The Twenty-First Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project

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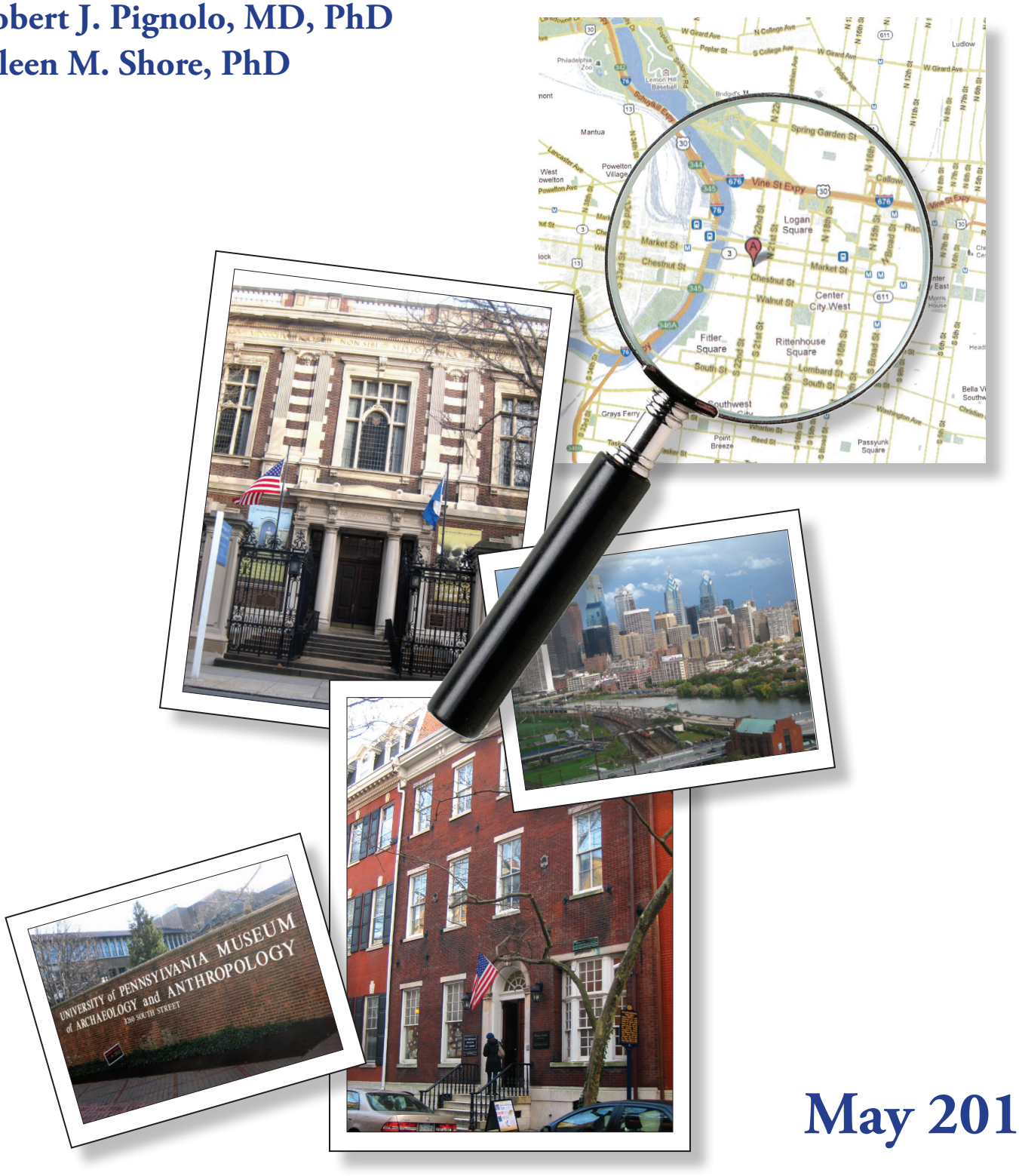

May 2012

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Introduction

Two thousand twelve years ago, during the reign of the Roman Emperor Augustus, the poet Ovid wrote:

"My soul would sing of Metamorphoses.
But since, o gods, you were the source
Of these bodies becoming other bodies,
Breathe your breath into my book of changes."

The professor surveyed the puzzled looks and addressed the class.

"The Metamorphosis may be a fantasy," she said, "perhaps even a lie. But 'Art is the lie that tells the truth,' said Picasso, and Joseph Campbell wrote in **The Power of Myth**, 'If you want to change the world, you first have to change the metaphor.'"

"Your assignment this term is to change the metaphor - breathe new life into the book of changes. I want each of you to grapple with the meaning of The Metamorphosis in the modern world. How does The Metamorphosis shape and alter our view of reality? Use examples from art, literature, and from everyday life. First, record your notes, ideas, and sources. Then, organize them into a coherent essay. It can be any length you wish. Be original and creative. Think broadly and deeply. The assignment is due on April 10th. Class dismissed."

Jenny Tang, an undergraduate student sitting in the first row, approached the professor. "Is this for real?" she asked. The professor smiled, "As real as you want it to be. You're a smart girl Jenny. Use your imagination. Dream a little. You won't have to look far, but you'll have to delve deep. Remember what Campbell said, 'Doors will open where you didn't know they were going to be'. "

Jenny shrugged. "Fair enough" she said as she replaced her I-Pad in her backpack, leapt up the same classroom steps that Albert Einstein climbed decades earlier, darted across campus, and entered the Starbucks on Nassau Street.

She Googled, "Metamorphosis," and noted a comment by Ann Druyan, a TV producer and Carl Sagan's widow: "For most of the history of our species, we were helpless to explain how nature works. We took every storm, drought, illness and comet personally. We created myths and spirits in an attempt to explain the patterns of nature."

"True, but this goes too far," Jenny thought. "Sure, science matters, but it's more than just science. Why do we still read myths? Believe in them? Why do they continue to exert so much power over us? Diseases, for example, are not just biological processes, but human experiences, and those human experiences, regardless of how primitive, are timeless - anchored in mythology."

D.H. Lawrence, the British novelist came to mind: "Myth is an attempt to narrate a whole human experience."

"A whole human experience…bodies becoming other bodies", Jenny kept repeating, as she left the coffee shop. No one even turned a head, no one, as if she had been speaking on her cell phone, speaking across twenty centuries to the poet himself.

For much of the next week, Jenny wandered through campus, stopping now and then at a statue or frozen pond to re-read and transcribe hastily-written notes she had scribbled on coffee receipts and unredeemed coupons – notes from every source conceivable without much thought to their origin or meaning. She was trying to make sense of it all . . .

The Metamorphosis: How does it shape and alter our view of reality?

- *Ovid's Metamorphoses?*
- *Lot's Wife?*
- *Michelangelo's Captives?*
- *Kafka's Metamorphosis?*
- *Harry Eastlack – Who was Harry Eastlack?*

She couldn't get her mind around it. "Okay; Ovid, Lot, Michelangelo, Kafka. All fiction, myth, art, literature. I can buy that – all of it. But, who was Harry Eastlack? Was he real? And, what does he have to do with the metamorphosis?"

"It's about a whole human experience," she kept thinking, "a whole human experience." Delve deeper." Her mind wandered.

The New York Times.

Friday evening, November 14, 1851 - two American authors - friends and neighbors -met for dinner at a village inn near Pittsfield, Massachusetts to celebrate the publication of a novel that one had written and the other had revised. The story told the adventure of a wandering sailor and his voyage on a whaling ship ("Now, there's a myth," Jenny thought!). The author had made formal arrangements to dine with his friend and neighbor; their wives were each nursing newborns and did not attend.

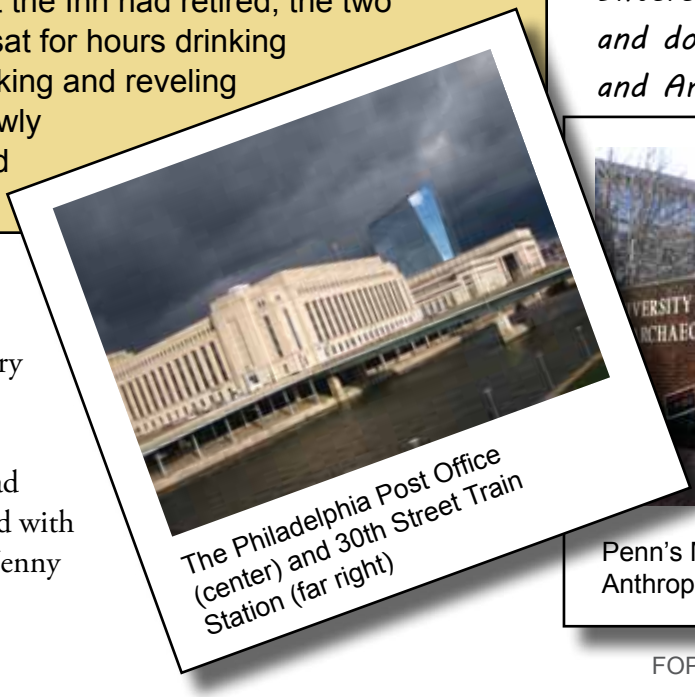
Near the end of dinner, the author presented a copy of the book, published that day, to his friend and neighbor. The book was inscribed with an extraordinary dedication, and the friend was profoundly honored by the tribute. The friend opened the book to Chapter 32, paused for a moment, and highlighted a sentence for the author. After all the other guests at the Inn had retired, the two authors sat for hours drinking and smoking and reveling in the newly published novel.

"It would take more than a century for others to understand what they had accomplished with that book," Jenny wrote. "They had changed the collective metaphor – boldly and dramatically, and it was all based on an idea, a myth, that was so incredibly real, about something that never happened, but always does. Generations of high school students would rue the day, but the world had a new metaphor – a new code to decipher reality, and it was embedded in a single sentence in Chapter 32."

Jenny was daydreaming. She inhaled the smell of varnished wood and old floor wax – the scents that lingered in all classrooms from the first day of kindergarten. The class was over and the teacher admonished, "Remember; the assignment is due April 10th. I hope you are all working on it. This is not one you want to leave to the last minute." She looked directly at Jenny, "I expect extraordinary things from you." And then added, quoting her mentor, Loren Eiseley from Penn: "Decipher only those secrets that you possess the power to endow with meaning."

"I'm confused," Jenny wrote in her diary. "Decipher only what secrets?" The entry continued . . .

February 11: "Took the train from Princeton Junction to Philly's 30th Street Station. An impressive place. Far nicer than the rat hole of a station in New York City. Walked past the post office to the University of Pennsylvania Museum of Archaeology & Anthropology across from Franklin Field. Entered the Courtyard, up to the Rotunda, and down to the Lower Egyptian Room and Archives. Scoured Eiseley's Notes & Memoirs."



The Philadelphia Post Office (center) and 30th Street Train Station (far right)

Penn's Museum of Archaeology and Anthropology.

"Nature teaches, but what it teaches is often hidden and obscure. It would be well to consider what may be called the hidden teacher, lest, we become too much concerned with the formalities by which we learn. We think we learn from teachers, and we sometimes do. But the teachers are not always to be found in schools or in great laboratories. Some times what we learn depends on our own power of insight."

– Lauren Eiseley – Anthropologist
The University of Pennsylvania
(The Unexpected Universe)

"Dig deeper", thought Jenny. "Dig deeper. Doors will open where you didn't know they were going to be."

She wandered into the courtyard, through the outer gates of the museum, across the newly renovated South Street Bridge and back into Center City, Philadelphia.

Skyline – Center City Philadelphia.

The Rosenbach Museum, Delancey Street, Philadelphia. A museum of rare books in an elegant downtown neighborhood of stately row houses. "A docent led me to the second floor, to an old bookcase, and handed me a pair of white cotton gloves," Jenny wrote. "I trembled as she opened the glass door and handed me the book. I had to see it myself. I opened the cover. A first edition.

The Rosenbach Museum: Delancey Street, Philadelphia.

MOBY DICK (OR THE WHALE) BY HERMAN MELVILLE

"But this was not Melville's personal copy," Jenny noted. "It was far more impressive than that."

". . . My heart stopped.

I turned the page . . . "

Friday, November 14, 1851
In Token Of My Admiration For His Genius
This Book is Inscribed
To
Nathaniel Hawthorne,
My Friend and Neighbor

"My hands were shaking," Jenny wrote. "I opened to Chapter 32, and flew through the paragraphs. There in the midst of a classification of whales, I found the sentence I had been looking for, had been dreaming about…"

"I am the architect, not the builder."

"In every work of genius," Emerson wrote, "we recognize our own rejected thoughts; they come back to us with a certain unalienated majesty."

"I handed the book carefully to the docent as if I was handing-off a sacred text, removed my gloves, offered a heartfelt thank you, flew down the steps of the town house, out onto Delancey Street, and headed straight for the Mütter Medical Museum at The College of Physicians on 20th Street. Everything I had done, everything I had researched pointed me to that place. It was like a wave carrying me along. I had to meet Harry Eastlack and find-out who he really was."

"It's an imposing building, stuck in the middle of an ordinary street. I entered the vestibule, showed my student ID, walked down an impressive staircase to the lower level where I met Anna Dhody, the curator of The Mütter Museum. Anna led me to the place I could only imagine; used a special key to open the glass closet in the southwest corner of the Museum. I recalled the words of my professor on the power of myth: "Doors will open where you didn't know they were going to be."

"**The Key to the Closet"** remembered Jenny**, "is the Key to the Kingdom."**

She had read those words before. They were vivid now - illuminating. Jenny glanced at her museum notes:

The Mütter Museum is located here at the College of Physicians of Philadelphia.

"Reality has a way of hiding even from its most gifted observers"

— Lauren Eiseley

"In the glass closet", Jenny wrote, "was the skeleton of a truly remarkable man named Harry Eastlack. Harry had fibrodysplasia ossificans progressiva (FOP). Harry willed his body to medicine so that future generations of doctors and scientists could learn about his condition and could observe the results of the metamorphosis that had ravaged his body during his lifetime."

Jenny recalled the words of Eiseley. They resonated in her mind like a parable as she repeated them over and over until they were inscribed indelibly in her memory: "One cannot help but dwell upon the hidden powers that produce so delicate a balance between freedom and catastrophe." "So delicate a balance between freedom and catastrophe," thought Jenny, "It's true after all. It's not art. It's not a lie. It's not a myth. It's a whole human experience. Decipher only those secrets that you possess the power to endow with meaning. The key to the closet is the key to the kingdom. This is the real metamorphosis. This is what shapes and alters our view of reality. Who are the architects? Who are the builders? Can it be stopped?"

Dear Doctors,

My name is Jennifer Tang. I am a junior at Princeton University, majoring in cultural anthropology. I recently received a fascinating assignment in my class on ANCIENT MYTHS AND URBAN LEGENDS. The assignment is based on The Metamorphoses by Ovid, but it's a little more complicated than that.

In doing research for my assignment, I discovered several papers you wrote that intrigue me. I have some ideas I wanted to run by you, and some extraordinary things I have seen along the way that I wanted to share with you. You probably know all about them already, but maybe not in the way that I found. I am writing to see if you might have time to meet with me. I can only imagine how busy you are, but I would love to meet you all in person and learn more about what you are doing. Your work is truly fascinating to me and the intrigue goes well beyond the classroom assignment. Would it be possible to visit the FOP Laboratory and meet an FOP patient? You don't know how important that would be for me. I just met Harry Eastlack - what a truly remarkable man he was.

I look forward to hearing from you.

Sincerely,

Jenny

. . . Three weeks later . . .

(How Does the Metamorphosis Shape & Alter Our View of Reality?)

FOP & the Metamorphosis: Architects & Builders

by Jennifer Tang

My soul would sing of Metamorphoses.

But since, o gods, you were the source

Of these bodies becoming other bodies,

Breathe your breath into my book of changes.

May the song I sing be seamless as its way

Weaves from the world's beginning to our day.

– Ovid

In their respective works, both Ovid and Kafka reveal a truth we know instinctively but are loathe to confront: that life can be transformed rapidly and tragically into a nightmare that redefines reality. Anyone who has ever met a child with the condition fibrodysplasia ossificans progressiva (FOP) knows that these stories were neither fiction nor myth. The condition has been known for centuries and its elusive mysteries have taunted physicians and scientists for as long. The childhood victims of this musculoskeletal sabotage seem normal at birth except for telltale malformations of the great toes. Soon, the children succumb to progressive waves of renegade bone formation that transform the body's soft connective tissues into an armament-like encasement of bone. Ribbons, sheets, and plates of ectopic bone seize the body's joints, and relegate its victims to a state of permanent and lifelong immobility. Dr. Jules Rosenstirn wrote in 1918: "One does not wonder that a disease, so baffling in its course from the first causes to its ultimate state, should invite the speculative as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle."

On Monday, April 24, 2006, **The Associated Press** reported:

"FOP Gene (ACVR1/ALK2) Discovered."

On Tuesday, May 9, 2006, **The New York Times**, reported:

"Finally, With Genetic Discovery, Hope for Escape from a Prison of Bone."

. . . Discovery . . . Hope . . .

ACVR1/ALK2:
"I am the architect, not the builder."

Cells, Triggers, Microenvironment:
"I am the builder, not the architect."

What kind of a year was 2011 for FOP research? A year when blueprints were drawn - when foundations were poured and superstructures emerged – when scientists and engineers measured progress in stories built - when the view got better the higher one reached - when architects and builders used their tools and powers of insight to shed light on the metamorphosis of FOP and move one level higher, one step closer to "solving this embarrassing puzzle."

The FOP gene discovery and the advances it has inspired have transformed thinking and have altered horizons. It has been six years since that momentous milestone, and I see now from the doctor's and the patient's perspective – that the world no longer looks the same. Ian Cali described it: "From Hopeless to Hopeful." You'll read more about that later!

The distinct structures that the doctors have told you are still there – genes, cells, pathways, models, triggers, treatments. But, they are not individual islands any more. They are a coherent skyline. An illuminating shift in perspective has occurred as knowledge of FOP has deepened from within traditional fields of study and from without. It's the difference between a countryside of castles and a city of skyscrapers. As the architect, Philip Johnson said, "I'm about four skyscrapers behind." The architect Frank Gehry countered, "You just gotta bumble forward into the unknown."

As the doctors explained to me, FOP research is an epic journey – an odyssey. As the patients and families taught me, FOP is a whole human experience. Myths and epics have always been about the fears and aspirations of a people just as in the time of Ovid. But, in the small yet global world of FOP, this is no myth. The most coveted aspiration is a simple four-letter word, *CURE*. It is a word filled with hope and peril – hope in its possibility for redemption; peril in the obstacles and dangers getting there. *CAUSE* and *CURE* are what FOP research is about – to truly understand the cause of FOP, not just at a genetic, cellular, and molecular level – but fundamentally and deeply in an interconnected way – how it all works together in an individual so that knowledge can be turned into wisdom – and wisdom into action. So that the builders can take the plans of the architects and alter the skyline to make a difference – for one person at a time. **It's about a whole human experience**.

In the following report, I will trace the fundamental outlines of FOP research since the gene discovery was made. First, I will review, using the metaphor of architects and builders, the basic blueprints of the extraordinary metamorphosis of FOP. Then I will explain what the newest discoveries have revealed, how FOP will, in time, be stopped, and of course, what still needs to be done to stop it. Ultimately, you the reader will understand how the metamorphosis of FOP shapes and alters our view of reality.

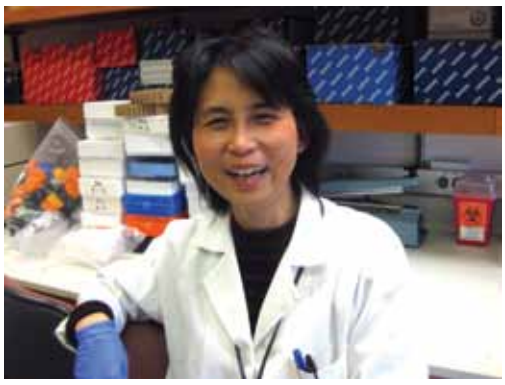
Part I – The Architects and the Builders

FOP: A Blueprint for the Metamorphosis

Physicist Erwin Schrodinger confused the program and the constructor in his 1944 book *What is Life?*, in which he saw chromosomes as "architect's plan and builder's craft in one." This is wrong. The code script contains only a description of the executive function, not the function itself.

– Sydney Brenner

The most important discovery in understanding FOP was the identification of the causative mutation, the architect of the second skeleton. However, such knowledge is insufficient to understand how the body builds a second skeleton. While activating mutations of the ACVR1/ALK2 receptor are necessary, disease activity and progression also depend on altered cell and tissue activity. Recent findings identify inflammatory and immunological factors, connective tissue stem cells, and a lesional microenvironment that triggers, promotes, and enables episodic progression of FOP in the setting of the genetic mutation. Effective therapies for FOP will need to consider these seminal interactions.



Research Scientist Meiqi Xu in The FOP Laboratory

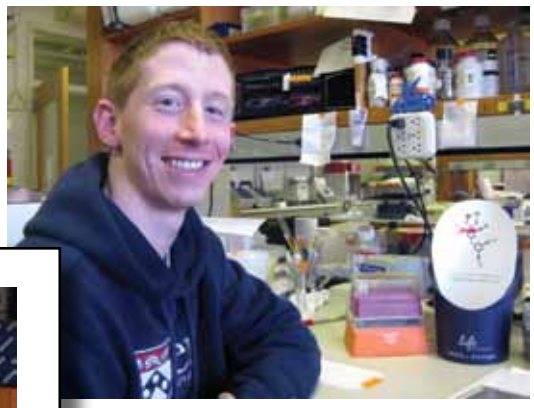
The Hidden Architect of Skeletal Metamorphosis in FOP

Most of the organism, most of the time
is developing from one pattern into another

– Alan Turing

In a strange way, FOP provides a glimpse into the protective mechanisms that nature has evolved to ensure tissue stability and to prevent the metamorphosis of one tissue or organ into another. In a world where FOP is unknown, these mechanisms would be completely hidden from view.

Skeletal metamorphosis in FOP is an incredibly complex pathological process in which the normal structure and function of one tissue (skeletal muscle, for example) is destroyed and replaced by that of another tissue (bone) through an intermediate cartilage scaffold. The process of skeletal metamorphosis in FOP begins with an intense destructive stage in which a soft tissue injury triggers an inflammatory cell infiltrate involving lymphocytes, macrophages, and mast cells. The inflammatory process is associated with muscle cell injury and death. Following the destructive phase, a formative phase occurs and is characterized by an explosive proliferation of stem cells (fibroproliferative lesion) that matures through a cartilage scaffold (endochondral process) and culminates in the formation of a new ossicle of heterotopic bone. As the process of metamorphosis spreads through contiguous and adjacent sites with subsequent flare-ups, new skeletal elements ramify to form a disabling second skeleton of heterotopic bone.



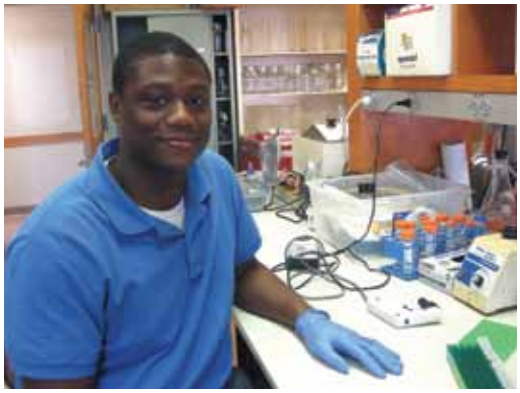
Graduate Student Michael Convente in The FOP Laboratory.

Inflammation and FOP: Triggering the Metamorphosis

Hence, the rapid and innumerable transformations of that architecture . . .

– Victor Hugo (Notre Dame de Paris)

The mutations in ACVR1/ALK2 that cause FOP are necessary but may not be sufficient to trigger the disabling, episodic, flare-ups of heterotopic bone. Activation of inflammatory pathways through the innate immune system appears to be an important trigger for flare-ups of FOP. Presently, several animal models reproduce various clinical and pathological features of FOP-like heterotopic ossification and in all, inflammatory triggers play a key role in lesion initiation and disease progression.



Pre-medical student and FOP Researcher Edwin Theosmy at the lab bench in The FOP Laboratory

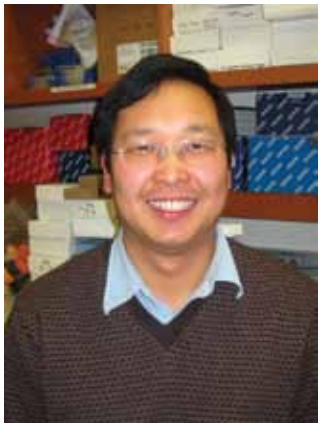
The Microenvironment of the Metamorphosis

And not only the form of edifices, but also the sites selected for them, revealed the thought which they represented.

– Victor Hugo (Notre Dame de Paris)

Generation of a low oxygen microenvironment in injured skeletal muscle appears to be an important step in the formation of heterotopic bone. The FOP scientists at Penn tested the hypothesis that a low oxygen microenvironment enhances BMP signaling through the mutant ACVR1/ALK2 receptor. Ongoing work supports an encompassing role for microenvironmental factors in the formation and maturation of FOP lesions.

Stem Cells and FOP: The Master Builders of the Metamorphosis



Postdoctoral fellow Haitao Wang in The FOP Laboratory

Do you mean to tell me that you're thinking seriously of building *that* way, when and if you are an architect?

– Ayn Rand (The Fountainhead)

BMP signaling is a well-established regulator of stem cell fate. Importantly, the FOP gene mutation leads to dysregulated BMP signaling and increases bone formation in targeted progenitor cells. These observations suggest that BMP signaling pathway regulates stem cell fate commitment, findings recently established in FOP-like animal models.

Recent studies have shown that progenitor cells associated with skeletal muscle can transform into multipotent stem-like cells by an ACVR1/ALK2 dependent mechanism. In lesions from individuals with FOP, or from transgenic mice expressing constitutively active ACVR1/ALK2, heterotopic cartilage and bone cells appear to be derived from these cells. Taken together, these studies suggest that connective tissue progenitor cells resident in skeletal muscle and closely associated with the microvasculature may be master builders of a second skeleton.

Emerging Principles of Skeletal Metamorphosis in FOP

Rules? said Roark. Here are my rules: what can be done with one substance must never be done with another.

– Ayn Rand (The Fountainhead)

Recent studies have elucidated a set of principles that guide our understanding of tissue metamorphosis in FOP. Data from FOP patients and from animal models of FOP support that inflammatory signals (in response to soft tissue injury) enhance the cellular response to microenvironmental changes, mobilize resident connective tissue progenitor cells and differentiate them to every stage in the development of heterotopic bone.

Treatment Strategies for Inhibiting Skeletal Metamorphosis in FOP

A real castle in the air?
Yes; one with a firm foundation under it.

– Ibsen (The Master Builder)

The discovery of the FOP gene and emerging insights into activity of ACVR1/ALK2-mediated heterotopic ossification reveals at least four plausible approaches to the treatment and/or prevention of FOP. These approaches include:

1. Blocking activity of the mutant FOP receptor (ACVR1/ALK2)

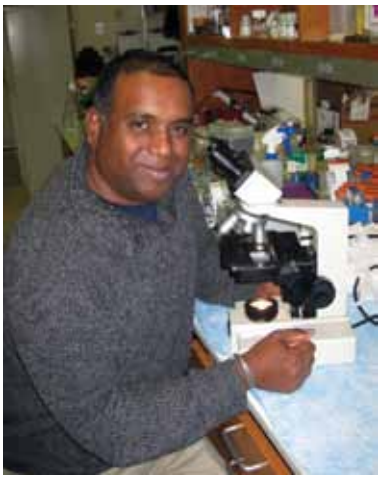
2. Inhibiting triggers of FOP flare-ups

3. Directing FOP stem cells to an alternate tissue fate

4. Altering microenvironmental signals that promote the formation of FOP lesions.

Presently, at least six classes of compounds are plausible candidates for FOP clinical trials within the next several years, and are all being pursued in pre-clinical studies. As always, there are daunting safety and regulatory hurdles that must be surpassed before a clinical trial to test potential drugs for FOP can begin.

Histologist Bob Caron in The FOP Laboratory



Postdoctoral fellow Salin Chakkalakal at work in The FOP Laboratory

Research Scientist Dr. Vitali Lounev at the work bench in The FOP Laboratory

Part II – Stopping the Metamorphosis

Workshop for a Cure

An architect's most useful tools are an eraser at the drafting board and a wrecking ball at the site.

– Frank Lloyd Wright

Just because we don't know everything, doesn't mean we can't do anything.

– An anonymous doctor

An FOP Scientific Retreat held this past August in Philadelphia consolidated new frontiers in FOP research, and identified new targets for therapeutic intervention. Never before, has the scientific and medical community had both the repertoire of potential candidates and the sound scientific foundations for testing new drugs in animal models of FOP. Now, with so many potential therapies available, the FOP Center and its collaborators have embarked upon a rational approach to prioritize the preclinical testing of these drugs.

In mid-August, 2011, 27 scientists (13 from the University of Pennsylvania and 14 from other institutions) met in Philadelphia for an informal, but intense two-day workshop on: **"Strategies for the Treatment of FOP."** The workshop was co-organized by Drs. Kaplan, Pignolo, and Shore with the tireless and gracious support of Mrs. Amanda Cali.

Mrs. Amanda Cali (IFOPA Board Member & Workshop Coordinator) meets with FOP researchers Dr. Jay Groppe (Baylor University) and Dr. Lixin Kan (Northwestern University).

Seated (from left to right): Mrs. Amanda Cali, Mr. John R. Cali, Dr. Robert Pignolo, Dr. Fred Kaplan, Dr. Eileen Shore, Dr. Aris Economides, Dr. Michael Zasloff. Standing (from left to right): Mr. Ian Cali, Mrs. Robin Gambaiana, Mrs. Jennifer Snow, Dr. Viet Le, Dr. Kristi Wharton, Dr. Bjorn Olsen, Dr. Jay Groppe, Dr. Vicki Rosen, Mr. Mark Gambaiana, Dr. Ernestina Schipani, Dr. Corey Hopkins, Dr. Karen Lyons, Mrs. Diane Weiss, Dr. Petra Seemann, Dr. Masahiro Iwamoto, Dr. Bettina Mucha-Le Ny, Mr. Robert Snow, Dr. Joseph Kitterman, Dr. Emile Mohler, Dr. Malek Kamoun, Dr. Maurizio Pacifici, Dr. Damian Medici, Dr. Lixin Kan, Dr. Ed Hsiao, Dr. Charles Hong, Mrs. Moira Liljesthrom

The workshop was sponsored by generous contributions from Mrs. Diane Weiss, the IFOPA, the University of Pennsylvania, and an anonymous donor. The primary goal of the workshop was to establish priorities for developing effective treatments and an eventual cure for FOP. An important secondary goal of the workshop was to stimulate and strengthen basic scientific and translational collaborations that will lead to the development of a cure.

Dr. Kristi Wharton (Brown) discusses FOP research with Dr. Ed Hsiao (University of California - San Francisco)

Participants were provided with an extensive reading list of the most up-to-date scientific articles in the field of FOP research a month prior to the meeting, and were encouraged to scour the details before arriving in Philadelphia. All clearly did.

Dr. Scott Levin, Chairman of The Department of Orthopaedic Surgery with FOP Patron Mrs. Diane Weiss, donor of The Isaac & Rose Nassau Professorship of Orthopaedic Molecular Medicine to Dr. Kaplan and supporter of the FOP Scientific Workshop, "Strategies for the Treatment of FOP"

Dr. Robert Pignolo conducting a session.

Discussions ensued in a series of small workshop sessions focused on four highly plausible areas of therapeutics, all bolstered by recent advances in FOP research.

The meeting was interactive and vibrant, highlighting an agenda that limited formal lectures and promoted brainstorming. The discussions and collaboration-building continued seamlessly well beyond the designated sessions. Participants discussed unpublished data and novel ideas in a dynamic interdisciplinary forum that began in a conference room environment and evolved in informal gatherings.

After brief introductions and scientific updates, the scientists self-assigned themselves to one of three small working groups (BMP pathways; Lesional stem cells; or the Microenvironment of early FOP lesions) for "shop talk" and a discussion of scientific and therapeutic priorities. Each workshop self-selected a group discussion leader who focused the conversation on the broad general question: "What is the biggest gap between what we know and what we need to know in order to achieve successful treatment and a cure for FOP? How do we get there in the short term (1-3 years) and in the long term (3-5 years)?"

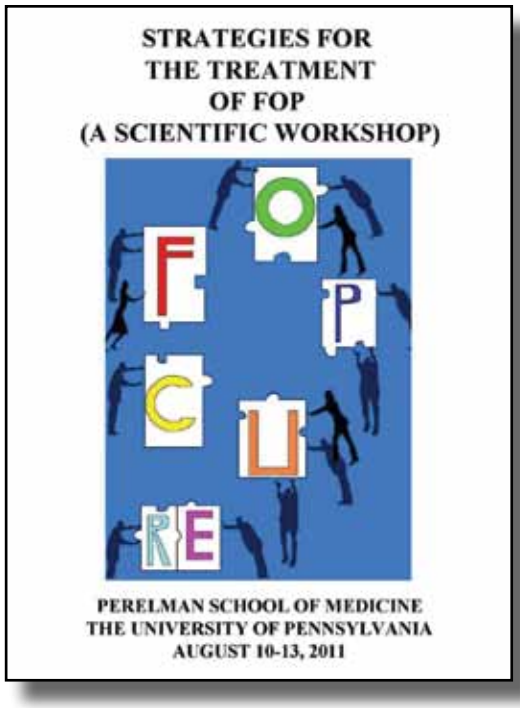
Dr. Petra Seemann (Berlin) on the left and Dr. Eileen Shore (Philadelphia)

Following the introductory workshops, the small working groups reconvened to summarize their proceedings for all in attendance. The remainder of the meeting was spent in several larger workshops where all of the scientists participated in the agenda of each of the smaller working groups.

The workshop participants represented diverse and far-ranging scientific fields relevant to the understanding and treatment of FOP including genetics, cell and molecular biology, immunology, neurology, vascular medicine, structural biology, biomechanics, animal model development, medicinal chemistry, pharmaceutical development, micro environmental biology, and clinical and translational medicine.

Manuel Robert, a 14 year-old young man with FOP from Buenos Aires, Argentina was commissioned to depict the theme of the workshop and the goal of all FOP research in a specially designed, computer-generated poster. Selected from among six renditions, the illustration joins the pantheon of work from historic FOP meetings:

- 1991: Save the FOP Children (Ashley Kurpiel)
- 1995: Accentuate the Positive (Sarah Steele)
- 2001: We are the World (Tiffany Linker)
- 2007: Together We Can Move Mountains (Hugo Fahlberg)
- 2011: Cure FOP (Manuel Robert)



The illustrated theme, a mandate in two words "Cure FOP," says all that needs to be said as the scientists moved the jigsaw pieces of the FOP puzzle into place. The meeting focused on critical pieces that still might be missing as well as currently available knowledge that could be translated most quickly into more effective treatments.

Recalling an earlier time, two decades ago (September, 1991), at the first FOP Symposium in Philadelphia when war was declared on FOP, the scientists recreated a war room atmosphere as they sat face-to-face around a large conference table and sketched the outlines for a final assault on a long-term enemy – FOP itself. The workshop culminated in an intense working session where treatment options, as presently conceived, were prioritized for further basic research and pre-clinical development. The workshop participants identified at least six available compounds with potential benefit for FOP (based upon their known molecular activities) that must be stringently tested in high-fidelity animal models of genuine FOP. That project, adapted with great enthusiasm by all, is presently ongoing in the core FOP laboratory.

The workshop think tank atmosphere had a verve and tone unparalleled in the history of FOP research. "The tools and enthusiasm were never more available to do so much," said one scientist commenting on the lightening exchange of ideas. "One could smell the ozone in the room."

The workshop was punctuated with a series of brief inspirational messages from members of the core FOP Laboratory and from The Center for Research in FOP and Related Disorders as well as from the Dean of the Perelman School of Medicine, the Chairman of the Department of Orthopaedic Surgery, members of the IFOPA Board, and from FOP patients Patrick Doerr and Ian Cali.

Dr. Petra Seemann (Berlin), Mr. Patrick Doerr (IFOPA Board Member) and Dr. Fred Kaplan (Penn)

Participants at the FOP Scientific Workshop from Left to Right: Dr. Aris Economides (Regeneron), Dr. Bjorn Olsen (Harvard), Dr. Vicki Rosen (Harvard), Dr. Karen Lyons (University of California - Los Angeles), Dr. Fred Kaplan (Penn)

Elevator greetings from the FOP Scientific Workshop. IFOPA board members left to right: Mrs. Amanda Cali (New Jersey), Mrs. Jennifer Snow (California), Mrs. Moira Liljesthrom (Argentina), Mr. Robert Snow (California), plus Dr. Jay Groppe (Texas) and Dr. Petra Seemann (Germany)

Dr. Bjorn Olsen (Harvard), Dr. Bettina Mucha-Le Ny (Penn) and Dr. Ernestina Schipani (Indiana)

Dr. Jameson, the Dean of the Perelman School of Medicine at the University of Pennsylvania wrote in his inaugural letter to alumni: "During the course of the summer, I had the opportunity to attend two events related to prominent donor-funded research initiatives. One of those was the Scientific Workshop on Fibrodysplasia Ossificans Progressiva (FOP). The work accomplished by this program is truly innovative, and it has been a distinct honor to meet the families involved, and to see firsthand the meaningful progress that they have enabled against this devastating disease. This is an example of how Penn scientists are changing our understanding of disease, and based on this knowledge, developing new treatments."

Dr. Robert Pignolo (Penn), Dr. Vicki Rosen (Harvard) and Dr. Viet Le (Brown)

The workshop, held at the Inn at Penn on the University of Pennsylvania campus, began with an informal reception at which the attendees were greeted by members of the Penn academic community and representatives of the IFOPA Board of Directors and culminated with a deep appreciation by all of the mysteries and miseries of FOP and the mandate and possibility for a cure. As FOP patient Ian Cali said, we have taken the step "from hopeless to hopeful."

With knowledge and hope inspired by the workshop, Ian expressed his thoughts in a moving and inspirational address to the scientists gathered at the meeting:

At the dinner reception seated from left to right: Mrs. Diane Weiss (FOP Patron and Workshop Sponsor), Dr. Eileen Shore and Dr. Petra Seemann. Standing: Dr. Fred Kaplan and Dr. Robert Pignolo.

"After I was asked to speak at this medical conference, I started thinking what I could say besides a genuine thank you that would not only catch all of your attention, but keep your interest. This conference is a very busy, but exciting time for everybody involved, and being one of the only FOP patients here, I feel I have a unique perspective on the potential these new discoveries hold. This is the first time in my life where a cure is actually something I can let myself believe may happen in the foreseeable future.

In the past, I was always hopeful that someday there would be a treatment for FOP, but it was a hope tainted with selfishness because I couldn't really do much to help discover it myself. After the gene discovery a few years ago, FOP research went from hopeless to hopeful. Scientists, researchers, FOP patients along with their family and friends instantly all had a piece of reality to base their hope on. Now that a bone-preventing compound is being investigated, it is as if scientists and

researchers such as yourselves have maybe found the key that will open the door to the treatment.

At the dinner reception seated from left to right: Dr. Robert Pignolo, Mr. John Cali, Mr. Ian Cali, Standing from left to right: Dr. Maurizio Pacifici, Dr. Ernestina Schipani, Mrs. Amanda Cali, Dr. Fred Kaplan and Dr. Tina Bales

A cure or treatment for FOP would be making my dream come true. Not the equivalent of a little boy wanting to be a fireman or a little girl wanting to become a ballerina, but bringing to life a dream that I don't even let myself think about. I've learned to live my life with the way things are, and even with how they may be once FOP progresses, but the possibility of a cure or treatment would help me accomplish new goals that wouldn't otherwise be possible, show love and affection towards those dear to my heart in ways I couldn't before, and allow my compassion and perseverance to spread into even more areas of life. Still being a young adult, I have a lot to look forward to in the rest of my life. When longterm goals are difficult or easy, fun or challenging, convenient or just worth whatever it takes, my mind is my battery when my body falls short of the task at hand.

I am lucky enough to have parents who duly supported my youthful desires before FOP prevented them from happening. They let me play soccer and football, never on a team, but always with friends and family, which is who I cared about doing those things with most. I ran as much as I could, rode a bike as fast as my legs would allow, scraped my knees, and got grass stains on my favorite jeans. While I have let go of all those things since my hip ossified in 8th grade, they are a cluster of fond memories that I will never regret or forget.

Since then, I have focused on genuinely appreciating the smaller things in life, perhaps at time giving the little things more credit than many of the others around me, but in the end, always learning to be happy and grateful for what I have instead of mourning what's been taken away.

As an FOP patient, I can assure you all that a big part of the roller coaster flare-ups take us on is often a big game of give and take. Some times we can do something to change the outcome, and the other times the only thing that comes to mind is the infamous question, "Why me?" In order to cope with this frustration, I try not to let myself get too hopeful that there will be a way to prevent FOP progression in the future because I don't want my current happiness to be tainted by the possibility of such a dream coming true.

To attempt to put this feeling into words would be cheating my elation, but think of it like this: being able to honestly tell an FOP patient that a cure has been discovered is the equivalent to successfully being able to show a sunset to a person who's been blind ever since they could remember.

I am truly grateful to all of you who are here trying to make a difference and I will be incredibly thankful for the rest of my life if your efforts are successful.

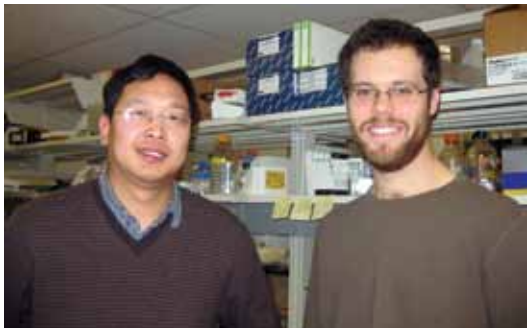
Mr. Ian Cali addressing physicians and scientists.

Thank you for giving me a chance to speak to all of you today."

Comprehensive Survey of FOP Flare-ups: Essential Background for the Design of a Clinical Trial

What, then? What will you build? Tell me at once.

— Ibsen (The Master Builder)



Postdoctoral fellow Dr. Haitao Wang and premedical student Carter Lindborg in the FOP Laboratory.

Student worker Xiaoyue Xie in the FOP Laboratory.

Flare-ups of FOP are sporadic and unpredictable, and there is great individual variability in the rate of disease progression. Several studies on the natural history of FOP have confirmed that it is impossible to predict the occurrence, duration, or severity of an FOP flare-up, although characteristic anatomic patterns of disease progression have been described. The rarity of FOP and the unpredictable nature of the condition make it extremely difficult to assess any therapeutic intervention, a fact recognized as early as 1916 by Jules Rosenstirn: "The disease was attacked with all sorts of remedies and alternatives for faulty metabolism; every one of them with more or less marked success observed solely by its original author but pronounced a complete failure by every other follower. In many cases, the symptoms of the disease disappear spontaneously so that the therapeutic effect (of any treatment) should not be unreservedly endorsed."

Comprehensive, contemporary knowledge of the occurrence and natural history of flare-ups is of paramount importance in the design of a clinical trial. Mechanism of action, safety, side effects and interactions of potential drugs needs to be understood in the context of spontaneous and induced FOP flare-ups.

In order to advance the design of meaningful clinical trials for FOP, it is absolutely necessary to obtain a contemporary understanding of the natural history of FOP with the present state of symptomatic management. Therefore, the FOP Center will be conducting an urgently needed international survey of FOP flare-ups. The results of this survey will be critical for designing much awaited clinical trials.

Regardless of whether or not one may be interested in participating in an eventual clinical trial, it is essential, that clinical information be obtained from all FOP patients worldwide so that the best possible comprehensive information about FOP is available. This is a very exciting time in FOP research, and the FOP community will be hearing about the survey in more detail in the near future.

Mrs. Kamlesh (Kay) Rai, Tim Hazlett (O'Fallon, Illinois), Dr. Fred Kaplan and visiting medical student Brendan Everett (Rutgers)

A Mouse with FOP

Riddle: "I am neither the architect nor the builder, but the product of both. Who am I?"

– The FOP Mouse

The most important scientific breakthrough this past year was the development of a genetically engineered mouse that mimics classic FOP.

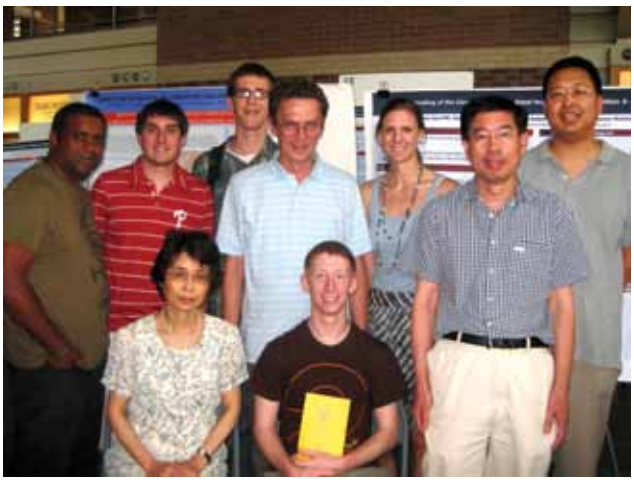
Lead author Salin Chakkalakal, PhD, postdoctoral fellow, and senior author Eileen M. Shore, Ph.D. unveiled the mouse model of FOP in a recent online edition of **The Journal of Bone and Mineral Research**.

Drs. Robert Pignolo, Haitao Wang, Fred Kaplan and Eileen Shore (far right) meet with visiting professor Dr. Ernestina Schipani (Indiana University) at the FOP Laboratory.

Until now, work on therapies for FOP has been hampered by the lack of a true mouse model containing the FOP mutation in which to test potential drugs. In this latest report, the scientists used a special gene targeting approach, called knock-in technology, to develop a precise mouse model of classic FOP. Unlike more common transgenic mouse models in which one or more copies of a mutant gene of interest are randomly inserted into the genome, the knock-in technology used by the Penn scientists exchanges one of the two normal copies of the mouse ACVR1/ALK2 gene with a mutant FOP copy of the gene in its natural chromosomal location, and in doing so preserves the precise genetic and molecular fidelity of the human disease. The resulting mice develop FOP, just like in people.

Animal models of human genetic disease are vital for validating the exact genetic cause of a condition, for understanding the cellular and molecular mechanisms of disease pathology, and for developing and testing translational strategies to prevent and treat affected individuals. Initial investigation of FOP used BMP protein implants to induce extraskeletal bone formation. More recent studies used transgenic mice that over-express BMP or that produces an artificially overactive BMP receptor. However, something critical was missing in all of those models. While they all produced heterotopic bone, none of them reproduced the detailed clinical features and inexorable progression of FOP in patients. In contrast, the new knock-in mice developed by the Penn scientists display all of the clinical and pathological features of FOP that are present in the human condition including the characteristic malformed toes and arthritic joints as well as the progressive and episodic heterotopic bone formation that is the devastating hallmark of the disease.

One remarkable difference though between FOP in mice and humans is that the mice are more sensitive to the mutation, particularly during embryonic development, an unusual finding in a mouse model of a human disease. The presence (from early development) of the FOP mutation in every cell of the mouse was lethal,



Members of the FOP Laboratory building the future at research day. Seated: Meiqi Xu and Michael Convente. Standing: Salin Chakkalakal, Andrew Smith, Brendan Everett, Vitali Lounev, Andria Culbert, Deyu Zhang, and Haitao Wang.

but mice that harbored the FOP mutation in just 70-90% of their cells still had all the features of human FOP, except more severe.

Sophia Castro-Anderson at her desk in the FOP Laboratory.

Addie Black of Lewisville, Idaho and her parents visit The University of Pennsylvania.

Unexpectedly, the scientists found that both healthy and mutant cells are present within the heterotopic bone, a finding that indicates that although the mutation is necessary to induce extraskeletal bone formation, the mutation is not required in every cell that becomes bone and cartilage. This remarkable finding sheds light on the cellular targets of the FOP mutation, an issue that could be addressed only in viable chimeras (mice containing both healthy and mutant cells).

Although FOP is exceedingly rare, affecting approximately one in two million individuals, it is illustrative of many more common conditions of extraskeletal bone formation that affect millions of individuals worldwide, and FOP may be a key to their understanding and solution. Such conditions include ectopic bone formation caused by brain and spinal cord injuries, athletic injuries, peripheral nerve injuries, burns, high impact war injuries, total joint replacement, valvular heart disease, and atherosclerosis.

The FOP knock-in mouse developed in the FOP laboratory at Penn is rare among animal models in its complete fidelity to all of the features of a complex human disease, and thus provides an invaluable tool to address therapeutic strategies for FOP and hopefully for more common forms of heterotopic ossification.

Architects of Sabotage: Backing-up the Runaway Train and Blowing-up the Bridge

Every assassin knows that it is futile to aim at a moving target; one aims at where the target will be when the bullet gets there.

– Anonymous

Be sure you positively identify your target before you pull the trigger.

– Tom Flynn

In a recent landmark study, Shimono et al. demonstrated a novel approach that blocks FOP-like bone formation, not prior to induction, but after the inflammation events leading to a flare-up have already occurred. The authors build on well-established findings that retinoic acid inhibits the cartilage scaffold of endochondral bone formation, a crucial function they exploit to derail heterotopic bone formation using potent and specific retinoic acid receptor gamma (RARg) agonists. Studies in mice show that both the pre-cartilage and cartilage stages of heterotopic bone formation are exquisitely sensitive to the inhibitory effects of RARg agonists, which block BMP signaling and the bone forming potential of progenitor cells.

RARg agonists effectively inhibit heterotopic bone formation in FOP animal models during a wide treatment window that begins at the pre-cartilage phase and continues up to (but not including) the bone-forming phase. Remarkably, when RARg agonists are discontinued, no significant rebound effect occurs, indicating that the RARg effect may be irreversible, perhaps through mechanisms that redirect cell fate decisions in pre-cartilage connective tissue cells.

The study by Shimono et al. thus identifies RARg agonists as a class of compounds that profoundly inhibit the cartilaginous scaffold of heterotopic bone formation. The beauty of this approach is that it does not just target the BMP signaling pathway that is dysregulated in FOP, but does so in the very cells that build a second skeleton. RAR-gamma agonists are potent weapons to stop a runaway train - derailing it before it reaches its dangerous and catastrophic destination.

During the past year, robust work has continued on the development of an RARg agonist for use in a clinical trial in FOP. One of these compounds has been through human safety trials in adults, and efforts are currently being directed towards the development of a clinical trial with this compound.

While there are many intangibles in the development of such a clinical trial, plans are proceeding, and updated information will be forthcoming, as progress is made. Presently, this is our highest priority in FOP therapeutics because we think that it has high potential to be effective for FOP and because we may be able to bring it to clinical trials more quickly than any other potential treatment. It is unlikely that any one medication will accomplish all of our goals, but that should not prevent us from starting.

Daniel Licht of Scarsdale, New York (3rd from right) and his parents Peter Licht (far left) and Jeri Licht (far right) visit with Kay Rai, and Dr. Kaplan and Rutgers medical student Brendan Everett at Penn.

FOP Patron Mr. Richard Simcox, Founder and Managing Director of Roemex Limited, Specialty Oilfield Chemicals of Aberdeen Scotland visits with Dr. Kaplan during a trip to Philadelphia.

Blocking Activity of the FOP Receptor (ACVR1/ALK2)

There was nothing to be said of them, except that each structure was inevitably what it had to be.

– Ayn Rand (The Fountainhead)

Signal transduction inhibitors (STIs) are important molecular tools for studying BMP signaling in FOP, and have the potential to be developed into powerful therapeutic drugs for FOP. Several years ago, the small molecule STI Dorsomorphin was identified in a screen for compounds that perturb BMP-regulated embryonic pattern formation in zebrafish. Dorsomorphin and its derivatives inhibit all type I BMP receptors (ALK2, ALK3, and ALK6), and completely blocks downstream BMP-signaling. However, a safe and effective STI for FOP must preferentially inhibit ACVR1/ALK2 (the FOP gene) over ALK3 and ALK6, rather than completely bock all BMP signaling, and must not affect other critical cellular receptors. STIs designed to specifically block ACVR1/ALK2 must have specificity, efficacy, tolerance to resistance, acceptable safety profiles, and be shown to lack rebound effects before they can enter clinical trials for FOP.

FOP: From A Fishing Expedition to a Master Plan

Treasure your exceptions! Keep them always uncovered and in sight. Exceptions are like the rough brickwork of a growing building which tells that there is more to come and show where the next construction is to be.

—William Bateson (Geneticist; 1908)

Nancy Humphrey, a journalist from Vanderbilt University, recently highlighted the work of Dr. Charles Hong, the discoverer of Dorsomorphin in a feature article in **Vanderbilt Medicine,** entitled, "Prison of Bone." Humphrey wrote: "A scientist and zebrafish offer the best hope for a cure for a rare and disabling bone disease. Greek mythology is rich with stories of gods and goddesses who suddenly and tragically turn to stone. But, for fewer than 3000 people in the world, this mythological metamorphosis to bone is no legend. A rare and disabling disorder, FOP replaces soft tissue-like muscle and connective tissues with bone. People with FOP basically form a second skeleton that locks the body in place."

Dr. Charles Hong (Vanderbilt University) and Dr. Eileen Shore at the FOP Scientfic Workshop, "Strategies for the Treatment of FOP."

Humphrey describes the pioneering work of Dr. Charles Hong, M.D., Ph.D., an Assistant Professor of Medicine, Pharmacology and Cell Biology, whose drug research has discovered a compound that could prevent the progression of FOP. Humphrey wrote, "In 2006, the FOP gene was discovered by Kaplan, Shore and their colleagues at The University of Pennsylvania. The scientists found that the exact same mutation occurred in the bone morphogenetic protein receptor ACVR1/ALK2 in every classically affected FOP patient. The same year, Hong (then at Harvard Medical School) and his colleagues discovered a compound they named Dorsomorphin that could inhibit all BMP receptors.

'We kind of stumbled upon it, and through our discovery have made some really good friends who have treated FOP patients for years', Hong said. 'I am new to this field but our friends at the University of Pennsylvania have dedicated their entire careers trying to find the cause and a cure.'

Hong's lab at Vanderbilt has its tanks of zebrafish, an important genetic animal model that was originally recovered from the Ganges River in India. Zebrafish embryos are used in understanding the process through which all vertebrates, including people, develop from the moment that sperm fertilizes an egg. The zebrafish eggs are clear and develop outside of the mother's body allowing scientists to watch them grow into newly-formed fish.

A cardiologist at the Vanderbilt Heart and Vascular Institute, Hong studies chemicals that control how different parts of the body form at precisely specified locations. When he found that Dorsomorphin was an inhibitor of the gene involved in FOP, his research suddenly went in a very different direction.

'We could wait for drug companies to do it, but they aren't going to spend a hundred million dollars on a disease that affects fewer than 3000 people. It is not cost effective for them. But, that is one of the great things about Vanderbilt. We have resources that other universities simply don't. We can take full advantage of the drug discovery expertise of The Vanderbilt Institute Chemical Biology and make improved versions of Dorsomorphin and test them on FOP mice with our colleagues at Penn, with the ultimate hope of delivering these in the first trials for people with this disease in the

next few years.' Kaplan says that, 'If we can effectively and selectively block this pathway, we might turn FOP from a catastrophic condition into something that is only a minor inconvenience.' "

In 2011, the NIH announced that Dorsomorphin-like compounds discovered by Hong and developed by his former colleagues at Harvard had been selected for further refinement in the Therapeutics for Rare and Neglected Diseases (TRND) program. The TRND program of the NIH is part of a congressionally-funded effort to encourage and speed the development of new drugs for rare and neglected diseases. As described by the NIH, "TRND will bridge the wide gap in time and resources that often exist between basic research and human testing on new drugs. The effort is grounded in, but aims to improve upon existing processes used for drug development in the pharmaceutical industry. TRND will concentrate its efforts on the pre-clinical stage of drug development. TRND's aim will be to move candidate drugs forward in a drug development pipeline until they meet FDA requirements for an investigational new drug (IND) application. Once TRND generates enough data to support an IND application for a candidate drug, the drug will then be handed off to an experienced organization outside of NIH, such as a pharmaceutical company, for human testing.

Typically, drug development begins when academic researchers studying the underlying cause of a disease discover a new molecular target. Too often the process gets stuck at the point of discovery because academic researchers can not conduct all the types of studies needed to develop a new drug. If a pharmaceutical company with the resources to further the research gets involved, substantial pre-clinical work begins with efforts to optimize the chemistry of the potential drug. This involves an iterative series of chemical modifications and tests in progressively more complex systems. Only if these stages are successful, can a potential treatment move to clinical trials in patients.

Unfortunately, the success rate in this pre-clinical process is low with 80-90% of projects failing in the pre-clinical phase and never making it to clinical trials. Drug developers colloquially call this: "The Valley of Death"

TRND works closely with disease specific experts on selected projects using both in-house scientific capabilities needed to carry out much of the pre-clinical development work. If a compound does survive this pre-clinical stage, TRND scientists at the NIH will work to find a company willing to test therapy in patients. The NIH's goal is to get new medications to people currently without treatment and thus without hope."

Scientists and Clinicians from Penn are working with both the Vanderbilt and Harvard groups to bring the best STIs (Signal Transduction Inhibitors) to clinical trials.

Kelsey Rettinger of Ashtabula, Ohio in Dr. Kaplan's office at Penn.

Foremen on the Construction Site: Nerves and Immune System Trigger the Building of a Second Skeleton

Everything needed to solve the problem is in the room.

– Edwin Land
(Inventor of the Polaroid camera)

In FOP and related common disorders of acquired heterotopic ossification, sensory nerves regulate the innate immune system and amplify the formation of heterotopic bone. That's right; the nervous system

and the immune system are in cahoots! Substance P, an 11 amino acid neurotransmitter and potent neuroinflammatory protein, plays a key role in this metamorphosis, and provides a critical link between the sensory branch of the nervous system and the innate immune system in the induction and amplification of heterotopic ossification. The dysfunctional sensory innervation of the innate immune system is BMP pathway dependent, and unveils a myriad of unanticipated new targets for the treatment of FOP and related disorders of acquired heterotopic ossification. This work establishes a common mechanism underlying lesion induction for nearly all forms of heterotopic ossification including brain and spinal cord injury, peripheral nerve injury, athletic injury, total hip replacement, and FOP. These novel findings ushered in a new era in the understanding of heterotopic ossification that were explored in two complementary articles published in the July 2011 online edition of **The Journal of Cellular Biochemistry**.

Heterotopic ossification, the formation of extraskeletal bone, is frequently associated with injuries to peripheral nerves, the spinal cord, or the brain; yet, a distinct causative relationship between heterotopic ossification and the nervous system has eluded discovery – until now. A new collaborative scientific study from Northwestern University and The University of Pennsylvania, and a complementary study from Baylor University - both published in the July online edition of **The Journal of Cellular Biochemistry** - lift the veil of obscurity that has plagued physicians and scientists for over a century, and places FOP at the bull's-eye of this astounding discovery.

Everyone who has FOP knows that disease progression can be triggered by minor soft tissue injury, and that flare-ups can be painful. What was not known - until now - is that the same sensory nerves that carry pain signals to the brain also amplify the inflammatory response that leads to catastrophic explosions of new bone formation.

The studies from two independent groups of investigators paint a broad and sweeping picture of a peripheral nervous system out of control, fanning the flames of inflammation, and amplifying the body's response to injury in common forms of heterotopic ossification as well as in FOP. The studies establish a common mechanism of lesion formation for sporadic forms of heterotopic ossification including brain and spinal cord injury, peripheral nerve injury, athletic injury, total hip replacement, as well as FOP.

Research scientist Dr. Petra Seemann of Berlin, Germany visits with Dr. Kaplan in his office at Penn.

Together, the two studies used four different mouse models of heterotopic ossification as well as early lesional biopsy specimens from FOP patients and those with various forms of acquired heterotopic ossification. The immense scientific power of these studies derives from their use of genetically engineered knockout mice to study the critical relay points in the neuro-inflammatory pathway.

The story begins with the arcane and colorfully named TRPV1 (Transient Receptor Potential Vanilloid 1) cationic channel receptor located on the sensory nerve endings in injured muscle and other soft connective tissue. The response of this receptor gets out-of-hand early when soft tissue injury produces prostaglandins and bradykinins that trigger the bone morphogenetic protein (BMP)-sensitized cationic channel receptor to release a flood of calcium and magnesium ions that travel up the sensory nerve as an electrochemical signal. A branch of this signal enters the spinal cord and continues up to the brain, causing the sensation of pain. However, heterotopic ossification is induced when another branch of the signal reaches the nucleus of the sensory nerve cells in the dorsal root ganglia near the spinal cord and

triggers the sensory neurons to manufacture and release Substance P, a potent and inflammation-inducing neurotransmitter. A flood of Substance P then travels back down the nerve and is released at the nerve ending in the injured muscle where it binds to Substance P receptors (NK1R) on tissue mast cells. Once bound to the mast cells, Substance P triggers the release of inflammation-inducing and edema-causing chemicals that ramp-up the innate inflammatory response, fanning the flames of heterotopic ossification.

Mya Watts of Powder Springs, Georgia meets with Dr. Kaplan at Penn.

The experiments in the genetically engineered and pharmacologically-manipulated heterotopic ossification forming mice show that blocking any major control point in the sensory nerve pathway - the TRPV1 ion channel, the dorsal root ganglion cells, the preprotachykinin (PPTA) gene that encodes Substance P, the neurokinin 1 receptor (NK1R; the receptor for Substance P), the tissue mast cells that express NK1R, or the c-kit gene (required for mast cell development) - curtails or abolishes heterotopic ossification. Thus, when the fire door of the sensory nervous system is shut, the innate immune response is extinguished, and heterotopic ossification ceases.

The neurological innervation of the innate immune system is a complex feedback system that allows the body to ramp-up an inflammatory response when needed, but control it so that it does not run amuck. In a recent article entitled *"Ancient Neurons Regulate Immunity,"* Kevin J. Tracey wrote: "A general principle in physiology is that neurological control of a system provides a regulatory framework that can fine tune responses over time and space." Such a mechanism likely arose to regulate the balance between fighting infection or healing wounds on one hand and controlling a runaway innate immune system that could kill the host on the other hand. However, complexity has its price. When such a system goes awry, disease processes such as heterotopic ossification and FOP occur. In health, the system likely functions to down-regulate inflammation rather than amplify it. Whatever details are yet to emerge about the neurological control of the innate immune system, it is clear that overactive BMP signaling turns a normally-functioning fire door into one that doesn't close and allows the fire to spread, sabotaging the integrity of the organism, mouse or human.

Taken together with other recent discoveries, these two studies expand the repertoire of cellular receptors that can be targeted for the treatment of heterotopic ossification in general and for FOP specifically. For individuals with classic FOP, the causative mutation in the ACVR1/ALK2 gene is upstream of all FOP activity. Far downstream in the pathway is the retinoic acid receptor gamma (RAR-gamma) gene, a nuclear receptor that regulates the fate of chondro-osseous progenitor cells that are likely recruited by the inflammatory process. Both receptors are druggable targets for heterotopic ossification, and intense work is underway in both of those arenas. To those already identified targets, we can now add TRPV1, a cationic channel receptor expressed in primary sensory neurons and NK1R, a G-protein coupled receptor expressed in tissue mast cells. This expanding list of receptors provides a tangible repertoire of targets for the treatment of FOP and other sporadic forms of heterotopic ossification. There will certainly be more.

These two new studies have enormous implications for all forms of heterotopic ossification. What do they mean specifically for those with FOP? Although initiated by a single nucleotide mutation in a single gene (ACVR1/ALK2), FOP is an extraordinarily complex disorder of tissue metamorphosis that involves environmental triggers, including a dysregulated neuro-immune system, and a stem cell response that leads to disabling heterotopic ossification. The solution for FOP - and likely for all common forms of heterotopic ossification

- will likely involve a multi-faceted approach that considers multiple targets that regulate critical events in the evolution of a lesion. The latest studies provide groundbreaking insight into a neuro-immune system gone haywire, and some exciting new leads into how to restore it to its proper function.

The Architect's Drawing Board

I am the architect, not the builder.

– Melville (Moby Dick)

If one wanted to know how an ancient organism – one that has been around for nearly a billion years - can help us understand FOP, Exhibit A might be Kristi Wharton's fruit flies. Although fruit flies don't have bones and people with FOP don't have wings, the similarity of the metamorphosis that occurs in flies and in humans with the FOP mutation is truly remarkable.

And, no wonder! The bone morphogenetic protein (BMP) signaling pathway involved in the development of the fly and in FOP has remained essentially unchanged for the past 800 million years, the last time that fruit flies and humans shared a common ancestor.

To paraphrase Michael Crichton (**Jurassic Park**). "People can not imagine geological time. Human life is lived on another scale of time entirely. An apple turns brown in a few minutes, silverware turns black in a few days, a compost heap decays in a season, a child grows up in a decade. None of these everyday human experiences prepare people to imagine the meaning of 80 million years."

Now, take that time span and multiply it by ten – that's right - 800 million years! The BMP signaling pathway has been around for that long, and the BMP signaling pathway in fruit flies is nearly identical to that in humans. In fact, tinker with the ACVR1/ALK2 gene in the fly (called Saxophone; or Sax) in just the right way and you get a fly with FOP.

Recently, scientists learned that a single or double dose of the mutant ACVR1/ALK2 receptor that causes FOP can lead to extraordinary increases in BMP signaling, and ultimately heterotopic bone in humans. But, what does a single or double dose of the wild type ACVR1/ALK2 receptor do? Well, the results are, to say the least, stunning, and unexpected. In a recent paper, in **Developmental Dynamics**, Dr. Kristi Wharton, and her postdoctoral fellow, Dr. Viet Le (supported by the Ian Cali Developmental Grants Program of the Center for Research in FOP & Related Disorders at Penn), have shown in fruit flies that a single wild type dose of ACVR1/ALK2 acts as a mild stimulant, but a double dose acts as a powerful inhibitor. In other words, one dose of wild type ACVR1/ALK2 gives cells a jump start; a double dose throws them into a brick wall.

When damaged in a very specific way (as in the FOP gene mutation), the ACVR1/ALK2 receptor no longer acts as an inhibitor, but as a powerful stimulator. In flies, the mutant form of the receptor causes a completely abnormal pattern to develop; in humans it causes extra bone to form that locks-up the joints. These unexpected findings raise the possibility that ACVR1/ALK2 evolved not to stimulate or inhibit developmental processes, but to do both - to act as a context-dependent developmental modulator.

It is not easy to think of a system in nature where one of something normally facilitates a process and two of that same thing dramatically inhibits it. But, for the moment, that appears to be what we have here. The Wharton-Le paper shows us that wild type ACVR1/ALK2 can antagonize as well as promote BMP signaling depending on whether it partners with itself (double-dose inhibitor) or another BMP type I receptor (single-dose stimulant). Most importantly, these findings have vital therapeutic implications – if we could only silence the damaged copy of the gene – and abolish the possibility of over-active signaling.

The Architects of Change & the Sounds of Silence

And the vision that was planted in my brain still remains,within the sounds of silence.

—Simon & Garfunkel
(The Sounds of Silence)

In the most direct approach yet to the treatment of FOP, scientists at the Center for Research in FOP and Related Disorders at the University of Pennsylvania and scientists working independently in Japan have developed a new genetic approach using small sequences of ribonucleic acid (RNA) to silence the damaged copy of the FOP gene in cells while leaving the normal copy untouched.

Every human being has two copies of the ACVR1/ALK2 gene in every cell in their body. Individuals with FOP have one normal copy and one damaged copy of the gene in each cell – a dangerous occurrence that causes over-activity of ACVR1 and that tips the scales to renegade bone formation, the dreaded consequence of FOP.

Using inhibitory RNA designed and engineered to specifically silence the damaged copy of the gene and not the normal copy (a process known as RNA interference or RNAi), the scientists restored the cellular function that was deranged by the FOP mutation by virtually ridding the cells of the damaged, mutant, and dangerous ACVR1/ALK2 mRNA. The cells were essentially left with only normal copies of ACVR1/ALK2 mRNA, thus adjusting the cellular activity to normal. A tremendous advantage of this approach is that ACVR1/ALK2 activity is not abolished in the cell, but brought to more normal levels, similar to that of cells without the FOP mutation.

Imagine identical twin pilots of a commercial jet airplane. The twins are both in the cockpit. For all outward appearances, they look identical and behave identically. However, one of the twins is a good pilot and the other is a terrorist. What distinguishes them is one letter in a simple instruction on how to fly the airplane, tattooed on each of their wrists.

And, as in all of genetics, the instructions are written in code words of three letters each. The good twin's tattoo says: "Now fly the jet." The tattoo of the terrorist twin says: "Now fry the jet." Just one letter difference, but the fate of the plane hangs on that one letter. The new approach developed by members of the Penn FOP research team uses allele-specific (twin specific) inhibitory RNA designed to recognize the one letter difference in the tattoos, and silence the evil twin so that the good twin can fly the airplane safely. After the preemptory stealth attack by the allele-specific inhibitory RNA (that identifies and silences the evil twin terrorist pilot) the plane is left with only one pilot, but a good responsible pilot. All is well!

In a landmark paper published in the Thursday October 20, 2011 online edition of **Gene Therapy** (a **Nature** journal), Dr. Josef Kaplan, Dr. Frederick Kaplan, and Dr. Eileen Shore, all from the FOP Research Laboratory of the Perelman School of Medicine at The University of Pennsylvania, describe in detail this new stealth-like proof-of-principle approach for treating FOP.

In their study, the authors generated specific inhibitory RNA (RNAi) duplexes capable of silencing the expression of the mutant copy of the gene in bone progenitor cells from FOP patients (while leaving the normal or good copy untouched) and importantly show that this approach decreased the elevated BMP signaling in FOP cells to levels observed in control cells. The cells used in the experiments were adult stem (or progenitor) cells obtained directly from discarded baby teeth of FOP patients and thus contained the exact combination of damaged and normal ACVR1/ALK2 receptors found in all classically affected FOP patients worldwide. The discarded teeth were obtained from FOP pediatric patients and normal controls in the ongoing "FOP Good Tooth Fairy Program."

While the approach outlined in this landmark study provides proof-of-principle for the use of allele–specific inhibition of ACVR1/ALK2 in the treatment of FOP, the *in vivo* utility of this approach must be confirmed in mouse models of classic FOP prior to its consideration for human use. Additionally, other hurdles stand in the way of human application at the present time, most notably safe delivery of the small RNA duplexes to cells

in the human body. "We have a very long way to go," acknowledge the investigators, "but we have taken a big first step."

Dr. Kaplan out for an early morning stroll in the mountains of Western Canada.

Improvements in RNAi design are advancing at a rapid rate and will enhance the stability, potency, and specificity of the inhibitory RNA allowing for long-term experiments both *in vitro* and *in vivo*. The new RNA interference approach developed by the Penn scientists can be applied to emerging mouse models of FOP providing hope for a novel therapeutic strategy to decrease and perhaps eliminate the catastrophic heterotopic bone formation in FOP patients.

In an editorial in **Gene Therapy**, Drs. Lowery and Rosen from the Department of Development Biology, Harvard School of Dental Medicine, wrote: "The discovery of the genetic mechanism of FOP in 2006 was a tremendous accomplishment and renewed the hope of finding a cure. In two separate reports, published in **Gene Therapy**, Kaplan *et al*. and Takahashi *et al*. provide preliminary evidence of the ability to selectively suppress constitutively active (ca)ACVR1/ALK2. Both studies utilize allele-specific RNA interference (ASP-RNAi) to target (ca) ACVR1/ALK2 mRNA for degradation. Importantly, careful design of the siRNAs allows the authors to discriminate between mutant and normal mRNAs, thus preserving expression of normal ACVR1/ALK2. By doing so, the level of BMP signaling in cells obtained from FOP patients, which are basically higher than control cells, can be reduced to normal levels. These studies are the most recent examples of the growing applicability of the use of ASP-RNAi for treating human disease. ASP-RNAi has been preliminarily applied to the study of several diseases, most often of a neuronal or nerve degenerative nature and a Phase I clinical trial determining the safety and toxicity of ASP RNAi for treatment of another rare disease was recently completed. Classic FOP is an ideal candidate disease for ASP-RNAi because of the strikingly common nucleotide mutation (c.617G>A) among FOP patients. This important direction has clear translational advantage, even over many other monogenic autosomal dominant diseases associated with heterozygous mutations, as it would allow for careful validation and clinical trial of a single set of small inhibitory RNAs (siRNAs) that could potentially treat all classic FOP patients.

Although the results of Kaplan et al and Takahashi et al provide promising proof- of-principle for the allele-specific silencing ACVR1/ALK2 in the treatment of FOP, there are outstanding questions that must be answered before this technology can be translated to humans. For instance, it is presently unclear how mild constitutive activation of ACVR1 leads to severe heterotopic ossification. It is noteworthy that (ca) ACVR1/ALK2 is likely expressed in all cells that also express normal ACVR1. However, heterotopic ossification only occurs in a considerably smaller domain in FOP patients. Collectively, these findings are highly suggestive that specific responses downstream of ACVR1 might be regulated in a cell type - and/or context-dependent manner. All of the above underscore the importance of identifying the cell types responsible for heterotopic ossification in FOP. Identification of the entire repertoire of cell types involved in heterotopic ossification will also aid in solving a general concern for the use of ASP-RNAi *in vivo* which is how to preferentially target RNA-mediated silencing to sites of disease. Previous approaches have included the use of viruses with significant tropism for cells/tissues of interest, and one could envision utilizing cell type-specific promoters to drive expression of siRNAs *in vivo*. With these considerations in mind, FOP therapy is a step closer to actuation."

Sheryl Hadley, Chairman of FOP Action - UK writes, "We are generally encouraged by the recent important and significant steps towards a search for the FOP cure,

but we must be cautious. The new work applying this (RNAi) approach to FOP is at a very early stage and is another sword in the armory of research strategies, aimed at stopping extra skeletal bone formation. Hopefully, now with different lead ideas for drug development, including the presently described technology, one can make it home. We are all committed to finding the fastest, most effective, and safest treatment for FOP."

Architecture at the Atomic Level

Form follows function

– Louis Sullivan (Architect)

Work in the US and UK in 2011 has highlighted the atomic microstructure and activity of the FOP receptor. X-ray crystallographic work at Oxford University under the direction of Dr. Alex Bullock has elucidated how Dorsomorphin fits inside of the working part of the ACVR1/ALK2 receptor to turn it off. Unfortunately, the Dorsomorphin molecule and its newer derivatives also fit into the working part of other BMP type I receptors and turns them off too, limiting the potential efficacy and safety of such an approach in treating FOP patients at the present time. Nevertheless, such molecular and atomic knowledge is stimulating the design of more specific inhibitors for eventual use in FOP patients. Dr. Jay Groppe and his colleagues at Baylor College of Dentistry are examining the function of the wild type and mutant ACVR1/ALK2 receptor and its molecular activity at the atomic level. Online and print publications from both groups have elucidated the workings of this most unusual receptor that is the ultimate architect of FOP. Additional robust work in this area will be forthcoming in 2012.

Shaking the Foundations

It was an earth-shaking and memorable experience for the medical students as FOP patients Holly Pullano and Laura Rossano met the first year students of the Perelman School of Medicine at the University of Pennsylvania and introduced them to FOP.

At the exact moment that a historic and rare 5.8 earthquake struck the east coast of the United States, Holly Pullano and Laura Rossano were meeting the medical students and beginning to share with them their life-altering experiences with FOP.

Danielle Graham, a first year Penn medical student wrote: "I just wanted to let you know how wonderful the talk was on Tuesday. It was incredibly moving, and I know many of my classmates felt the same way. A huge thanks go to Laura and Holly and their friends and family for coming to speak to us. It was such a great experience for all of us. Their willingness to share their stories was both touching and inspiring."

Laura Rossano wrote about the experience: "It was the most unbelievable experience and I was so honored to do it. To say, I had an amazing time, doesn't seem

Dr. Eileen Shore, Ms. Holly Pullano, Ms. Laura Rossano, and Dr. Fred Kaplan after the 5.8 earthquake and the "earth-shattering " FOP Session with medical students at Penn.

fitting. It was absolutely incredible! Thank you for giving me this opportunity to speak to the medical students. It is something I don't think I will ever forget. It was an experience of a lifetime!"

The Construction Site

Why, I am going to build that myself.

– Ibsen (The Master Builder)

After 20 very busy and exciting years, the FOP Core Laboratory at **The Center for Research in FOP and Related Disorders** is being renovated. The architects have completed their plans and the builders are busy at work. The renovations will provide a state of the art laboratory for all core FOP research activities. The wonderful pictures that make the FOP laboratory unique are safely in storage during the renovation and will be displayed for the re-dedication of the laboratory later this summer.

FOP research continues at a lively pace in temporary laboratory space in the Department of Genetics at Penn's Perelman School of Medicine. The Penn FOP team thanks the Genetics Chairman, Steve Liebhaber, and the entire genetics faculty for their hospitality and support to keep the work moving forward. The FOP team hopes to return to the renovated FOP laboratory by late spring 2012, and will bring you pictures of the re-dedication later in the year.

Blueprints for renovation of the FOP Laboratory.

The Penn FOP Research Team steps-in to inspect the ongoing renovations of the FOP Laboratory.

FOP Treatment Guidelines: Revised and Updated

The discovery of the FOP gene established a critical milestone in understanding FOP and has propelled approaches for developing novel therapies for this disabling disorder of tissue metamorphosis.

While effective treatments for FOP will likely be based on interventions that modulate overactive ACVR1/ALK2 signaling or that specifically block heterotopic ossification, present management is focused on early diagnosis, assiduous avoidance of injury and iatrogenic harm, symptomatic amelioration of painful flare-ups, and optimization of residual function. These comprehensive management principles are outlined in the **Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations (FOP Treatment Guidelines)** by the International Clinical Consortium on FOP (May 2011). The updated guidelines are available to all patients, families, and physicians worldwide on the IFOPA website: www.ifopa.org .

FOP: The Written Word – 2011

In 2011, major publications on FOP appeared in peer-reviewed journals including **Nature Medicine; Gene Therapy; Cells, Tissues and Organs; Journal of Cellular Biochemistry; The Journal of Bone & Mineral Research; Annals of the New York Academy of Sciences; Current Osteoporosis Research; Orphanet Journal of Rare Diseases; Pediatric Bone Biology & Diseases; Cell Stem Cell; and Kidney International.** As of January 1, 2012, the classic paper in **Nature Genetics** (April 2006) describing the discovery of the FOP gene has been cited in more than 250 major scientific publications worldwide. The much awaited, updated, and revised fourth edition of **The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations** (The FOP Guidelines) has been completed and is available on the IFOPA website.

FOP: The Spoken Word – 2011

During 2011, major lectures on FOP were presented at the:

- Advances in Mineral Metabolism Annual Meeting; Snowmass, Colorado
- American College of Rheumatology; Chicago, Illinois
- American Society for Bone & Mineral Research Annual Meeting; San Diego, California
- Children's Hospital of Philadelphia; Philadelphia, Pennsylvania
- FOP Italia Annual Meeting; Rome, Italy
- Gordon Research Conference on Bone and Teeth; Les Diablerets, Switzerland
- Harvard School of Dental Medicine; Boston, Massachusetts
- Heritable Disorders of Connective Tissue Translational Research Conference; Portland, Oregon
- International Workshop on FOP; Philadelphia, Pennsylvania
- Latin American FOP Meeting; Buenos Aires, Argentina
- Mercy Medical Center; Sioux City, Iowa
- Mutter Museum at the Philadelphia College of Physicians; Philadelphia, Pennsylvania
- New York Skeletal Biology and Medical Conference; New York City,
- New York
- Odense University; Odense, Denmark

- Perelman School of Medicine at the University of Pennsylvania; Philadelphia, Pennsylvania
- Thomas Jefferson University; Philadelphia, Pennsylvania
- University of Delaware; Newark, Delaware

During 2011, highlights of FOP research were presented at local, regional, national, and international FOP family meetings and gatherings in:

- Allentown, Pennsylvania
- Buenos Aires, Argentina
- Mountainside, New Jersey
- Orlando, Florida
- Philadelphia, Pennsylvania
- Rome, Italy
- Sioux City, Iowa

Danilo Conde of Columbia, South America (center with 3D glasses) and his mother (second from left) met with Dr. Robert Pignolo (left) and Dr. Fred Kaplan (right) at the Second Latin Americn FOP Familly Meeting in Buenos Aires, Argentina.

The FOP Team: Architects and Builders

The fate of the architect is the strangest of all. How often he expends his whole soul, his whole heart and passion, to produce buildings into which he himself may never enter.

– Goethe

A team of incredibly dedicated colleagues, collaborators, consultants, research scientists, physicians, post doctoral fellows, doctoral candidate students, undergraduate students, high school students, technicians, research assistants, administrative assistants, and volunteers contribute every day to the mission of caring for FOP patients, deciphering the cause of FOP, and applying that knowledge to the development of preventions, treatments, and eventually a cure for FOP. These are the human architects and builders of FOP research. These are the individuals who have the vision, draw the blueprints, and construct the foundations and the skyline that are the future of FOP. They are the fountainhead and backbone of FOP research at home and around the globe. The pictures of some are on these pages and the names of all indelibly inscribed in the annals of science with important accomplishments and discoveries. We honor them for their service and commitment to the FOP cause, and we are proud of them all.

FOP: Everyone Can Help

Patients, families, friends, even casual visitors to the FOP laboratory often ask: "What can I do to help?" The answer is simple. "Anything you can."

Research is laborious, time consuming, often frustrating and costly, filled with false starts, blind alleys, glimmers of hope and the fog of frustration, but so too is the FOP we are trying to cure. Formidable enemies require formidable opponents, and teamwork requires resources. When seminal discoveries are made and ignorance is extinguished, the fog lifts, and the summits, and the paths between them become clear. When knowledge advances, it successfully illuminates the way ahead to the next horizon and there is nothing like it. It is a powerful beacon that changes the world like nothing else can. The feeling of accomplishment for all who contribute in any way 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.

Where would we be without vaccines, antibiotics, CT scans, MRIs, recombinant proteins like insulin, growth hormone erythropoietin, medications to raise our blood count and to lower our blood pressure, small molecule inhibitors to combat certain leukemias? Where would we be without the basic research that made it all possible? All of these efforts started on a small scale because something had to be done, and with commitment and resources they were done.

When modern FOP research began 20 years ago in a small laboratory at the University of Pennsylvania, there was little basic knowledge about this terrible disease, and little hope outside an infinitesimally small inner circle of believers who knew in their heart that something could be done to change it. Hope prevailed - hope fueled by the faith and commitment of a dedicated/persistent few who year after year funded studies to create and sustain a team dedicated to make a difference. Over the years, that team has grown and expanded and its reach now extends around the world.

Dr. Kaplan at the Allentown Fair Grounds for Bingo for a Cure in honor of Joshua Scoble to benefit the IFOPA.

A cheerful contingency greets Dr. Kaplan at Bingo for a Cure. Back row left to right: Patrick Doerr (King of Prussia, PA); Lindsay Ruiz (Somers, NY); Kathy Hall (Somers Point, NJ). Front row left to right: Joshua Scoble (Allentown, PA); Joey Hollywood (Bridgewater, NJ).

Through a sustained effort at the core FOP laboratory and at The Center for Research in FOP & Related Disorders, research is eradicating the stifling ignorance that was prevalent just two decades ago. Barrier after barrier has fallen and achievable goals are in reach. FOP research holds real promise of preventing, treating, and curing FOP. It is no longer an imaginary dream. We need your help now more than ever to make this a reality. The often-heard comment, "Call us when you have a treatment or a cure," is an option, but not one that will get us there. Everyone has a stake in this effort. We need your help in getting there: bake sales, Burns' Suppers, barn dances and bingo; chicken barbeques and spaghetti dinners, garage sales and silent auctions; country fairs and benefit concerts at the Metropolitan Opera; raffles and rodeos, sales of holiday cards and embroidered quilts, 5K runs and ice fishing contests; chamber music benefits and Hard Rock concerts; horse-ploughing contests and competitive swims; golf tournaments and bowling parties; wine tasting events and lemonade stands on busy street corners. No idea or endeavor is too small or too outlandish to help. Polio was cured with dimes and dollars, so, too will FOP.

Everyone can help.

Having fun at a great fundraiser for the IFOPA. Back row left to right: Patrick Doerr, Lindsay Ruiz, Kathy Hall. Front row left to right: Joshua Scoble, Dr. Fred Kaplan and Joey Hollywood.

Bingo for a Cure at the Agri-Plex Hall, Allentown Fairgrounds, Allentown, PA is the largest FOP Fundraiser in the world with more than 1,100 people in attendance!

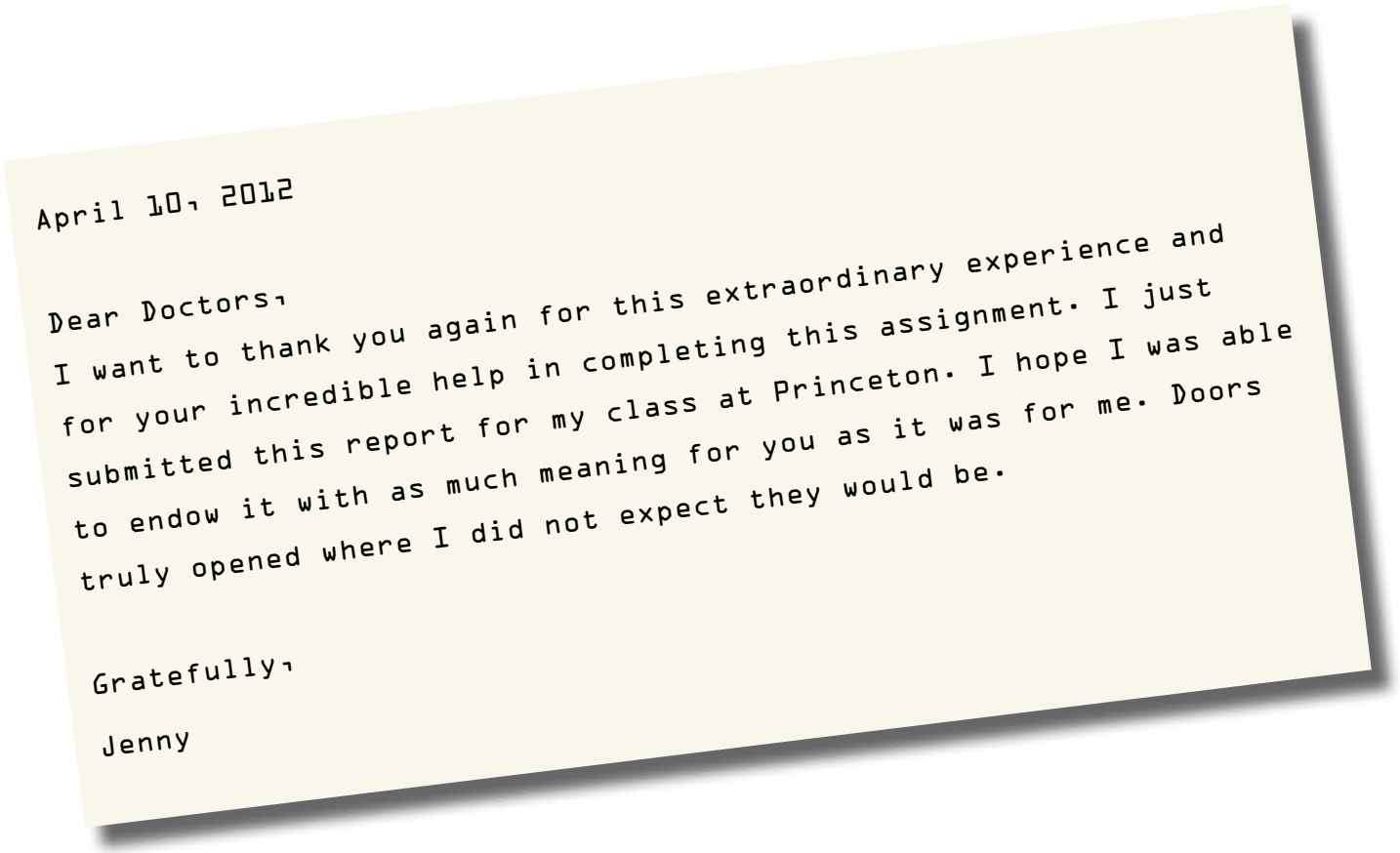
Joshua Scoble with his parents David and Stacy Scoble at Bingo for a Cure.

Many Thanks

The members of the core FOP Laboratory in Philadelphia, and at collaborating laboratories around the world are extremely proud to be a part of this mission, and are enormously grateful to those who support this vital research effort:

- The International FOP Association (IFOPA)
- The Center for Research in FOP & Related Disorders
- The National Institutes of Health (The People of the United States of America)
- The Cali Family Endowment for FOP Research
- The Weldon Family Endowment for FOP Research
- The Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine
- The Roemex & Grampian Fellowships in FOP Research
- The Canadian FOP Families & Friends Network
- FOP Italia
- The FOPeV (Germany)
- FOP France
- A Generous and Anonymous Donor from Caldwell, New Jersey
- The People of Santa Maria (18 years of extraordinary service)
- And the many individuals, families, friends, and communities throughout the world who contribute generously and tirelessly to the FOP effort

Thank you, as always, for your continued generous and heartfelt support of this vital and urgent mission.


April 10, 2012

Dear Doctors,

I want to thank you again for this extraordinary experience and for your incredible help in completing this assignment. I just submitted this report for my class at Princeton. I hope I was able to endow it with as much meaning for you as it was for me. Doors truly opened where I did not expect they would be.

Gratefully,

Jenny

Greetings from the FOP Clinical and Laboratory Team at the University of Pennsylvania in Philadelphia, PA.

Seated left to right: Dr. Fred Kaplan, Dr. Eileen Shore, Dr. Robert Pignolo.
Standing left to right: Dr. Deyu Zhang, Dr. Haitao Wang, Bob Caron, Meiqi Xu, Carter Lindborg, Dr. Salin Chakkalakal, Dr. Josef Kaplan, Kamlesh Rai, Edwin Theosmy, Michael Convente, Dr. Vitali Lounev, Ruth McCarrick-Walmsley, Andria Culbert, Xiaoyue Xie and Sophia Castro-Anderson.

Front Cover Images from top to bottom:

- Map of Philadelphia showing Mütter Museum location.
- The Mütter Museum is located here at the College of Physicians of Philadelphia.
- Skyline – Center City Philadelphia.
- The Rosenbach Museum: Delancey Street, Philadelphia.
- Penn's Museum of Archaeology and Anthropology.

Penn Medicine

ifopa

Support Families, Fund Research, Find A Cure.

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