29TH EDITION
FEB 15 '95 - MAY 15, 1995

THE F.O.P. CONNECTION

BY AND FOR PEOPLE WITH F.O.P. AND P.O.H.

1994 ANNUAL F.O.P. RESEARCH REPORT

Pictured above at the F.O.P. lab at the University of Pennsylvania are: (standing left to right) Adam Shafritz, B.A., Jennifer Moriatis, B.A., Gregory Hahn,M.D., Hal Janoff, B.A., and Fred Kaplan, M.D. (sitting) Eileen Shore, Ph.D., and Betsy Olmstead.

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THE CONNECTION IS PRODUCED AND FUNDED BY
THE INTERNATIONAL FIBRODYSPLASIA OSSIFICANS PROGRESSIVA ASSOCIATION, INC. (IFOPA)
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The Fourth Annual Report of the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project, January, 1995

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Mission Statement for the Laboratory of Molecular Orthopaedics

1. To determine the genetic defect in fibrodysplasia ossificans progressiva (FOP) and the developmental pathways leading to disease expression.
2. To establish effective treatments based on the molecular cause of FOP.
3. To understand the molecular and developmental basis for the formation of a heterotopic and normotopic skeleton.
4. To use that knowledge to explore the molecular pathogenesis of related developmental diseases of the skeleton and to establish effective treatments for these currently untreatable disorders.
5. To provide the most compassionate treatment and medical advise for our patients who have FOP and other related disorders of bone formation.

1994 was a very productive year for FOP research with several exciting developments. In this report, we will outline the major work and accomplishments of our laboratory during the past year, and discuss the overall progress of the FOP project.

I. When we began our work in the laboratory several years ago, we hypothesized that a bone morphogenetic protein (BMP) gene would likely be involved in causing bone formation in FOP. The BMPs are a set of master genes involved in the embryonic formation and repair of the skeleton. Last year we reported the discovery that abundant amounts of BMP-2 or BMP-4 protein were produced by the cells of the earliest FOP lesions (the soft nodules that appear suddenly, that are often painful, and that can grow to a large size within a day or less) long before there was any microscopic evidence of cartilage or bone. That discovery was the first tangible evidence connecting a BMP gene with the earliest development of FOP. That single discovery also greatly advanced our understanding of early signalling molecules in FOP, and was a striking contrast to the absence of BMP molecules in lesions of aggressive fibromatosis (a condition often confused with FOP).

This year we learned that the BMP-4 gene specifically is dysregulated in FOP and that the BMP-4 protein is over-produced in living cells from the earliest FOP lesions, but not from the unaffected muscle, tendon, ligament or skin of FOP patients. (The tissue used for this analysis was obtained at the time of emergency surgery for problems not directly related to FOP.) While these additional discoveries provided important clues to the role of the BMP-4 gene and its protein product in the earliest identifiable FOP lesions, they provided little direct evidence for the cause of the lesions themselves. That frustration set the stage for a recent serendipitous discovery that promises to be the most interesting finding to date in FOP research — the discovery that BMP-4 messenger RNA (a precursor to the protein) is produced in lymphocytes (a type of circulating white blood cell) of most patients who have FOP but almost never in individuals who do not have FOP. This surprising discovery arose from studies on immortalized cells from blood samples that so many in the FOP community kindly provided to us. These samples were originally collected so that we could study the gene(s) that are involved in causing FOP. All cells in the body, regardless of what type they are (for example a white blood cell or a skin cell), contain the same genes, so the genes can be studied from any cells. Blood cells are commonly used for this purpose because they are relatively easy and safe to obtain, even from a person who has FOP. What makes cell types within an individual different from each other are not the genes that the cells contain but the subset of genes that are activated to produce messenger RNAs and proteins.

We therefore thought it unlikely that a gene for an important bone protein would be activated in a circulating blood cell. And we were even more surprised to learn that this gene was activated in cells from persons who have FOP but not in others (controls) who did not have FOP. An enormous amount of work needs to be done now to verify, clarify, and extend these findings. This discovery raises numerous important questions, some of which include:

Is the BMP-4 gene also activated in other types of blood cells, and if so, which ones? Do normal blood cells produce BMP in response to bone injury? Why and how is the gene activated in FOP? Can it be turned-off? Is there something wrong (or different) with the BMP-4 gene itself in FOP, or is it's activity the result of an earlier switch? Is BMP-4 in high concentrations in the blood plasma, or is it released by the cells at the sites where heterotopic bone is formed? The potential implications of our recent findings are clearly of enormous importance for FOP research, but also for research on many more common skeletal diseases such as osteoporosis and osteoarthritis. We are all very excited about these recent discoveries and about the insight they provide for understanding FOP.

II. Our laboratory discovered recently that there are at least three different BMP-4 mRNAs in humans, all coded from the single BMP-4 gene on chromosome 14. [An mRNA or messenger RNA is an intermediate molecule between a gene (DNA) and its protein product.] Important questions to investigate this next year include:

What is the total repertoire of BMP-4 mRNAs in humans? What controls when and how each one is used? Do people who have FOP have yet additional types of BMP-4 mRNAs or

do they utilize the same forms in different ways? What is the genetic switch that determines how the various BMP-4 mRNAs are regulated under normal circumstances and in FOP? Which forms of BMP-4 mRNAs are being produced in the circulating blood cells of some patients who have FOP?

III. Our laboratory has completed DNA sequencing all of the currently known regions of the human BMP-4 gene. This important sequence information will allow us to begin our study of the various regulatory or switching regions of the gene, so that we can determine what factors turn the gene on and off in different cells. We have also continued our work in determining the precise positions in the gene where the various on-off switches are located. We know now that there are at least three such locations within this complex gene. There may be more. We have also begun similar work on the human BMP-2 gene, an important sister-gene to BMP-4 and one with which it appears to interact in many developmental processes of bone formation and tissue patterning. The protein products of the two genes (BMP-4 and BMP-2) are very similar in their structure and it is likely that an understanding of the coordinate regulation of both genes will greatly enhance our understanding of the pathophysiology of FOP.

IV. We have begun an international collaborative research study to determine if the BMP genes are directly responsible for FOP. This genetic linkage analysis can only be done using DNA analysis of blood samples from families having more than one affected family member. To date, there are only four such families known in the world. Three of the families have been identified by our group in Philadelphia and one of the families by Dr. Connor in Scotland. Blood samples are available on all family members relevant to the study, and we are collaborating to complete this work. While the paucity of large families affected by FOP is a definite hindrance to this type of analysis, recent advances in gene mapping and linkage technology make it more likely for us to determine whether these candidate BMP genes (and specifically BMP-4) are directly, or indirectly, involved in causing FOP. If BMP-4 is directly involved in causing FOP, then we can avidly pursue the site and nature of the mutation(s). This will undoubtedly lead us to the best understanding of what is causing bone to form in persons who have FOP and how this bone formation can be prevented. If BMP-4 is indirectly involved in causing FOP, then we will determine what factors regulate the BMP-4 gene. Each of these areas of laboratory investigation reveal important pieces of the puzzle that appear to be essential in solving the mystery of FOP.

V. We have learned a great deal in the past year from the "fos" transgenic animal model of heterotopic ossification. This exciting work is conducted in collaboration with scientists in London, England and Vienna, Austria. Our work has revealed that the protein product of the fos nuclear proto-oncogene, a powerful and ubiquitous transcription factor that is able to turn other genes on and off, is able to directly or indirectly activate the BMP-2 and/or BMP-4 genes resulting in heterotopic cartilages and bones in the mouse. Our preliminary studies indicate that the fos gene is relatively inactive in early FOP lesions in humans, and that the overproduction of BMP-4 may interact with the fos gene. Much more work is needed to understand the functional inter-relationships of these two critical genes in bone formation, especially as it relates to FOP. This work has provided us with extremely valuable insight into the interactions of two distinct classes of molecules involved in the regulation of bone formation.

VI. Five new BMPs have been discovered in the past year (BMP-8, BMP-9, and Growth Differentiation Factors 5, 6, 7). We are in the process of mapping these genes to the human chromosomes in order to determine possible genetic linkage with disorders of bone formation. The exact role of these genes in bone formation has not yet been determined. This work is being conducted in collaboration with consortium members in Boston and Baltimore.

VII. We are investigating possible FOP treatment strategies based upon interruption of the capillary blood supply to the early FOP lesions. While this work is in its earliest stages, we hope to provide a much more detailed progress report on this topic at the FOP symposium in October.

VIII. Preparation continues for The Second International Symposium on FOP which will be held at the Wyndham-Franklin Plaza Hotel on October 29-31, 1995. Invitations have been extended to participating scientists and physicians, and favorable responses have been received from all invitees. The major goal of this meeting is to stimulate research in basic bone biology that is applicable to the study and treatment of FOP and other disabling diseases of heterotopic bone formation. Our specific aims are:

1. To define the current knowledge of bone morphogenesis that is applicable to the study of FOP and other disabling disorders of bone development.
2. To explore and define the future directions of research in this area of bone biology.
3. To stimulate novel multidisciplinary approaches to the understanding and treatment of FOP and related disorders of heterotopic ossification.
4. To foster seminal contributions from broad areas of bone biology in order to better understand and treat FOP.
5. To disseminate knowledge on these multidisciplinary interactions through the publication of abstracts and proceedings of this symposium in order to attract new ideas and investigators to this exciting area of bone biology.

A distinguished group of investigators will be assembled from a wide spectrum of basic biological and applied medical sciences including: molecular biology, cell biology, developmental biology, pathology and laboratory medicine, genetics, oncology, pediatrics, rheumatology, orthopaedics, oral biology, physical medicine and rehabilitation, endocrinology, cardiopulmonary medicine, otorhinolaryngology, nursing and statistics.

As with the extremely successful First International Symposium on FOP (September 25-26, 1991; Philadelphia, Pennsylvania), our goal is to assemble experts both inside and outside the field of bone biology to participate in a vibrant and robust discussion of FOP and genetically induced heterotopic ossification that will further invigorate the exciting research developments in this field of bone biology.

The assembly of such an eclectic group of scientists with vast expertise in numerous disciplines relevant to this devastating human affliction, and to the more general concepts of the genetic regulation of osteogenesis to which it pertains, will permit a highly valuable interchange of new information and ideas. Such an exchange will aid in understanding the molecular pathophysiology of the disease, in developing relevant transgenic animal models, in formulating practical approaches to prevention of disabling complications, and in achieving the ultimate long-term goal of developing more effective treatment strategies. Such achievements will not only stimulate scientific understanding of genetic forms of heterotopic ossification, but are also likely to advance our understanding of even more common disorders of osteogenesis. Directions for future research will be emphasized in all of the sessions.

IX. In addition to determining the molecular, genetic, and cellular defects in FOP, and to establishing effective treatments genuinely useful to the patients, it is also our mission to provide the FOP community with the best current medical advise on the management of the condition. During the past year, we have written several major articles on the subjects of immunizations, dental injections, submandibular swelling, genetic transmission, mild expression, fractures, remodeling, scoliosis, and accutane treatment. Some of these articles have been published. Many others will be published in 1995, and others are being prepared for peer-review and submission in 1995. We include here abstracts of these papers for your review and use. An updated bibliography of papers published or in press is also included.

A. Permanent Heterotopic Ossification at the Injection Site after Diphtheria-Tetanus-Pertussis Immunizations in Children who have Fibrodysplasia Ossificans Progressiva

In patients who have fibrodysplasia ossificans progressiva, routine childhood Diphtheria-tetanus-pertussis immunizations administered by intramuscular injection pose a significant risk of permanent heterotopic ossification at the site of injection ($p<10^{-8}$), while Measles-mumps-rubella immunizations administered by subcutaneous injection pose no significant risk. Intramuscular injections should be avoided, if possible, once a diagnosis of FOP has been established.

B. Temporomandibular Joint Ankylosis Following Routine Injection of Local Anesthetic In Patients Who Have Fibrodysplasia Ossificans Progressiva

Spontaneous ossification of the temporomandibular joint occurs late in the course of fibrodysplasia ossificans progressiva but has been reported following dental procedures or oral trauma at any age. .A postal survey of the sixty patient-members of The International Fibrodysplasia Ossificans Progressiva Association was conducted in order to determine the relationship of dental procedures to subsequent ossification and ankylosis of the jaw. Thirty-six of the forty-one patients who completed the survey had dental work performed. Twenty-one of the thirty-six patients who had dental work performed (58 per cent), had received an injection of a local anesthetic in association with a dental procedure. Five of the twenty-one patients (24 per cent) had an immediate flare-up of the disease at or near the site of a routine injection of local anesthetic (expected occurrences, 1.65; $p< 0.05$). Flare-ups were characterized by immediate post-injection swelling and subsequent ossification leading to permanent ankylosis of the jaw. None of the twelve patients who had comparable dental work but who did not receive a local anesthetic injection developed heterotopic ossification (expected occurences, 1.09; NS). We conclude that injections of local anesthetic during dental procedures pose serious and immediate risk for inciting heterotopic ossification and subsequent ankylosis of the temporomandibular joints in patients who have fibrodysplasia ossificans progressiva, and should be assiduously avoided.

C. Submandibular Swelling in Patients With Fibrodysplasia Ossificans Progressiva

Although ankylosis of the temporomandibular joint occurs commonly in the late stages of the disease, there is only one well-documented case of submandibular heterotopic ossification in the world's literature. Twelve of our 107 patients who have FOP (11%) experienced submandibular heterotopic ossification which was mistaken initially in seven of the patients for mumps, angioneurotic edema, abscess, mononucleosis, or neoplasm. There were 2 males and 10 females, and ages varied from 6 to 47 years (mean: 21 years). Ten patients survived following assiduous precautionary measures. One patient who required emergency tracheostomy and ventilatory support also survived. Another patient succumbed to inanition from chronic swallowing difficulty. An effective treatment program included early identification of the submandibular flare-up, avoidance of lesional manipulation, nutritional support, glucocorticoid therapy, and measures to avoid airway obstruction. Submandibular swelling is a medical emergency requiring intensive precautionary measures in order to avoid potentially catastrophic clinical

deterioration, and should be recognized as a variable feature of fibrodysplasia ossificans progressiva.

D. Fibrodysplasia Ossificans Progressiva in Two Half-sisters: Evidence For Maternal Mosaicism.

We observed classic features of FOP in 2 native American half-sisters from the same unaffected mother and different unaffected fathers. This is the first report of FOP in siblings from different pregnancies whose parents were unaffected. The findings in this family suggest the occurrence of maternal gonadal mosaicism in FOP and provide important new data for genetic counseling in this disease.

E. Mild Expression of Fibrodysplasia Ossificans Progressiva

We describe three unusually mild cases of fibrodysplasia ossificans progressiva (FOP) in an 80-year-old man, a 44-year-old woman, and a 17-year-old woman. The man, whose daughter had classic features of FOP, lacked malformation of the great toes and experienced unusually slow progression of the disease. Both women displayed late onset of heterotopic ossification. The older woman also displayed an unusually slow progression of the disease. All three patients remained ambulatory at the time of examination. Recognition of a mild form of FOP will influence diagnosis, counseling, and research in this rare condition.

F. Radiographic and Scintigraphic Features of Modeling and Remodeling in the Heterotopic Skeleton of Patients who have Fibrodysplasia Ossificans Progressiva

To characterize the radiographic and scintigraphic features of modeling and remodeling in the heterotopic skeleton of patients who have fibrodysplasia ossificans progressiva, radiographs from 47 patients and radionuclide bone scans from 12 of those patients, all of whom had a confirmed diagnosis of the disease, were reviewed. A wide range of normal bone modeling and remodeling features was seen in the heterotopic skeleton of all but the youngest two (age, 1 year) of the 47 patients. Characteristic features of normal bone modeling identified on radiographs of the heterotopic skeleton included: (a) the development of tubular and flat bones with mature cortical and trabecular organization; (b) the presence of well-defined cortical-endosteal borders enclosing medullary canals; and (c) the presence of metaphyseal funnelization in isolated ossicles or at sites of synostoses. Characteristic features of normal bone remodeling identified on radiographs of the heterotopic skeleton included: (a) the response of heterotopic bone to weight-bearing stress with osteosclerosis of use and osteopenia of disuse, and (b) the resistance of heterotopic bone to fatigue failure with the absence of pathologic fractures and stress fractures. Radionuclide bone scans in 12 patients showed that remodeling of mature heterotopic bone occurred at a rate consistent with that of mature normotopic bone. This study documents the radiographic and scintigraphic features of a heterotopic skeletal system in 47 patients who have fibrodysplasia ossificans progressiva. These data provide additional support for the hypothesis that the genetic defect leading to the formation of a heterotopic skeleton involves normal skeletal morphogenesis at heterotopic sites.

G. Traumatic Fractures of Heterotopic Bone in patients who have Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva is an extremely rare genetic disorder characterized by the formation of a heterotopic skeleton that is histologically, biomechanically, and metabolically indistinguishable from the normotopic skeleton. Isolated cases of traumatic and pathologic fractures have been reported in the normotopic skeleton of patients who have fibrodysplasia ossificans progressiva, but to our knowledge there have been no detailed reports of traumatic fractures in the heterotopic skeleton of patients who have this disease. We report here two children with fibrodysplasia ossificans progressiva who sustained traumatic fractures of heterotopic bone around the elbows. In both children the fractures healed uneventfully with normal appearing callus. These two extremely rare cases suggest that the biological response to fractures in the heterotopic skeleton appears indistinguishable from that in the normotopic skeleton in patients who have fibrodysplasia ossificans progressiva.

H. Spinal Deformity in Patients Who Have Fibrodysplasia Ossificans Progressiva

We reviewed roentgenograms and clinical records in order to characterize the spinal deformity in forty patients who had an established diagnosis of fibrodysplasia ossificans progressiva. Twenty-six (65 per cent) of the patients had scoliosis, which, according to clinical records and the recollection of the patients, had been present during childhood. Twenty-three (88 per cent) of the twenty-six curves were unbalanced c-shaped curves, while the remaining three (12 per cent) were balanced s-shaped curves. Twenty-one (91 per cent) of the twenty-three c-shaped curves involved the thoracolumbar or lumbar spine. The c-shaped curves ranged in magnitude from 15 to more than 80 degrees. Curves became rigid by early adulthood and many resulted in severe pelvic obliquity with impaired sitting or standing balance. An osseous bridge developed between the posterolateral aspect of the iliac crest and the posterolateral aspect of the rib cage in twenty-two (55 per cent) of the forty patients. Nineteen (86 per cent) of these twenty-two patients had scoliosis; there was a significant association between the development of scoliosis and the presence of the osseous bridge ($p<0.005$).

Ossification of the paravertebral muscles and fascia during the first decade limited the development of a normal thoracic kyphosis in ten (42 per cent) of twenty-four patients for whom lateral roentgenograms of the spine were available.

A spinal orthoses was used to treat scoliosis in two patients, but this method resulted in breakdown of the

skin and failed to halt progression of the curve. Five patients had operative procedures to correct the scoliosis, in the hope of obtaining a balanced fusion of the spine. Five of the procedures either failed to halt progression of the curve or were associated with exacerbation of heterotopic ossification at sites remote from the operative field.

While our series is small, and while we cannot completely dismiss the option of operative treatment of scoliosis in patients who have fibrodysplasia ossificans progressiva, we believe that operative intervention is rarely indicated because of the numerous and severe complications: most notably, the exacerbation of heterotopic ossification at sites remote from the operative field.

I. Treatment of Patients who have Fibrodysplasia Ossificans Progressiva with 13-cis-Retinoic Acid (Isotretinoin)

Retinoids are a plausible family of therapeutic agents for this condition, due to their ability to inhibit differentiation of mesenchymal tissue into cartilage and bone. We conducted a prospective study to assess the efficacy of 13-cis-retinoic acid in the prevention of heterotopic ossification in patients who had fibrodysplasia ossificans progressiva.

Twenty-one patients who had fibrodysplasia ossificans progressiva (thirteen males, eight females) ranging in age from three years to twenty-one years (mean age=twelve years) were treated with steady-state doses of 13-cis-retinoic acid ranging from 0.5 milligrams per kilogram per day, to eight milligrams per kilogram per day (mean=2.8 milligrams per kilogram per day; median=1.7 milligrams per kilogram per day) for durations between four months and ten years (mean duration=three years; median duration=three years). Eleven anatomic regions were assessed in each of the twenty-one patients (total=231 anatomic regions) by clinical examination, plain roentgenograms, and radionuclide bone scans. An anatomic region was considered to be involved if there was clinical, roentgenographic or radionuclide evidence of orthotopic or heterotopic ossification anywhere in that region. There were 143 involved anatomic regions and eighty-eight uninvolved regions in the twenty-one patients at the beginning of the study.

Only one of the eighty-eight anatomic regions that was completely uninvolved at the beginning of the study became involved (secondary to trauma) during the study. However, thirty-eight of the 143 anatomic regions that were involved at the beginning of the study (27 per cent) sustained a severe flare-up of fibrodysplasia ossificans progressiva during the course of the treatment. Sixteen of the twenty-one patients (76 per cent) developed major flare-ups in previously involved anatomic regions while on isotretinoin therapy.

Our data indicate that 13-cis-retinoic acid at steady-state doses of one to two milligrams per kilogram per day decreased the incidence of heterotopic ossification at uninvolved anatomic regions by more than five-fold (82 per cent reduction; 95 per cent confidence interval: 27 per cent to 96 per cent reduction) compared to an age-controlled and disease severity-controlled external control group ($p=0.0013$). However, 13-cis-retinoic acid had no protective effect at those regions even minimally involved at the beginning of therapy. Thus, 13-cis-retinoic acid provided some protection against regional activation of heterotopic ossification, as long as the medication was started prior to the appearance of any orthotopic or heterotopic ossification in that anatomic region. The regions that were most protected by the use of oral 13-cis-retinoic acid therapy were the major joints of the lower limbs, especially the hips and knees.

During the past four years, the working group on FOP has:

1. Defined the Mendelian genetics of FOP.
2. Described a form of mosaicism in the transmission of the disease.
3. Defined the histopathology of heterotopic osteogenesis in FOP.
4. Defined the developmental gradients of heterotopic osteogenesis in FOP.
5. Established age and joint-specific risk profiles for heterotopic ossification in patients who have FOP.
6. Defined the modeling and remodelling characteristics of the heterotopic skeleton in patients who have FOP.
7. Defined the complications of injections for dental work in patients who have FOP.
8. Defined the complications of childhood intramuscular immunizations in patients who have FOP.
9. Described the manifestations and treatment of submandibular swelling in patients who have FOP.
10. Described several mild variants of disease expression in FOP.
11. Defined the utility and limitations of 13-cis-retinoic acid in the prevention of new regional heterotopic ossification in patients who have FOP.
12. Defined the natural history and pathogenesis of spinal deformity in patients who have FOP.
13. Described Progressive Osseous Heteroplasia (POH), a newly characterized developmental disorder of heterotopic ossification in humans and compared this condition with FOP.
14. Formulated an hypothesis on the molecular pathogenesis of FOP.
15. Demonstrated the presence of BMP-2/4 in pre-chondral and pre-osseous FOP lesional tissue, thereby providing the first tangible evidence of the inappropriate expression of BMP in patients with FOP.
16. Demonstrated the over-production of BMP-4 mRNA in cells from the earliest FOP lesions.
17. Demonstrated the dysregulation of BMP-4 in mRNA in white blood cells of patients who have FOP.
18. Discussed the implications for BMPs as morphogens in vertebrate embryonic and postnatal bone induction.

19. Mapped eight bone morphogenetic proteins (BMP-1 through BMP-8) to the human chromosomes using somatic cell hybrid panels and standard molecular techniques.

20. Defined RFLPs for human BMPs in the normal population.

21. Produced immortalized lymphoblastoid cell lines from 40 FOP patients and 25 family members.

22. Performed extensive RFLP analyses of the BMP genes in FOP patients, as a preliminary screen for gross molecular abnormalities.

23. Recovered a human BMP-4 genomic clone and completed determination of its DNA sequence.

24. Discovered at least three mRNAs (alternate splicing variants) of the human BMP-4 gene.

25. Recovered a human BMP-2 genomic clone and began determination of its DNA sequence.

26. Discovered that embryonic over-expression of the c-fos proto-oncogene in the mouse leads to an FOP-like condition; and that c-fos over-expression in that animal model may lead directly or indirectly to the activation of BMP-2 and/or BMP-4 genes.

27. Organized and hosted The First International Symposium on FOP (Philadelphia; September 25-26, 1991) in order to bring together scientists, patients, and physicians to focus attention on the rare disorder FOP, and to seek a broad multi-disciplinary perspective that would foster a better understanding of the condition. Accordingly, a distinguished group of experts from a broad spectrum of biological and medical sciences were assembled to discuss their work and to exchange ideas. Patients, family members, and caretakers participated in the historic proceedings that united all factions of the FOP community.

28. Organized and planned the Second International Symposium on FOP (Philadelphia; October 29-31, 1995).

29. Wrote FOP: A Guidebook for Families. This book of commonly asked questions with accessible answers will be published in conjunction with the Second International Symposium on FOP and will be made available to all interested families.

Recent Publications By the FOP Basic Science/Clinical Consortium

1. Campbell JT, Kaplan FS (1992). The role of morphogens in endochondral ossification. **Calcif. Tissue Int.**, 50:283-289.

2. Cohen RB, Hahn GV, Tabas JA, Peeper J, Levitz CL, Sando A, Sando N, Zasloff MA, Kaplan FS (1993). The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva - a study of 44 patients. **J. Bone Joint Surgery**, 75-A: 215-219.

3. Cohen RB, Kaplan FS (1993). Diagnosis: Natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. **Orthopaedics and Rheumatology Digest**, 8: 18-19.

4. Connor JM, Skirton H, Lunt PW (1993). A three generation family with Fibrodysplasia Ossificans Progressiva. **J. Med. Genet.**, 30: 687-689.

5. Einhorn TA, Kaplan FS (1994). Traumatic fractures of heterotopic bone in patients who have fibrodysplasia ossificans progressiva. **Clin. Ortho. Rel. Res.**, 308: 173-177.

6. Hahn GV, Cohen RB, Wozney JM, Levitz CL, Shore EM, Zasloff MA, Kaplan FS (1992). A bone morphogenetic protein subfamily: chromosomal localization of human genes for BMP5, BMP6, and BMP7. **Genomics**, 14: 759-762.

7. Hahn G, Kaplan FS: Heterotopic Ossification; in Basic Science of Osteogenesis, Brighton, CT, ed., **American Academy of Orthopaedic Surgeons**, 1994.

8. Janoff H., Shah P, Cohen R, Shafritz A, Bleier J, Wozney J, Zasloff M, Kaplan F and Shore E (1994). Isolation and characterization of human BMP-4 genomic DNA. **J. Bone and Min. Res.** 9 (Suppl. 1), S373.

9. Janoff H, Cohen R, Shafritz A, Shore E, Zasloff M, Kaplan F (1994). Submandibular swelling in patients who have fibrodysplasia ossificans progressiva: a life threatening complication. **J. Bone and Min. Res.** 9 (Suppl. 1), S428.

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12. Janoff HB, Zasloff MA, Kaplan FS (1995). Submandibular swelling in patients who have fibrodysplasia ossificans progressiva. **J. Oto.**, submitted.

13. Kaplan FS, Tabas JA, Zasloff MA (1990). Fibrodysplasia ossificans progressiva: A clue from the fly? **Calcif. Tissue Int.**, 47:117-125.

14. Kaplan FS, Tabas JA (1991). Mapping the human BMP genes: Communication and collaboration in the age of biotechnology. **Univ. Pa. Ortho. J.** 7:32-34.

15. Kaplan FS, Zasloff MA (1992). First annual report of the fibrodysplasia ossificans progressiva collaborative research project. **Univ. Pa. Ortho. J.**, 8:84-86.

16. Kaplan FS, Zasloff MA (1992). Proceedings of The First Int. Symp. on F.O.P., **Univ. Pa. Ortho. J.**, 8:87-91.

17. Kaplan FS, Tabas JA, Gannon FH, Finkel G, Hahn GV, Zasloff MA (1993). The histopathology of fibrodysplasia ossificans progressiva: an endochondral process. **J. Bone Joint Surgery**, 75-A: 220-230.

18. Kaplan FS, Zasloff MA (1993). The Second Annual Report on the Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project. **Univ. Pa. Ortho. J**, 9:70-72.

19. Kaplan FS; Zasloff MA, Shore EM (1993). The Fibrodysplasia Ossificans Progressiva (FOP) Collaborative Research Project: An Interim Progress Report (Jan. 1993). **Univ Pa. Ortho. J.**, 9: 78-80.

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