The Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project: An Interim Progress Report January 1993

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The new year begins with great hope for FOP research. While 1992 was productive, the coming year promises to be even more so. Our new FOP research laboratory opened in May 1992. The laboratory is co-directed by

FOP Patient Carol Orzel cuts the ribbon at the dedication of the new Molecular Orthopaedics - FOP Research Laboratory. Witnessing the event are Drs. Michael Zasloff, Eileen Shore, and Fred Kaplan, as well as numerous FOP fellows, friends, and well-wishers. At the McKay Laboratories; Friday, May 8, 1992.

Drs. Kaplan, Zasloff, and Shore. Dr. Shore has a Ph.D. in molecular biology, and she joined our research group in 1991, after serving a post-doctoral fellowship at the Fox Chase Cancer Center. The FOP laboratory was established with the enthusiastic support of the entire FOP community. Funds for laboratory construction and purchase of major equipment was provided by the research and development fund of the Department of Orthopaedic Surgery. The continued focus of the laboratory on FOP will depend on the establishment of successful extramural funding for ongoing and future projects. We hope eventually to establish an endowment which will provide the laboratory with funds to pursue many new avenues of FOP research. The continued help and support of the entire FOP community will be needed.

During the past year, we have enjoyed continued success in recruiting and retaining FOP investigators. Jeffrey Tabas, our first FOP fellow, is a resident in internal medicine at The University of California. He continues to work with us on numerous ongoing FOP projects. Randy Cohen completed his American Heart Association Fellowship in FOP last June and is currently

Welcome to the Dedication and Grand Opening of the Molecular Orthopaedic - FOP Research Laboratory. From Left to Right: Randolph Cohen (FOP fellow), Michael Zasloff (co-director), Eileen Shore (co-director), Carol Orzel (patient and friend), Fred Kaplan (co-director), Greg Hahn (FOP fellow), Craig Levitz (FOP fellow), Chris Strear (FOP fellow). At the McKay Laboratories; Friday, May 8, 1992.

an intern at The University of Pennsylvania. He continues to work with us on several FOP projects, and is looking forward to reentering the laboratory for a full one-year NIH-funded research fellowship beginning in July 1993. Gregory Hahn completed his American Heart Association Fellowship in the laboratory last June, and will continue working this year as an IFOPA-funded fellow. Greg recently published a paper on the localization of bone morphogenetic protein (BMP) genes 5, 6, and 7, to the human genome and is currently working with Eileen Shore on analyzing the complex regulatory control regions of the BMP genes. Chris Streer, our current American Heart Association FOP Fellow, is working on the genetics of Progressive Osseous Heteroplasia, a condition similar to FOP. Our discovery of Progressive Osseous Heteroplasia is an important milestone in understanding the spectrum of developmental disorders of heterotopic ossification in humans. It is even rarer than FOP (only seven known cases in the world) but provides a vital link in our understanding of the genetics of FOP.

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Binny Shah joined our laboratory on January 2, 1993, and is working on determining the molecular control switches of the bone morphogenetic protein (BMP) genes in man. So far, we know that the BMP genes stimulate bone formation. However, we must understand how the body normally turns these genes on and off. That is not a trivial matter and one that may take several years to determine. However, such an approach offers us the best opportunity to understand the genetic regulation of normal and abnormal bone formation (FOP) in humans. Binny's work will be funded by the National Institutes of Health and the National Cancer Institute. Beginning in July 1993, two additional FOP fellows will join our laboratory research program. Ross Milner and Adam Shafritz will each spend a year with us in the laboratory studying the molecular genetics of FOP. Ross Milner has applied for a prestigious Howard Hughes Foundation Fellowship, and Adam Shafritz has applied for a prestigious American Heart Association Student Fellowship.

Last year was a successful one for publications related to FOP. Two major articles were published in 1992. One pertained to the role of morphogens (bone morphogenetic protein, for example) in the formation and regeneration of the skeleton. The other major paper concerned the genomic localization of the BMP 5, 6, and 7 genes in man. These are potential candidate genes for FOP. In addition, there were four major FOP-related papers accepted for publication in 1993. They are: "The Genomic Localization of the Bone Morphogenetic Protein 4 Gene In Humans, The Natural History of FOP, The Histopathology of FOP, and The Genetics of FOP." Three of these papers will be published in *The Journal of Bone & Joint Surgery*, one of the most prestigious journals in the field of orthopaedics and skeletal research. In addition, we have recently submitted a paper on Progressive Osseous Heteroplasia. This disease is similar to FOP but different in a few important ways. For example, bone forms by a different process in POH than it does in FOP. In addition, the disease progresses asymetrically and does not follow the anatomic patterns usually seen in FOP. Finally, the toes are not involved but bone does form in the skin. We feel that the clinical and molecular differences between FOP and POH will provide vital insight into the genetic control of heterotopic bone formation.

The major focus of our current laboratory work is the regulatory region of the bone morphogenetic protein (BMP) genes and their possible relationship to FOP. The BMP genes appear to be the master genes for the formation and regeneration of the skeleton, and are likely involved in the pathogenesis of FOP. Whether or not the BMP genes are the ultimate cause of FOP remains to be determined. So far, we have identified one child with FOP who has a unique pattern in one of his BMP genes. The exact abnormality remains to be determined and must be compared with the normal structure of the same gene. This finding provides one of the most important clues we have in trying to unravel the mysteries of FOP. In addition, we will begin examining available tissue specimens from early FOP lesions to see if they produce abundant amounts of bone morphogenetic protein. And, finally, we are fortunate to collaborate with Dr. Max Muenke (of Children's Hospital of Philadelphia) who has been instrumental in establishing immortalized cell lines from blood samples in children and adults with FOP. These cell lines are a vital resource in our ongoing study of the molecular genetics of FOP. Much of the funding currently provided by the IFOPA supports the continuation of this extraordinary resource.

During 1993, we will continue to expand our work on important clinically-related projects including the FOP-dental study. We will embark upon at least two new clinical projects related to FOP. These will involve the study of spinal deformity (scoliosis) in FOP (and possible recommendation of early spinal fusion in some patients), as well as the study of hearing abnormalities associated with FOP. Your help will be needed in recruiting information for these studies, and you will be hearing more about them in later editions of the Newsletter.

At the present time, we are cautiously encouraged about the prospect of funding for FOP research. In addition to fellowship support from the American Heart Association and the National Institutes of Health, our greatest current funding source comes from the IFOPA itself. The University of Pennsylvania has just been awarded a major grant from the IFOPA to continue its research into the molecular genetics of FOP. This funding will support an FOP fellowship, partial salary for our full-time molecular biologist (Eileen Shore), continued development of vitally-important immortalized (FOP) cell lines, and the procurement of perishable supplies necessary to conduct the FOP research. We are most grateful for the extraordinary commitment by the FOP community.

At the present time, all departmental funds for the purchase of new equipment have been exhausted, and we will need even more robust funding support to purchase

Fred Kaplan, Carol Orzel, and Michael Zasloff in the newly dedicated Molecular Orthopaedics-FOP Research Laboratory, May 8, 1992.

needed equipment for ongoing research. Total funding support of approximately $200,000 per year will be necessary to sustain our current focus on FOP research. Such funding would be used for the purchase and replacement of equipment and supplies, salary support for at least two additional full-time scientists, and the development of new projects. It is important to remember that thousands of researchers world-wide are working on diseases such as cystic fibrosis and muscular dystrophy. At present, only a handful of people are working on FOP. Clearly, the problems related to FOP are as complex (if not considerably more complex) than other genetic disorders. Although FOP is a rare condition, the answers to FOP will help us understand and eventually treat even more common conditions such as osteoarthritis and osteoporosis which affects tens of millions of people world-wide.

The establishment of an endowment for FOP research will be a difficult task but one that we believe is essential. During this past year, we have submitted two additional major grant applications related to FOP. One of these grant applications has been submitted to the Orthopaedic Research and Education Foundation. The other has been submitted to the National Institutes of Health and represents a major international collaboration with Drs. Kaplan, Zasloff, Shore, and Muenke (Philadelphia); Drs. Gelbart and Wozney (Boston); and Dr. Connor (Glasgow, Scotland).

As further major funding becomes available, we will be able to undertake several important studies related to the treatment of FOP. These include the study of medications such as Indomethacin, thalidomide and angiostatic steroids. This work is extremely costly as it involves long-term animal research, and currently cannot be undertaken with the funds available. Also, it will be essential in the next several years to establish a transgenic animal model for FOP, and that too, will require major funding support.

In summary, great progress has been made in 1992 in the basic science and clinical studies of FOP. Our beautiful new laboratory is focussed entirely on FOP-related research and is poised to make even greater contributions in 1993. We look forward to an exciting year and are grateful for the enthusiastic help and support of the entire FOP community. Research into the fundamental molecular and genetic mechanisms of FOP offers the best opportunity to eventually establish a cure.