The Center for Research in FOP and Related Disorders

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Our collaborative work is to identify the cause of fibrodysplasia ossificans progressiva (FOP) and to use that knowledge to advance the treatment and cure for this debilitating disease. We began with the founding of our research program focused on this rare disorder of heterotopic ossification at Penn in 1991; we became the Center for Research in FOP and Related Disorders in 1998 with a generous gift from the Cali Family. Our critically important discovery in 2006 of the genetic mutation that causes FOP has allowed us to rapidly expand our research efforts. These efforts have led to discovery of new drug targets for FOP and to take the first steps into clinical trials, as well as to successfully promote interest in FOP research and drug development by scientists and researchers from around the world.

At Penn, work at the Center for Research in FOP & Related Disorders is broad, comprehensive, and evolving as research advances are made and clinical treatments are developed; some of our activities during the past year are highlighted:

Clinical Care and Consultation

The Center is the largest clinic and referral center for FOP worldwide, and provides guidance to physicians, families, and patients living with FOP. Furthermore, the Center coordinates the medical management of FOP patients with physicians from around the world.

Clinical Research and Infrastructure Development

Important recent advances that support current and future clinical trials include a global survey of FOP patient disease flare-ups, the first patient-reported longitudinal natural history study for FOP, and development of a Cumulative Analogue Joint Involvement Scale (CAJIS) to rapidly and informatively evaluate FOP disease progression.

Basic Research

The goals of our basic laboratory research are to understand the effects of the FOP mutation in promoting disease and to identify druggable pathways and targets for therapeutic intervention. Our work includes developing *in vitro* and *in vivo* models for investigational and pre-clinical studies and using these systems to understanding how the FOP mutation alters tissues, cell functions, and molecular pathways to initiate and support the progression of heterotopic bone formation. Over the past year, areas of focus have included: defining changes in immune cells in response to the FOP mutation and identifying the cellular response to tissue hypoxia and inflammation; examining changes to the tissue microenvironment and the molecular mechanisms by which the mutant FOP gene alters biomechanical signaling in response to the physical environment; initiating genome wide approaches to identify genetic modifiers of FOP clinical progression and investigating the molecular mechanisms by which ultra-rare FOP variants trigger promiscuous BMP signaling and subsequent heterotopic ossification. Our work has been highly recognized within the bone and musculoskeletal field; of the five 'most talked about articles in The Journal of Bone & Mineral Research (JBMR) in 2016', two were research publications from our laboratory.

Translational Research

These studies focus on pre-clinical testing of potential treatments for FOP in animal models and investigation of biomarkers for FOP that could be used to inform diagnosis and disease onset and progression. A key, recently published study investigated the effects of a small molecule currently used in clinical trials for effects on growth plate chondrogenesis, providing valuable insight for use of this drug in children.

Developmental Research Grants Program

This outreach program encourages investigators working in fields related to FOP research to apply their knowledge and perspectives to FOP and establishes collaborative interactions with the Center. During the past year, the Center supported three innovative projects: "Molecular Basis of Pathogenic Signaling and High Throughput Testing of FOP Therapies in a Zebrafish Model System" (Mary Mullins, PhD at Penn); "Identifying Alternative Therapeutic Targets and Genetic Interactors in FOP" (Dr. Ed Hsiao, MD at UCSF); "Novel Allosteric Destabilizers as Therapeutics for FOP" (Jay Groppe, PhD at Texas A&M).

Clinical Trials

The FOP Center at the University of Pennsylvania is the principle clinical site for the first clinical trial for FOP. We have enrolled and followed patients in two sponsored interventional clinical trials and in a sponsored longitudinal natural history study. We have additionally consulted with pharmaceutical/biotech companies on the study design for pending clinical trials, and have advised 30 pharmaceutical and biotech companies on the development of novel drugs for clinical trials in children and adults with FOP.

Education

The Center continues to mentor the next generations of physicians and scientists in the classroom, clinic, and laboratory. Postdoctoral researchers and graduate, undergraduate, and high school students work on research projects in our laboratory. We annually present FOP patients cases to first

year medical students. Additionally we educate physicians, scientists, researchers, and regulators at medical and scientific forums, meetings, and conferences worldwide.

Although FOP is the founding and primary focus of the Center, we additionally investigate a second rare genetic disorder of heterotopic ossification, progressive osseous heteroplasia (POH). Work in POH during the past year has continued to advance our understanding of how the underlying genetic mutations lead to induction of ectopic osteogenesis and how these mutations impact the formation and maintenance of the skeleton.