

**THE SEVENTEENTH ANNUAL REPORT  
OF THE FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)  
COLLABORATIVE RESEARCH PROJECT**

**APRIL 2008**

**FREDERICK S. KAPLAN, M.D.**

**ROBERT J. PIGNOLO, M.D., Ph.D.**

**DAVID L. GLASER, M.D.**

**EILEEN M. SHORE, Ph.D.**

## **Introduction**

In late September at a mountain lodge high-up on the Continental Divide in Western Canada, Glen Boles, a good friend and accomplished mountain climber from British Columbia, recounted the three rules of mountaineering:

- It's always farther than it looks.
- It's always taller than it looks.
- And, it's always harder than it looks.

Then, he added, "Prepare for the journey, and with good luck and hard work, you will get there." He was talking not only about the highest mountain in the range, but about the treatment and cure of FOP. Glen's words are filled with wisdom, and we have no delusions about the challenges of the mission.

The discovery of the FOP gene, two years ago, has provided an unparalleled view from the summit, and has determined the destiny of FOP research. Quite simply, it would be impossible to find a cure without it. As Justice Oliver Wendell Holmes said, "A mind that is stretched by a new idea can never go back to its original dimensions."

We are now deep within a range of towering mountains, armed with critical knowledge, enlightened with a novel perspective, and embarked on a unique expedition to the ultimate summit – the treatment and cure of FOP.

“On the mountain of truth,” said the German philosopher, Friedrich Nietzsche (1844-1900), “you can never climb in vain: either you will reach a point higher-up today, or you will be training your powers so that you will be able to climb higher tomorrow.”

So it is with FOP research, but it cannot be done alone. The term “collaborative research,” has never held greater meaning. Research groups from five continents and many nations are working together now to solve what Jules Rosenstirn from Mount Zion Hospital in San Francisco described nearly 100 years ago as “the embarrassing puzzle of FOP.” It is now time for the puzzle to be solved once and for all. That mission is underway.

There has never been a time in FOP research with so much excitement or hope. The identification of the FOP gene has allowed us to see farther and more clearly than ever before. An effective treatment and a cure now seem so much closer through the telescope and microscope of scientific discovery. Two years after identifying the FOP gene, we have moved beyond the historic summit where the howling winds of discovery mark the site that changed FOP research forever.

Last summer, we came down from the mountain to regroup, to re-supply, and to re-outfit ourselves for the ultimate journey. We returned for a brief and inspiring visit at sea level, at one of the flattest places on Earth - Orlando, Florida, for **The Fourth International FOP Symposium**. There, we reflected on where we have been, and where we are going – TOGETHER - as a worldwide community with a focus, a verve, and a determination that is unstoppable.

But, perhaps the most important reason we returned from the summit was to receive our new mission maps for the journey ahead, not from clandestine cartographers in a secret mountain hideaway, but from three children: Hugo Fahlberg of Sweden, Carli Henrotay of The United States, and Manuel Robert of Argentina. Hugo, Carli, and Manuel know well, as every child with FOP knows, what this mission is all about, and what is truly at stake. Their winning pictures from **The Fourth International FOP Symposium** are not mere decorations but encoded destination maps that will guide and inspire us on the journey ahead. And, each picture is marked with the same indelible clue: **TOGETHER, WE CAN MOVE MOUNTAINS.** As Glen Boles cautioned, “it will not be easy, but it can and must be done.”

As the Cali family wrote in their year-end newsletter, “Although 2006 will forever be remembered as the year that the FOP gene was discovered, 2007 was marked by a new-found energy and focus on research. The prospects for a treatment and a cure for FOP have never been better. When Ian was asked, ‘What does the gene discovery mean to you?’ he replied: Hopeless to hopeful.” And Amanda added, “It is no longer a question of *if*, but a matter of *when*.” With that spirit of hope and optimism, we present you with: **2007 – This Year in FOP.**

### **First, the Headlines:**

1. Compassionate Corporate Chemistry Provides Hope for FOP
2. FOP World Leadership Program Established: Research Frontiers Expand with Collaborators from Five Continents
3. FOP Gene Switch Deciphered in Lab and in Life
4. A Visit from the Tooth Fairy: Adult Stem Cells from Baby Teeth Reveal Clues to Classic FOP
5. Mutant FOP Gene Enhances Cartilage and Bone Formation
6. Zebrafish Provide Knock-out Model for Study of FOP Gene
7. Powerful Inhibitory Protein Binds Less Effectively To Damaged FOP Receptor Than to Normal Counterpart: Molecular Mechanisms of a Mutant Receptor
8. Computer Modeling Provides Insight into Overactive FOP Receptor Switch
9. FOP Toe Malformation Studied in Chickens: Developmental Actions of Mutant Receptor Confirmed
10. Studies in FOPPY Mice Reveal Contribution of Normally Silent Cells
11. Fly Me to the Moon: Playing the Sax to Decipher the Tune
12. Receptor Partners Alter Amplitude of BMP Signals in FOP Cells
13. FOP Patients from China, Japan, and Vietnam Support Universality of FOP Mutation
14. Diagnostic Gene Test Developed for Classic FOP
15. Novel Mutations in FOP Gene Identified in Rare FOP Variants
16. A Peripheral Feature of FOP Enters Center Stage

17. Negative Result Reveals Important Clues: Bone Marrow Transplantation Does Not Cure FOP, but Normal Marrow Derived Stem Cells Can Trigger FOP in Genetically Susceptible Individuals
18. FOP Mice Near Delivery Room: Hope for Next Generation
19. Cartilage Cultures Developed to Screen Drugs for FOP
20. Novel Signal Transduction Inhibitor Stops BMP Signal in FOP Cells: Clues for Drug Development
21. FOP Gene: Bonanza for Bioengineers
22. Heterotopic Ossification in Combat Amputees, Hip Replacement Patients, Head Injury Victims, Heart Valve Replacement Patients, and a New Jersey Governor May All Have Connections to FOP
23. FOP Gene Identified as First Human Metamorphogene: A Skeleton Key to the Metamorphosis
24. FOP Skeleton Continues to Reveal Clues Following Gene Discovery
25. Penn Post-Doc Procures Prestigious Prize: Young Investigator Award to M.D., Ph.D. for Groundbreaking FOP Research
26. Extraordinary Journalists Honored with Distinguished Media Award
27. Steady Stream of Students Select FOP for Study: Elementary, High School, College, and Graduate Students Warm to Dangers, Dilemmas, and Discoveries
28. From Baltimore Harbor to Tokyo Bay: Educating Patients, Doctors, and Researchers about FOP
29. FOP in Print - 2007
30. FOP Reaches Primetime: Fact and Fiction Collide

### 31. Worldwide Holiday Greetings Express Spirit of Hope

In this 17<sup>th</sup> Annual Report, we will briefly outline each headline. Our goal is not to overwhelm with technical detail, but to provide a snapshot of the work - of the breadth and depth of the commitment, of the extraordinary focus and collaborative nature of the mission, and of the immediate insight and longterm value of the discoveries - while keeping in mind our shared and common goal – the treatment and cure of FOP. For those who wish to delve deeper, we refer you to previous Annual Reports, especially to numbers 15 (2006) and 16 (2007) for background information on the FOP gene discovery, and to our detailed published papers with abundant technical information. For those, who wish to go even further, feel free to write or phone. We will do our very best to answer your questions.

## **1. Compassionate Corporate Chemistry Provides Hope for FOP**

The Greek mathematician and inventor Archimedes (c.250 B.C.) exclaimed, “Give me where to stand and I will move the Earth.” More than two thousand years later, a famous advertisement proclaimed, “When the human element is added to the equation, everything changes.” May 30, 2007 will forever be noted in the annals of FOP history as one of those rare and defining moments when one could hear and feel the earth-shattering movement of something one could barely see – the massive and powerful engines of corporate capitalism locking in place on a new track, being nudged into a purposeful articulation by revelational biology, compelling chemistry and most importantly by the undeniable valence and compassion of the human spirit.

While no miracle drugs have yet been developed, promised, or even begun, one of the highlights of 2007 was a unique and mind-boggling meeting on FOP with a focus on FOP patients, sponsored and hosted by the research division of a major US pharmaceutical company. The company’s senior vice president and director of worldwide development was instrumental in organizing the historic meeting which took place at corporate research headquarters near Philadelphia, and was attended by senior corporate executives, research scientists, medicinal chemists and physicians. Three FOP patients (an adult, a teenager, and an infant) were invited to attend with family members, and provided, in the words of the senior executive, “a powerful day that we hope will lead to an improved approach to addressing a terrible unmet medical need.” And, she continued, “We all feel deeply passionate about helping patients.”

The medicinal chemists of the pharmaceutical company have developed inhibitors for overactive receptors very similar to the kinds of receptors that cause FOP. Motivated by the FOP gene discovery, the compelling need of FOP patients, and the widespread utility of an orphan drug for FOP that might be used to treat more common conditions of heterotopic ossification, the company was eager to explore the feasibility of entering a new frontier of pharmaceutical development. During the remainder of 2007, tantalizing collaborative experiments, conducted at the pharmaceutical company and in the FOP laboratory, provided important insight into possible drug development for FOP. This exciting work continues. The Earth has begun to move, one mountain at a time.

## **2. FOP Research Frontiers Expand with Collaborators from Five Continents**

“There is no national science, just as there is no national multiplication table; what is national is no longer science,” said Anton Chekhov, the Russian author and physician. More recently, Linus Pauling wrote, “The best way to have a good idea is to have lots of ideas.” Different laboratories excel in different areas, and have different ideas, and their interactions, both formal and informal, promote progress.

Worldwide research collaborations expanded dramatically following the FOP gene discovery, fostered in part by Developmental Research Grants from The Center for Research in FOP and Related Disorders. Presently, physicians and scientists from the United States and from many nations around the world participate in a collaborative network that highlights the expertise of each group, the ingenuity of individual contributions, and the common goals and aspirations of a thriving international community. FOP collaborative research partners include physicians and scientists from Aberdeen, Amsterdam, Athens, Austin, Berlin, Boston, Buenos Aires, Beijing, Chicago, Dallas, Genoa, Garmisch, Glasgow, Los Angeles, London, Melbourne, Nashville, New York, Oxford, Paris, Providence, San Francisco, São Paulo, Seoul, Stockholm, Sydney and Tokyo. The list is expanding rapidly.

### **3. FOP Gene Switch Deciphered in Lab and in Life**

A series of seminal collaborative experiments were conducted in 2007 in Philadelphia, Tokyo, and Berlin, and established a central dogma of FOP research in the post gene discovery era: that the FOP mutation activates the ACVR1 receptor in the absence of bone morphogenetic protein (BMP) and leads to the promiscuous stimulation of BMP signaling. Additionally, experiments performed in Philadelphia confirmed that the mutated FOP receptor stimulates leaky BMP signaling in cells from FOP patients and explosive signaling when FOP cells are activated by BMPs. These studies provide the first insight into a signaling pathway that when damaged in a specific manner, orchestrates the promiscuous differentiation of soft connective tissues into a disabling second skeleton of heterotopic bone. Furthermore, they provide the basis for developing model systems for testing drugs that might block this renegade receptor.

#### **4. A Visit from the Tooth Fairy: Adult Stem Cells from Baby Teeth Reveal Clues to Classic FOP**

FOP is a challenging condition to study. Since physical and surgical trauma exacerbates FOP by inducing bone formation, it has been difficult to safely obtain biopsy samples from FOP patients for detailed biochemical and molecular analyses. In a report published as the lead article in **The Journal of Bone and Mineral Research**, we described adult stem cells that were derived safely and non-traumatically from the dental pulp of discarded primary teeth of FOP patients and unaffected controls. These are the first FOP connective tissue cells that have been used to study BMP signaling and bone differentiation. The study showed that connective tissue stem cells from FOP patients transmit increased BMP signals through both developmental and inflammatory signaling pathways downstream of the mutant receptor and respond to BMP treatment by dramatically over-expressing BMP responsive genes. FOP cells demonstrate leaky signaling at rest and hyperresponsive signaling when stimulated by BMPs. FOP cells also showed more rapid differentiation to bone cells than normal control cells. Future studies with these cells should substantially increase our understanding of FOP, providing novel insights and screening tools for testing new therapies.

## **5. Mutant FOP Gene Enhances Cartilage and Bone Formation**

Heterotopic bone in FOP patients develops from an intermediate cartilage stage. Recent studies in adult stem cells indicate that the mutant FOP gene can in fact induce cartilage as well as bone formation. Most importantly, these studies make it possible to screen for drugs that will inhibit not only bone formation but also the intermediary stage of cartilage formation, and thus inhibit heterotopic ossification at an earlier stage of development than might otherwise be possible. The detailed results of these landmark studies will soon be submitted for publication.

## **6. Zebrafish Provide Knock-out Model for Study of FOP Gene**

Cells from the blood and from the dental pulp have been invaluable in studying FOP, but animal models of human disease provide the possibility of studying the developmental effects and implications of genetic diseases that are impossible to study in cell culture.

The tiny zebrafish is an extremely valuable animal model for studying the effects of BMP signaling during development. Importantly, zebrafish development occurs externally and can be monitored under laboratory conditions. As in humans, zebrafish have two copies of ACVR1, the FOP gene. The world's expert on the ACVR1 gene in zebrafish, Dr. Mary Mullins, a Professor of Developmental Biology, is at the University of Pennsylvania, a serendipitous occurrence that facilitates close collaborative interactions with the FOP Core laboratory.

When both copies of the ACVR1 gene are knocked-out or removed from the zebrafish embryo, severe developmental malformations occur due to the absence of BMP signaling from the ACVR1 receptor. Microinjection of messenger RNA encoded by the normal human ACVR1 gene into the zebrafish embryo partially rescues the developmental abnormality. However, microinjection of RNA encoded by the mutant FOP gene into the zebrafish embryo over-corrects the ACVR1 deficiency. These important experiments, conducted in collaboration with Dr. Mullins' laboratory, demonstrate that the mutant FOP gene is overactive in a living experimental animal during development. These experiments are vitally important not only in elucidating the developmental effects of the FOP gene mutation, but also in screening large pharmaceutical libraries for compounds that can block overactive BMP signaling in a living organism, as we will see later in this

report. These data provide the first experimental evidence that the FOP gene is overactive within the cells and tissues of a living organism.

## **7. Powerful Inhibitory Protein Binds Less Effectively to Damaged FOP Receptor Than to Normal Counterpart: Molecular Mechanisms of a Mutant Receptor**

Did the assassin work alone? Was there more than one bullet? Who fired the fatal shot? Conspiracy theories abound. No, we are not talking about the Kennedy assassination, but about FOP. How can one misspelled genetic letter cause all that mischief? Well, actually it doesn't! It has a partner in crime, who has been booked and charged. The name of the co-conspirator? Let's call it factor F, or to be more precise, the absence of factor F, working where it should.

Remember the metaphors from previous years of the atom bomb, the runaway car, the leaky faucet, the broken garage door, and the damaged TV remote control? What all of those metaphors have in common with FOP is a broken switch. But, in FOP, we have evidence that the switch is broken in a very special way. The FOP switch is normally protected by an armed guard who is handcuffed to the switch and prevents it from being activated except by an explicit presidential order. When the order comes from the President, the armed guard unlocks the switch so that it can be activated. Now, suppose that the switch was broken in such a way that the armed guard could not be handcuffed to it, and therefore could not protect it from promiscuous activation in the absence of a presidential order. It might then be possible to trip the switch accidentally and trigger an explosion of an atom bomb (an FOP flare-up). Well, in our metaphor, ACVR1 is the switch, factor F is the armed guard, and BMP is the presidential order. In FOP, the ACVR1 receptor is broken in such a way that factor F, the armed guard, can not protect it. As a result, the switch is always active at a low level when it should be "off," and

highly vulnerable to be triggered when BMP is present. In fact, when BMP is present, the switch goes “haywire” and triggers an atom bomb (a flare-up).

Thus, factor F, a protein that interacts with and normally protects the ACVR1 switch from being activated in the absence of BMP (a presidential order), also controls access to the switch on the cell surface. In FOP, due to the single letter mutation in the FOP gene, factor F, the protein that should normally guard the switch cannot properly do so. It’s like creating nuclear weapons, but leaving them unguarded – not a good thing!

As the Editors of the journal **Cell** wrote in a recent editorial, “Elucidation of molecular mechanisms inevitably creates exciting new questions and insights into biology and is a prerequisite for applied research, such as mechanism-based drug discovery. It is also at the level of molecular mechanisms that different fields can most easily learn and borrow from each other, and even sometimes meld.” Or, as Albert Einstein said, “Something deeply hidden had to be behind things.”

## **8. Computer Modeling Provides Insight into Overactive FOP Receptor Switch**

ACVR1, a bone morphogenetic protein receptor, is a switch that determines the fate of cells. In individuals who have FOP, a single misspelled letter in one of the two copies of the ACVR1 gene causes the ACVR1 switch to be made incorrectly. That single misspelled letter causes the ACVR1 switch to send a signal to the inside of the cell telling it to make a new bone where it should not. As we just learned, factor F, a protein that interacts with the switch, acts like an armed guard to protect the switch and keep it shut off until it is properly activated by a BMP molecule. In the presence of an FOP mutation, factor F (the armed guard) cannot properly bind to the broken ACVR1 switch and the switch is unprotected and active even in the absence of BMP.

But, why exactly does factor F not bind properly to the mutant receptor? Dr. Jay Groppe, a biochemist and x-ray-crystallographer from Baylor College of Dentistry in Dallas, has used computer modeling to predict the structure of the normal and mutant ACVR1 receptor at the atomic level in order to determine why factor F can not bind properly to the mutant receptor. Dr. Groppe, supported in part by a Developmental Grant from The Center for Research in FOP and Related Disorders, predicts that a previously unidentified pocket within the normal ACVR1 receptor is critically disrupted by the FOP mutation. Dr. Groppe's studies further predict that the FOP mutation creates a pH-sensitive switch that regulates whether or not factor F will properly bind to the mutant receptor. The model shows that a more acidic environment (such as might be encountered in an FOP flare-up) might disable the mutant switch (but not the normal switch) and make it impossible for factor F to bind properly. In other words, in an acidic environment, the

mutant switch might be much more vulnerable to being triggered and creating an atomic explosion (an FOP flare-up).

This important theoretical modeling of the FOP switch was described in a major paper entitled, “**Functional Modeling of the ACVR1 (R206H) Mutation in FOP**” that was published in the journal **Clinical Orthopaedics & Related Research** in 2007. The article explains that if x-ray crystallographic and biochemical studies (presently underway) prove the existence of this predicted pH-sensitive switch, it might be possible to modulate the local pH of cells in an FOP flare-up to suppress or diminish the extent of heterotopic ossification.

## **9. FOP Toe Malformation Studied in Chickens: Developmental Actions of Mutant Receptor Confirmed**

One of the most perplexing quandries of FOP is the great toe malformation. “Okay,” one might say, “too much BMP activity causes too much bone. That is easy to understand; but what’s going on with the big toe?”

While we do not yet know all of the answers, we do know this: Mutant ACVR1 is involved in the malformation of the great toe. When normal copies of the ACVR1 gene are injected into the developing limb buds of chicken embryos, not much happens, but when mutant (FOP) copies of the ACVR1 gene are injected into the developing limb buds, the chickens are born with malformation of the great toes. These extraordinary findings from the laboratory of our collaborators Drs. Petra Seemann and Stefan Mundlos at the Max Planck Institute of Molecular Biology in Berlin are beginning to dramatically enhance our understanding of the actions of the overactive FOP gene and receptor during development. You will be hearing much more about this exciting work in future reports.

## **10. Studies in FOPPY Mouse Reveal Contribution of Normally Silent Cells**

FOPPY mice have been developed to produce extra BMP protein in mouse muscles and they form heterotopic bone very similar to FOP bone. While awaiting the arrival of mice with real FOP, the well-known and beloved FOPPY mice continue to enlighten us. In collaboration with Dr. Lixin Kan and his colleagues from Northwestern University in Chicago, we conducted detailed studies (supported by a grant from The Center for Research in FOP and Related Disorders) to examine the origin of inflammatory cells that trigger heterotopic ossification following injury as well as the origin of cells that respond to the increased BMP signal to form cartilage and bone. While the results are preliminary, there are some major surprises. For the meanwhile, let's just say that some normally silent progenitor cells (or stem cells) in connective tissue are recruited into action following injury to carry-out the detailed instructions of cellular and molecular sabotage necessary to form heterotopic bone. Our ongoing work in the FOPPY mice is aimed at identifying these cells, deciphering their clandestine molecular conversations, and using them to probe the process of heterotopic ossification in FOP. If the same cells are involved in real FOP, molecular "silver bullets" to "take out" those sleeper cells may be a therapeutic approach worth pursuing.

## **11. Fly Me to the Moon: Playing the Sax to Decipher the Tune**

Dr. Kristi Wharton, Professor of Medical Sciences at Brown University in Providence, Rhode Island is the recipient of a Developmental Grant from The Center for Research in FOP and Related Disorders to study the role of the FOP gene (called saxophone; or sax, for short) in the fruit fly. So, what are flies doing with the FOP gene? That is a great question, and has been a major focus of Dr. Wharton's investigations. Flies don't have bones and people don't have wings, but just as humans have an internal skeleton, flies have an external skeleton, and the ACVR1 gene (sax) seems to play a critical role in its formation and maintenance.

The discovery of the FOP gene brought our two worlds together. ACVR1, the FOP gene, is the human counterpart of the saxophone gene in the fruit fly. The high conservation of not only the ACVR1/sax gene sequences but also the complete BMP signaling pathway between humans and flies makes it possible to use the fruitfly model system to dissect the molecular details of ACVR1 signaling and to do so in the context of the developing organism, an approach not possible with many other experimental systems. Recently, Dr. Wharton has been studying the function of FOP mutations in the fruit fly. With available tools and the short lifecycle of fruit flies, she is making rapid progress in deciphering molecular clues from this most extraordinary multicellular organism. So, how are the FOP mutants behaving in the fly? Well, Dr. Wharton has been listening to the sounds of the sax from the little buggers and will begin to decipher the tune in future reports. We'll all be eager to listen!

## **12. Receptor Partners Alter Amplitude of BMP Signals in FOP Cells**

An important paper was published from the FOP laboratory in 2007 documenting the role of cell surface sugar-protein complexes (called heparan sulfate proteoglycans or HSPGs) in modulating the activity of the mutant FOP receptor. The paper, **“HSPG Modulation of BMP Signaling in FOP Cells,”** was published in **The Journal of Cellular Biochemistry**. The significance of the study is that although the FOP mutation causes tremendous harm, FOP cells attempt to modulate the harm, albeit ineffectively. Thus, FOP cells try to block the abnormal signal using HSPGs, but cannot quite muster the resources to do it. These findings provide important insight into the body’s ability to buffer harm from mutations in signaling pathways and provide avenues that might be exploited in developing drugs to prevent or treat FOP. The ACVR1 gene and the associated BMP signaling pathways have evolved over 500 million years, and are hard-wired into cells. Thus, there has been ample time for the cell to figure-out ways to bypass attempts to block it. With these caveats in mind, we have been conducting experiments in conjunction with research scientists at a major pharmaceutical company to identify possible detours that could frustrate drug development. So, FOP cells beware; we have discovered some of your little tricks, and we are on to you!

### **13. FOP Patients From China, Japan, and Vietnam Support Universality of FOP Mutation**

The FOP gene discovery showed that patients with classic features of FOP (malformed great toes and progressive heterotopic ossification) all have the same gene mutation.

While our original FOP population was assembled from around the world, patients from a few key geographic regions were notably missing. The recent FOP mutational data from patients in China, Japan, and Vietnam now provides additional strong support that all classically-affected FOP patients worldwide carry the same genetic change in the ACVR1 gene. This remarkable finding confirms that the FOP mutation is one of the most specific point mutations in the human genome, a finding with important therapeutic implications. An FOP patient from Beijing or Yokohama is no different than an FOP patient from Baltimore or Chattanooga. FOP exhibits no ethnic, racial, or geographic boundaries clinically or at the molecular level. Thus, definitive treatments, when available, should be applicable to patients worldwide.

#### **14. Diagnostic Gene Test Developed for Classic FOP**

The single recurrent mutation in the *ACVR1* gene in patients with classic FOP is particularly amenable to clinical genetic testing. In 2007, a reliable diagnostic genetic test for FOP was developed and used to diagnose FOP in seven children who were suspected of having FOP on the basis of malformed great toes, but prior to the onset of heterotopic ossification. Genetic testing thus provides a level of molecular certainty at an early stage in the disease process that can be used to prevent unnecessary harm.

## **15. Novel Mutations in FOP Gene Identified in Rare FOP Variants**

Erez Lieberman, who studies the evolutionary dynamics of language at Harvard University said, “Every rule is the tombstone of a thousand exceptions.” Last year, we found twelve exceptions.

In 2007, we performed extensive genetic analysis on patients with classic FOP (malformations of the great toes and progressive heterotopic ossification), patients with atypical FOP (those with classic features who additionally have physical findings not commonly associated with FOP), and those with FOP variants (those with major variations in the classic defining features of FOP). While all patients with classic FOP and most with atypical FOP have the same FOP mutation, we have identified twelve people with FOP variants who have different mutations in the FOP gene. In some cases, there was a correlation between the location of the mutation on the ACVR1 gene and the physical features of the patient (especially the severity of the toe malformations), illustrating that small gene variations can give rise to large variations in clinical features.

Identification of disease-causing mutations in the FOP gene has important diagnostic and therapeutic implications for patients with all forms of FOP. Although FOP is one of the rarest and most disabling conditions known to mankind, its importance to clinical medicine far exceeds the paucity of affected individuals. The FOP variants provide extraordinary insight into the embryonic and postnatal effects of altered ACVR1 function and dysregulated BMP signaling. Presently, we are targeting the development of treatments to cover all patients with classic FOP, atypical FOP, or FOP variants.

## **16. A Peripheral Feature of FOP Enters Center Stage**

As the saying goes: If you want to hide something, put it where everyone can see it. And, the most obvious things are often the last to be discovered. So it is for the little (and sometimes not so little) bumps that are found on the inside of the leg bones, just below the knees, in more than 90 per cent of FOP patients worldwide. Even more astonishing, these bumps are found not just below the knees, but can occur on any bone of the skeleton - dwarfed by the heterotopic bone that has masked their presence for more than 300 years. These bumps called osteochondromas, or exostoses, are the most frequent benign tumors of bone, and can be felt easily on physical examination. Osteochondromas initially were considered an unusual feature of FOP, but were under-diagnosed due to their often asymptomatic nature. In fact, they are the most common clinical feature of FOP after the malformations of the great toes.

Our findings on FOP osteochondromas will be published soon in **The Journal of Bone and Joint Surgery**, and demonstrate a previously unrecognized and robust occurrence of proximal tibial osteochondromas in patients with FOP. The results have important clinical implications. Because of the rarity of FOP, physicians often fail to recognize the disorder in patients who have congenital malformations of the great toes or soft tissue masses during childhood. The remarkable association of osteochondromas with FOP adds a simple, diagnostically useful aspect to the disease, raising the physician's level of suspicion and allowing an earlier recognition of FOP, helping to preclude inappropriate and dangerous invasive procedures.

FOP is on a short list of hereditary disorders in which osteochondromas occur. The most common disorder is multiple hereditary exostoses (MHE), a distinct genetic condition characterized clinically by numerous osteochondromas throughout the skeleton. The discovery of this prominent clinical finding in FOP also has important basic science implications. The molecular mechanisms that cause multiple hereditary osteochondromas involve highly conserved cell signaling pathways. The association of osteochondromas with FOP adds the BMP signaling pathway to the network of interacting developmental pathways that are required to form these cartilage/bone growths. This is yet another example of how research in a rare condition (FOP) can reveal knowledge about a very common disorder (osteochondromas).

In summary, we showed that proximal tibial osteochondromas are a common clinical feature of FOP, a finding that has important clinical, pathological, and basic science implications. The study expands the range of disorders caused by recurrent activating mutations in *ACVR1* to include not only congenital skeletal malformations (the great toes) and progressive heterotopic bone formation, but also benign osteochondral lesions of skeletal formation. This finding provides insight into the genetic cause of osteochondromas and is therefore of great interest not only to physicians who treat patients with FOP, but to all orthopaedic physicians, pediatricians, geneticists, and surgeons worldwide who will encounter more common conditions in which these lesions occur. Finally, the discovery illustrates that the molecular basis of a disease can be revealed not only by discovering the genetic cause of the disease, but by discovering unanticipated clinical features of a condition whose genetic cause is already known.

As the Editors of the **Journal of Bone & Joint Surgery** said in their review of the article, “Thank you for submitting your manuscript entitled: **Proximal Tibial Osteochondromas in Patients with FOP**. Your observations of this rare group of patients continue to enhance our understanding of orthopaedic basic science, and we are sure that many readers of the **Journal** will be interested in this manuscript. The study is well-defined for an unusual entity. The in-depth discussion of genetic factors and their role in normal and abnormal bone formation is clear. The manuscript thoughtfully extends the description of a rare but important condition (FOP), by adding observations from a significant subpopulation about the association with proximal tibial osteochondromas. Since the genetic defect for FOP has been tenaciously pursued, and masterfully defined, it is logical to propose that this same defect plays a role in the development of osteochondromas, a far more frequent clinical entity (throughout the world). Despite the rarity of patients with FOP, it is of enormous value and relevance to our understanding of bone biology. The manuscript is written with balance and clarity, as it describes this additional feature of the disease. The impact of FOP and the biology of BMPs and their receptors may well provide insight into other skeletal disorders including the pathophysiology of osteochondromas.”

## **17. Negative Result Reveals Important Clues: Bone Marrow Transplantation Does Not Cure FOP, but Normal Marrow Derived Stem Cells Can Trigger FOP in Genetically Susceptible Individuals**

A major paper on FOP stem cells entitled **Hematopoietic Stem-Cell Contribution to Ectopic Skeletogenesis** was published in 2007 in the prestigious **Journal of Bone & Joint Surgery**. The study showed that although bone marrow transplantation does not cure FOP, at least two populations of stem cells - one derived from circulating cells of bone marrow origin, and the other derived from a population of connective tissue progenitor cells - are necessary to form an ectopic skeleton. Intriguingly, even normal bone marrow derived stem cells can trigger FOP flare-ups in genetically susceptible individuals. We learned this information from a series of detailed bone marrow transplantation experiments in mice and from clinical observations in an FOP patient who underwent bone marrow transplantation for treatment of an unrelated bone marrow disorder. Results from this complex study strongly suggest that therapeutic regulation of connective tissue progenitor cells and the use of drugs to influence inflammation, stem cell function, bone formation, and BMP signal transduction hold great promise for controlling ectopic bone formation relevant for FOP and perhaps for many common disorders of heterotopic ossification in humans.

## **18. FOP Mice Near Delivery Room: Hope for Next Generation**

Most people want to get rid of mice; we can't wait till they arrive and flourish!

Throughout 2007, we have performed genetic studies of stealth-proportion to stack the deck for the birth and propagation of mice with real FOP. Our work has taken us a giant step towards that goal. It has been a long and arduous process but ultimately one that should bring great rewards for FOP research. Some would say, in fact, that it is a necessary step to the next summit, the effective treatment and cure of FOP.

In 2007, the Nobel Prize in Medicine honored three scientists: Martin Evans, Oliver Smithies, and Mario Capecchi, "for their discovery of principles for introducing specific gene modifications into mice by the use of embryonic stem cells." The work of these three pioneering scientists made possible the construction of genetically engineered animals using molecular technology and embryonic stem cell developments. The conceptual and technical advances honored by the Nobel Prize in Medicine in 2007 have direct practical application to our generation of FOP knock-in mice.

So, where are the mice? As of the first week in January 2008 (when this report was written), we became the parents of the first "pre-FOP" baby mice. But, let's not get too excited yet. There are still many obstacles to overcome in what is, without doubt, one of the most technically difficult types of engineering feats in molecular genetics.

## **19. Cartilage Cultures Developed to Screen Drugs for FOP**

During FOP flare-ups, undifferentiated cells expand in number and transition through a cartilage stage before heterotopic bone is formed. To study early molecular events in the process of cartilage and bone formation in FOP, assays have been developed in which the FOP gene is introduced into adult connective tissue stem cells and then monitored as those cells begin to express cartilage and bone proteins. With support from The Center for Research in FOP and Related Disorders, Dr Robert Mauck and colleagues from the University of Pennsylvania have developed a cartilage-based assay system to screen a large chemical library (from The National Institutes of Health) containing more than 100,000 compounds of unknown action. Dr. Mauck is presently transitioning from the assay development phase of the project to the chemical library screening phase. With this chemical screen, he hopes to identify novel compounds that can influence cartilage and bone formation, and in so doing, identify potential medications for the treatment of FOP.

## **20. Novel Signal Transduction Inhibitor Stops BMP Signals in FOP Cells: Clues for Drug Development**

In 2007, Dr. Charles Hong, from Vanderbilt University in Nashville, Tennessee visited the FOP lab at the University of Pennsylvania to describe the ground-breaking discovery of dorsomorphin, the first small molecule inhibitor of BMP receptors. Dorsomorphin was identified from among thousands of compounds by screening for a molecule that could block BMP signaling in zebrafish development. Dorsomorphin selectively inhibits all BMP receptors including ACVR1. Preliminary experiments being performed in collaboration with Dr. Take Katagiri and colleagues from Saitama Medical University in Saitama, Japan are investigating whether dorsomorphin can block BMP signaling in mouse muscle stem cells into which the FOP gene is artificially introduced. If successful, dorsomorphin and related compounds might be tested in mouse models of FOP and further investigated for therapeutic use. The discovery of dorsomorphin was described in a major article by Dr. Hong and colleagues in the January 2008 issue of **Nature Chemical Biology**.

## **21. FOP Gene: Bonanza for Bioengineers**

For every person with FOP desiring to rid themselves of unwanted bones, there are millions more who desperately need to form new bones – children with skeletal malformations, old people with osteoporotic fractures that do not heal, middle-aged individuals with spinal arthritis who need spinal fusions to mitigate their misery, and patients who lose bone as a result of cancer. For those individuals, the work of Jason Burdick, Ph.D., an assistant professor of bioengineering at The University of Pennsylvania, holds much promise. Supported by a Developmental Grant from the Center for Research In FOP and Related Disorders, Dr. Burdick and his colleagues are using polymer scaffolds to transport the mutant FOP gene to stem cells at bone interfaces in attempt to create new skeletal elements. This novel and exciting tissue engineering work is in its early stages of development, and you will be hearing much more about it in future reports.

## **22. Heterotopic Ossification in Combat Amputees, Hip Replacement Patients, Head Injury Victims, Heart Valve Replacement Patients, and a New Jersey Governor May All Have Connections to FOP**

FOP may be the tip of an iceberg of conditions in which individuals form heterotopic bone. Drs. Robert Pignolo, Mary Ann Keenan, and colleagues from The University of Pennsylvania are investigating the role of ACVR1 in non-hereditary forms of heterotopic ossification that plague millions of individuals worldwide including athletes, amputees, hip replacement patients, head injury victims, patients who have endstage valvular heart disease, and even a New Jersey governor who sustained severe bone and soft tissue injuries in an automobile accident and who subsequently developed massive heterotopic bone. While specific mutations in ACVR1 have not been found in this patient population, the ACVR1 receptor and downstream BMP signaling pathway are highly likely to be involved in these non-hereditary forms of heterotopic ossification. If pharmaceutical companies are to derive an economic benefit in developing drugs that block the formation of heterotopic bone in FOP, it will be in this very large and diverse patient population who have more common forms of heterotopic ossification and whose bodies are likely to use the same molecular blueprints (as in FOP) in forming their extra and unwanted bones. We will keep you informed about this exciting new area of investigation in future reports.

### **23. FOP Gene Identified as First Human Metamorphogene: A Skeleton Key to the Metamorphosis**

“When I use a word,” Humpty Dumpty said, in a rather scornful tone, “it means just what I choose it to mean – neither more nor less.” The word *metamorphogene* entered the medical lexicon in 2007 at a scientific meeting in New York City and later in print in an article entitled: **Morphogen Receptor Genes and Metamorphogenes: Skeleton Keys to the Metamorphosis** (by Drs. Kaplan, Groppe, Pignolo and Shore) in **The Annals of the New York Academy of Sciences**.

The term *metamorphosis* refers to any striking developmental change of an animal’s form or structure. While the only defined biological examples of metamorphoses are those in insects and amphibia, the medical concept of metamorphosis implies a pathological process that transforms one normal tissue or organ system into another, as in FOP.

Just as proto-oncogenes (normal cellular genes that regulate cell division) become oncogenes (cancer causing genes) when they are damaged in very specific ways, morphogen receptor genes (normal cellular genes that regulate cell fate) become metamorphogenes (genes causing metamorphosis, as in FOP) when they are damaged in very specific ways.

Genetic changes occur when a proto-oncogene becomes an oncogene and send cells hurdling down dangerous pathways that result in malignancy. Similarly, genetic changes occur when a morphogen receptor gene (such as ACVR1) becomes mutated. The

changed metamorphogene dramatically shifts and distorts the differentiation repertoire by which connective tissue stem cells and progenitor cells respond to injury and trauma, leading to the transformation of one normal tissue into another normal tissue through a pathological process of metamorphosis.

The study of metamorphosis in FOP provides profound insight into the molecular mechanisms that ensure the stable identity of tissues following their formation and that regulate the repertoire of cellular responses to environmental signals. These mechanisms, just now beginning to be understood as a result of the FOP gene discovery, ordinarily lay deeply hidden in the highly conserved signaling pathways that regulate cell fate. It's as if a trap door in development, firmly sealed for over 500 million years of evolution, were suddenly unlocked by a single misspelled letter in the genetic code and in so doing revealed a previously unknown process of both terrifying mortal danger (as in FOP), or dazzling therapeutic potential (as in the construction of new skeletal elements).

Metamorphosis (as a result of the action of metamorphogenes) thus joins the ranks of wound healing, regeneration, tumor formation, and aging as one of the key biological processes in which to study and therapeutically manipulate tissue behavior following morphogenesis (tissue and organ formation). As Thomas Maeder wrote in an article in the **Atlantic Monthly** (February, 1998): "FOP and its problems lie at the crossroads of several seemingly unrelated disciplines. Answers to questions that FOP poses will also address grander issues of how the body first creates its shape and then knows where to

stop, how tissues decide how to become what they are, and why they don't turn into something else.”

## **24. FOP Skeleton Continues to Reveal Clues Following Gene Discovery**

Many important FOP discoveries began with simple observations, and there is no better way to continue that tradition than with a man who wanted those observations to be made. Harry Raymond Eastlack, affectionately known as “Harry,” had FOP and died in 1972, a few weeks short of his fortieth birthday. Despite the physical limitations of his mortal life, Harry has enjoyed a resurrection at The Mutter Museum of the College of Physicians of Philadelphia where his skeleton resides at his request. In his last will and testament, Harry donated his skeleton to medicine so that physicians and scientists could learn from it and make observations that would help others with FOP in future generations.

Harry’s last wishes have already been fulfilled many times over. Harry’s skeleton, like the oracles of ancient times, continues to enlighten. If one asks the right questions, Harry’s skeleton likely holds the answers – answers waiting to be revealed. Many believed that after the FOP gene discovery, there would be few important observations to be made from Harry’s skeleton. How wrong they were. Members of the FOP research team in Philadelphia make frequent visits to The Mutter Museum to examine Harry’s skeleton and to illustrate features of FOP to inquiring students and visiting physicians and scientists. At nearly every visit, some new feature of FOP is discovered. During visits with Harry in 2007, there were tantalizing clues that degenerative joint disease that affects millions may be related to FOP. Degenerative arthritic changes were noted not only in the great toe and thumb of Harry’s skeleton, but also in the joints of the neck, jaw, shoulders, elbows, wrists, hips, knees, and ankles and in many joints where the ribs join

the spine. These observations have profound implications for understanding how ACVR1 affects joint development and maintenance for all humans. From a basic science standpoint, the critical observations made possible by Harry's skeleton are leading us to more carefully consider these issues on a deeper molecular basis and on a larger scale. The significance of the discovery is that FOP not only causes heterotopic bone formation, but predisposes affected individuals to the development of degenerative arthritis, a finding that has dramatic implications for millions of individuals worldwide. These observations from Harry's skeleton are presently being pursued at a cellular and molecular level in the FOP laboratory. Harry Eastlack was an enlightened individual who willingly bypassed the grave in order to reside in posterity at an institution of higher learning. We are all extremely grateful for his immortal contribution.

**25. Penn Post-Doc Procures Prestigious Prize: Young Investigator Award to M.D., Ph.D. for Groundbreaking FOP Research**

Qi Shen, M.D., Ph.D., a former post-doctoral fellow from the FOP laboratory at the University of Pennsylvania, received a prestigious **Young Investigator Award** of The American Society for Bone and Mineral Research (ASBMR) for her landmark study “**Activation of BMP Signaling by the FOP ACVR1 Mutation.**” The award was presented at the annual meeting of the ASBMR in Honolulu, Hawaii in September 2007, where Qi presented her paper to an overflow international audience of skeletal biologists and physicians.

Qi’s excitement in receiving this award can be felt in her accompanying email.

“Dear Fred and Eileen:

The abstract we submitted to the ASBMR was selected for an oral presentation and I got the **Young Investigator Award!** I could not wait to tell you this great news. Although the award is given to me, it brings honor to our laboratory and to the entire FOP community. I am so happy that I have been involved in this wonderful project. Thank you very much for accepting me into the laboratory in the first place and for all of the support in my research and life.

With best regards,

Qi.”

Congratulations Qi and to all of your collaborators. We are very proud of you!

## **26. Extraordinary Journalists Honored with Distinguished Media Award**

Last May, at an elegant ceremony in Washington, DC, the American Academy of Orthopaedic Surgeons honored two extraordinary journalists with **MORE** (Media Orthopaedic Reporting Excellence) **Awards**, the Academy's highest distinction for excellence in medical journalism. Claudia Kalb of **Newsweek** magazine and JuJu Chang of **ABC News** received the prestigious **MORE Award** for their feature stories on FOP in print and broadcast journalism respectively.

The **MORE Awards** were created to honor outstanding contributions made by journalists whose extraordinary work has educated readers and viewers about important musculoskeletal issues. The American Academy of Orthopaedic Surgeons notes: "The **MORE Awards** symbolize the lasting impact that media stories have on furthering public understanding of orthopaedic health and related conditions."

Winners were chosen from more than 90 nominations in a range of media presentations including newspaper, magazine, television, radio, and online formats. After a thorough review of all nominees, the board of directors of the American Academy of Orthopaedic Surgeons selected 13 entries to receive **MORE Awards**.

A surprise 14<sup>th</sup> Award was presented to Dr. Kaplan for "outstanding contributions to medical journalism."

## **27. Steady-Stream of Students Select FOP for Study: Elementary, High School, College, and Graduate Students Warm to Dangers, Dilemmas, and Discoveries**

One of the most surprising day-to-day changes in life since the discovery of the FOP gene has been the nearly steady-stream of requests for information on FOP from students from all over the world - from elementary school students through post-doctoral trainees. It is particularly gratifying to hear from elementary school, junior high school, and high school students who write to tell us that they have selected FOP for their research project or term paper. They often pose fascinating and challenging questions to supplement their on-line reading.

One elementary school student's request was particularly amusing. His letter arrived informing one of us that we had been selected as his hero for a school project and that in order to complete the project, he would appreciate it if we could answer 20 questions on FOP that he had listed. The letter was opened late one evening, and it was clear that the project was due the next morning – so a phone call was made to his home at 10 pm. When the student was informed that his “hero” would be happy to answer the questions by phone so that he would have his assignment completed by the next day (when it was due), the student replied: “Gee, thanks; I am very tired now, and I have to go to sleep. Would you mind faxing me the answers?” The midnight oil was burned, and the request was obliged. A few weeks later a letter arrived informing us of our official “hero” status, and the “A” he received on his project.

## **28. From Baltimore Harbor to Tokyo Bay: Educating Patients, Doctors, and Researchers about FOP**

During 2007, we were proud to present major lectures on FOP at the:

- American Academy of Orthopaedic Surgeons; Washington, D.C.
- Annual Meeting of Advances in Mineral Metabolism; Snowmass, Colorado
- Annual Meeting of the American Society for Bone & Mineral Research; Honolulu, Hawaii
- Children's Hospital of Boston; Boston, Massachusetts
- Eastern Orthopaedic Association; Victoria, Canada
- Fourth International Symposium on FOP; Orlando, Florida
- Glaxo-Smith-Kline Pharmaceuticals; King of Prussia, Pennsylvania
- Gaslini Children's Hospital; Genoa, Italy
- Harvard University; Cambridge, Massachusetts
- International Conference on Children's Bone Health; Montreal, Canada
- Johns Hopkins University School of Medicine; Baltimore, Maryland
- Massachusetts General Hospital; Boston, Massachusetts
- Max Planck Institute for Molecular Genetics; Berlin, Germany
- Morphotek Pharmaceuticals; Exton, Pennsylvania
- Mount Sinai School of Medicine; New York, New York
- New York Academy of Sciences; New York, New York
- Osaka University Medical School; Osaka, Japan
- Saitama Medical University; Saitama, Japan
- Taijen Pharmaceuticals; Osaka, Japan

- University of Aberdeen; Aberdeen, Scotland
- University of California San Francisco School of Medicine; San Francisco, California
- University of Genoa; Genoa, Italy
- University of Texas Health Science Center; San Antonio; Texas
- Wyeth Pharmaceuticals; Collegeville, Pennsylvania

During 2007, we were honored to present highlights of FOP research at regional, national, and international FOP family meetings and gatherings in:

- Aberdeen, Scotland
- Bedminster, New Jersey
- Genoa, Italy
- King of Prussia, Pennsylvania
- Orlando, Florida
- Osaka, Japan
- Plainfield, New Jersey
- Santa Maria, California
- Staten Island, New York
- Tokyo, Japan

In addition to lectures on FOP by doctors and scientists, students also spoke and held audiences captivated. To quote from a holiday newsletter:

“In 2007, both Jason and Ian Cali highlighted their mission with FOP by speaking in front of 350 people at **The Fourth International Symposium** about their personal journey with FOP. The very next week, they traveled to Philadelphia at the invitation of Drs. Kaplan and Shore to share their experiences and emotions

with 150 first year Penn medical students following a brief introductory lecture on the genetics of FOP to the freshmen genetics class at Penn. Most recently, Ian spoke in front of his entire school of 500 students encouraging them to participate in the school's 5K run for FOP. He said, 'FOP turns things that are often taken for granted, like walking a dog or playing sports, or even tying your own shoes, into a privilege. Because of this, I have learned to appreciate everything I can do at any specific point in my life, because some day I might not be able to do them any more. It's scary to think that your range of motion can get taken away, but it just makes every step, or reach, that much better.' "

This is one of many stellar examples of young people with FOP throughout the world who have reached-out to their own communities with candor and enthusiasm about their personal struggles and triumphs with FOP and about the global urgency of the FOP mission. We applaud each of you for helping to educate physicians and scientists, colleagues and peers, and others in your own and extended communities. Your own words and experiences motivate physicians and scientists to work on FOP and help us better understand the human element that propels this work. Our marching orders and our mission come from you. You make us all very proud!

## **29. FOP in Print - 2007**

Since the last Annual Report, there have been 12 publications on FOP, six of which appeared in major peer-reviewed journals. There were several major reviews on bone morphogenetic protein signaling in which the FOP gene discovery was highlighted. As of January 2008, the FOP gene discovery paper in **Nature Genetics** (2006) has been cited in 27 major scientific publications worldwide and has been quoted in many languages.

### **30. FOP Reaches Primetime: Fact and Fiction Collide**

There are approximately 700 known patients with FOP worldwide and one (Cathy Rogerson) with fictional FOP. While real people are far more important to us, fictional characters, like Cathy Rogerson, help bring FOP to the attention of the public.

When we were contacted by the writers and producers of **ABC Television**, about their script for the FOP episode of *Grey's Anatomy*, we were happy to help them revise the script to make the program medically correct. We did what we could within the limits that the script allowed, but the bottom line was that FOP was introduced to millions of people, who would not otherwise have heard of it. The response was sudden and dramatic, and the request for information following the broadcast came from all corridors of society, with enormous enthusiasm, and even some contributions for research. Our own Jud Bogard from Hollywood, CA volunteered to help educate the writers, producers, and actors who played in the historic FOP episode of *Grey's Anatomy*. In all, it was a positive experience, and we are grateful that it helped introduce, inform, educate, and expand our outreach to the world.

### **31. Worldwide Holiday Greetings Express Spirit of Hope**

The spirit of hope is most often expressed at holiday time, but is relevant all year long. Each year, we receive numerous cards, letters, and emails from around the globe. We truly love hearing from you. Through such communications, we gain access in a very personal way to those who are the sole reason for what we do. Regardless of the native language or the country of origin, the primary message is the same worldwide – the spirit of hope.

While most will not read this report until the spring or summer of 2008, it is being written in the depths of winter - during the earliest days of January 2008. There is no time like the holidays, when the global nature of the FOP community is more apparent. The internet and email have connected our world like no other. What is even more apparent – immediately, and at the speed of light – is that the wishes are the same worldwide – for a treatment and cure for FOP. They are number one on everyone’s list –

- From Avio to Anchorage
- From Benghazi to Boston
- From Berlin to Burbank
- From Brisbane to Bangor
- From the Congo to Cedar Rapids
- From Eskilstuna to Ellicott City
- From Henvic to Hudsonville
- From Melbourne to Meridian
- From Osaka to Oyster Bay

- From Petoskey to Petaluma
- From Pori to Porterville
- From Rome to Redondo Beach
- From Sao Paulo to Seal Cove
- From Sierra Leone to San Diego
- From Santa Maria to Staten Island
- From Vancouver to Victor
- From Summerfield to Winter Springs

We want you to know that your wishes and hopes resonate throughout every season and inspire us in all we do.

## **What Needs To Be Done**

The FOP gene discovery is relevant to every disease that affects the formation of bone and every disease that affects the formation of the skeleton. Answers to FOP are relevant to many common skeletal conditions such as unwanted bone growth that forms after hip replacement surgery, athletic injury, brain injury, spinal cord injury, soft tissue injury, burns, war wounds, valvular heart disease, and even bone spurs from osteoarthritis. Eventually, through progress being made in FOP research, some of which has been highlighted in this report, it might be possible to harness the FOP gene, and create bone in a more controlled way where it is desperately needed such as in fractures that do not heal, surgical spine fusions, severe bone loss from trauma, osteoporosis, tumors, and congenital malformations. The FOP gene discovery is a great beacon of hope for all of us in the FOP community, and for all of us in a much wider global community who are affected with common skeletal disorders. Better treatments for FOP are not just a dream – they are now a likelihood, and a cure is a distinct possibility.

During this past year, we have begun to turn the FOP gene discovery into insight, and insight into development. We have set our sights on the distant horizon. But, we won't get there by wishing it, and we cannot do it alone. We need your help.

**What needs to be done?** During this past year, we have expanded the network of physicians and scientists who are working on FOP through targeted identification and funding of those who can help most and who can help the fastest – wherever they may be. We need to expand that program, and we need your help.

**What needs to be done?** During the past year, we have begun to develop cellular and animal models to determine how the renegade FOP gene acts at the molecular level. We need that knowledge and those critical models to design new drugs and to test them. We need to continue that work, to expand it, and we need your help.

**What needs to be done?** During this past year, we have begun to crystallize the mutant FOP protein to study its atomic structure, its catalytic domains, and its interactions with other key proteins in the molecular relay-switch that triggers catastrophic new bone formation. Such knowledge will be needed to custom-design the best medications to block the mutant switch. We need to continue that work, to expand it, and we need your help.

**What needs to be done?** During the past year, we have begun to model the active site of the broken switch, and are beginning to use that knowledge to design the best methods to block, jam, or bypass it. We need to continue that work, to expand it, and we need your help.

**What needs to be done?** During the past year, we have begun to study the mechanisms by which the inflammatory microenvironment of an injury triggers the renegade FOP switch to form new bone. When we understand that better, we'll be able to use that knowledge to apply the brakes to a run-away process. We need to continue that work, to expand it, and we need your help.

**What needs to be done?** During the past, year, we have begun to scour the world's available libraries of medicinal compounds to identify those that may block the abnormal FOP switch and its downstream molecular circuits. We need to continue that work, to expand it, and we need your help.

These goals and the tasks they imply are easy to articulate and all have been started, but they need funding to be fulfilled. We need your help to continue these vital programs and ensure their success, to do more, to do it faster, to expand our horizons, and to make sure that no clue is ignored.

Our research budget of 1.5 million dollars annually supports a core laboratory of 15 scientists as well as collaborators around the world. Each year, we struggle to find the funds to persist. But we need to do more than persist. We need to prevail. We need your help.

FOP is an uncommon condition of uncommon brutality, but there is finally a chance to do something intelligent and rational to interrupt the inexorable progression of what has been described as a "horrible nightmare disease." Chemistry combined with compassion will lead to orphan drug development, to more effective treatments for those with FOP, and for those with more common forms of heterotopic ossification. We have worked hard to get this far, and your generosity has helped get us there. But, we need your help to go farther. We all know what needs to be done, and we need your help to prevail.

As we have said many times, *cause* and *cure* are the two words that propel us and provide the guiding principle for all we do: to discover the cause of FOP, and to use that knowledge to develop effective treatments and eventually a cure. Many said that identifying the gene mutation that causes FOP couldn't be done. In 2006, with your help, we reached the summit of a great mountain and discovered the genetic cause of FOP. In 2007, we headed for a higher and more distant summit – the treatment and cure of FOP. We need to continue that journey, to expand it, and we need your help.

**What needs to be done?** As David Ben Gurion, the first Prime Minister of Israel said, “The difficult we do immediately; the impossible takes a little longer.” With your help, we plan to do the impossible, not just climb mountains, but move them. Finding an effective treatment and cure for FOP is not a job; it is a mission.

All of us at the FOP Center, in the Developmental Grants Program, and in the affiliated collaborative ventures around the world are extremely proud to be part of this mission, and are enormously grateful to those who support this vital research effort:

- The International FOP Association (IFOPA)
- The National Institutes of Health (The People of the United States of America)
- The University of Pennsylvania
- The Center for Research in FOP & Related Disorders
- 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 Allison Weiss Fellowship in Orthopaedic Molecular Medicine

- The Born-Lotke-Zasloff Fellowship in Orthopaedic Molecular Medicine
- The Whitney Weldon - Stephen Roach Fellowships in FOP Molecular Genetics
- The Roemex Fellowship in FOP Molecular Pathophysiology
- The Grampian Fellowship in FOP Molecular Pathophysiology
- The Medical Research Council and The University of Oxford (United Kingdom)
- The Association Pierre-Yves (France)
- FOPeV (Germany)
- FOP Italia
- The Brazilian FOP Association
- Canadian FOP Families & Friends Network
- The Pittsburgh Foundation
- The Max Planck Institute for Molecular Biology
- Saitama Medical University
- The Sarah Cameron Fund (U.K.)
- The Scandinavian FOP Association
- Members of the FOP International Research Consortium
- The People of Santa Maria (15 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.