THE SIXTEENTH ANNUAL REPORT

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COLLABORATIVE RESEARCH PROJECT

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"All truths are easy to understand once they are discovered," said the 16th century Italian physicist, astronomer, and philosopher, Galileo Galilei, "The point is to discover them." In modern times, the writer and philosopher, E.O. Wilson, said, "Great scientific discoveries are like sunrises; first they touch the tips of a few peaks and steeples; then they illuminate the whole world." Those two bits of wisdom embody the story of FOP research for 2006.

In science, discoveries are not official until they are published. On Sunday, April 23, 2006 at 6 PM Greenwich Mean Time, a brief article was published online by the prestigious journal **Nature Genetics** of London, and marked the moment that a team of researchers from the University of Pennsylvania and their international collaborators from five continents (North America, South America, Europe, Asia, and Australia) planted the FOP flag at the summit of one of the highest, most remote, and most forbidding mountains in all of skeletal biology and medicine.

The news spread at the speed of light around the globe, and captured headlines from London to Los Angeles, from New York to New Delhi, from Minneapolis to Moscow, from San Francisco to Sydney, from Chicago to Cairo, from Philadelphia to Paris, and from Baltimore to Buenos Aires. Like an informational tsunami, doctors, scientists, patients, families, friends, strangers, and communities across the planet learned of the discovery of the FOP gene - the elusive Holy Grail in the scientific pantheon of one of medicine's greatest mysteries. Suddenly, a great secret of nature had been revealed – the

key to a catastrophic and normally forbidden biological process of metamorphosis in humans - the transformation of one normal organ system into another.

After fifteen long years, the discovery team had finally arrived at the mountain top and announced to the world that the FOP gene had been discovered. Reinhold Messner, one of the greatest mountaineers of all times, said in speaking of the greatest summits, “If you have to crawl on your hands and knees, you are going to get there.”

But, distance and altitude can be deceiving in the mountains. And with the revelation of that momentous discovery, the biggest to occur since FOP was first described nearly 300 years ago, the outlines of the most distant range became visible – the mountains that would have to be scaled to achieve a cure. Isaac Newton, the great genius of 17th century physics, wrote to Robert Hooke, the inventor of the microscope, “If I have seen further, it is by standing on the shoulders of giants.” From the summits of great mountains, we can see even further.

Some years change little; some years change history. Now, a year after the most momentous discovery in the history of FOP, the seismic aftershocks continue to reverberate through the scientific and medical world. Dr. Thomas Einhorn, the chairman of Orthopaedic Surgery at Boston University wrote: “The contribution of this discovery to the understanding of FOP and the ripple effects this will have on our understanding of bone biology in general are enormous.”

M.K. Timmerman, a scientist from the Netherlands, wrote, "The discovery of the FOP gene has the potential to tell us something fascinating about the nature of bone formation. Furthermore, the identification of this mutation has potential implications for the treatment not only of patients with FOP, but also, perhaps, of patients with osteoporosis or others who might benefit from an increase in bone formation."

Patrick Warnke of the University of Kiel in Germany, stated in an editorial in the journal **Science,** "The newly discovered gene mutation described in **Nature Genetics** not only has potential therapeutic implications for this currently untreatable disorder, but may also reveal novel avenues for harnessing the tragic talent of FOP patients to produce prolific amounts of bone. We are always in need of hard tissue. The FOP gene defect could show us the way to induce bone growth."

William Gelbart, a professor of genetics and developmental biologist from Harvard University said, "That the gene defect is so specific is pretty amazing. It is my hope that an FOP mouse model can now be created, allowing for deeper study of the disease and potentially drug development."

In an editorial in the journal **Orthopaedics**, Dr. Jennifer Wolf from the Department of Orthopaedics at the University of Colorado Health Sciences Center in Denver Colorado wrote, "The identification of the specific gene mutation that causes bone to form in FOP has great implications for orthopaedics as a whole. Knowing the genetic basis for this rare but catastrophic disorder of heterotopic ossification can guide us in the treatment of

more common entities. Imagine the ability to cause a tibia to heal, a spine to fuse, or a delayed union to stabilize in a predictable fashion by turning on the switch of bone formation! In the FOP community, the next goal is to learn how to block or bypass the abnormal ACVR1 receptor to stop the progressive heterotopic bone formation that occurs in these patients. What we can learn from this process is how and when to stimulate bone formation. The genetic key to FOP has the potential to demonstrate how to control and modify bone formation at the molecular level, which could revolutionize the way we perform surgery and treat patients."

The FOP gene discovery heralds new approaches for developing treatments and eventually a cure for FOP, our ultimate mission. But, this too will take time and will require much additional work. Cellular and animal models will be developed. New drugs will be designed, and screened, and safety testing will be conducted and completed before any new medications are used in a patient with FOP.

The identification of genes of clinical relevance is critically important for drug development for diseases like FOP, and for more common disorders that share parts of the same molecular pathway. In essence, 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 will be important for many common conditions such as non-hereditary heterotopic ossification that forms after total hip replacements, brain injury, spinal cord injury, soft tissue injury, burns, valvular heart disease, and even bone spurs from osteoarthritis. Eventually, 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 spinal fusions, severe bone loss from trauma and osteoporosis, 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 those in a much wider community worldwide who are affected with common skeletal disorders.

Together we have reached the summit of a great mountain, but we still have an even greater peak to conquer. During the past year, we have established base camp near the summit, surveyed the horizon from the mountain top, documented our treacherous and exhilarating climb, and told the world where we are, what we have accomplished, and where we are going. We have called for reinforcements, recruited new climbers with special expertise, consulted with experts near and far, and formed new collaborations with colleagues far and wide. We have planned our next steps on this journey, and sent out advance teams to scout the way. We have studied our maps and redrawn them almost daily as new data are discovered and new knowledge emerges on this next phase of the journey. And through this all, we have charged ourselves and you, the members of our FOP community and our scientific and medical team, with the grandest of all challenges - the final assent to the ultimate summit – the most distant and highest peak on the horizon, the treatment and eventual cure of FOP.

The place: London, England.

The date: April 14, 1736.

John Freke, a London surgeon wrote: "There came a boy of healthy look and about 14 years of age, to ask of us at the hospital, **what should be done to cure him** of many large swellings on the back which began about three years since, and have continued to grow as large on many parts as a penny-loaf, particularly on the left side. They arise from all the vertebrae of the neck, and reach down to the os sacrum. They likewise arise from every rib of his body, and joining together in all parts of his back, as the ramifications of coral do, they make, as it were, a fixed bony pair of bodices."

Today, 271 years later, our knowledge is infinitely greater, but the challenge remains. **"What should be done to cure him?"** The question is as relevant now as it was nearly three centuries ago, but our hope has a new dimension. As the Snow family from Santa Maria, California, stated so eloquently in their 2006 holiday letter, "Hope sees the invisible, feels the intangible, and achieves the impossible."

The place: Philadelphia, Pennsylvania.
The date: Sunday, April 23, 2006.
What kind of a day was it? To paraphrase a journalist of great renown, "It was a day unlike any other, filled with the events that alter and illuminate our time." It was a day that might have left Dr. Freke speechless. It was a day that left all of us in awe.

The discovery of the FOP gene is not only a monumental milestone in the history of FOP, but a vital focal point for all FOP research from this time forward. We urge all readers – those who are new to the FOP world, and those who are veterans of this venerable

community - to carefully read (and re-read) the 15th Annual Report of the FOP Collaborative Research Project in its entirety. It will enable a deeper and more comprehensive understanding of all that follows in this report. In the body of this 16th Annual Report, we will highlight some of the other major research developments and perspectives of this amazing and historic year.

Computer Modeling of the Mutated ACVR1 (R206H) Receptor Switch in FOP: The Shape of Things to Come

Soon after the discovery of the FOP gene, we contacted Jay Groppe, one of the foremost x-ray crystallographers in the world in the field of BMP signaling, and asked him to help us better understand how the ACVR1 mutation causes FOP. Almost immediately, Jay embarked upon a complex study called protein homology mapping that predicted the atomic structure of the mutant ACVR1 switch and extended the original observations published in the historic paper describing the discovery of the FOP gene.

In his study of the structure of the mutant ACVR1 protein, Jay discovered a feature of the receptor that had gone unnoticed until now. This discovery allowed him to predict that the FOP mutation would have profound consequences on the function of the ACVR1 receptor. This discovery has led to a novel hypothesis about the immediate chemical environment of the receptor that suggests why the mutated ACVR1 receptor may be "leaky at rest" but not wildly hyperactive except under conditions of stress and soft tissue injury. You will be hearing a lot more about this as the work evolves. This is an extraordinarily exciting new area of research that has the potential to identify precisely how the FOP mutation alters the atomic structure and function of the ACVR1 receptor,

and how the local environment of the receptor (as in the setting of tissue injury) alters the functional stability of the receptor switch. This fascinating new perspective provides a basis for the rational design of drugs targeted to disrupt the renegade activity of this mutant switch that triggers explosive new bone formation.

Variations in FOP Reveal New Mutations in ACVR1

The FOP gene discovery is a tough act to follow, but we were not about to rest at the summit! After we identified the FOP gene mutation in individuals who had classic FOP (typical malformed great toes and characteristic patterns of progressive heterotopic ossification), we extended our investigation to individuals who had atypical FOP (classic FOP plus other clinical features not usually seen in FOP) and to individuals who had FOP variants (variations in the classic clinical features of the disease). We found that everyone with classic FOP, atypical FOP, and FOP variants had mutations in the ACVR1 gene. That itself is remarkable. However, a few individuals who had atypical FOP and all individuals who had FOP variants, instead of having the classic R206H mutation, had novel mutations in the ACVR1 gene. We were amazed. In every individual, the mutation occurred in a functional region of the protein that is predicted to affect BMP signaling.

The discovery of unique ACVR1 mutations in individuals who have variations in the classic clinical features of FOP is an extremely important finding and an exciting new development in FOP research. These ongoing genetic studies are vitally important in helping us better understand the spectrum of clinical effects attributable to mutations in ACVR1 and in helping us better design strategies to treat them. We anticipate that many new insights will emerge from this ongoing area of investigation and you will be hearing a lot more about them as the work evolves.

Genetic Testing for FOP is Now Possible Prior to the Appearance of Heterotopic Ossification

The correct diagnosis of FOP cannot be made if it is not first suspected. Clinical awareness of the classic clinical features of FOP – the great toe malformations and the soft tissue swellings, ensures that FOP will be properly diagnosed. Once FOP is suspected, genetic testing can be performed to confirm or exclude the diagnosis of classic FOP. Such early diagnostic assurance at the molecular level will provide clinicians and parents with an element of certainty that will allow them to approach the preventative aspects of FOP in a timely and rational manner.

Attention to easily identifiable signs and symptoms of FOP early in life, before the appearance of disabling heterotopic ossification, can limit the disability and lifelong harm that results from diagnostic errors and inappropriate invasive procedures. While definitive therapies for FOP are not yet available, early clinical diagnosis and genetic testing can provide a high degree of diagnostic certainty that can be used to prevent unnecessary harm.

A Gift from the Tooth Fairy: Cells from Baby Teeth of FOP Patients Hold Vital Clues About the Functioning of the Renegade ACVR1 Gene

FOP is a challenging condition to study. Since physical and surgical trauma exacerbates FOP by inducing bone formation, it has been difficult to obtain tissue samples from FOP patients for detailed biochemical and molecular analysis. An understanding of the molecular havoc caused by the ACVR1 mutation in FOP has thus been limited by a lack of readily available connective tissue cells from FOP patients.

In order to better understand the mischief of FOP at the molecular level, we have safely derived connective tissue precursor cells from the baby teeth of FOP patients and unaffected individuals and examined differences in the BMP signaling pathway under resting conditions and after simulation with BMP. Cells obtained from the pulp of baby teeth grow well under laboratory conditions and have the capacity to differentiate into several different connective tissue cell types including cartilage cells and bone cells. These cells have recently been proposed as a human adult stem cell source for tissue engineering.

Baby teeth provide a safe and abundant source of cells to study the abnormal behavior of the FOP gene. Cells from these baby teeth express bone proteins when grown under laboratory conditions, and activate both major branches of the BMP signaling pathway. In our preliminary studies, we found that the ability to activate downstream target genes in the BMP pathway was consistently higher in FOP cells than in control cells. Importantly, baby teeth cells from FOP patients demonstrate a remarkable change in the set-point and sensitivity of BMP signaling compared to cells from children who did not have FOP.

What exactly do we mean when we say that FOP cells demonstrate a remarkable change in the set-point and sensitivity of BMP signaling? Imagine, for a moment, that ACVR1 (the protein made by the FOP gene) is a light switch that turns the lights on and off in a room. One can even imagine that the light switch has a dimmer that allows the brightness of the light to be adjusted according to the needs of the cell, tissue, or organ in

which it is expressed. In individuals who do not have FOP, the switch is off most of the time, and is turned on when the cell or tissue needs it to be turned on. What we have found in FOP cells is that when the switch is turned off, the lights still flicker. And, when the switch is turned on, the lights not only go on to the brightest setting, but the washing machine turns on, the television and the stereo turn on, and the neighbors' garage door opens! Thus, the FOP gene is not only overactive, but is also doing things that it should never do in places it should never do them.

For those who prefer a plumbing analogy, imagine a faucet. In the case of FOP, the faucet leaks when it is turned off, but gushes water everywhere (not only in the sink but all over the room), when it is turned on. That's what we mean when we say that FOP cells demonstrate a change in the set-point (flickering lights or leaky faucet) and sensitivity (neighbor's garage door opens or water spurts everywhere) in BMP signaling. The study of bone-forming cells from baby teeth provides a cell system for us to use to expand our understanding of the ACVR1 gene mutations in FOP, provides important new insight into the dysregulated BMP signaling pathway in FOP, and pays dividends of knowledge that will be invested in drug development for the future.

The FOP Zoo

Animal studies are vital to the progress of FOP research, but no one animal model can address all of the important questions that need to be answered. Therefore, we would like to introduce the concept of an FOP zoo. Zoos are not just places to observe rare animals, but places to better understand the unique relationships between animals and humans.

There are many great zoos around the world, but soon none will rival the FOP zoo for its creative use of animal models for understanding the molecular mischief of FOP. Genetic modification of animals is a powerful tool for the study of development and is beginning to contribute substantially to our understanding of the FOP mutation and the process of metamorphosis caused by it.

The development of relevant animal models for FOP is a necessity. Animal models are essential for understanding the FOP gene mutation and for testing treatments that will eventually be used in children and adults who have FOP. While experiments using cells in culture are helping us better understand the molecular activity of the FOP gene, they are not sufficient to probe the activity of the mutant ACVR1 gene in tissues, organs, and organisms. In addition, cell culture studies are insufficient to understand the potential side-effects or complications of potential therapies for FOP.

During the past year, we have expanded our use of animal models to include those that will help us better understand the BMP signaling pathway, ACVR1-related developmental processes, and postnatal heterotopic ossification that occurs as a result of the ACVR1 mutation in FOP. Relevant animal models will include genetically-engineered mice, but will also include chickens, fish, and flies. We are preparing a new sign for the entrance to the lab which will read: "No fly swatters, fishing poles, or mouse traps allowed!….and don't count your chickens before they hatch!"

Designer Genes for the FOP Zoo:
The Development of a Knock-In Mouse Model for FOP

We have begun to develop an FOP mouse – not just an ordinary FOP mouse – but one that is genetically identical to FOP in humans. The easiest way to make a mouse that is similar to FOP is to make what is called a transgenic mouse. In such a mouse, extra copies of the mutant ACVR1 gene are introduced into an embryonic stem cell and a mouse is generated after implantation. The transgenic approach may create a close look-alike, but it is not good enough. With such an approach, one is never sure how many extra copies of the gene are introduced into the mouse genome or exactly where the mutant genes are incorporated into the mouse DNA. Also, with such an approach, it is possible that the "shot-gun" introduction of a mutant ACVR1 gene into the mouse might interrupt the organization of other critical genes in the mouse DNA. One could also never be certain that any resultant clinical features that the mouse developed were due to the ACVR1 mutation or were due to the unanticipated insertion of the gene into an unknown location in the mouse DNA.

In order to avoid this potentially confusing situation, we have taken special precautions to introduce the mutant ACVR1 (FOP) gene into the exact spot in the mouse genome where one of the two normal copies of the ACVR1 gene resides. We, therefore, have to "knock-in" a mutant copy of the FOP gene, at the exact location in the mouse genome where one of the two normal copies resides, and swap it with a normal copy of the mouse ACVR1 gene that normally resides at that exact spot. Such stealth molecular targeting ensures that the mutant gene is inserted at exactly the right genomic address and is exchanged for a normal copy of the ACVR1 gene that normally resides there. These

molecular manipulations are extremely time-consuming, tedious, and technically difficult, but they are necessary to ensure the fidelity of the resulting mouse model for FOP.

This stealth molecular technology we are using should provide the best chance of developing an FOP mouse that is genetically identical to FOP in humans. Such a mouse is called an "FOP knock-in mouse." Eventually, we will have a contest to name the mouse. There is no guarantee that the mouse genome will cooperate and produce the exact clinical features of FOP that we see in humans, and it would not be surprising if an FOP mouse had some clinical features that were different in scope and magnitude from those seen in individuals who have FOP.

Nevertheless, the generation of such an FOP knock-in mouse, if it can be achieved, will be an extraordinary achievement in FOP research. Preliminary names for an FOP mouse suggested by patients and families around the world include: "lucky mouse", "special bones", "bumpy mouse", and "ultra-fop." If and when FOP mice are born, these mice will be bred and a colony established, making these the most valuable members of our FOP zoo.

Pending development of "FOP knock-in mice", other mouse models that continue to provide important insight into the mechanisms of heterotopic ossification include the FOPPY mice and the BMP4 implant mice. Until real FOP mice are developed, the

FOPPY mice and the BMP4 implant mice will continue to be valuable animal models for FOP research as well as for research on post-traumatic heterotopic ossification.

Expanding the FOP Zoo: Alternate Approaches

We must be careful not to count our mice before they are born. Recreating the sequence of genetic mishaps in a mouse is not necessarily enough to replicate human FOP. The physical differences between humans and mice can be a daunting obstacle. We therefore need to consider alternative approaches and other animal models for FOP that can also provide important insight into how the FOP mutation affects tissues and organs. As one scientist said recently, "Genetically engineered mice are valuable, but they are, after all, still mice."

The FOP Zoo and the Chicken Coop

If we must be careful not to count our mice before they are born, we must also be careful not to count our chickens before they hatch! But, they have hatched! It was, in fact, a study of overactive ACVR1 in embryonic chickens that identified the functional capacity of mutated ACVR1 to act as a BMP receptor in the formation of heterotopic cartilage and bone. This finding, by colleagues at the University of Rochester in Rochester, NY, allowed us to more seriously consider ACVR1 as a prime candidate gene for FOP and its subsequent identification as the causative gene for the condition. While we do not presently have chickens in the FOP lab, they have become honorary members of our FOP zoo!

Catch of the Day: Little Zebrafish in the FOP Aquarium

The 18th century novelist, Oliver Goldsmith, said to his nemesis, the English poet Samuel Johnson, "If you should write a fable for little fishes, you would make them speak like great whales." Well, little fishes have entered the FOP laboratory, and for us, they are as powerful and interesting as great whales.

Every great zoo needs an aquarium, and the FOP zoo just acquired one. The ACVR1 gene is highly conserved in the animal kingdom all the way back to fish (and even farther back than that)! Zebrafish, a well-studied animal model for vertebrate development, have a gene similar to ACVR1 in humans. Dr. Mary Mullins, a professor of developmental biology at Penn, showed that inactivating mutations of the zebrafish ACVR1 gene lead to a condition called "lost-a-fin." The "lost-a-fin" mutant fish provides a convenient animal model for testing the function and potency of the FOP mutation, specifically to determine if the overactive FOP gene can rescue (or prevent) the effects of the "lost-a-fin" zebrafish mutant.

In collaboration with the Mullins' laboratory, we are beginning to perform experiments in this animal model. Preliminary data suggest that the human ACVR1 gene partially rescues the loss-of-function mutation caused by an inactivating mutation of the zebrafish ACVR1 gene, and that the FOP mutation in ACVR1 provides a super-rescue! These preliminary experiments in the zebrafish provide strong evidence that support our hypothesis about the functional consequences of the FOP mutation.

These preliminary findings will guide us in generating genetically-engineered zebrafish that actually have FOP, or as close to it as a fish can get (fish don't have toes)! Such fish will be extremely helpful in understanding the early embryonic and late developmental effects of the FOP mutation. Unlike many other vertebrates, zebrafish develop externally, and their bodies are translucent so that developmental events can be monitored easily. Also, zebrafish breed rapidly and in large numbers, thus facilitating experimental studies. Thus, the "foppish fish" will join the "FOPPY mice" and the soon-anticipated "FOP knock-in mice" in our new FOP zoo. As Mollie Steele, sister of FOP patient Sarah Steele, said 15 years ago at an FOP family meeting on a hot summer day in Nashville, Tennessee, "Let's go swimming!"

No Zoo is Complete Without Flies, and the FOP Zoo is No Different

Saxophone, thickveins, wishful thinking, decapentaplegic, and *glass bottom boat* - a New Orleans reverie gone wild? Not at all! These are the names of genes in Drosophila (or fruit flies) that control BMP signaling in those little bugs and are nearly identical to their more soberly-named counterparts in humans, conserved over nearly half a billion years of evolution. *Saxophone,* for example, is the fly equivalent of our ACVR1 gene; and *thickveins, wishful thinking, decapentaplegic,* and *glass bottom boat* are its molecular "partners in crime." So, the more things sound different, the more they may actually be the same in a jazz festival of molecules shared by animals down through the ages. As Shakespeare said, "What's in a name? That which we call a rose by any other word would smell as sweet."

Kristi Wharton, a professor of developmental biology at Brown University in Providence, Rhode Island, studies the function of *Saxophone* (ACVR1) and *thickveins* (BMPRIA) and their mutations in fruit flies. Upon learning of the FOP gene discovery, Dr. Wharton contacted us to learn of our interest in studying the FOP mutation in fruit flies. Unlike vertebrate animal models, of course, the fruit fly does not have bones. And, people, of course, do not have wings! But, flies do have skeletons of a sort, and their skeletons are on the outside of their bodies, like armor (exoskeletons). In humans, the skeletons are on the inside of the body (endoskeletons), and the genes that regulate their formation are almost identical to those in flies. The molecular tool kits for building the fly and human skeletons are different, but the molecular blueprints are essentially the same. The study of *saxophone* gene mutations in Drosophila will thus allow us to better understand the ACVR1 gene mutation in humans in one of the simplest animal models possible for deciphering the molecular physiology of FOP. Thus, in our zoo, flies are welcome!

Fruit flies breed even faster than fish, and it should be possible to rapidly decipher some of the molecular workings of the FOP gene in Drosophila. A lesson that we have learned repeatedly is that nature is resourceful and conservative. Once nature has worked-out a system for communication between cells, it is likely to preserve that system, and modify it rather than change it completely. Therefore, studies of the molecular mischief of the FOP mutation in fruit flies are likely to be highly relevant to our understanding of the wayward ways of the same gene mutation in individuals with FOP.

The fruit fly has already illuminated the path of FOP research. In fact, the very first paper we ever wrote on FOP in 1990, was entitled, **"FOP: A Clue From the Fly."** As our friend and colleague, Dr. William Gelbart from Harvard University advised many years ago, "As you move forward in your work on FOP, do not forget the fruit fly. It has provided important clues that have taken you far, and it will likely continue to provide important clues that will take you even farther." Wise advice from a wise friend.

Bone Marrow Transplantation Does Not Cure FOP. However, Even a Normal Immune System is Sufficient to Trigger FOP in a Genetically Susceptible Individual

We recently (Feb, 2007) published a landmark study in the prestigious **Journal of Bone and Joint Surgery** on the role of adult stem cells in FOP. The article is based upon observations made in a unique patient who has FOP and in corresponding studies in mice. Blood-making cells from the bone marrow have long been implicated in the ectopic bone formation of FOP. The replacement of these blood-making stem cells by bone marrow transplantation has been postulated by some as a possible cure for FOP. However, the definitive contribution of blood-derived cells to the formation of heterotopic bone has remained obscure. In this newly published study, we made careful clinical observations in a unique FOP patient who underwent a life-saving bone marrow transplantation for an unrelated but fatal bone marrow disorder.

This extraordinary FOP patient underwent a bone marrow transplantation 25 years ago (in his childhood) for the treatment of aplastic anemia, a fatal condition in which the blood making stem cells in the bone marrow suddenly stop making blood. We asked whether the clinical course of his FOP had been influenced by the bone marrow

transplantation that he needed to save his life. In complementary studies, we transplanted blood-making stem cells from the bone marrow of genetically labeled mice into unlabeled mice to identify the contribution of blood making stem cells to BMP4-induced heterotopic ossification, a well-described model of FOP.

Interestingly, we found that replacement of the FOP patient's bone marrow with normal bone marrow from his unaffected sister cured his fatal bone marrow condition but was not sufficient to prevent further heterotopic ossification and progression of his FOP. However, the powerful immunosuppressive medicines that he received following his bone marrow transplantation, and that he needed for 15 years to prevent his new immune system from destroying his body's tissues, seemed to quiet the activity of his FOP. In complementary transplantation studies in mice, we found that blood cells derived from the bone marrow contributed to the early inflammatory and to the late marrow repopulating stages of BMP4-induced bone formation, but were not present in the early FOP-like lesions.

Taken together, these amazing findings demonstrated that bone marrow transplantation did not cure FOP in this patient, most likely because the blood-making stem cells from the bone marrow were not the cells that became the FOP lesions. Following his life-saving bone marrow transplantation (from his normal sister), he had to receive powerful immunosuppressive medications to prevent his new and overactive immune system from destroying the rest of his body. Over time, his new immune system got used to his body, and when the immunosuppressive medications were eventually tapered and stopped after

15 years, the FOP flare-ups resumed with a vengeance. Thus, in this patient who has an ACVR1 (R206H) mutation, immune cells from his new bone marrow (without any ACVR1 mutation) contributed to the formation of an ectopic skeleton. These immune cells only trigger ectopic bone in the context of the ACVR1 mutation in other cells of the body. In other words, the immune cells may be the match that lights the fire, but they're not the fuel that keeps it burning. Or, looking at it another way, even a normal match can light a fire in an FOP gas station!

At first glance these findings seem to suggest that intense immunosuppression (as this patient received and needed for 15 years to prevent his new immune system from destroying his body) could have a strong beneficial effect on the clinical course of FOP. However, such chronic immunosuppression could also lead to fatal complications (luckily in this one patient, it did not).

It is also unclear whether immunosuppression in the absence of bone marrow transplantation would be sufficient to reduce progressive heterotopic ossification in a patient with FOP whose blood is formed normally. While it is assumed that the immunosuppressive therapy had a direct action on the normal blood-making stem cells that our FOP patient received from his sister and an indirect effect on his FOP connective tissue progenitor cells, a more direct effect of the immunosuppressive medications on his connective tissue cells cannot be ruled-out on the basis of this one patient. At the present time, (and until further studies are performed in appropriate animal models), all members of the international consortium of FOP physicians feel that use of chronic

immunosuppressive medications is not a wise approach for the routine management of FOP.

These findings are of immense research interest and vital clinical importance, and they illustrate vividly how much can be learned by careful observation in an individual patient. They also illustrate the importance of the immune system in triggering FOP flare-ups. For the meanwhile, however, the general use of powerful immunosuppressive medications such as used in the patient described in this study is not advocated in the routine management of FOP, and would likely be extremely dangerous and possibly life-threatening if it were applied to the general FOP community.

In summary, we showed through the careful study of a unique FOP patient and in complementary animal studies that at least two populations of stem cells, one derived from the blood (immune cells), and another derived from the soft connective tissues (muscle, tendon, and ligament cells) are necessary to form an ectopic skeleton. Furthermore, lymphocytes or immune cells with the FOP ACVR1 mutation are not needed to trigger this process. Even normal lymphocytes and normal immune cells can trigger an FOP flare-up in a genetically susceptible individual. Therefore, therapeutic regulation of the immune system may hold promise for controlling ectopic bone formation relevant to FOP and perhaps for many other common disorders of extra bone formation in humans. Once again, extreme caution is necessary. Additional studies are mandatory before the approaches described in this study can be safely applied to others who have FOP.

FOP Treatment: the Overall Picture

The ultimate mission of FOP research is the treatment and cure of FOP. That mission will ultimately be based on four principles: blocking the renegade ACVR1 signaling pathways in FOP cells, suppressing the immunological triggers, altering the relevant osteoprogenitor cells in the target tissue(s), and modifying the tissue environment so that it is less conducive to heterotopic ossification.

The FOP Gene is the Key to the Pharmacy

"With so much being discovered about how the BMPs act," wrote Bridget Hogan more than a decade ago, "it might be possible to develop drugs that will block some part of the BMP pathway and therefore prevent the progression of what is a horrible nightmare disease." The recent discovery of the FOP gene and the specific mutation that causes FOP brings that elusive goal closer to reality.

The recent discovery of the FOP gene mutation provides stunning new insight that strongly suggests that a small molecule signal transduction inhibitor (STI) against ACVR1 (also known as Activin-like kinase 2 or ALK2) might be the most promising approach to block the renegade BMP signaling pathway in FOP. Similar approaches have been used to develop STI medications for other renegade receptors that cause diseases in humans, and some of those STIs are now life-saving drugs.

ACVR1/ALK2: A Druggable Target for the Second Skeleton

The identification of the recurrent point mutation that causes FOP in all classically affected individuals provides a specific druggable target and a rational point of intervention in a critical signaling pathway in nature. The discovery of the FOP gene

immediately identifies ACVR1/ALK2 as a specific and ideal drug target for FOP. Plausible therapeutic approaches to inhibiting promiscuous ACVR1/ALK2 signaling in FOP include soluble BMP antagonists like Noggin, inhibitory RNA technology (the Nobel prize in medicine for 2006), monoclonal antibodies directed against ACVR1/ALK2, and most plausibly, orally available small molecule STIs for ACVR1/ALK2 - even cherry flavored ones!

Small Molecule STIs for ACVR1/ALK2

Small molecule STIs have proven invaluable for investigating signal transduction pathways in a host of human diseases. Such molecules have the potential for development into powerful medications that can be taken orally. Small molecule STIs designed to specifically block ACVR1/ALK2 signaling need to be designed, developed, and tested in cell and animal models of FOP. The opportunity to arrest disease progression during childhood highlights the urgent need to develop specific ALK2 inhibitors for preclinical and clinical testing in this catastrophic human condition.

There are seven receptors similar to ACVR1/ALK2 in humans. In other words, if you entered the molecular hardware store, and went to the shelf where the ACVR1/ALK2 receptor was found, you would find six other similar receptors or switches on the same shelf. The ALK receptors or switches function in a wide array of cells and tissues during development and throughout life to determine the fate of cells and to regulate the activity of those cells. One of these receptors, called ALK5, plays a major role in wound healing and inflammation as well as in many cancers.

The development of selective small molecule STIs for activin-like kinases (ALKs), the group of molecular switches that ACVR1/ALK2 belongs to, is not a new concept. Selective inhibitors have been developed by at least four pharmaceutical companies for three of the seven ALKs (ALKs 4,5,7). At the present time, there are no known selective inhibitors of ACVR1/ALK2 or the other three ALKs involved in BMP signaling (ALKs 1,3,6). One is desperately needed.

Recently, we have been talking with medicinal chemists at several pharmaceutical companies who have expressed interest in this work. Orphan drugs that are useful for treating FOP will likely be useful for treating more common forms of heterotopic ossification as well. It is our highest priority to move this work forward. As the ancient Chinese proverb says: a journey of a thousand miles must begin with a single step.

An Interference Pass on the FOP Football Field: Gene Knock Down and the Nobel Prize in Physiology and Medicine-2006

Mr. Raihan Adil, brother of FOP patient Hassan Adil of Haryana, India, wrote on October 12, 2006, "Dear Dr. Kaplan: How are you? There was news published in one of the newspapers here in India that two Americans, Andrew Fire and Craig Mello, got the Nobel Prize for medicine. They have discovered how to switch off genes, a potential road to new treatments for various diseases from AIDS to blindness to cancer. After reading this news, we got a little excited and curious to know more about this discovery and if this is helpful in any way in treating FOP? Please let me know if this discovery is actually relevant to a cure for FOP?"

A similar email was recently received from Manuel Robert, a ten-year-old child from Buenos Aires, Argentina. Manuel wrote: "Dear Fred, I am Manuel. I want to ask you about a possible cure for FOP. If every cell has two copies of the same gene and one is defective, is it possible to eliminate the defective copy of the gene and let the normal copy assume its work? I have another question for you too. Is it possible to use the discovery of the doctors that won the Nobel Award to cure FOP? Your friend. Manuel."

Heidi Zumfeld from Hamburg, Germany, the sister of Roger Zumfeld wrote, "Dear Fred, When I read about the new Nobel Prize winners of 2006, especially in medicine, it reminded me of what you told us in Valbert regarding the pathways in FOP, and it occurred to me that the findings of Professors Fire and Mello might have something in common with your search for the treatment of FOP? Love Heidi."

And, finally from Sausalito, California, Sandra Olsen, grandmother of little Hayden Pheif wrote. "Hi Fred, I was reading the **San Francisco Chronicle** this morning, and saw this article, and thought it was so exciting about the possibilities it holds. The Nobel Prize this year seems fantastic. I know it may not work for FOP, but wondered whether it might be possible."

Each of these emails arrived soon after the 2006 Nobel Prizes were announced. These thoughtful inquiries from FOP patients and family members in India, Argentina, Germany, and the United States are a wonderful testimony to the enlightened awareness of our FOP community in identifying new research developments that may impact the

development of therapies. And, we might add, your observations are absolutely on target. The simple answer to these remarkable questions is that, "Yes, the discovery honored by the 2006 Nobel Prize in physiology and medicine provides important clues for the development of treatments for FOP." Let us explain.

The 2006 prize in physiology and medicine was awarded to Andrew Fire of Stanford University School of Medicine and Craig Mello of the University of Massachusetts Medical School for discovering a new way of inactivating or silencing genes. If the genes (DNA) are the cookbooks, then the cellular mechanisms described by Fire and Mello are a way of destroying the copied recipes (RNA) so that they cannot reach the cook (ribosomes). If the recipes (RNA) are destroyed before they reach the cook (ribosomes), the poisoned soup (mutant ACVR1 protein, for example) can not be made.

In a letter to the journal **Nature** in 1998, Fire, Mello, and their colleagues reported that exposing cells of the microscopic soil-dwelling worm *Caenorhabditis elegans* (pronounced Sy-anno-rab-dee-tees el-ah-ganz) to double-stranded RNA resulted in specific and efficient gene silencing, or, in other words, destruction of specific recipes. This process was dubbed "RNA interference (RNAi)," because it interfered with the normal transmission of the genetic "recipes" (RNA) from the cookbook to the cook. Because RNAi rarely leads to the complete silencing of gene expression, the technique essentially is described as a "knock-down" of gene expression. Thus, this technique can target the destruction of specific recipes, but is rarely 100 per cent effective. This technique, although used in an artificial manner in their worm experiments, was soon

recognized to exist in nearly all animals as a primitive immune system protecting against viruses. In higher animals, RNAi has an important role in regulating gene expression.

In an editorial in the **New England Journal of Medicine** on December 7, 2006, René Bernards, Ph.D., wrote, "RNAi has many applications in biomedical research, including drug development. Researchers can knock-down the expression of a gene of interest (in cell culture or in animal model) and observe the consequences. Many diseases are caused by the inappropriate activity of specific genes" (such as ACVR1 in FOP), "and a selective silencing of such genes through RNAi represents a potential therapeutic strategy for such diseases. However, the road to successful therapeutic application of RNAi is likely to be treacherous, and those who attempt to travel it will encounter at least three obstacles.

First, … further improvement is required for its systemic delivery *in vivo.*… Second, the problem of unpredictable off-target effects (the silencing of genes other than the intended transcript) must be addressed. Finally, the question of potential toxic effects must also be laid to rest. Nevertheless, the successful application of RNAi to a broad range of animal models of disease…augurs well.

It is unusual for the Nobel Committee to award a prize in medicine so soon after the relevant discovery. But, then hardly ever has such a discovery given rise so quickly to such a broad range of promising medical applications."

Thus, in a series of experiments on worms, Fire and Mello stumbled on a naturally occurring mechanism that allows cells to shut down individual genes like a secret police force that enters the kitchen and tears-up the extra copies of a dangerous recipe. The mechanism of RNAi appears to have first evolved more than a billion years ago helping plants and fungi defend themselves against invading viruses. In more complex organisms, including humans, the molecular machinery of RNAi has taken on new and complicated functions including the delicate job of gene regulation. After discovering the mechanism, Fire and Melo, and many other scientists around the world quickly figured how to harness it, so that it can be used to study and treat diseases. Presently, RNAi is becoming an essential tool in laboratories of genetics and molecular biology worldwide to understand how various genes function.

In the FOP laboratory, we have been using RNAi for the last two years to study the function of various genes in the BMP signaling pathway. Additional work in this area will continue as we use RNAi to investigate the function of normal and mutant ACVR1/ALK2. It may indeed be possible to use RNAi to downregulate the activity of ACVR1/ALK2 in cell culture and possibly in an FOP mouse. RNA interference holds great promise for the study of FOP and potentially for developing effective treatments. While the development of orally effective STIs remains the most promising approach at the moment for the treatment of FOP, the development of RNAi remains an intriguing alterative. We have recently recruited a new post-doctoral fellow to the FOP laboratory to focus on this exciting new aspect of FOP research. You will be hearing more about this in the years ahead.

The Broad Implications of FOP Treatment

A complete understanding of the genetic and molecular basis of FOP will likely have broad therapeutic implications for patients with more common forms of heterotopic ossification. Such knowledge will be important not only for understanding and treating FOP, but for treating many common disorders of heterotopic bone formation - conditions such as non-genetic forms of heterotopic ossification that may occur following total hip replacement, head injuries, spinal cord injuries, athletic injuries, blast injuries from war, and endstage valvular heart disease.

It may even be possible some day to harness the gene mutation that causes the renegade bone formation in FOP to create bone in a controlled way – for patients who have osteoporosis, for those with severe bone loss from trauma or tumors, for those with fractures that fail to heal or spinal fusions that are slow to heal, or for those with congenital malformations of the spine and limbs. We have recently reached a monumental milestone on our epic journey to understand FOP - knowledge that we desperately need to help the children with FOP and that has the potential to help many others.

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 inevitably to orphan drug development and to more effective treatments for

those with FOP and for those with more common forms of heterotopic ossification. That journey has begun.

In summary, the discovery of the FOP gene reveals a highly conserved druggable target in the BMP signaling pathway that compels therapeutic approaches for the development of small molecule STIs for ACVR1/ALK2. Effective therapies for FOP and likely for a vast array of more common conditions of heterotopic ossification will be based on blocking ACVR1/ALK2, a critical target in the BMP signaling pathway. Such work is presently underway.

PRESENTATIONS, MEETINGS, REPORTS, AND PUBLICATIONS

During 2006, we were privileged to present major lectures on FOP at the:

- Annual Meeting of Advances in Mineral Metabolism; Snowmass; Colorado
- Annual Meeting of the American Society for Bone & Mineral Research; Philadelphia, Pennsylvania
- Annual Meeting of the FOPeV; Valbert, Germany
- Brown University; Providence, Rhode Island
- Case Western Reserve University; Cleveland, Ohio
- Children's Hospital of Philadelphia; Philadelphia, Pennsylvania
- Eskilstuna General Hospital; Eskilstuna, Sweden
- European Neuromuscular Center; Naarden, The Netherlands
- German Consulate of the United Nations; New York, New York
- Karolinska Institute; Stockholm, Sweden
- Rhode Island Hospital; Providence, Rhode Island

- Royal Children's Hospital; Melbourne, Australia
- Sixth International Conference on Bone Morphogenetic Proteins; Dubrovnik, Croatia
- University of Arkansas; Little Rock, Arkansas
- University of California-San Diego (UCSD); La Jolla, California
- University Hospitals of Cleveland; Cleveland, Ohio
- University of Medicine & Dentistry of New Jersey (UMDNJ); Newark, New Jersey
- University of Melbourne; Melbourne, Australia
- University of Wisconsin; Madison, Wisconsin

During 2006, we were honored to present highlights of FOP research at regional, national, and international FOP family meetings and gatherings in:

- Aberdeen, Scotland
- Bay Head, New Jersey
- Bedminster, New Jersey
- Melbourne, Australia
- Naarden, The Netherlands
- Oamaru, New Zealand
- Philadelphia, Pennsylvania
- Santa Maria, California
- Sausalito, California
- Stockholm, Sweden
- Valbert, Germany

Papers Published

Since the last annual report, there were eleven publications on FOP, five of which appeared in major peer-reviewed journals. Major publications included:

Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho T-J, Choi IH, Connor JM, Delai P, Glaser DL, Le Merrer M, Morhart R, Rogers JG, Smith R, Triffitt JT, Urtizberea JA, Zasloff M, Brown MA, Kaplan FS. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. **Nature Genetics** 38: 525-527, 2006

Fiori JL, Billings PC, Serrano de la Peña L, Kaplan FS, Shore EM. Dysregulation of the BMP-p38 MAPK signaling pathway in cells from patients with fibrodysplasia ossificans progressiva (FOP). **J Bone Miner Res** 21: 902-909, 2006

Kaplan FS, Fiori J, Serrano de la Peña L, Ahn J, Billings PC, Shore EM. Dysregulation of the BMP4 signaling pathway in fibrodysplasia ossificans progressiva. **Ann NY Acad Sci** 1068: 54-65, 2006

Kaplan FS, Glaser DL, Shore EM. Fibrodysplasia (myositis) ossificans progressiva. pp. 450-453. In Favus MJ (ed). **Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism - Sixth Edition.** The American Society for Bone and Mineral Research, Washington, DC., 2006

Kaplan FS, Glaser DL, Shore EM, Pignolo RJ, Xu M, Xhang Y, Senitzer D, Forman SJ, Emerson SG. Hematopoietic stem-cell contribution to ectopic skeletogenesis. **J Bone Joint Surg** Am 89:347-357, 2007

Your FOP Laboratory

During 2006, the staff of the FOP Research Laboratory included as many as 16 researchers: four principal investigators, four research specialists, four post-doctoral fellows, two graduate students, one medical student, and one pre-medical student. During a very busy summer following the FOP gene discovery, we welcomed Vincent Whelan, a pre-medical student from UC-Berkeley and UC-Santa Clara, who joined us for a thoroughly enjoyable week in the laboratory. Vincent wrote a beautiful article in the **FOP Connection** (November 2006), about his summer experience in the FOP laboratory.

Jennifer Fiori, a graduate student at Penn, completed her Ph.D. thesis on BMP Signaling Pathways in FOP and earned her Ph.D. degree at the University of Pennsylvania in April 2006. Jennifer's family and friends along with Mr. and Mrs. Richard Simcox from Aberdeen, Scotland (benefactors of Jennifer's graduate studies in FOP and donors of the Roemex and Grampian Fellowships) joined us for her magnificent thesis defense and for a wonderful celebration immediately thereafter. Jen has made major contributions to FOP research that were documented in her first-authored paper in the **Journal of Bone and Mineral Research.** Jennifer's paper won the prestigious **Raisz-Drezner First Author Journal Award** of the **American Society for Bone and Mineral Research.** This is one of the most prestigious awards given to young investigators in the field of musculoskeletal research and was highly deserved for her groundbreaking work on the molecular dissection of the BMP signaling pathway in FOP cells. Congratulations, Jen; we are all extremely proud of you!

We are also extremely proud of Jen's fiancé, Dr. Michael O'Connell, (who she met in our laboratory!). Michael, a former graduate student at The University of Southampton (England, U.K.), has worked with us in the FOP Laboratory for a wonderful two years. Michael studied the role of cell surface heparan sulfate proteoglycans (complex protein-sugar molecules) in modulating BMP4 signaling in FOP and control cells. Michael successfully defended his Ph.D. thesis and was awarded his Ph.D. degree from the University of Southampton in the summer of 2006. Michael completed his doctoral thesis under the mentorship of Professor Trudy Roach in Southampton, U.K., and Drs. Kaplan and Shore in Philadelphia. Congratulations Michael! We are extremely proud of you as well for your groundbreaking research on BMP signaling in FOP! Michael's

important research findings have recently been accepted for publication to a major peer-reviewed scientific journal.

We are thrilled for Jennifer and Michael as they embark on the next phase of their scientific careers at the National Institutes of Aging, a branch of the National Institutes of Health, in Baltimore, Maryland. We know that they will carry the message of their work and their heartfelt commitment to the FOP community throughout their lives, and we know that their brilliant thoughts and loving care will always be with the FOP community.

Pictures of the FOP children adorn the hallways of our core FOP Laboratory and are a constant reminder of our goals and our mission. As we tell the children and adults who visit the FOP Center and Laboratory, "This is really ***your*** Center and ***your*** Laboratory." We love when you come and visit, and now we have a new stop on our FOP tour; we can show you where the FOP gene was discovered!

Center for Research In FOP and Related Disorders

While the core FOP Laboratory occupies approximately 2000 square feet of space at The University of Pennsylvania, our space is now virtually limitless with the establishment of the intramural and extramural components of The Developmental Grants Program for FOP Research. Through this remarkable program, sponsored by The Cali Family Endowment and administered through the Center for Research in FOP and Related

Disorders, we have been able to expand collaborations with colleagues in many departments and schools throughout The University of Pennsylvania, and now elsewhere.

In 2006, the Developmental Grants Program funded continuation of the extramural collaborative research grant on the FOPPY mice at the laboratory of Dr. Lixin Kan at Northwestern University in Chicago, Illinois. Projects involving the molecular mechanisms of heterotopic ossification in the FOPPY mice continue to be conducted collaboratively at Northwestern University and at The University of Pennsylvania.

In 2006, a new extramural grant was awarded to Dr. Jay Groppe from the University of Texas Southwestern in Dallas, Texas for work on "x-ray crystallographic studies on the normal and mutant ACVR1/ALK2 receptor." This fascinating new area of collaborative research, described in this report, holds great promise for understanding the three dimensional structure of the normal and mutant ACVR1/ALK2 receptor, knowledge that will be critical in the design of STIs to inhibit the mutant receptor in FOP.

In 2006, two intramural grants were awarded at the University of Pennsylvania; one to Dr. Mary Mullins for her work on the zebrafish model of FOP, described in this report, and the other to Dr. Jason Burdick for his work on a novel approach to harness the FOP mutation to engineer new bone development.

Since its inception, the Developmental Grants Program of the Center for Research in FOP and Related Disorders has supported 15 novel projects relevant to our long-term mission. Many of these projects were highlighted in previous annual reports, and have produced important insights for FOP research. We are extremely excited about the new projects that have been funded during this past year and that have been featured throughout this report. You will certainly be hearing more about them.

ACKNOWLEDGEMENTS

FOP continues to be one of the most obstacle-ridden and perplexing quandries of the human condition, but with the discovery of the FOP gene, it is a much less perplexing quandry than it was a year ago. FOP research is the key to understanding not only FOP, but also many other common conditions that affect the formation of bone and the formation of the skeleton. We recently discovered the skeleton key, a molecular switch that determines the fate of cells. That skeleton key will be used to unlock the secrets of FOP as well as the secrets of many common skeletal conditions in the years ahead.

As we have stated many times before, *cause* and *cure* are the two words that motivate us and provide the guiding principle for all we do: to discover the exact genetic and molecular cause of FOP and to use that knowledge to develop effective treatments and eventually a cure. In 2006, we reached the summit of a great FOP mountain. We discovered the genetic cause of FOP. But more difficult work lies ahead – the treacherous trip across the mountain range to the next summit – one of the highest peaks in the scientific and medical world – where we look forward one day to planting the flag that says: "FOP cured."

It is not a simple task to successfully treat or cure a genetic condition, and it will likely take many more years. But, it will be done. We will need the continued help and support of many scientists and many laboratories, and the continued generosity of benefactors, families, and communities throughout the world, more now than ever. We have entered a new era of FOP research. The FOP Center and Core Laboratory continue to be unique resources for FOP patients and for the medical community worldwide. As always, we strive for excellence and leadership in all areas vital to our mission: patient care, education, and the generation of new knowledge.

In summary, 2006 was a year of astonishing milestones for FOP research, clearly the most momentous in more than 300 years. The year 2006 was highlighted by the announcement of the discovery of the FOP gene, the most important discovery in the history of FOP research. We are hopeful that 2007 will also be a year of great milestones in FOP research and that exciting advances and discoveries will occur in the year ahead.

The FOP research community has charted a long and difficult journey over the past 16 years, but it is amazing how far we have come. We continue to be a robust and vibrant community that spans the globe. We are united in our mission and we possess the momentum and verve to accomplish the goals we have set for ourselves. We are reminded each day that we have a long journey ahead to achieve those goals, but we are encouraged by our accomplishments and we are energized by our challenges. As always, our heartfelt thanks go to the children, adults, and families who live with FOP every moment of their lives. Their equanimity and nobility provide the perpetual inspiration that dignifies this work and all who are privileged to participate in it.

Again, this year, we wish to extend a special thanks to Jeannie Peeper, the founder of the IFOPA, who remains in her lifetime role as President, spokesperson, and spiritual leader of our worldwide FOP community. We wish to extend special thanks as well to Amanda Cali, the outgoing Chairman of the Board of the IFOPA, and to Linda Daugherty, the Executive Director of the IFOPA, who have provided a seamless and magnificent transition during these challenging times. We thank Don Brister as well. Don is the new Chairman of the Board of the IFOPA who has graciously and magnanimously agreed to serve in that important position. Jeannie's, Amanda's, Linda's, and Don's visionary devotion to FOP research and to the FOP community worldwide brings clarity to our mission, and hope to future generations.

The FOP Collaborative Research Project arose out of a mutual desire to find the cause and to establish a cure for this disabling condition. The words *care*, *collegiality*, *compassion*, *creative chemistry*, and *collaboration* are the working glue that link *cause* to *cure*. We are grateful for many colleagues and collaborators at medical offices, clinics, hospitals, research laboratories, centers and universities around the world without whose help and brilliance this ongoing effort would be even more difficult - if not impossible. Together, we have accomplished the goal of discovering the genetic cause of FOP, and together we will find a cure for this disabling condition. We will prevail. As David Ben-Gurion, the first Prime Minister of Israel said, "The difficult we do immediately; the impossible takes a little longer." As always, finding an effective treatment and cure for FOP is not a job, it is a mission.

All of the work we have done, and all of the knowledge we have gained is for one purpose, and one purpose only – to help design better treatments and eventually a cure for FOP. A physician from sub-Saharan Africa asked one of us recently, "Why do you do what you do?" The question is startling enough, but the answer is simple. "So that there will come a time when no one has to suffer from FOP- so that a terrible disease becomes nothing more than an inconvenience – so that childhood can be returned to children from whom it has been stolen – so that physical freedom can be restored to those from whom it has been taken – so that those who have been imprisoned in a second skeleton can be liberated – so that the oppressed can be set free." This is not just a dream; it is a mission, and together we will achieve it.

Michael Mason, a correspondent for **The New York Times**, wrote a brilliant feature article on FOP following the FOP gene discovery. The article focused on how FOP affected little Hayden Pheif, a six year-old child from Sausalito California, and how the

FOP gene discovery provided a beacon of hope for Hayden and all of the other children who have FOP worldwide. The title of the article said it all: **"Finally, With Genetic Discovery, Hope for Escape From a Prison of Bone."**

Many did not believe that it would be possible to find the FOP gene so quickly; others wondered why it took so long – but all of us who have been to the mountain top understand the promise, the inspiration, and the hope of the summit - the beautiful view of the horizon that just two years ago was shrouded in clouds. We have at least one more horizon, one more mountain top, and one more summit to conquer – and one great mountain to move. We have come this far. Together, we can move mountains.

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 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)
- The Brazilian FOP Association
- The Pittsburgh Foundation
- The Sarah Cameron Fund (U.K.)
- The Scandinavian FOP Association
- Members of the FOP International Research Consortium
- The People of Santa Maria (14 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.