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The Twentieth Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project

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Introduction

Lessons from the Outfield...

During a childhood summer, more than half a century ago, one of us, who was not a talented baseball player, was banished by the coach to a permanent position in the distant outfield, so far away from home plate that no human being could have possibly hit the ball there. If home plate was the sun, then the distant outfield was far beyond the orbit of the since- demoted Pluto, and any connection to the rest of the solar system seemed almost imaginary.

The journey back to the dugout each inning was a chore and often abandoned. Many possible "at bats" were sacrificed and spent in exile in the weeds of the distant outfield, watching grasshoppers, frogs, and butterflies, and swatting mosquitoes, gnats, and flies. The receding Doppler effect of the coach yelling, "Stand-up out there, and look like you are playing ball," was muffled like a radio signal from the distant cosmos and, if at all decipherable, was laughable. For one child, there was no ball to play in this twilight zone at the outer limits of athletic exile.

One day, towards the end of this long summer of baseball cards, bubble gum, and boredom - while faithfully serving time at this remote outpost of athletic isolation, something remarkable happened – something that would change forever, the way one child would view the world.

One of the authors at seven years of age in the far outfield

In clear daylight, and from a direction totally unexpected, a giant flying object, spherical and much bigger than a baseball, soared overhead - not from home plate, but from the distant outfield, towards home plate - as if coming from another universe, with different rules and different laws. It made no sense at all. It wasn't from outside the box; it was from outside the ballpark, and clearly the most activity and excitement that occurred in the distant outfield all summer - and possibly ever.

Soaring overhead was a giant rotating, flying object – a large white spherical ball, with prominent interconnected segments. The object was coming from the volleyball court, just behind the weeds, at the edge of the distant outfield. Suddenly, a different world came alive. Diving towards the falling object with arms outstretched, the young, would-be athlete in exile flung the giant white, rotating ball backwards over the net. Miraculously, the ball fell into the volleyball court, scoring a point that somehow counted – changing the nature of the moment, both games, the coaching narrative, summer sports legends, and a lifetime that followed.

What might have been the distant outfield in one game became center court in another.

Revolutionary advancements and insights do not happen in a field. They happen between fields, at the boundaries of fields, in the weeds, where the rules applicable to each field no longer apply.

Serendipity plays a large role in science and in life. Most games, much work, and many endeavors in life occur in an infield, a circumscribed area, or proverbial "box." However, some of the most important insights arise from outside the box, the diamond, or the field - from the distant outfield, and they can be lost, if one is not prepared to recognize them.

Enter the world of FOP research, where the unexpected and the revolutionary are often the rule of the day - and the story and theme of the year.

The acclaimed science writer, Isaac Asimov said, "The most exciting phrase to hear in science, the one that heralds new discoveries is not "Eureka; I found it," but rather, "Hmm… that's funny..."

2010 was a "funny" year on the rapidly changing frontier of FOP research, where volleyballs flying backwards into the outfield were as notable as home runs hit out of it.

The FOP gene discovery and the advances it has inspired have transformed our way of thinking, and have altered our horizons. Five years after the FOP gene discovery, the world no longer looks the same; the horizons no longer distinct and discernible. Previous landmarks that seemed compartmentalized and isolated: genes, cells, pathways, models, triggers, treatments – now seem curiously interconnected like a range of mountains rather than a series of distinct peaks, with a clearer path between and through them. This illuminating shift in perspective has occurred as our knowledge and insight have deepened from within our traditional fields of study and from without, and mostly on the border between seemingly unrelated fields, much like a child standing in the weeds at the boundary of a baseball field and a volleyball court, struggling to understand the rules that apply in each.

The FOP gene is needed to make FOP animal models; FOP animal models are needed to understand the triggers and the microenvironments that induce and sustain the formation of FOP lesions; cells from FOP lesions are needed to decipher the signaling pathways that propel FOP flare-ups, and understanding of FOP flare-ups is needed to design the compounds that will halt progression of FOP. And, that is just the beginning.

As the naturalist, John Muir, said, "When one tugs at a single thing in Nature, one finds it attached to the rest of the world." That revelation occurs best at boundaries, places between fields where the weeds are highest, and one is not sure which field one is in anymore.

FOP research is a highly interconnected and epic journey, and epics have always been about the

Greetings from The FOP Laboratory at The University of Pennsylvania School of Medicine in Philadelphia, PA.
Seated in the front row from left to right: Dr. Robert Pignolo, Dr. Eileen Shore, and Dr. Fred Kaplan.
Standing from left to right: Bob Caron, Dr. Deyu Zhang, Dr. Jan-Jan Liu, Dr. Bettina Mucha-Le Ny, Edwin Theosmy, Kamlesh (Kay) Rai, Dr. Josef Kaplan, Meiqi Xu, Fiachra Malone, Dr. Salin Chakkalakal, Michael Convente, Dr. Vitali Lounev, Dr. Lakshman Singh, Kevin Egan, Becky Billmire, Andria Culbert and Ruth McCarrick-Walmsley

aspirations of a people. In the small but global world of FOP, our most coveted aspiration is a simple four-letter word, *CURE*. It is a word filled with hope and peril – hope in its possibility for redemption; peril in the obstacles and dangers getting there. *CAUSE* and *CURE* are what FOP research has always been about – to truly understand the cause of FOP, not just at a genetic, cellular, and molecular level – but fundamentally and deeply in an interconnected way, so that summary knowledge can be turned into wisdom – and wisdom into action.

IFOPA Members, Justin Henke (left) of Middletown, Delaware and Nathaniel Padilla (right) of Port Deposit, Maryland show their new trucks and cars to Dr. Kaplan

In 2010, we boldly moved in that direction, propelled by discoveries that were sensational, serendipitous, and simple. But, FOP is not simple. We can and we must simplify things, break them down into their component parts - to study them, and then reassemble them for understanding. Einstein had it right: "Things should be made as simple as possible, but not any simpler."

Mariette DiChristina, the Editor-In-Chief of **Scientific American** speaks of, "The utility of looking at an area of science anew by coming at it from a different perspective. In this, I realize, I am hardly the first person to notice that when attempting to solve a problem, changing your physical vantage point or mental framework can loft you past perceived limits."

Sort of like a child in the distant outfield of a baseball game; a child who sees a volleyball coming from the wrong direction and realizes in fact it is coming from the right direction and that it is part of an entirely new game.

"In some cases," Dr. DiChristina continues, "It may be difficult to recognize evidence that may be right before your eyes because you fail to appreciate it for what it is." As philosopher Redelmeier noted, "Do not get trapped into prior thoughts. It is perfectly okay to change your mind as you learn more." Oh, indeed we are!

2010, like every year, was a year of notable advancements and accomplishments. But, 2010 was also a year of unanticipated discoveries – a "funny" year, as Isaac Asimov said, in which unexpected volleyballs flew backwards into the outfield and changed the nature of the game in a way that Nobel Laureate Joseph Goldstein would say, fulfills G.H. Hardy's axioms for scientific greatness: significance, generality, and unexpectedness. These insights from the distant outfield are essential ingredients on our journey for a cure.

In this annual report, we will focus on two unexpected volleyballs that are likely to be game-changers in this kaleidoscopic and interconnected landscape of discovery where cells lead to pathways; pathways lead to models, models lead to medicines, and medicines hopefully lead to cures. As Dorothy said in the ***Wizard of Oz***, "Toto; I don't think we are in Kansas anymore."

INSIGHTS FROM THE OUTFIELD

FOP Cells Re-Write Their Own Destiny; Reveal New Paths For Creating Stem Cells

Collaborators Dr. Damian Medici (left) and Dr. Bjorn Olsen (right) of Harvard University

A most unexpected scientific breakthrough in FOP research was heralded in the world press and published in the pages of the world's leading biomedical research journal, **Nature Medicine**, in December 2010.

This groundbreaking work was the product of a collaboration of two research teams – the FOP laboratory at the University of Pennsylvania, and the Olsen Laboratory at Harvard University, and it was a collaboration that led to fundamental new insights into bone biology and tissue regeneration.

High School Student Henry Gadsden visits with Dr. Eileen Shore in the FOP Laboratory

This wonderful collaboration was the product of two laboratories with slightly different perspectives; one, whose major goal is to understand the genetic, molecular, and cellular basis for building a skeleton, and to use that knowledge to enhance the process for those who need it, and the other laboratory whose major goal is to understand the genetic, molecular, and cellular basis for building a second skeleton and to use that knowledge to stop it from happening. The stimulus for the collaboration was the discovery in 2009 by the FOP Laboratory that cells of blood vessel origin contribute to every stage in the formation of the cartilage scaffold of the second skeleton of FOP. But, how do they do that?

The major finding of the collaborative work was that the FOP mutation rewinds the internal clock of a blood vessel cell (from the damaged muscle of a flare-up) and drives it back into an adult stem cell. Yes; a stem cell! In other words, the FOP mutation re-directs cells of blood vessel origin from muscle and other connective tissues, not to form bone directly, but to form stem cells that are the direct precursors of all of the stages of the second skeleton of FOP. The study shows that the early fibroproliferative cells of the FOP lesion (the ones that are often misdiagnosed on biopsies as being aggressive fibromatosis or fibrosarcoma) are not simply fibrous connective tissue cells, but stem cells that have arisen in part from vascular lining cells of the original muscle and connective tissue. Why is this discovery so important? For at least three reasons:

1. Mesenchymal (connective tissue) stem cells are created in FOP by the de-differentiation of vascular lining cells. Unexpectedly, during the earliest stages of an FOP flare-up, the vascular lining cells from the affected muscle tissue appear to be re-programmed into mesenchymal (connective tissue) stem cells that can differentiate into bone, cartilage, muscle, fat, and even nerve cells. In other words, in order to create a second skeleton, cells from the affected muscle tissue don't simply turn into bone cells, they first de-differentiate into stem cells, and then re-differentiate through a series of cartilage cell intermediates to form bone. Think of it this way: imagine you wanted to wage a war. You wouldn't go to every house and deliver a gun to every citizen. You would first draft the citizens (differentiated cells) into basic training, de-program their civilian tasks, train them to be soldiers (mesenchymal stem cells), issue a gun to each new soldier, teach them how to use it, and then send them out to do something different than they did in civilian life. Nevertheless, some identification markers of their former civilian life might still remain, even as they became effective soldiers. That is similar to what happens in FOP.

2. **FOP may be most easily manipulated at the stem cell stage**. The early pre-cartilage FOP lesions consist largely of undifferentiated stem-like cells and seem to be among the most sensitive cells for manipulating and possibly treating FOP. We are finding that it is at or near this de-differentiated mesenchymal stem cell

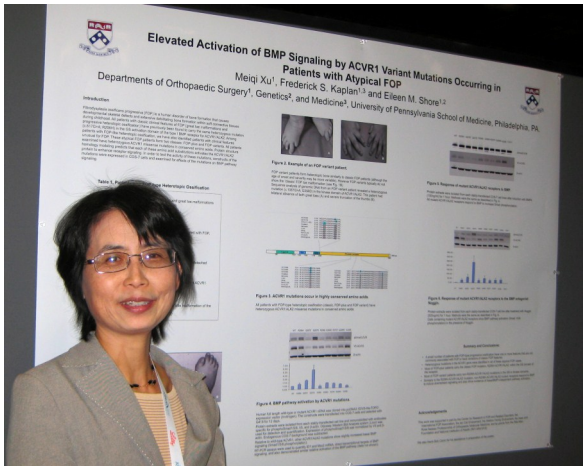
Scientists Vitali Lounev (background) and Kevin Egan (foreground) examine an FOP lesional biopsy specimen under the microscope in the FOP Laboratory

stage when various cellular re-differentiation programs seem most accessible to manipulation by medications.

Penn Medical Student Danish Nagda (left) and Visiting Medical Student Lydia Pathmanathan (right) meet with NY Yankees fans Anthony Barbera and his father of Elmont, New York

3. **De-differentiated FOP mesenchymal stem cells provide a vital clue on how to regenerate cartilage and bone.** The experiments published in **Nature Medicine** showed that vascular lining cells could be exposed to specific bone morphogenetic proteins (BMPs) whose actions mimic, in part, the effect of the mutated FOP gene and thus provide a more efficient way to reprogram cells. The immediate application for these findings is in the field of tissue engineering and personalized medicine. It is conceivable that transplant patients may one day have some of their own vascular lining cells extracted, reprogrammed and then grown into the desired tissue type for implantation. Host rejection would not be an issue. Thus, this discovery opens a window of opportunity not only for understanding and treating FOP, but also for tissue engineering and personalized medicine, for individuals who may desperately need new connective tissue body parts.

In an accompanying editorial in **Nature Medicine**, entitled, "Building bone from blood vessels," Edwin M. Horwitz of Children's Hospital in Philadelphia writes, "In the fields of observation, chance favors only the prepared mind. This famous quote from Louis Pasteur in 1854 emphasizes how some of the most important discoveries in biomedical research begin as key observations during studies focused on an entirely different question." (Sort of like discovering misplaced volleyballs when you're looking for baseballs). "Such may now be the case in the field of stem cell therapy. In this issue of **Nature Medicine**, authors from Harvard and Penn, while investigating the cause of FOP, uncovered a new source of mesenchymal (connective tissue) stem cells that could revolutionize regenerative medicine for bone and cartilage. The authors have identified a new source and processing protocol to generate mesenchymal stem cells. Endothelial (vascular lining) cells from people with FOP carrying a specific ACVR1/ALK2 mutation undergo a remarkable transformation that results in the regeneration of mesenchymal stem cells. This finding alone is quite interesting as the current thought is that the end product of endothelial-mesenchymal transformation (as in the formation of the heart valves) is a generic fibroblast (connective tissue cell), which lacks stem cell capacity. In FOP, endothelial-derived stem cells differentiate first into cartilage-forming cells followed by bone forming cells, presumably under the regulation of inflammatory chemicals, as inflammation triggers the formation of heterotopic bone in FOP. Also, the authors showed that ACVR1/ALK2 activation (as in FOP) is necessary and sufficient for this stem cell transformation. Using this signaling mechanism, they showed how treating human vascular lining cells with BMP4 activates ACVR1/ALK2 (without the FOP mutation) and induces this transformation *in vitro,* generating vascular derived stem cells with cartilage and bone potential.

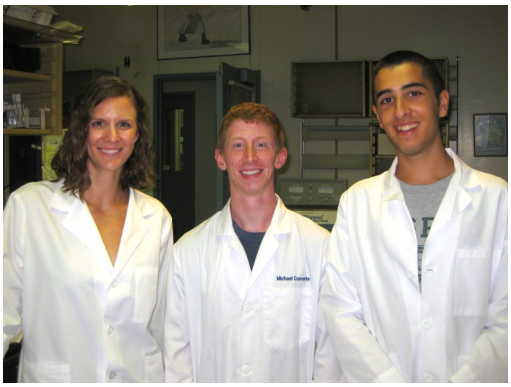


Research Scientist Meiqi Xu at her poster at The Annual Meeting of The American Society for Bone and Mineral Research; Toronto, Canada; October, 2010

Friends of the Cali Family pause for a picture with members of the FOP Laboratory during a visit to Penn

The findings uncovered by the study could markedly alter our approach to cell therapy and tissue engineering. These observations suggest that vascular lining cells may be a physiologic reservoir of FOP generated stem cells that differentiate under the appropriate environmental cues to bone precursor cells and then mature bone cells during physiologic stress, such as bone fracture. These new FOP-like stem cells may lead to the use of generated stem cells as progenitors to regenerate damaged tissue. This amazing vascular lining cell to stem cell transformation was uncovered by the mutation in the ACVR1/ALK2 gene that causes FOP. Turning off the gene turns off the process. This work shows that the BMP signaling pathway, under the influence of the mutant FOP gene, plays an unexpected role in transforming vascular lining cells into stem cells. This discovery is the first to show that the effects of a disease-causing genetic mutation can be replicated in vitro and might be used to treat other diseases. Triggering the formation of these stem cells could help generate tissues to treat other ailments. And, of course, shutting down the process could curtail FOP."

In another editorial on the work entitled, "Transition of endothelium to cartilage and bone" in the prestigious journal, **Cell Stem Cell**, Ofer Shoshani and Dov Zipori from the Department of Molecular Cell Biology of The Weizmann Institute of Science in Rehoboth, Israel, write, "A recent **Nature Medicine** study shows that mislocalized bone in the human disease FOP, originates from vascular lining cells that gives rise to mesenchymal (connective tissue) stem cells. Ectopic bone formation in soft tissues is a common occurrence following trauma, internal muscular bleeding, osteoarthritis, inflammation, and also in specific genetic disorders such as FOP, where cartilage and bone form pathologically within soft tissues."



Graduate students Andria Culbert (left) and Michael Convente (middle) with high school student Aziz Kamoun (right) in FOP Laboratory

The editorial postulates a "stem cell cycle" that allows de-differentiation of mature cells back to a stem cell state that can then be re-differentiated to build an entirely different organ system (such as the second skeleton of FOP). "During tissue repair, cells downstream in a differentiation cascade "turn back" and re-exhibit stem cell characteristics by regaining additional lineage potentials that have previously been lost. The "stem cell cycle" notion predicts that de-differentiation is possible in mature mammalian tissues, and this proposal is supported by the current findings from the collaborative research paper that supposedly unipotent adult blood vessel cells can, when prompted, re-exhibit multipotency."

The authors of the editorial note that, "Future studies should explore the possibility that other cases of ectopic ossification might be due to this type of transformation. In osteoarthritis (wear and tear arthritis), as one example, ectopic ossification causes severe pain and disability. The mechanism of osteoarthritis is not well understood and elucidation of the possible contribution of the microvasculature is now necessary. This work on FOP has important implications not only for FOP but also for extremely common conditions such as osteoarthritis or bone spurs that can cause pain and limit mobility. Osteoarthritis affects hundreds of millions of patients worldwide and is a source of severe morbidity to the human population."

In yet another editorial vignette entitled: "Developmental biology: blood vessel cells turn to bone," the editors of **Nature,** wrote: "In the rare disease, FOP, a mutation in the ACVR1/ALK2 gene results in the formation of bone in soft tissues. Now researchers show that the bone cells derive from the inner lining of blood vessels, called endothelial cells. These become stem-like cells before redifferentiating into cartilage and bone. This process could be important in normal tissue repair." The team (from Penn and from Harvard) found that cells from bony lesions in patients with FOP express marker proteins specific for blood vessel cells. And, when mutant ACVR1/ALK2 was introduced into normal human endothelial cells, it conferred characteristics of connective tissue stem cells. When they were cultured in appropriate conditions, the endothelial-derived stem cells transform into bone, cartilage, and fat cells."

Derailing Heterotopic Ossification and RARing to Go From left to right, Dr. Maurizio Pacifici, Dr. Fred Kaplan, Dr. Eileen Shore, Dr. Masahiro Iwamoto and Dr. Robert Pignolo meet to explore new opportunities with RAR-gamma agonists

II. Derailing Heterotopic Ossification and RARing to Go

(adapted, in part, from: Kaplan & Shore. Nature Medicine 17: 420-421, 2011)

Heterotopic endochondral ossification (HEO), the formation of bone in soft tissues by a cartilaginous scaffold, can lead to catastrophic disability and enormous human misery. Conditions that predispose to HEO range from FOP to relatively common athletic injuries, total joint replacements, traumatic brain injuries, strokes, paralysis, high velocity war wounds, and endstage valvular heart disease. In each of these conditions, common or rare, metamorphosis of soft connective tissues into heterotopic bone occurs by a process of endochondral ossification.

The process of HEO resembles the process by which the normal skeleton forms in the embryo, but differs by induction through an inflammatory trigger. The inflammation leads to tissue destruction and activation of mesenchymal (connective tissue) stem cells that differentiate into a second skeleton of heterotopic bone. Attempts to effectively prevent and treat all forms of HEO have been frustrating, if not elusive. Steroidal and non-steroidal anti-inflammatory medications have produced equivocal results, most likely because inflammatory events that initiate HEO may not be clinically apparent until after the key steps of the induction process are complete. Radiation has limited application to some forms of sporadic HEO, but has potential long-term side effects and no plausible role in the treatment of FOP. Further, the promise of small molecule signal transduction inhibitors of BMP receptors (such as the dorsomorphin class of molecules) is presently limited by the non-specific nature of available compounds, their inability to completely suppress HEO, the rebound phenomenon that occurs after cessation of use in animal models, and a myriad of off-target effects. Nevertheless, there is much promise for the development of more specific inhibitors in the dorsomorphin class of molecules that would directly target the mutant, overactive FOP receptor, ACVR1/ALK2. There is presently an intense focus on this area of research, but optimal solutions are not yet available.

As far back as the 1980s, retinoids, used for the treatment of acne, were known to cause skeletal birth defects if taken during pregnancy because they interfere with the formation of the cartilaginous scaffold on which the embryonic skeleton is built. The idea of using retinoids to treat FOP flare-ups was simple, and elegant: if retinoids caused birth defects by disrupting the formation of the cartilaginous scaffold of the normal skeleton, perhaps they might retard the formation of the cartilaginous scaffold of the heterotopic or second skeleton of FOP.

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

In the mid-1980s, more than 20 years before the FOP gene was discovered in our laboratory, Dr. Michael Zasloff, then at the National Institutes of Health, conducted a clinical trial of isotretinoin (13-cis-retinoic acid; accutane), a powerful retinoid, for the prevention and treatment of FOP. Zasloff and colleagues published the results of the FOP clinical trial of isotretinoin in 1998. Although the results of the clinical trial were equivocal and the side effects of high-dose isotretinoin generally intolerable, the idea of using a retinoid to prevent or treat FOP flare-ups was far ahead of its time.

Over the past 30 years, nuclear receptors for retinoids have been discovered, and specific agonists (molecules that activate specific retinoid receptor subtypes) that possess far greater specificity and far fewer side effects than isotretinoin have been developed.

In the April, 2011 issue of **Nature Medicine**, Dr. Maurizio Pacifici (a former Cali Developmental Grants recipient), Dr. Masahiro Iwamoto (senior author) and their colleagues (recently from Thomas Jefferson University in Philadelphia and now from the Children's Hospital of Philadelphia and the Department of Orthopaedic Surgery at the University of Pennsylvania School of Medicine) offer a novel approach to derail

Rebecca Ellis (center), President of the Newark Academy Student Government class of 2011, and Jason Cali (left) present Dr. Kaplan (right) with a souvenir T-shirt from the November 2010 Newark Academy 5K Run for FOP

heterotopic ossification, not prior to induction, but rather, after the process of building a second skeleton has begun. The authors build on previous work from the FOP laboratory, that retinoic acid is a potent skeletal poison that can be exploited to interfere with the cartilage scaffold of HEO before the dreaded endstage of disabling heterotopic ossification is reached.

In their landmark study, the authors show that the early chondrogenic (cartilage producing) stage of the pre-bone scaffold is exquisitively sensitive to the inhibitory effects of retinoic acid receptor gamma (RARγ). By using compounds that specifically activate the RARγ receptor, the authors are able to critically target the pre-cartilage and cartilage cells that follow from the inflammatory start signals and that are used as the scaffold to form mature heterotopic bone, sort of like blowing up the runaway train of HEO after it has left the station but before it reaches its undesired destination of mature bone formation.

A previous study by the same research group showed that compounds that activate the retinoic acid receptor alpha (RARα) inhibit HEO, but do so in an incomplete manner, much like isotretinoin. In contrast, RARγ is more specifically expressed in cells that form the cartilage scaffold. Therefore, the authors postulated that RARγ agonists might possibly be more effective in inhibiting HEO.

In their mouse experiments, the authors employ a comprehensive approach using implanted stem cells, BMP induction of HEO, and a conditional transgenic mouse that forms FOP-like HEO and show that RARγ agonists potently inhibit HEO. Remarkably, when the RARγ agonists are stopped, no significant rebound effect occurs, indicating that the RARγ effect may be irreversible.

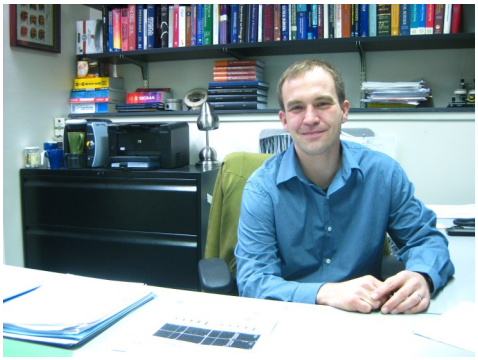
Importantly, the authors show that this class of compounds is effective in inhibiting HEO in animal models during a wide treatment window that includes the pre-cartilage mesenchymal stem cell phase (see previous section), up to, but not including, the bone formation phase. These tantalizing findings suggest that the successful inhibition of HEO in patients may be possible even after the clinically elusive induction phase has occurred.

Most remarkably, the authors show that this class of compounds may actually redirect cell fate decisions in mesenchymal stem cells to a non-bone lineage, an observation with wide-reaching implications for skeletal oncology, vascular biology, and tissue engineering, and one that builds on the revolutionary stem cell discoveries described in the previous section of this report. Thus, the RARγ agonists may prevent HEO by two distinct cellular mechanisms: sabotaging pre-cartilaginous and cartilaginous scaffold formation once the train has reached the bridge, and/or backing-up the train to the station before it has reached the bridge.

Taken together, the authors provide a tour-de-force in identifying a potent, orally available class of compounds that can prevent HEO in animal models by inhibiting the cartilage scaffold, and by diverting stem cells to a more benign soft tissue fate while avoiding the rebound phenomena seen in other classes of experimental medications.

The authors' remarkable findings raise intriguing questions. Most importantly, given that the formation of heterotopic bone requires participation of the BMP signaling pathway, how might RARγ agonist compounds impair HEO from a constitutively active

Carla Miranda of Philadelphia (center) with her mother and sister during a visit to Penn



Dr. Robert Mauck in his office at the FOP Laboratory at the University of Pennsylvania

BMP type I receptor as in FOP, or in the FOP-like transgenic mouse model in which the constitutively active ACVR1/ALK2 receptor is conditionally activated by inflammation? The answer lies, at least in part, with an unusual mechanism of action. The authors show that the RARγ agonists dramatically and irreversibly down regulate BMP signaling by promoting the degradation of molecules in the molecular relay race immediately downstream of the overactive FOP receptor. These activated molecules, called "phosphorylated BMP-pathway specific Smads," are thus blocked from entering the nucleus of the mesenchymal stem cells and early cartilage cells, and thus prevented from activating heterotopic ossification. Dr. Pacifici and his colleagues also speculate that another important signaling pathway called the Wnt/b-catenin signaling pathway, known to inhibit cartilage formation, is activated by these compounds. Thus, the RARγ agonists likely block the cartilaginous scaffold of heterotopic ossification in an encompassing manner by both inhibiting BMP signaling (that is overactive in FOP) and stimulating the Wnt/b-catenin signaling pathway (that is inhibitory); molecular sabotage at its best!

The therapeutic implications of this work for preventing HEO in common, sporadic forms of the condition and in FOP are enormous, but some clinical caveats remain. First, RARγ agonists, like the earlier molecules used, cause birth defects and their use in woman of childbearing age must be monitored carefully. Second, the authors predictably show that RARγ agonists delay endochondral bone formation during fracture repair. Thus, these agents may have limited applicability in patients with long bone fractures in addition to their heterotopic ossification-prone injuries (such as wounded soldiers and civilians with multiple traumatic injuries). Third, long term use of these compounds may adversely affect the cartilaginous growth plates, and additional studies in knock-in mice with the classic FOP mutation are necessary before RARγ agonists can be considered for long-term use in children. Nevertheless, RARγ agonists are presently in clinical trials for other disorders, likely expediting their application to FOP and other HEO conditions.

Scientist Deyu Zhang in the FOP Laboratory

It is difficult to find effective molecular targets for intractable diseases. Successful therapeutic sabotage of highly conserved signaling pathways, as in FOP, requires exquisite planning and good fortune. Pacifici and his colleagues combine both in their elegant study. They identify RARγ agonists as a class of compounds that profoundly inhibit the BMP-induced cartilage scaffold of FOP. The beauty of this approach is that it does not just broadly target the BMP signaling pathway in many tissues in the body, but rather it targets a specific pathological process of tissue metamorphosis (cartilaginous scaffold formation) that requires the BMP signaling pathway to cause disabling disease. Thus, it has the desired features of targeting the molecular basis for FOP in the very cells that cause HEO, hopefully with minimal collateral damage. Talk about an unexpected volleyball flying backwards through the outfield heading towards home plate! The authors have thus identified a new and powerful class of compounds to derail the cartilaginous scaffold of HEO in FOP. Without the cartilage scaffold, there is no HEO in FOP. With some additional work, these

compounds seem RARing to go in clinical trials for FOP patients and others, who are desperately waiting for clinical answers.

Jeannie Peeper, the founder and President of the IFOPA stated in her annual letter, "Our mission to find a treatment and cure for FOP is our driving force and we won't stop until our mission is complete." As recently as several years ago, this degree of hope was not possible, because the FOP gene had not yet been discovered, and the molecular basis for FOP was completely unknown. Today, we are in a different land.

Dr. Kaplan visits with IFOPA President and Founder Jeannie Peeper and her mother, Mrs. Marie Peeper in Orlando, Florida

This new work with RARγ agonists provides an exciting and unexpected therapeutic horizon for FOP that is being assiduously pursued. Other compounds, like the dorsomorphin class of molecules, are also being pursued with great excitement. We may reach the day when, not one but several medicines are used to effectively prevent and treat flare-ups of FOP. Although we have new and unexpected knowledge at the threshold of therapeutic investigation, no one yet has the wisdom to know which compounds will be most effective and safe. As Banquo said in Act I, Scene III of **Macbeth**, "If you could look into the seeds of time and say which grain will grow and which will not, speak then to me." For now, we are boldly pursuing these new discoveries to establish more effective treatments and a cure for FOP.

NOTES FROM HOME PLATE

Not every discovery or advance in 2010 was a volleyball flying through the distant outfield. There were some notable base hits and home runs, straight from home plate.

Knock Knock: Who's There?

The discovery of the FOP gene in 2006 was not the end of the story; it was the beginning of a new chapter. There are many outstanding questions:

- How does the FOP gene mutation lead to bone formation?
- What cells receive the message?
- From what tissues do the cells arise?
- Why is there so much inflammation with most flare-ups?
- Why do some flare-ups occur spontaneously?
- What triggers a flare-up?
- Why do flare-ups stop?
- Why do some flare-ups disappear spontaneously without forming bone?
- Why do flare-ups occur in specific patterns throughout the body?
- How does the BMP pathway drive the progression of the disease, and what other interacting pathways are involved?
- Why do some flare-ups respond to steroids while others do not?

What are the most effective therapies to prevent or abort FOP flare-ups?

Mohamed Esau Abduol of East Bank, Demarara, Guyana visits with Dr. Kaplan in his office

Kelsey Rettinger of Ashtabula, Ohio visits with Dr. Kaplan in Philadelphia

For some of these questions, rudimentary answers exist. For others, there are no definitive answers yet, but they are beginning to emerge. Answers to most of these incredibly complex questions can come only from animal models of FOP.

There is no perfect animal model for FOP, but some are better than others for answering specific questions. Some models, such as the fruit fly, the zebrafish, and the chicken (more on those later) are well suited to answer fundamental questions of disease mechanisms and drug screening. Other models, such as the mouse models of FOP, are best suited to address complex issues of disease flare-ups and response to therapy.

Vitally important clues to FOP have come from early mouse models of heterotopic ossification using BMP implantation into skeletal muscle and genetically regulated BMP over-expression in muscle (the FOPPY mice). Other, more recent clues have come from mouse models that harbor a mutation in the ACVR1/ ALK2 gene (a mutation that is similar, but not identical to the one that occurs in FOP). However, until now, there has been no mouse model with the exact mutation that occurs in individuals with FOP. We have been developing such a mouse model, called a knock-in FOP mouse, and this year we saw great progress towards that goal. The knock-in FOP mouse is the newest and rarest member of the FOP zoo, and already is helping us answer many of the critically important questions noted above.

In individuals with FOP, every cell in the body has one damaged copy (and one normal copy) of the FOP gene. In order to make FOP mice, we created mice in which one of the two copies of the ACVR1/ALK2 gene (the gene that is damaged in FOP) remained normal, while one gene, that was mutated in exactly the same way it is in people with FOP, was knocked-in to the genome of the earliest mouse embryo to replace a normal copy of the gene. The resulting mice were born with malformed toes, and developed heterotopic ossification early in life – often spontaneously and almost always following injury - exactly as in individuals with FOP. Quite remarkable!

Postdoctoral fellow Salin Chakkalakal presenting research findings at the Annual Meeting of The American Society for Bone and Mineral Research in Toronto, Canada; October, 2010

Post Doctoral Fellow Salin Chakkalakal presented the seminal findings of the study entitled, "The ACVR1 R206H mutation recapitulates the clinical phenotype of FOP in a knock-in mouse model" at the annual meeting of the **American Society for Bone and Mineral Research** in Toronto, Canada in October 2010. The study was heralded as a great advancement in FOP research. Dr. Chakkalakal concluded his presentation by saying that the FOP knock-in mouse provides the first direct *in vivo* evidence that the classic FOP mutation induces the characteristic clinical

phenotype of FOP and is responsible for the pathophysiology of FOP. The full paper describing this landmark mouse model has been submitted for publication.

Zebrafish Swim into Drug Development

As volleyballs sail through the outfield, zebrafish swim into drug development. An article by Leigh MacMillan of Vanderbilt University Medical Center highlights the work of collaborator Dr. Charles Hong and his colleagues from Vanderbilt - work supported by a Cali Developmental Research Grant from the Center for Research in FOP & Related Disorders.

Graduate Student Michael Convente in the FOP Laboratory

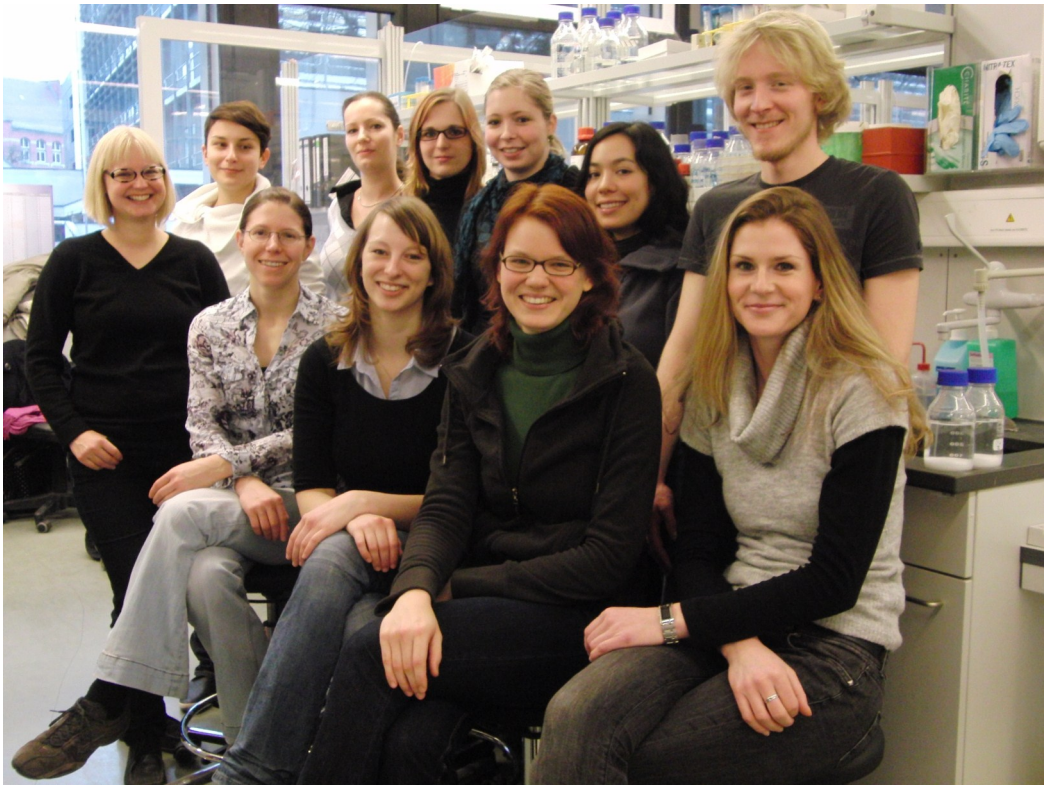
Macmillan writes: "By combining the tools of medicinal chemistry and zebrafish biology, a team of Vanderbilt investigators has identified compounds that may offer therapeutic leads for bone-related diseases such as FOP. In 2007, Charles Hong, M.D. Ph.D., and colleagues described using zebrafish embryos to screen for compounds that interfere with signaling pathways involved in early development - pathways known to play a role in a variety of disease processes including FOP. In this work, the investigators discovered the compound "dorsomorphin" and demonstrated that it blocked BMP signaling which is critical for the development of FOP. But, in examining dorsomorphin further, the investigators found that it had other "off target" effects that would limit its therapeutic potential. To find compounds that were more selective BMP inhibitors without such off-target effects, Hong and colleagues opted to use their zebrafish drug discovery screen once again as a drug development and optimization tool.

The zebrafish embryo, Hong said, is very good at assessing a compound's selectivity for the BMP signaling pathway. Mixed signals from compounds that are not selective are toxic to the embryo and shut down its development. Hong's colleagues, Craig Lindsley, Ph.D., Director of Medicinal Chemistry for the Vanderbilt Drug Discovery Program, and Corey Hopkins, Ph.D., Associate Director, used the dorsomorphin "backbone" as a starting point to synthesize many different analogs, subtly different dorsomorphin-like compounds that might have a more specific effect on desired pathways to shut down FOP. Traditionally, pharmaceutical companies perform these studies *in vitro* with isolated proteins or cells. But Hong points out those *in vitro* studies assess only one dimension of biology. Compounds that have great activity *in vitro* often fail later because they have poor selectivity or because they do not have chemical properties that make them good drugs. The living zebrafish assesses selectivity and drug desirability at the same time, Hong says. 'What the traditional approach takes months to do, the zebrafish does in a day.' Hong praised his associates at Vanderbilt for putting into place the drug discovery infrastructure that makes this work possible. 'Having medicinal chemists and zebrafish biologists together in the same building fosters our collaboration,' he said."

The work of Hong and colleagues has advanced greatly during the past year and involves synthetic chemistry to develop improved dorsomorphin analogs, *in vivo* and *in vitro* analysis for optimization of compounds, and *in vivo* testing of the compounds in pre-clinical models being developed at the University of Pennsylvania FOP laboratory. This work holds great promise for developing specific dorsomorphin-like compounds that have selectivity and effectiveness in blocking the FOP mutation while minimizing the side effects in the process.

While no one class of compounds is likely to be the "ultimate medication" for FOP, many different approaches are necessary in order to target such a complex disease. Some compounds might be better for targeting long-term prevention while others; such as RARγ agonists might possibly be more effective in shutting down the process once it has started. All may be needed to ultimately tame, suppress, and arrest the runaway train of bone formation in FOP.

The work on dorsomorphin and related analogs is further enhanced by discoveries of the molecular mechanisms of the damaged FOP receptor described



Dr. Petra Seemann (far left) and her research team at the Berlin-Brandenburg Center for Regenerative Therapies of the Charite University of Medicine in Berlin, Gemany

in previous annual reports. This work is an excellent example of how the tiny zebrafish can be used to screen the most promising compounds for further drug testing in mouse models of real FOP flare-ups. The use of several animal models (fruit flies, chickens, zebrafish, and mice) will help optimize drug selection, minimize side effects, and optimize dose, duration and delivery. It is a great testimony to how work in multiple fields and at the boundaries of seemingly unrelated fields can intersect to achieve the final common goal of developing more effective treatments for FOP.

Chickens with FOP

Dr. Petra Seemann's laboratory in Berlin is dedicated to identifying disease mechanisms of FOP and other bone disorders that are associated with dysregulated BMP signaling, by using the chicken as a model system. By overexpressing the FOP receptor in chicken embryos, Dr. Seemann and her colleagues follow the effects of the FOP mutation on embryonic development and cellular differentiation. Currently, Dr. Seemann's team is investigating the effects of FOP on bone marrow stromal cells, a natural source of stem cells in the body. So far, they have observed that chicken cells, in which the FOP mutation is artificially introduced, have an enhanced tendency to differentiate into cartilage and bone, as compared to wild type cells. Currently, the team is dissecting the molecular signaling pathway downstream of the FOP mutation in the chicken cells, which hopefully will reveal new clues on how to inhibit the process.

Petra Seemann and her research team recently moved from the Max Planck Institute of Molecular Genetics to the Berlin-Brandenburg Center for Regenerative Therapies, a new institute of the Charité University Hospital in Berlin focused on regenerative medicine. The studies are supported by a developmental grant from the Center of Research in FOP & Related Disorders.

FOP Gone Bananas

Fruit fly larvae live and thrive in rotten bananas, a natural source of sustenance for a very special type of FOP animal model. Professor Kristi Wharton from the Department of Molecular Biology at Brown University, and her graduate students continue to make major advances in FOP animal model development using the fruit fly (Drosophila) as a model organism. Dr. Wharton described this in a recent report: "Funding from an FOP Center Developmental Grant has enabled us to make significant progress in our efforts to unravel the molecular mechanisms responsible for FOP. These studies increase the likelihood of finding a therapeutic for FOP patients. While Drosophila or fruit fly cells do not make bone, the BMP cell communication pathway that signals specific cells in vertebrates to begin the synthesis of heterotopic bone is completely conserved in fruit flies. In fact, many of

the proteins that we now recognize as critical for BMP signaling in humans were first identified in fruit flies. The beauty of the Drosophila model system is that we can study, in a matter of weeks, processes that may take months to years in mice or humans. In addition, we can manipulate the genes and physiological conditions of fruit flies quite easily. This allows us to assess the consequences of various gene mutations or changes in physiology within an entire organism. This is critical because in the living fly cells are in their normal anatomical and physiological context and thus, continue to receive other signals or information that could modify the manipulations we have induced - something that would not happen if we were examining individual cells grown in a culture dish. Furthermore, the fact that we can examine many different fruit flies means we can make sure our results and conclusions are statistically significant and valid.

Dr. Jay Groppe reviews data with Dr. Eileen Shore in the FOP Laboratory

Specifically, fruit flies have an ACVR1/ALK2 BMP type I receptor (nearly identical to that which is mutated in FOP) called Saxophone (or Sax for short). Other studies from our lab have shown that Sax is an unusual receptor in that when it acts alone, it blocks BMP signaling, but when it is in a complex with another BMP type I receptor, it can transduce a strong BMP signal. We have now discovered that ACVR1/ALK2 behaves in a similar way. It can both antagonize signaling and facilitate signaling. The mutations that damage the ACVR1/ALK2 receptor in FOP patients appear to make the receptor signal when it shouldn't be signaling. Our finding that wild type ACVR1/ALK2 has two functions while the mutated ACVR1/ALK2 receptor in FOP appears to have only one (overactive) may explain a vital mechanistic aspect of FOP. It is also very interesting because once we understand how the antagonistic function of ACVR1/ALK2 is lost in FOP, we may be able to find ways to recover that behavior or find ways to alter molecules in the downstream signaling cascade that block the consequences of the hyperactive receptor. Our recent studies also indicate that we can use the Drosophila system with confidence to identify factors and conditions that trigger the hyperactive signaling associated with FOP flare-ups. This work compliments beautifully the work done in the core FOP laboratory, and will provide great depth to our understanding of this process for the benefit of the FOP patients."

Gulliver's Travels into the FOP Receptor

FOP patients have a mutation in the gene that makes a receptor (ACVR1/ALK2) for BMPs. The receptor is a protein embedded in the membrane of cells. The part of the receptor that is outside the cell is recognized by BMPs produced in the vicinity of those cells (often as a result of highly regulated developmental processes in the embryo or as a result of injury after birth); the region of the receptor that is inside the cell sends signals to the nucleus, or control center of the cell, when BMPs trigger the receptor. When BMPs are not around, a safety lock protein, called FKBP12 (or FKBP1A) is bound to the inside of the receptor, keeping it quiet or "off." In FOP, the specific mutation affecting the ACVR1/ALK2 receptor prevents the FKBP12 safety-lock protein from binding properly, thus allowing the receptor to be active or "on" when it should be inactive or "off." Further, when BMPs do bind to the damaged receptor, signaling is even further enhanced, triggering the renegade cartilage and bone formation of an FOP flare-up.

Ruth MCarrick-Walmsley in the FOP Laboratory

In 2010, there continued to be surprises at every turn from the strange subatomic world of the mutated FOP receptor. Studies conducted by Dr. J. Groppe and colleagues at Baylor University revealed a myriad of bizarre activation scenarios and Rube-Goldberg-like machinations from the damaged receptor. Data from X-ray crystallographic studies and other *in vitro* experiments are presently being analyzed. Attention is focused on internal factors within the mutated FOP receptor as well as external factors and associated proteins that interact with the receptor, and ultimately lead to a loss of auto-inhibition and an altered threshold for heterotopic ossification. Detailed analysis of these fascinating findings will be published in 2011.

Medical Student Danish Nagda (left) meets with Ian Cali (right) after Ian's blockbuster lecture to the medical students

The Keys to the Closet are the Keys to the Kingdom

Vital lessons continue to be learned from the rarest variants of one of the world's rarest conditions. A rare disease is defined as one that affects less than one in 50,000 individuals. FOP affects approximately one in two million individuals, thus making it one of the rarest diseases in the world.

Approximately 98 percent of individuals with FOP have classic clinical features of the condition caused by the classic FOP mutation. Approximately 2 percent of individuals with FOP have major clinical and genetic variants of the condition. Frances Collins, M.D., Ph.D., Director of the National Institutes of Health, said, "What we learn from rare disorders often has profound consequences for our understanding of more common conditions." Taken to its extreme, the rarest of the rare disorders teach us even more.

Rare conditions provide insight into cause and complexity in biological systems. The specificity of the rare condition often permits a causative genetic factor to be isolated in a complex regulatory network, thus identifying and defining the network itself. This is exactly what happened with FOP. Such insight is often the catalyst for dissecting the signaling network that is so critical for designing promising therapies, as with Dorsomorphin-like compounds and RARγ agonists in FOP.

Bobby Johnson of Warren, Pennsylvania relaxes atop Dr. Kaplan's desk

The keys to the closet are often the keys to the kingdom. In other words, identifying the cause of a rare disease will often unlock the mysteries of more common ones. And it is even more so with the rarest of the FOP variants. Members of our community harbor these exceptionally rare genetic mutations that cause their clinical variations in FOP, and we are learning more about them. They tell us a great deal about the FOP receptor (the broken switch) that causes so much havoc. Every person with FOP has a mutation in the gene that encodes ACVR1/ALK2, the FOP receptor. Ninety-eight per cent of individuals who have FOP harbor a mutation at the exact same place in

the ACVR1/ALK2 gene. But, the remaining two per cent of patients who have mutations in different places in that same gene teach us even more. How do differences in the sites of damage (mutation) translate into different clinical features of FOP? Do these sites of damage have something in common, and if so, what are they? What do they tell us about how the broken switch causes unwanted bone formation, and how can we use that knowledge to fix it or bypass it?

Kurt Kysar of Davenport, Washington dives into the toy box and plays with a new stuffed animal friend (courtesy of a generous gift from Amie Darnell Specht of Hillsboro, Oregon) during a visit to Penn

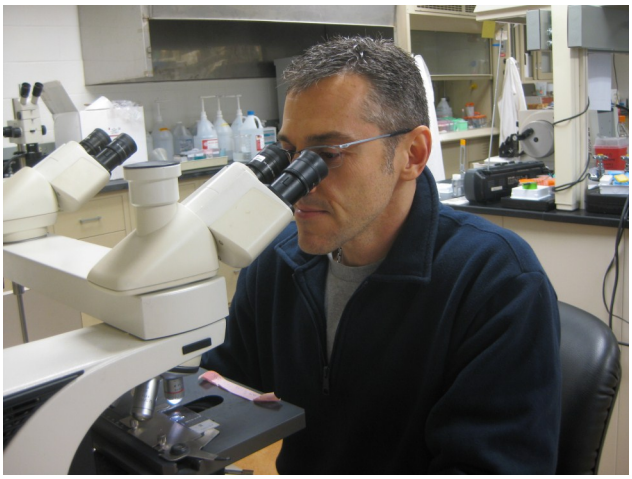
During the past year, we have been examining both the structural features and the molecular mechanisms behind the rarest genetic variations and we are learning a lot about them. This knowledge is being used to draw more detailed maps and diagrams of the damaged FOP receptor and its working parts, and to design newer approaches to jam and bypass the broken switch. Interestingly, all of the damage appears to occur in a very narrow portion of the switch that controls its access to downstream signaling molecules that ultimately determine (and in FOP, alter) the fate of cells. The more we know about the overactive switch, its function, and the various sites of damage, the better able we will be to hack into the genetic program and shut it down.

We are studying these variations not only *in vitro* but also *in vivo*, in animal models that are easily amenable to genetic manipulation such as the fruit fly, the zebrafish, and the chicken. These model systems are invaluable in rapidly gaining functional information about the variations in the FOP switch.

Our colleagues and collaborators at the University of Pennsylvania (Drs. Mary Mullins and Bettina Mucha-Le), our colleagues at Brown University, (Drs. Kristi Wharton and Viet Le), and our colleagues at the Max Planck Institute for Molecular Biology, and the Charité Hospital in Berlin (Drs. Petra Seemann and Julia Haupt), as well as our colleague Dr. Jay Groppe at Baylor University, and numerous members of our core FOP laboratory at the University of Pennsylvania contribute vitally to this ongoing effort.

The Handwriting of FOP

Every disease has a signature, or at least a characteristic handwriting. These molecular and biochemical features, called biomarkers, are indicators of disease course and activity and may change with a pharmacological response to an intervention such as a preventative medication or treatment. The opportunity to identify biomarkers of genetically regulated and inflammation-induced heterotopic ossification is now possible given the recent development of animal models that reproducibly form heterotopic bone in a predictable FOP-like manner. In late 2010, we began work to identify biomarkers of FOP disease activity. Such biomarkers will be invaluable in assessing the efficacy of drug development and in monitoring medications in future clinical trials.



Histologist Bob Caron examining an FOP lesion under the microscope in the FOP Laboratory

Dr. Fred Kaplan and Kamlesh Rai

Prestigious NIH Grant Renewed for Five Years

The NIH grant, "The Cellular & Molecular Basis of FOP Lesions," was favorably reviewed and renewed for five years (2010-2015). The aims of the competitive renewal are to investigate the cellular and microenvironmental conditions that induce the formation of FOP lesions. The reviewers noted that the application addresses, "significantly important questions in regenerative medicine. The successful completion of the project is likely to provide important new information on mechanisms of heterotopic ossification that will be useful in developing an effective prevention for debilitating heterotopic bone."

Graduate student Andria Culbert at work in the FOP Laboratory

The reviewers further noted, "This application is from a group who discovered the genetic cause of FOP, published in **Nature Genetics** in 2006. This was a major advancement in the understanding of this rare, devastating disease. This new application is a carefully crafted strategy to exploit the breakthrough discovery that ACVR1/ALK2 is the gene that causes FOP with experiments designed to identify the key players (cell types, molecules, and internal cell signals) that combine to trigger an FOP flare-up because of the lowered threshold of BMP receptor activation. The current work is focused on determining how the tissue microenvironment, specifically inflammatory growth factors, tissue hypoxia, and tissue specific stem cells spur development of lesions during flare-ups. The specific aims are novel and well designed, and the overall approach is visionary. The environment of the University of the Pennsylvania School of Medicine is outstanding for the completion of a project of this nature, as it is the preeminent laboratory in the world for this work.

The principal investigators are the world's authority on FOP, clinically and scientifically. This is an outstanding, proven investigative team. Their predictions and past strategy have proved insightful, highly productive, and have advanced the field greatly. This new proposal promises more to come. This is an outstanding, proven investigative team. Further, they have assembled an outstanding array of collaborating experts to help deliver on the aims and translate the findings into clinical practice."

Jacelane Clark of Oakdale, Louisiana visits with Dr. Kaplan

During 2010, important discoveries were made in all three major areas of this new proposal (immunological triggers, responding cells, and micro environmental factors). These discoveries will be reported in peer-reviewed publications and summarized in future annual reports.

Student Edwin Theosmy in the FOP Laboratory

FOP: The Written Word – 2010

In 2010, publications on FOP appeared in major peer-reviewed journals including: **Nature Medicine**, **Nature Reviews Rheumatology, The Journal of Bone & Mineral Research, The Journal of Bone & Joint Surgery, Methods In Enzymology,** and **Bone & Development**. As of January 1, 2011, the classic paper in **Nature Genetics** (April 2006) describing the discovery of the FOP gene has been cited in 168 major scientific publications. The much waited, updated, and revised fourth edition of **The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations** (The FOP Guidelines) is nearing completion and will be posted soon on the IFOPA website.

FOP: The Spoken Word – 2010

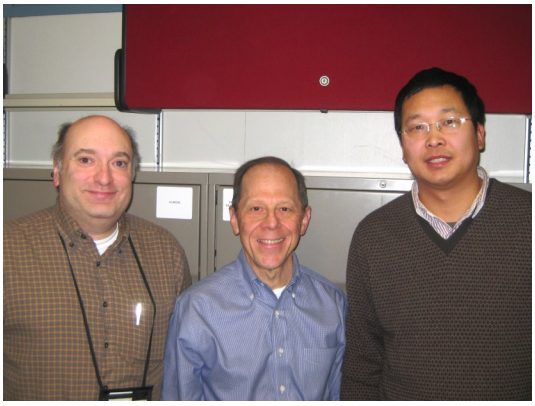
During 2010, we were proud to present major lectures on FOP at the:

- American Society for Bone & Mineral Research; Toronto, Canada
- Annual Meeting of Advances in Mineral Metabolism; Snowmass, Colorado
- Annual Meeting of the FOPeV; Valbert, Germany
- Annual Meeting of FOP Italia; Verbania, Italy
- Gordon Research Conference on Musculoskeletal Biology; Andover, New Hampshire
- International Conference on Bone Morphogenetic Proteins; Leuven, Belgium
- International Conference on the Chemistry & Biology of Mineralized Tissues; Carefree, Arizona
- National Institutes of Health; Bethesda, Maryland
- Novartis Institute for Biomedical Research; Basel, Switzerland
- Philadelphia Rheumatism Society; Philadelphia, Pennsylvania
- University of Alabama at Birmingham; Birmingham, Alabama
- University of California, Los Angeles (UCLA); Los Angeles, California
- University of Delaware; Wilmington, Delaware

University of Pennsylvania; Philadelphia, Pennsylvania

During 2010, we were honored to present highlights of FOP research at local, regional, national, and international FOP family meetings and gatherings in:

- Livingston, New Jersey
- New York City, New York
- Orlando, Florida
- Philadelphia, Pennsylvania
- Sausalito, California
- Valbert, Germany
- Verbania, Italy
- Wilmington, Delaware



Dr. Robert Pignolo, Dr. Fred Kaplan, and Dr. Haitao Wang at the FOP Laboratory

Our FOP Team: The Human Element

A team of incredibly dedicated colleagues, collaborators, consultants, research scientists, physicians, post doctoral fellows, doctoral candidate students, undergraduate students, high school students, technicians, assistants, secretaries, and volunteers contribute every day to the mission of deciphering the cause of FOP and of using that knowledge to develop preventions, treatments, and a cure for FOP. These are the individuals who do the research that transports us from one summit to another. These are the individuals who hit home runs and chase stray volleyballs in the outfield. Their pictures are on these pages and their names are

Dr. Kaplan at a toy store in Canada, daydreaming about the FOP zoo

indelibly linked to these accomplishments and discoveries. We honor them for their service and commitment to the FOP cause, and we are proud of them.

FOP: Everyone Can Help

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

FOP research is labor intensive, time consuming, and costly; filled with glimmers of hope and the fog of frustration. A formidable enemy like FOP requires a formidable opposing team, and teamwork requires resources. When seminal discoveries are made and ignorance is extinguished, the fog begins to lift. Summits and the paths between them become clear. New knowledge is a powerful beacon that illuminates the way ahead and changes the world like nothing else can. The feeling of accomplishment for all who contribute to this endeavor brings fulfillment and assurance that they have contributed something important and enduring for other human beings for generations to come.

When modern FOP research began 20 years ago in a small laboratory at the University of Pennsylvania, there was little basic knowledge about this terrible disease, and little hope outside of a small inner circle of believers who knew in their heart that something could be done to change it. Hope prevailed - hope fueled by the faith and commitment of individuals and families who sustained a team dedicated to make a difference. Over the years, that team has grown and expanded, and its reach now extends around the world. Through a sustained effort at the core FOP laboratory, at the Center for Research in FOP & Related Disorders in Philadelphia, and at satellite laboratories around the world, research is eradicating the stifling ignorance that was prevalent just two decades ago. Barrier after barrier is falling, and achievable goals are now in reach. FOP research holds real promise of preventing, treating, and curing FOP. It is no longer an imaginary dream.

We need your help now more than ever to make this a reality. The often-heard comment, "Call us when you have a treatment or a cure," is an option, but not one that will get us there. Every patient and every family has a stake in this effort. We need your help in getting there: bake sales, Burns' Suppers, barn dances and bingo; chicken barbeques and spaghetti dinners, garage sales and silent auctions; country fairs and benefit concerts at the Metropolitan Opera; raffles and rodeos, sales of holiday cards and embroidered quilts, 5K runs and ice fishing contests; chamber music benefits and hard rock concerts; horse-ploughing contests and competitive swims; golf tournaments and bowling parties; wine tasting events and lemonade stands on busy street corners. No idea or endeavor is too small or too outlandish to help. An FOP penny for every gallon of gasoline has taken us miles. Polio was cured with dimes and dollars, so, too will FOP. The finish line is in site. We can't afford to rest now. Everyone can help.

Many Thanks

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

The International FOP Association (IFOPA)

The Center for Research in FOP & Related Disorders

The National Institutes of Health (The People of the United States of America)

The Cali Family Endowment for FOP Research

The Weldon Family Endowment for FOP Research

The Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine

The Rita Allen Foundation

The Roemex & Grampian Fellowships in FOP Research

The Association Pierre-Yves (France)

The FOPeV (Germany)

The Canadian FOP Families & Friends Network

A Generous and Anonymous Donor from Caldwell, New Jersey

The People of Santa Maria (17 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.

FOP Patron, Mrs. Diane Weiss, donor of The Isaac & Rose Nassau Professorship of Orthopaedic Molecular Medicine at The University of Pennsylvania stops for a visit at Dr. Kaplan's office.