Zasloff, Meiqi Xu, Dr. David Glaser, Dr, Bob Pignolo, Dr. Mona Al Mukaddam, and countless students, fellows, scientists and most importantly patients (including patient-R) who joined in this heroic effort over the decades.

The title of the lecture came from an article written by the journalist Michael Mason and published in ***The New York Times*** to commemorate the historic FOP gene discovery in 2006. The article featured the story of Hayden Pheif who passed away from complications of FOP in summer 2024, and the headlines read, **"Finally, with Gene Discovery, Hope for Escape From a Prison of Bone."**

The lecture was attended by students, fellows, faculty members, and major benefactors of our FOP efforts over the decades including Mrs. Diane Weiss (Patron of The Isaac & Rose Nassau Professorship of Orthopaedic Molecular Medicine—currently held by Dr. Kaplan), Mrs. Amanda Cali (representing The Cali Family and Radiant Hope Foundation who have created and supported the FOP Center since its inception, established the Ian Cali Endowment, as well as granted major support for The FOP Resilience Project), and the Martucci, Segal, and Maracic families (Benefactors of The Ashley Martucci Research Fund that has been a major supporter the FOP Resilience Project), as well as an anonymous patron from Caldwell, New Jersey, and Mrs. Julie Haddad who joined virtually.

Nadine Großmann (Germany), Vice Chair of the IFOPA and Vice Chair of FOP Germany, presents Dr. Kaplan with the Roger Zum Felde Award of FOP Germany.

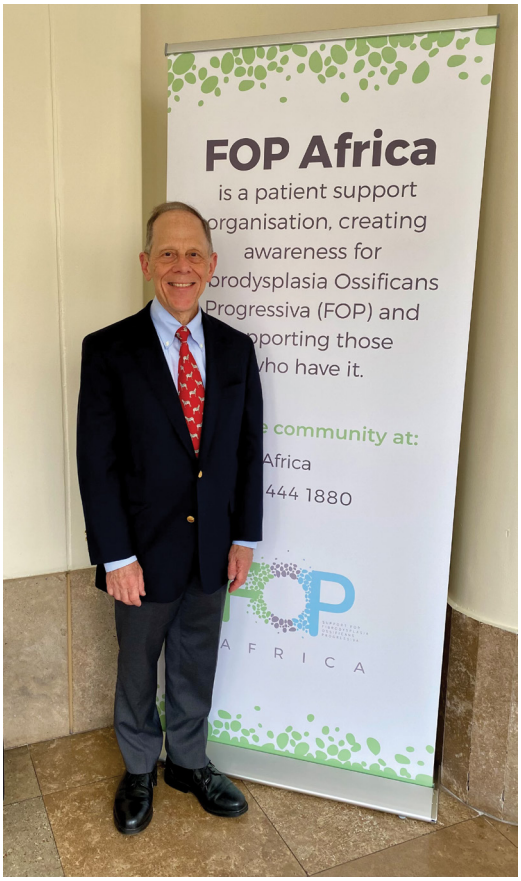
The Roger Zum Felde Prize of FOP Germany

The *Roger Zum Felde Prize* of FOP Germany honors the memory of the late Roger Zum Felde, an icon of the FOP international community, and past President of FOP Germany. The prize was awarded to Dr. Frederick Kaplan in 2024 for exemplary service to the worldwide FOP community.

PART 11 FOP—The Spoken Word

From 2022-2024, lectures on FOP were presented either in-person and/or virtually at:

- Advances in Mineral Metabolism; Snowmass, Colorado
- American Association for Anatomy & Experimental Biology; Philadelphia, Pennsylvania
- American Association of Clinical Endocrinology
- American Society for Bone and Mineral Research; Austin, Texas
- American Society for Bone and Mineral Research; San Diego, California
- American Society for Bone and Mineral Research; Toronto, Canada
- American Society for Bone and Mineral Research; Vancouver, Canada
- Ashley's Cure Fundraiser; New York, New York
- Biomedical Engineering Society Annual Meeting; Baltimore, Maryland
- BMP Signaling in Development and Disease FASEB Conference; Malahide, Ireland
- Bones and Teeth Gordon Research Conference; Galveston, Texas
- 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
- Coriell Institute for Medical Research; Camden, New Jersey
- David Smith Workshop on Malformations & Morphogenesis; Norfolk, Virginia
- Endocrine Society Annual Meeting; Boston, Massachusetts
- Endocrine Society Annual Meeting; Atlanta, Georgia
- Endocrine Society Annual Meeting; Chicago, Illinois
- FOP Argentina; Buenos Aires, Argentina



Dr. Fred Kaplan at the inaugural meeting of FOP Africa; Cape Town, South Africa.

- FOP Africa; Cape Town, South Africa
- FOP France; Nantes, France
- FOP Friends; Manchester, United Kingdom
- FOP Germany; Valbert Germany
- FOP India; Vellore, India
- FOP Spain; Madrid, Spain

Drs. Staci Kallish and Mona Al Mukaddam at The IFOPA Drug Development Forum in Stockholm, Sweden.

- FOP Sweden; Stockholm, Sweden
- FOP Switzerland; Ticino, Switzerland
- George Washington University; Washington, D.C.
- Icahn School of Medicine at Mount Sinai, New York, New York
- IFOPA FOP Drug Development Forum; Stockholm, Sweden
- IFOPA Family Gathering; Dallas, Texas
- IFOPA Family Gathering; Denver, Colorado
- IFOPA webinar on The FOP Treatment Guidelines; Kansas City, Missouri
- International Association for Dental Research; New Orleans, Louisiana
- International BMP Conference; Dubrovnik, Croatia
- International Federation of Musculoskeletal Research; Brugge, Belgium
- Jefferson University; Philadelphia, Pennsylvania
- Mütter Museum of The College of Physicians of Philadelphia; Philadelphia, Pennsylvania
- National Institutes of Health; Bethesda, Maryland
- Nemours Children's Hospital; Wilmington, Delaware
- Nobel Symposium; Sollentuna, Sweden
- Orthocorps, The Journal of Bone & Joint Surgery; Baltimore, Maryland
- Orthopaedic Research Society; Tampa, Florida
- Orthopaedic Research Society; Dallas, Texas
- Orthopaedic Research Society; Long Beach, California
- Queens College, City University of New York; New York, New York
- Sanford School of Medicine; Sioux Falls, South Dakota
- Society of Muscle Biology; Montreal, Canada
- South High Community School; Worcester, Massachusetts
- Rare Bone Disease Alliance Scientific Symposium; Gaithersburg, Maryland
- Tin Soldiers Clinicians Champion Alliance Summit; Cape Town, South Africa
- University of California, San Francisco; San Francisco, California

- University of Massachusetts Chan School of Medicine; Worcester, Massachusetts
- University of Michigan School of Medicine; Ann Arbor, Michigan
- University of Pennsylvania; Philadelphia, Pennsylvania
- University of São Paulo; São Paulo, Brazil
- Wayne State University; Detroit, Michigan

The FOP Clinical Trials Team assembles to hear Ian Cali's Distinguished Annual Lecture to the first rear medical students at the Perelman School of Medicine at the University of Pennsylvania. From left: Kay Rai, Nathalie Richter, Dr. Fred Kaplan, Ian Cali, Sarah Vanasse, Dr. Staci Kallish, and Raissat Abdallah.

PART 12 FOP—The Written Word

In 2023-2024, publications from numerous groups on FOP and FOP-related issues appeared in peer-reviewed journals. There were more than 195 papers published on FOP worldwide–a continuing tribute to the broad international interest and awareness of FOP.

As of January 1, 2025, the classic article in ***Nature Genetics*** (April 2006) describing the discovery of the FOP gene has been cited in 1,334 major scientific publications worldwide. The FOP gene discovery article ranks in the 99th percentile of the 94,000 tracked articles of a similar age in all journals and ranked 1st among articles of a similar age that were published in ***Nature Genetics***.

As of January 1, 2025, the recently published article in ***The Journal of Bone & Mineral Research*** (February, 2025) describing the discovery that MMP-9 deficiency confers resilience in FOP in a man and mice has been downloaded more than 3,000 times.

PART 13 "What Can We Do to Help?"

Patients, families, friends, even casual visitors to the Center for Research in FOP & Related Disorders often ask: "What can we do to help?" The answer is simple. "Anything you can."

It is even more urgent now as several of our critical projects, including the Resilience Project, are in great need for funding for the work to continue.

The Resilience Project addresses six of the seven stated IFOPA research priorities:

- Biomarkers
- Genetic Modifiers
- Immune System & Inflammation
- New Druggable Targets
- Repurposed Drugs
- Muscle Regeneration

The remarkable findings from phase 1 of the Resilience Project discussed in this report strongly suggests that a simplified form of gene therapy or available pharmaceutical therapy may be possible in FOP.

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.

Because of a funding lull, we may have to put critically important projects on hold.

Research is laborious, time consuming, often frustrating, and costly, but so too is the FOP we are trying to cure. 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 35 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 more than 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.

No idea or endeavor is too small or too outlandish to help.

Please help cure FOP.

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

PART 14 Many Thanks to You

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

Much has been accomplished, thanks in large part to the 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 began for FOP—a major step forward. As this report documents, we continue to make monumental discoveries that have a real chance of affecting the natural history of this brutal condition.

Now, as a comprehensive center, we manage and coordinate care for FOP patients, not only at Penn, but globally, and also engage in vital clinical, basic science, and translational research that can change the course of this rare and debilitating condition. We are vitally committed to education. We want to ensure that the next generation of physicians and scientists is as passionate about FOP research as we are.

Despite the progress we have made, there are still many unanswered questions and more important 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 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 current and past generous support of:

- The International FOP Association
- The Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine
- Mrs. Diane Weiss
- The Cali Family Endowment for FOP Research
- The Weldon Family Endowment for FOP Research
- The Cali-Weldon Professorship of FOP Research
- The Radiant Hope Foundation
- The Ashley Martucci Fund for FOP Research
- The Martucci, Segal, and Maracic Families

- The Roemex Fellowship
- Canadian FOP Network
- FOP Australia
- FOP Germany (eV)
- FOP France
- FOP Italia
- Svenska FOP-föreningen (Sweden)
- Gary Whyte
- Michael & Donna Gordon
- A Generous and Anonymous Donor from Caldwell, New Jersey
- A Generous and Anonymous Donor from Australia
- The National Institutes of Health (The People of the United States)
- The Snow Family and The People of Santa Maria
- And the many individuals, families, friends, and communities throughout the world who contribute generously and tirelessly to the FOP effort.

PART 15 A Special Tribute to Amanda Cali on Her Retirement

We have known Amanda Cali for more than three decades. She is our friend. There is no one in our FOP world who is more inspired, more committed, more passionate, and more visionary than Amanda Cali. She has done more for the global FOP community than any person in the world—and she has done it with grace, commitment, compassion, and love. Her heartfelt empathy and philanthropy has reached FOP families on every continent—in major cities as well as the villages and huts in remote regions of the globe. Amanda has played a vital role in every facet of FOP life, at home and around the world. Through her relentless and tireless work for more than 30 years, Amanda has created, connected, empowered, and inspired the entire global FOP community. She is respected and loved by all—doctors, scientists, patients and families—in every corner of the world. We pledge to her legacy a vast, eternal debt of gratitude. She is truly a saintly and wonderful human being.

Amanda Cali (Past Chair of the Board of Directors of the IFOPA) at the inaugural Tin Soldiers Clinician Champions Alliance Summit; Cape Town, South Africa.

Among Amanda's legendary contributions:

- Chair of the Board of Directors of the IFOPA
- Creator of the International Presidents' Council of the IFOPA
- Creator and Patron of the International Clinical Council on FOP (ICC)
- Creator and Patron of the Mother's Retreat
- Patron of the worldwide search for multigenerational FOP families, critical for finding the elusive FOP gene
- Benefactor of the Center for Research in FOP & Related Disorders at the University of Pennsylvania

Members of the FOP Adult Clinical Trials Team greet Amanda Cali at Penn. From left: Katherine Toder, Mona Al Mukaddam, Amanda Cali, Raissat Abdallah, Sarah Vanasse, and Nathalie Richter.

Dr. Mona Al Mukkaddam?

- Benefactor of the Cali-Weldon Chair in FOP Research at the University of Pennsylvania
- Founder of The Radiant Hope Foundation
- Benefactor of more than 60 Ian Cali Research Awards (>$3 million) in basic and applied research to scientists worldwide for over 20 years
- Funded more than $17 million of FOP causes over 30 years
- Creator and organizer of the Meet the Doctors Clinics at FOP Family Meetings around the globe for nearly three decades
- Organizer of the 2nd and 3rd International FOP Symposia attended by more than 100 families worldwide
- Creator and Patron of the workshop "Strategies for the Treatment of FOP"—the inspiration for the FOP Drug Development Forums
- Creator and Patron of the FOP Ability Toolbox Program
- Founder of Tin Soldiers
- Inspiration, Patron and Co-Producer of the Documentary ***Tin Soldiers*** about the FOP patient voice worldwide
- Inspiration, Patron and Co-Producer of the Documentary ***The Whisper*** about the FOP patient voice in underserved areas of the world
- Championed the search for FOP patients on the continent of Africa
- Sponsored the first family meeting of FOP patients on the Indian subcontinent
- Comforter-in-chief to new FOP families worldwide
- Organizer of the FOP Friend Raiser in the US Congress
- Creator of the Library & Resource Center for FOP
- Visionary patron for the establishment of the IFOPA's FOP Registry
- Inspiration for the worldwide search to find undiagnosed and unconnected patient and connect them to pathways of care
- Patron of the First Adult FOP Meeting
- Patron the First South American Family Meetings
- Benefactor of The FOP Resilience Project
- Mother of Ian Cali

It has been said and written by others that "Amanda sees not only what is, but what could be. She envisions obstacles that stand in the way of fulfilling dreams and builds bridges of hope that others can't even envision. She has envisioned, funded and created countless infrastructures in the FOP community for research, education, and patient care. The centers, libraries, resource centers, professorships, clinics, symposia and retreats have become virtual highways of hope that Amanda has envisioned and built—and that has inspired generations of doctors, scientists, philanthropists, and FOP families throughout the world."

PART 16 The Last Word

The assembled audience of distinguished scientists and physicians listens in rapt attention to a humble superhero, Andrew Davis (Alabama), speaking during the Q&A portion of the special invited session on Disease Resilience in FOP at the IFOPA Drug Development Forum in Stockholm, Sweden. Also listening are Dr. Fred Kaplan (left) and Dr. Bob Pignolo (right).

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

This year, a patient has shown us all a better way. This year, that patient, immortalized in the scientific and medical literature as patient-R is in real life known as Andrew Davis—a superhero—to us, and to the entire FOP community. We asked Andrew about his unlikely journey—and his legacy. These are his words:

> "My name is Andrew Davis and I live near Birmingham, AL. I am 37 years old and work as a Database Manager/IT at a nonprofit. My journey with FOP has been a weird and extraordinary experience.
>
> I grew up having a normal childhood. I played outside, participated in sports (baseball and soccer), rode a bike, got bumps and bruises, all the kid stuff. Nothing seemed too out of the ordinary, as I had no flare-ups to speak of, even with some bad falls or things falling on me. I've never had any broken bones, thankfully.

That all changed in 2007. At age 20, I woke up one morning and the right side of my neck (from my collarbone to below my ear) was swollen. I had to turn my whole body to look to the right. We ended up seeing an ENT doctor who suggested surgery to have it removed. The mass was removed and I was diagnosed with fibromatosis. I had a little nub on my collarbone, but no other post-surgery problems afterward. Life continued on as normal.

Later in 2008, I was in a very stressful job. It became so stressful that I threw up before I went into work. That's when the little collarbone nub began growing. We went back to the ENT doctor and he was completely unsure as to what it could be. He referred us to a geneticist and an oncologist. The oncologist thought it sounded like FOP and gave us some info on it. On the way home from that appointment, the geneticist called to confirm that it was indeed FOP.

Needless to say, that news shocked me to the core. I could no longer look at life the same way. Thankfully, it sent us on the path to meeting with Dr. Kaplan and his team at UPenn. Since then, I've been able to watch, and participate in, the research that has happened over the years. Never would I thought to have seen the progress that's been made for FOP treatments. To see the multiple ongoing clinical trials and to have an FDA-approved treatment is so wonderful. Hope and persistence are truly glorious catalysts.

That's what I feel sums up being someone with FOP—hope and persistence. There's hope that a cure will one day be discovered, hope in the future treatments that will diminish FOP effects, and hope for future generations. Without the persistence of families, doctors, researchers, etc., there would be little to no hope. Without the persistence of men like Dr. Fred Kaplan, we would not be where we are today. Our hope would definitely have faded long ago.

I have been very happy and honored to contribute my samples over the years. There's a reason that the FOP gene was discovered in 2006 and my diagnosis being in 2008. And that reason is coming to fruition with the recent research talked about in ***The Power of One*** (in this annual report). I hope my story lights a fire in the hearts of others, including patients, doctors, and researchers, to not give up. To be willing to give of yourself to help those in need, especially when you are able to do so, no matter how small or great the impact may be.

Hope is defiant and I will hold onto it."


Penn Medicine