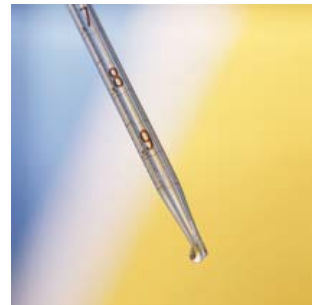


Oxford Thinking

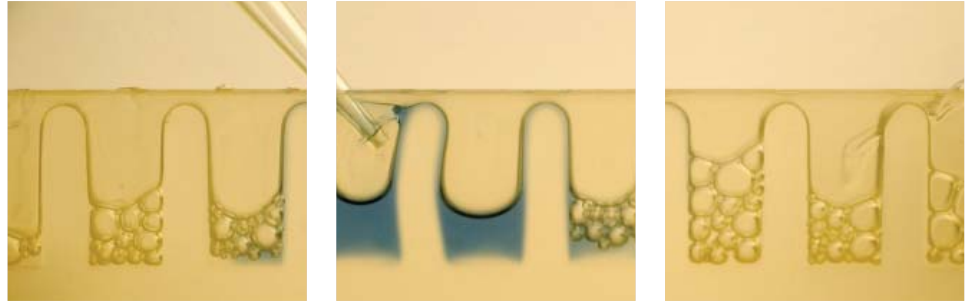
The Campaign for the University of Oxford



Supporting research into Fibrodysplasia Ossificans Progressiva (FOP)



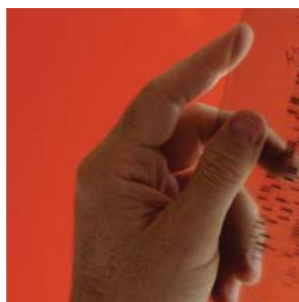
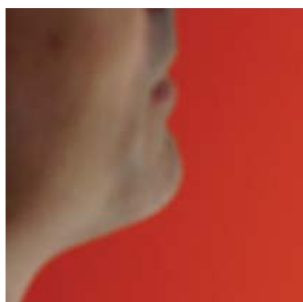
Medical Sciences
Division
May 2010



Fibrodysplasia ossificans progressiva (FOP)

Fibrodysplasia ossificans progressiva (FOP) is a very rare disorder in which skeletal muscle tissues and other associated connective tissues such as tendons and ligaments are gradually replaced by bone (ossified). This bone formed outside the skeleton (extra-skeletal, ectopic or heterotopic bone) significantly constrains movement. The pathogenic process generally becomes noticeable in early childhood, starting with bone developing as hard lumps in the neck and shoulders and proceeding down the body and into the limbs. Heterotopic bone formation occurs in a variety of other orthopaedic conditions also but in the rare heritable condition of FOP bone formation in abnormal tissue sites is one of the most severe and leads to a most distressing clinical condition.

FOP affects approximately one in two million individuals worldwide, with those influenced being gradually and increasingly afflicted throughout life. By the time they are 50 years of age, most patients are almost completely immobile as the joints become fused by bands of bone. Here in the UK, there are fewer than 40 affected individuals and support for research into FOP is limited to fund-raising by patients, families and friends, with little support from public funding agencies. This is despite the fact that a number of rare diseases provide fundamental knowledge that aids understanding of the pathogenesis of other more common disorders. Further knowledge of the underlying mechanisms that result in FOP may not only improve the management of this rare disease but may also throw light on the pathogenesis of many disorders that result in altered bone formation from whatever cause.



A remarkable breakthrough



Professor James Triffitt (picture, left) at the University of Oxford's Botnar Research Centre is one of the few scientists in the world conducting research into FOP. The genetic cause of FOP was discovered in 2006 by international collaborative efforts led by research centres in Philadelphia and Professor Triffitt's small team at the University of Oxford. It was identified as a defect in the bone morphogenetic protein receptor ACVR1, which is a signalling protein that influences bone formation. The methods of genetic analysis used by the Oxford Group at the Botnar Research Centre played a central and pivotal role in this remarkable breakthrough.

The identification of this gene is a major step in understanding how FOP occurs and how it may possibly be cured. It should also improve our understanding and possible future treatment of a wide range of more common skeletal conditions such as osteoporosis. However, much more support will be needed in the future to undertake further research to help all sufferers of FOP. It will be essential to limit the immobilising effects of the excessive bone formation as this is the central debilitating feature of the distressing condition.



Current research projects

FOP is caused by a mutant form of the ACVR1 receptor with constitutive kinase activity and was originally shown by genetic analysis to be the result of a single specific mutation in the gene in all the patients studied. With the recent completion of a doctoral student research project, funded by donations to the University of Oxford FOP Research Fund, we have discovered new mutations in patients in the UK, while others have been reported worldwide.

A newly appointed doctoral student has now begun investigations of protein structure and drug discovery in the TGF- β /BMP receptor family of serine/threonine kinases together with Dr Alex Bullock at the Structural Genomics Consortium within the Nuffield Department of Clinical Medicine at the University of Oxford. Mutations in the TGF- β /BMP receptor family also underlie a variety of cancers and proliferative diseases. The Structural Genomics Consortium has identified a series of compounds that inhibit ACVR1 and offer hope for further drug development to limit resultant bone formation in FOP.

The doctoral project will focus on the structure determination of the TGF- β /BMP receptor kinases to understand the mechanisms of activation, the basis for signalling specificity and the optimisation of small molecule inhibitors with potential to treat FOP and other diseases. These studies will include X-ray crystallography, biophysical studies of protein-protein and protein-inhibitor interactions and mass spectrometry to identify protein phosphorylation. Inhibitors may also be tested in cells to determine their efficacy.



Future direction and goals

With these and future investigations, researchers at the University of Oxford are determined to discover effective therapies for patients through better understanding of the physiological effects of mutations causing FOP. We are confident that this is an achievable goal since various specific inhibitors of the cell receptor related to FOP are now fully identified. In addition, since bone is deposited following inflammatory flare-ups, these warning signals may provide a window of opportunity for developing an acute therapy.

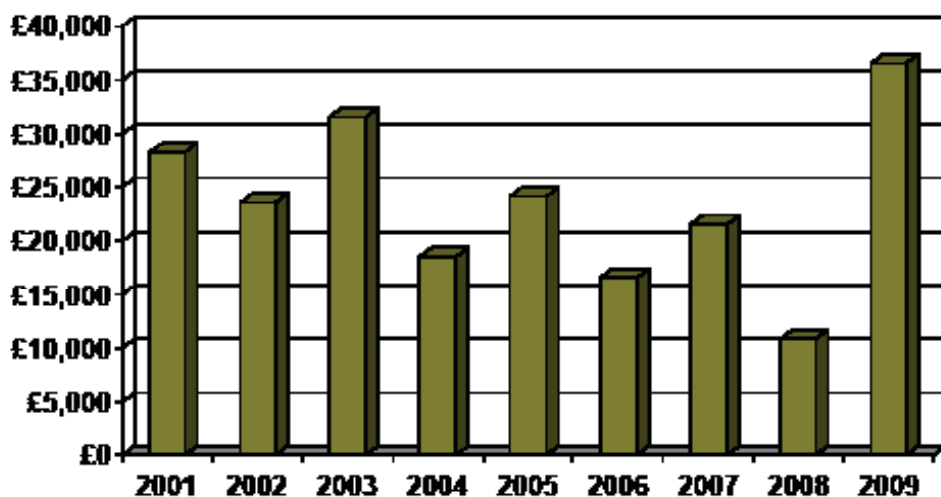
Towards this goal, we seek to develop even better inhibitors and understand more adequately the functioning of the mutant gene. This will be performed in structural genomics and biochemical laboratories within the University of Oxford that specialise in the study of the structure of proteins and cell signalling mechanisms, and by fostering future collaborative research with international colleagues. The aims will be to determine the precise chemical structures of the normal and wild type proteins produced and to see how the resultant activities may be effectively controlled. We will also undertake research on the altered cell signalling pathways in FOP-affected tissues.

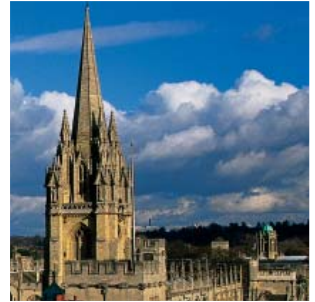
For this, we are grateful for funds that are being raised by patients and friends through the newly created body, FOP ACTION UK, which supports FOP research at the University of Oxford. With these funds, we will soon be appointing two postdoctoral scientists to push the research forward as soon as feasible financially. These researchers will work on the two major aspects: protein structure and control of cell signalling by the mutant receptors. This will create a unique and effective core Oxford team focussed on future research into FOP to help patients in both the UK and around the world. The major aim within this context is to discover the means to halt the progress of the debilitating bone deposits in affected patients without affecting the normal functioning of the skeleton. In all aspects of this work, as in the past, close collaboration with international FOP research laboratories and scientists worldwide, together with close interaction with the patients and families involved, will continue to be central to our success.



Income from donations

Below is a chart showing annual donations to FOP research at the University of Oxford since 2001. The majority of our donations are from patients, families and friends, many of whom are fundraising on our behalf. Without this generous support, FOP research at Oxford would not be possible.





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