

Big Steps Being Taken In 2016

Paul Brinkman, IFOPA Board Chair, Introduces IFOPA's Executive Director



Paul Brinkman

The IFOPA has been in a long arc of transition following the retirement of Jeannie Peeper, our founder and long-time leader. Recent years have brought exponential leaps forward in our prospects for a treatment, thanks to the hard work of the many families, researchers and IFOPA leaders who guided the organization in its first 25 years. Now, in the dynamic and evolving era of clinical trials, we are facing increased demands on the community and the IFOPA as an organization. We must rise to the demands of clinical research without losing sight of our roots as an organization that supports patients and families. Through our strategic planning process, it became clear that hiring an Executive Director would be a critical step forward.

We are delighted to have found Michelle Davis. She brings deep experience in nonprofit leadership and an extensive background in fund development. When you get to know her, I think you will find her to be warm, engaging and thoughtful. We are confident that Michelle's experience, enthusiasm and engaging personality are a great match for the work, staff and supporters of the IFOPA. Together with our Board of Directors, membership, donors and research partners, she will continue to advance our dual mission to find a cure while supporting families.

Executive Director's Message

Thank you for making me feel so welcome. I have met many individuals living with FOP, parents, siblings, grandparents, supportive friends and colleagues and dedicated clinicians, researchers and pharmaceutical companies. I am inspired to work harder and lead our staff



Michelle Davis

team to do more to fight this disease and support you on your journey with FOP.

I also want to thank Jeannie Peeper, the IFOPA's Board, numerous volunteer fundraisers, the University of Pennsylvania FOP team and all clinicians and researchers working

on FOP, as well as the IFOPA staff, consultants and advisors. The IFOPA has and continues to make an incredible impact on individuals living with FOP and their families. The research work and participation of those living with FOP in clinical studies and trials has resulted in tremendous revelation about the disease and potential treatments. I am grateful for the opportunity to now work alongside you.

You, the FOP community, have accomplished some amazing things so far this year! I'm excited to share about your accomplishments.

Advancing Research

Without patient participation in research, medical breakthroughs can't happen and new therapies won't be approved for patient use. With such a small patient population, it is critical that everyone living with FOP consider what part they can and want to play in advancing medical research. There are two types of clinical studies:

- Observational studies where data is collected but there is no attempt to alter the disease progression. The FOP Connection Registry and Clementia's Natural History Study are both examples of observational studies.
- Clinical trials require that a drug be given or a device used to alter the course of the disease (e.g. Clementia's palovarotene clinical trials).

As of June 15, people living with FOP from 28 countries are part of the FOP Connection Registry. Since launching in July 2015, 174 people have registered, 97 have completed enrollment surveys and 50 have completed the six-month follow-up survey. Through your generous support, we will

launch the Registry in six new languages later this year – Italian, Spanish, Portuguese, German, Russian and French.

You can add your name to the FOP Connection Registry at fopconnection.org. The Registry collects data to better understand FOP and its impact on the body and physical function, as well as the emotional impact of the condition. It is a global registry open to all individuals with FOP. To make the process as easy as possible, Registry surveys can be completed by patients, parents and caregivers. You can get your questions about the Registry answered by emailing registry@ifopa.org. Your funding and participation have built the FOP Connection Registry – thank you!

On February 29, which also happened to be Rare Disease Day, Clementia Pharmaceuticals announced that the 40th and last study participant enrolled in its Phase 2 clinical trial investigating palovarotene for the treatment of FOP. On June 13, Clementia also announced the modification of the open label extension study to investigate new palovarotene dosing regimens and enroll up to 20 new adult and nearly grown teens. Also of note, as of July 1, 2016, 84 participants have enrolled in Clementia's Natural History Study.

The best way to find Information about all FOP clinical studies and trials available worldwide is at clinicaltrials.gov (type "FOP" in the Search for Studies box).

Raising Awareness and Raising Funds



Betina Charis Ramirez
Jamba Juice Fundraiser

Congratulations and thank you for a very successful FOP Awareness Day on April 23! I am thrilled to report that not only did the IFOPA raise \$10,000 to secure a \$10,000 match from a generous donor, the FOP community actually gave \$24,450. That means that during the month of April, a total of nearly \$35,000 was given to support the IFOPA's mission.

Your support helps the IFOPA fulfill its mission to fund research to find a cure for FOP while supporting individuals and their families through education, public awareness and advocacy. This year, thanks to you, IFOPA will invest \$1.5 million a year in our top five mission-driven programs:

www.ifopa.org

1. FOP Research Lab at the University of Pennsylvania
2. FOP Connection Registry
3. 2016 FOP Drug Development Forum
4. FOP education, support and awareness programs and materials
5. IFOPA Competitive Research Grant program

It was also exciting to see how active the FOP community was in raising FOP awareness as we celebrated the 10th anniversary of the FOP gene discovery and the announcement of that discovery on April 23. From April 15 to 30, the IFOPA posted an FOP fact on Facebook and Twitter. There were nearly 1,000 "likes" and 950 "shares" and 81,000 Facebook users were reached with facts about FOP. If you missed the interview with Meiqi Xu, the UPenn researcher who discovered the FOP gene, you can read it in the "Latest IFOPA News" section on the home page of ifopa.org.

In support of FOP Awareness Day, the IFOPA also offered FOP awareness items free of charge. The FOP community ordered and shared nearly 1,000 bracelets and 700 FOP fact cards. If you missed out and would like to order items to continue spreading FOP awareness, please contact us at together@ifopa.org or (407) 365-4194.

We were also thrilled to see the FOP community excited to order FOP "Have you seen these toes?" t-shirts and hoodies; more than 120 were sold. The IFOPA will be launching a new website in early fall which will include more FOP merchandise.

We are grateful to the amazing families that hosted fundraising events Jan. through June raising nearly \$512,000:

- Cure FOP Team at the Delaware Marathon
- Euclid Middle School FOP Awareness Day Fundraiser
- FOP Ashley's Cure Finding a Cure Charitable Event
- Griffin's Fun Run
- Jamba Juice Fundraiser
- Joshua's Future of Promises Bingo for a Cure
- Kordylia's Kure Poker Run
- Samson Strong 5K

You too can support IFOPA's work to bring treatments and a cure for FOP by hosting your own fundraising event. Contact Michelle Davis at michelle.davis@ifopa.org or (816) 809-2772.

Providing Education and Support

It was an honor to attend the FOP Italia meeting in Livorno, Italy in April along with several other representatives of the IFOPA. This meeting is an incredibly exciting, important and growing forum. The more than 75 attendees included families, leaders of the FOP International President's Council (leaders of FOP patient groups from countries around the world), clinicians, academic researchers and pharmaceutical companies. In May, we attended the FOP UK Friends and Family Gathering with more than 100 attendees. Although the IFOPA was unable to attend in person, we were there in spirit with FOP Australia as they hosted their second-ever patient and family meeting with 65 attendees. Betsy Bogard, IFOPA's Global Research Director, provided a recorded presentation about the FOP Connection Patient Registry. The annual German FOP meeting was held at the end of July and FOP France will meet in October. As the IFOPA continues its strategic planning, the committee and Board are discussing the need for regional patient and family meetings in the United States.

I look forward to meeting more of the FOP family – by phone, in person or virtually. If you have ideas about how the IFOPA can better fulfill our mission, I hope you'll reach out to me. I work out of my home in Kansas City, Mo. and you can reach me by phone at (816) 809-2772 or michelle.davis@ifopa.org.

2016 FOP Drug Development Forum



of its \$10,000 goal. Our friends at FOP Friends® UK know how critically important it is to bring clinicians,

On June 30, the IFOPA announced a special matching gift challenge to support the 2016 Drug Development Forum (DDF). Thanks to the generosity of 23 donors, within six days, the campaign had raised 71 percent

academic researchers and biopharmaceutical companies together to share with and learn from one another and what a perfect opportunity the DDF provides to do just that. You can learn more about the power of the DDF in the article below.



Just like the IFOPA, FOP Friends® UK wants to see the patient community step out as the largest supporter of the DDF. When FOP Friends® UK

saw that the matching funds were almost gone, they committed another \$15,000 to the match pool. Now is your chance to make your gift to the DDF have double the impact. Give now at <https://donate.ifopa.org/2016DDF>. The first \$25,000 in gifts will be matched.

“Effective disease nonprofits bring a lot more than just money to the table. They bring laser focus on treatments and cures and an innate sense of urgency. They bring a big-picture perspective.

They identify the knowledge gaps and figure out how to fill them. They realize that focusing on clinical research such as natural history studies, outcome measures, and biomarker development is equally important to basic science. They recruit scientists and clinicians into the field and foster collaborations, not by imposing but by nurturing.”

Monica Coenraads, mother and founder of the Rett Syndrome Research Trust in the Human Gene Therapy Commentary, March 30, 2016

In Nov. 2014, the International FOP Association's inaugural **Drug Development Forum** did just what Monica Coenraads suggests effective disease nonprofits should do and **brought together more than 100 researchers from academic institutions and pharmaceutical companies from around the world who are working to solve FOP.**

This coming October we're doing it again, doing it bigger, and you can help make it happen!

It's a big commitment to offer a scientific meeting of this caliber, and the IFOPA is up for the challenge. While the DDF receives support from the pharmaceutical industry, in 2014 the largest block of supporters were members of the FOP community. Community support keeps the IFOPA and FOP patients in the driver's seat facilitating collaboration and learning among many different entities.



Your gift brings together scientists and doctors from leading universities and biopharmaceutical companies worldwide, as well as relevant experts from the government and venture capital firms. The DDF:

- Addresses questions and knowledge gaps that exist in FOP drug development
- Stimulates new ideas to help advance development of potential therapies as quickly and efficiently as possible
- Facilitates dialogue, fosters collaboration and forms connections among interested researchers

You can create opportunities for researchers and pharmaceutical companies to be inspired to work harder and faster through your support of the 2016 Seed the DDF Campaign. The first \$25,000 given will be matched so your gift has twice the impact!

Check out the work inspired by the 2014 Drug Development Forum! Ben Levi, MD, University of Michigan, sent the IFOPA this note following the last event:

Hope you have had a chance to sit back and celebrate the incredible meeting you organized.

I can say honestly it was the most inspiring and informative meeting I have ever attended without question.

It was truly transformative for me as a person, surgeon and scientist. To meet and get to talk to the patients was fun, educational and inspiring. I really feel as if I bonded with several of the patients and hearing their insight about temperature and the nervous system has given me new ideas to investigate in the laboratory.

Drs. Fred Kaplan and Bob Pignolo and I sat for two hours after dinner continuing our conversations and discussing ways we can improve research and treatment strategies. I can't wait to get back into the laboratory and start making new discoveries to help FOP patients.

I plan to show my lab the video that was shown at the DDF this week in our lab meeting. Keep doing the wonderful things that you do and I look forward to keeping in touch as we work together to improve the care of people we are both passionate about.

Dr. Levi acted on his promise to investigate new ideas. In 2015, Dr. Levi and his colleague, Yuji Mishina, PhD, applied for and were awarded one of the IFOPA's inaugural Competitive Research Grants for their project "Validation of Novel Diagnostic and Targeted Prophylaxis for FOP Related Heterotopic Ossification." At the 2016 DDF, all researchers in attendance will hear about the results of their research work.

An Update on FOP Drug Development: News from the FOP Italia Annual Meeting

from the IFOPA Research Committee

The FOP research landscape is evolving at a rapid pace in many wonderful ways. Global efforts to develop therapies for FOP are stronger than ever among academic and biopharmaceutical teams. The IFOPA works continuously to monitor and support these efforts, serve as an advocate for the FOP community and inform you of progress, whenever possible.

The annual FOP Italia meeting has become one of the key places to hear the latest news in FOP drug development. It is always an extraordinary gathering, to the credit of the entire FOP Italia team, and the 2016 meeting, held on April 15 and 16 in Livorno, Italy, was no exception.



Research presentation at FOP Italia

This year's meeting was marked by an increase in participation from the biopharmaceutical industry, with representatives from Clementia Pharmaceuticals, Regeneron Pharmaceuticals, Alexion Pharmaceuticals, Blueprint Medicines and Novartis in attendance. Chris

Bedford-Gay, Betsy Bogard, Michelle Davis, Moira Liljesthröm, Neal Mantick and Eric Otto all participated in this year's meeting on behalf of the IFOPA. Here are some of the highlights.

- **Clementia Pharmaceuticals** will be analyzing data from their Phase 2 clinical trial of palovarotene and completing enrollment in their FOP natural history study in the coming months. They expect to share the results from their Phase 2 program by the end of this year. If data are supportive, they expect their Phase 3 program will include two trials, one of which will be a surgical trial. For the latest update from Clementia, please read "Next Step in Clementia's Clinical Program for FOP" at ifopa.org on the home page under Latest IFOPA News.
- Following their publication in 2015 about the role of Activin A in FOP, **Regeneron Pharmaceuticals** has continued to evaluate a potential therapy for FOP, an anti-Activin A antibody, in an FOP mouse model. At the FOP Italia meeting, they presented new data from this mouse model showing potential benefit of the antibody in early heterotopic bone lesions and, separately, in conjunction with surgical removal of heterotopic bone. Regeneron is preparing to publish these findings. For the latest update from Regeneron, please read "Regeneron's Work in FOP" at ifopa.org on the home page under Latest IFOPA News.
- **Blueprint Medicines** and **Alexion Pharmaceuticals** disclosed a partnership to develop a custom-designed drug for FOP in the class of compounds known as kinase inhibitors. Blueprint and Alexion are both publicly-owned biotechnology companies based in the northeastern United States. In the partnership, Blueprint is responsible for creating the molecule and conducting all preclinical research and Alexion will be responsible for clinical trials.
- Harvard and Oxford are collaborating to explore the potential use of saracatinib for the treatment of FOP. Saracatinib is an experimental kinase inhibitor developed by **AstraZeneca** and previously tested in 28 clinical trials.

- Vanderbilt continues their ongoing efforts to develop a potential drug for FOP, a novel kinase inhibitor, in partnership with **La Jolla Pharmaceutical Company**. In case you missed the announcement about their partnership, you can read about it on their website. In addition to this news from FOP Italia, the University of Pennsylvania team recently shared new findings in FOP mouse models about palovarotene and, separately, the potential benefit of HIF-1-alpha inhibitors. You can read more about this at ifopa.org/2016pennannualreport.

While there is much work ahead before we can understand whether any of these possibilities might one day become an approved therapy for FOP, we are heartened by the progress so far. We are fortunate to have many different teams working on a therapy, and even more so, to have many different types of therapies being considered. We are grateful to the countless talented, bright, and hard-working professionals who give their time and expertise to finding a therapy for FOP. Their devotion, persistence and determination give us all hope.

We are equally grateful to the community members who participate in clinical trials, the FOP Connection Registry, and other research projects. You are heroes for all of us, giving so much of yourselves — your time, energy, biological samples, images and data — and participating on behalf of those who can't. We would be nowhere without you.

As the FOP research landscape has become more complex, leaders of the IFOPA have discussed our philosophy for engaging drug developers. Our goal in any dialogue or partnership is to enable development of therapies while maintaining our independence as a patient organization. We collaborate with drug developers who are conducting ethical, high-quality research in a responsible manner according to industry and international regulatory standards. When we have dialogue, it is to seek insight into the developer's objectives, plans and the potential drug being evaluated and to provide community-wide insight and perspective as needed and appropriate. Our sole incentive in these interactions is the eventual treatment of our loved ones with a safe and transformative therapy.

We are developing the details around this philosophy into guidelines to be sure it is clear, for ourselves and any

current or potential partners, how we wish to operate. We will make these available on our website when they are ready, and will welcome comments and feedback on them.

Competitive Research Grant Program Continues in 2016

Research has been and continues to be the focus of the IFOPA's programmatic investments. The attention over the years has been on basic research, an effort to understand the fundamentals of how FOP works. Enormous progress has been made, jump-started by the discovery of the genetic basis for the disease by researchers at the University of Pennsylvania's Center for Research in FOP and Related Disorders. There is still much to learn, and the IFOPA continues to support a variety of research projects at the Center that are designed to increase our understanding of FOP.

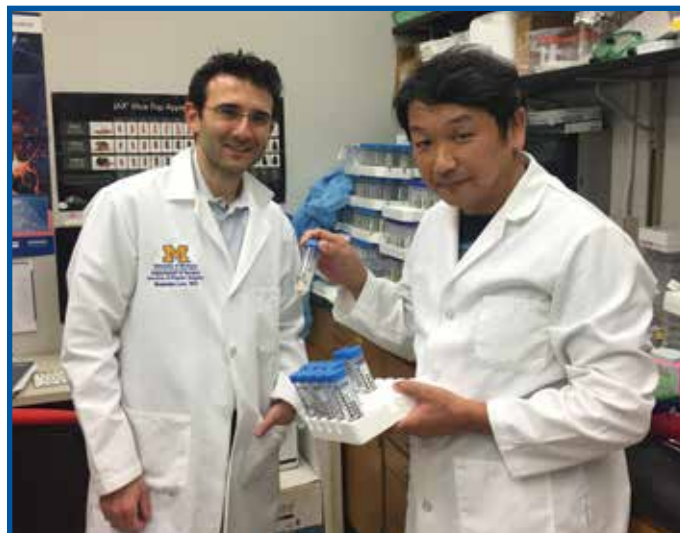
Starting in 2015, the IFOPA added a modest focus on translational research to our research funding portfolio by launching the Competitive Research Grants (CRG) Program. The CRG is an effort to move as rapidly as possible toward effective treatments and a cure, even in the absence of a full understanding of the fundamentals. The IFOPA started this new initiative following the lead of others in the rare disease community.

The Faster Cures publication "Why Translational Research Matters," highlights the role for nonprofit organizations in translating science into cures.

"Forward-thinking philanthropic funders of disease research – foundations such as the Michael J. Fox Foundation for Parkinson's Research, the Cystic Fibrosis Foundation, and a growing number of others – can play an absolutely critical role in stimulating research in under-resourced disease areas, and helping to bridge the Valley of Death," that is, the place between the lab bench and the marketplace where many good biomedical ideas wither away and die.

Serving the FOP community as a forward-thinking funder of disease research is the goal of the IFOPA's CRG Program – accelerating development of a safe and transformative therapy for FOP through a competitive application process. Applications are reviewed and funding

recommendations made by the CRG Scientific Advisory Board, which includes Dr. Michael Zasloff who introduced Dr. Kaplan to FOP.



2015 CRG Recipients: Ben Levi, MD & Yuji Mishina, PhD

The CRG program was launched in 2015 and three grants totaling nearly \$125,000 were provided in the program's inaugural year. The researchers who received these three grants will present on the findings of their research at the 2016 DDF.

In spring 2016, the IFOPA announced its second Competitive Research Grant program. Applications were due by July 1 and the number of entries nearly doubled from 2015. The CRG Scientific Advisory Board will review the applications and make funding recommendations to the IFOPA's Board of Directors this fall.

The IFOPA currently has \$100,000 available to support the 2016 research grants. With additional funding for the Competitive Research Grant program, the IFOPA could fund bigger projects and/or fund more projects moving the research needle more rapidly. Donations of any amount to this vital program are deeply valued and can be made via the IFOPA website at <https://donate.ifopa.org/CRG>.

You can learn more about the Competitive Research Grant Program at ifopa.org/research/competitive-research-grant-program.html, or you can contact Michelle Davis, Executive Director, at (816) 809-2772 or michelle.davis@ifopa.org.

FOP Connection Registry

**One coordinated and shared
Registry program
benefiting FOP patients,
physicians, researchers and
the biopharmaceutical industry worldwide.**

**Every person has a unique
experience with FOP.**

**Share yours at
fopconnection.org**

Brave New World

**A segment from the Twenty-Fifth Annual Report
of the Fibrodysplasia Ossificans Progressiva (FOP)
Collaborative Research Project**

by Frederick S. Kaplan, MD^{1,2,4}
Robert J. Pignolo, MD, PhD^{1,2,4}
Eileen M. Shore, PhD^{1,3,4}

From The Departments of ¹Orthopaedic Surgery,
²Medicine and ³Genetics, and ⁴The Center for Research
in FOP and Related Disorders, The Perelman School of
Medicine, The University of Pennsylvania, Philadelphia



FOP Clinical and Laboratory Team at UPenn

Two notable discoveries this past year – one from the pharmaceutical industry and one from the FOP Center – are likely to transform the basic understanding and

therapeutic landscape of FOP. In a nutshell, these discoveries showed that 1) the pathological activity of the mutant FOP receptor (mACVR1) is sensitive to an unsuspected extracellular hormone-like protein and immunological mediator, Activin A (Act A). Blocking the activity of Act A blocks heterotopic ossification (HO) in a mouse model of FOP; and 2) early FOP lesions are profoundly hypoxic (oxygen starved). The intracellular ‘alarm’ protein, HIF1- α which regulates the cellular response to hypoxia, retains mACVR1 in a signaling capacity when it should be destroyed, thus dramatically amplifying mutant BMP pathway signaling and stimulating HO. Blocking the activity of HIF1- α substantially diminishes HO in a mouse model of FOP.

The ideas behind these transformative insights have the strange quality of an Escher painting – one is able to see something – and then to see something else. The broadest brushstrokes suggest a picture in which inflammation and the extracellular hormone-like molecules (called ligands) such as BMP4 and Act A play a key role in initiating flare-ups from the mutant receptor– while the intracellular hypoxia alarm HIF1- α plays a key role in amplifying and fueling flare-ups. The first reaction requires ligand; the second reaction is completely independent of ligand – much like a match may be needed to start a fire but is not needed to sustain it.

Thus, in the complexity of an FOP lesion, both ligand-sensitive and ligand-independent processes are paramount in amplifying BMP signaling from the mutant FOP receptor (ACVR1). That means that not only the ACVR1 receptor, but the Act A ‘fuse’ and the HIF1- α ‘amplifier’ (both denizens of the inflammatory response) are – along with mACVR1 itself – robust targets for therapy of FOP.

These discoveries subtend a deeper understanding of FOP. The elucidation of these complimentary ideas have captivated our research world recently, and are a major focus of the 25th Annual Report.

Therapeutic Horizons

Worldwide interest in FOP research skyrocketed in the wake of the historic discovery of the FOP gene in 2006. FOP research is now a worldwide enterprise. The concept of orphan drugs for treatment of orphan diseases has been widely-embraced in just the past several years – a

concept that is leading to massive research investment on the part of industry. Pharmaceutical and biotechnology companies have expressed keen interest in FOP and are highly engaged in research efforts to bring the first-ever treatments, and ultimately a cure, for FOP.

In this year's Milestones, we focus on major new findings reported recently in a published study from **The Center for Research in FOP & Related Disorders**.

Scientists from The Center for Research in FOP and Related Disorders at the University of Pennsylvania, writing in *The Journal of Bone and Mineral Research*, announced a major breakthrough in understanding the role of palovarotene in FOP. In their paper, **“Palovarotene inhibits heterotopic ossification and maintains limb mobility and growth in mice with the human *ACVR1R206H* FOP fibrodysplasia ossificans progressive (FOP) mutation,”** lead author Dr. Salin Chakkalakal, senior scientist Dr. Eileen Shore and their colleagues Masahiro Iwamoto, Maurizio Pacifici and Fred Kaplan reported that palovarotene prevented spontaneous HO in a novel conditional knock-in mouse model carrying the classic FOP mutation. In addition, palovarotene restored long bone growth, maintained growth plate function, and protected growing newborn FOP mice when given to lactating mothers. Importantly, palovarotene maintained joint, limb and body motion, providing clear evidence for its encompassing therapeutic potential as a treatment for FOP.

In an explanatory editorial, “Learning more about Palovarotene,” the authors write: *Heterotopic ossification (HO) in fibrodysplasia ossificans progressiva (FOP) is a multi-step process that includes an intermediate stage of cartilage formation and concludes with the formation of mature mineralized bone in soft tissues such as skeletal muscles. This cartilage-to-bone process is known as endochondral ossification. The primary goal of research for FOP is to identify effective treatments to prevent the extra-skeletal endochondral bone formation that begins early in childhood and progresses throughout life. A milestone was reached in July 2014 with the beginning of a multicenter phase 2 clinical trial for FOP. The drug that is being evaluated in the phase 2 trials is palovarotene, a retinoid agonist that activates a specific component of the retinoic acid signaling pathway (RAR γ) in cells and tissues.*

The clinical trial for FOP was initiated based on the strength of previous studies by Drs. Iwamoto and Pacifici and their coworkers demonstrating that RAR γ agonists are particularly powerful to prevent HO at the cartilage stage and were effective in blocking it in injury and genetic mouse models. Palovarotene is a drug that was previously tested for emphysema. Although the drug did not achieve the targeted efficacy for emphysema, it was shown to produce few side effects in phase 2 clinical trials in adults.

*However, many questions remained unanswered about palovarotene and its use for treating FOP, including whether the drug would be effective in preventing HO triggered by the most common FOP *ACVR1R206H* human mutation, whether it would also improve skeletal function and joint movement, and whether it may actually impair the normal process of endochondral ossification required for skeletal growth and elongation during childhood.*

In order to answer these questions, and using the recent animal results, and the emerging clinical data, Clementia Pharmaceuticals is continuing its phase 2 dose-exploration program, which now includes chronic daily dosing (in adults and nearly grown teenagers) as well as higher dosing at the time of flare-up symptoms.

Kaplan commented, “The ravages of FOP can be successfully treated and prevented in mice. The discovery of the FOP gene, the use of that knowledge to successfully engineer FOP in a mouse model, and the identification of central and collateral targets for therapy provide hope and guidance for the greater challenge of successfully treating and preventing FOP in people.”