FOP Research Update 2024

From the
University of Oxford Research Team

Meet the team!

Monies raised by FOP Friends and a Simcox Family Scholarship have been supporting the new dynamic research team trio of Julien, Will and Carrie (pictured). The team is supervised by longstanding FOP scientists Professor Alex Bullock and Dr Ellie Williams at the Centre for Medicines Discovery at the University of Oxford.

Julien (pictured left) says, " I moved from France to Oxford in August 2022 after finishing a PhD in structural biology and drug discovery. My research aims to identify and characterise potential drug compounds for FOP, including how they stop the unwanted activity of the FOP-causative protein ACVR1. In my spare time I enjoy reading and playing friends at chess."

Will (pictured centre) tells us, "I grew up in Devon with three brothers. My family lives on the edge of North Dartmoor, a very beautiful national park with a lot of open spaces where our two mad spaniels love to go running. Growing up there had a big effect on me and is most likely why I am still happiest when I'm outside in wild places. In my spare time, I enjoy reading, biking and have published several articles about climbing in the Alps. I obtained a degree in biochemistry at the University of Oxford before joining the FOP team as a PhD student in October 2022. In my research, I use complementary structural, biophysical and cell biology methods to study ACVR1 and the wider family of receptor kinases to which it belongs. These proteins are fascinating to me and it is important for FOP research to understand how they work, how genetic variants in FOP patients alter this function to cause unwanted bone and how this can be controlled by drug molecules. The ultimate purpose of my research is to speed up the discovery of medicines to treat FOP."

Carrie (pictured right) explains, "I studied molecular biology and biotechnology at the beautiful Hong Kong University of Science Technology where I obtained my PhD. I joined the Oxford FOP team in October 2022. My most recent work has involved helping clinicians diagnose new potential cases of FOP by testing novel genetic variants in ACVR1 for FOP-like behaviour in human cells. I am also interested in developing cell-based detection tools for identifying new treatments for FOP. Finally, I enjoy painting as a hobby".

Update on the STOPFOP clinical trial for FOP

Alex continues to participate weekly in the management of the STOPFOP phase 2A clinical trial, which is testing the AstraZeneca drug "saracatinib" for the treatment of FOP. Recruitment is now completed and the trial is progressing as hoped. The STOPFOP trial differs from other clinical trials because it is designed and run by University academics rather than the pharmaceutical industry. It was initially funded by an academic grant from the EU. Alex and the STOPFOP team have just secured further philanthropic funding to cover the extra costs incurred due to delays arising from the COVID pandemic (official announcement to follow).

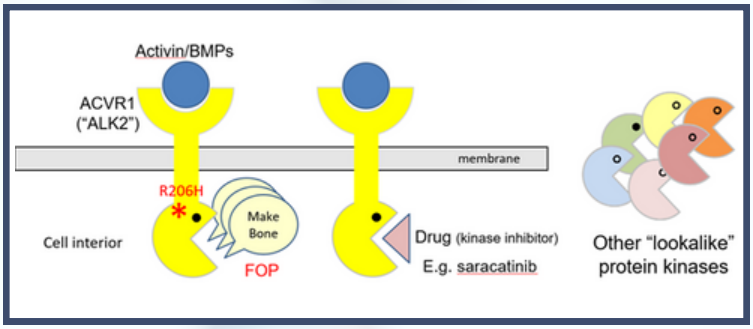
The trial adopts the gold standard "double-blind" approach, which means for the duration of the trial, the identity of which patients are initially assigned to a drug or placebo group is hidden.

This prevents the trial team members from introducing bias towards the outcome they want to make it as fair and rigorous as possible. Unfortunately, this also means that we have to wait through 2024 for the final results. Our fingers and toes are crossed for good luck.

Could other approved drugs be a treatment for FOP?

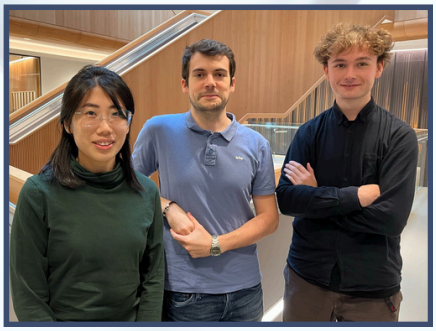
The FOP gene ACVR1 carries the genetic instructions to make a protein which we call the ACVR1 protein, or sometimes ALK2. FOP results from this protein being hyperactive. Scientifically, we classify genes and their protein products into families in which family members have similar 3D structures and functions. The FOP-causative protein ACVR1 belongs to the "protein kinase" family (this family stamps other proteins with phosphate to pass on messages, such as the message in FOP to make bone). Our STOPFOP clinical trial drug saracatinib is a type of drug called a kinase inhibitor that blocks this messaging activity. About 100 drugs of this type have been approved to date, making this type of drug both one of the most studied and most successful. Nearly all drugs are developed to work on one protein linked to one disease. However, they often struggle to distinguish this intended protein from others that are close family members (which appear as protein "lookalikes"). Sometimes this drug promiscuity can provide extra treatment benefit, but it can also sometimes introduce unwanted side effects. Therefore, much research focuses on these types of promiscuity analyses.

In the past year, this lookalike effect has suggested two newly approved drugs of potential relevance for ACVR1 and FOP. These drugs are called momelotinib and pacritinib, respectively. Both have been approved by the US Food and Drug Administration for the treatment of myelofibrosis, a rare form of blood cancer. This cancer is linked to the excessive activity of a protein kinase called JAK2. The drugs momelotinib and pacritinib were therefore developed to block the activity of the JAK2 protein. Recently, the respective drug manufacturers GSK and CTI BioPharma reported that these drugs also blocked the activity of the ACVR1 protein kinase as a lookalike effect. Furthermore, they concluded that blocking ACVR1 activity was beneficial as it reduced the anaemia side effect commonly observed with myelofibrosis.



This raises the question of whether these approved drugs could be used to block the hyperactive ACVR1 protein in FOP and therefore be of benefit to patients. One big concern is that these newly approved medicines may induce more unpleasant side effects than currently tested drugs and be rather toxic for long-term treatment of FOP.

Learning more about these approved drugs would be beneficial to make judgement on risk/benefit. We have now determined precisely how these drugs stick to the ACVR1 protein and measured how strongly they block its activity compared to other kinase inhibitors in clinical trials such as saracatinib. PhD student Will comments, "I have really enjoyed testing these medicines on cells and seeing their dramatic effects. They work in a very similar way to saracatinib, the drug that our group identified several years ago and that is now being tested in the STOPFOP clinical trial. It is important to find but if medicines that already exist could help FOP patients. They may be able to provide much needed treatment options for patients and I find that really motivating."

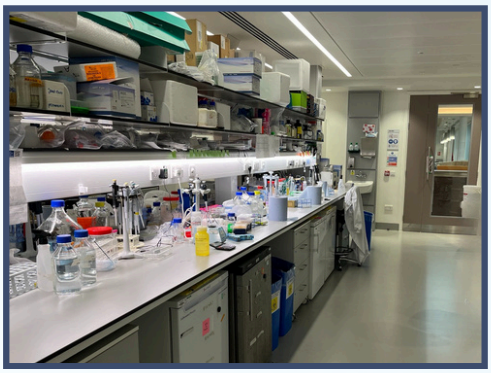


Our work shows that pacritinib blocks ACVR1 more strongly than momelotinib, but both are notably weaker than currently tested drugs like saracatinib. This is consistent with reports from the drug manufacturers. It seems they overcome the weaker activity by giving patients higher drug doses. If not a potential long-term

treatment, the use of these approved medicines could also be assessed and discussed as an option for short-term use, perhaps to enable interventions such as emergency dentistry without the surgical trauma inducing unwanted bone. Thus, we next aim to have momelotinib and pacritinib tested in the FOP mouse model to further scrutinise their value.

Towards a future with a more affordable drug for FOP

Drugs developed for rare diseases can be extraordinarily expensive. We have been collaborating with a project funded by a not-for-profit charitable Trust fund, organised under the banner of "M4KPharma" (Meds4Kids). They aim to develop an affordable drug for the ACVR1 protein that simply recovers costs rather than maximum profit.



Our latest published work with them involved a collaboration with chemists at the University of Toronto and reported further progress towards achieving this long-term goal. There are two key points of interest for this new drug design series. First, if drugs are flexible in shape they can adapt to fit the shape of a protein they need to stick to, such as ACVR1. This can be useful in early drug design work. However, a flexible drug is more likely to adapt to fit other unintended proteins too making them promiscuous which increases the risk of drug side effects. In our collaboration, the goal was to make the structure of the current drug prototype more "rigid", fixing it in the precise conformation that fits the shape of the ACVR1 protein. Our X-ray crystallography experiments showed that the design was successful. A rigid drug also has the benefit of sticking to its intended protein more tightly and we were able to measure this effect too.

Secondly, the Meds4Kids team are designing their future drug to be able to cross over the blood-brain barrier to enable its potential future use in both FOP and childhood brain tumours such as diffuse midline glioma (both conditions have the same ACVR1 genetic variants and overactive protein). The team are just planning the next steps for development towards a drug suitable for testing in clinical trials. The recent work was published in the Journal of Medicinal Chemistry and is available here: www.ncbi.nlm.nih.gov/pmc/articles/PMC10983009/

Helping clinicians with FOP diagnosis

Our recent work has also involved helping clinicians with diagnoses of uncertain FOP cases. Genetic analyses in Oxford have revealed a new variant of the ACVR1 gene that has not been seen in FOP before.

In response to the clinical referral, we further characterised the functional significance of this novel ACVR1 alteration. Akin to other known variants of ACVR1, such as the classic R206H, this novel ACVR1 variant exhibited evidence of hyperactivity (as evidenced by its activity in human cells exposed to the growth factor Activin A and by it sticking less to the inhibitor protein, FKBP12). Our results confirmed the likely clinical importance of this ACVR1 variation for FOP diagnosis. We hope to publish these findings in the near future.

The Oxford team greatly appreciates the FOP Friends community for their support and looks forward to further explaining their recent work with everybody in Manchester at the FOP Family Gathering 2024.

Photo: FOP Families meeting the Oxford Team, November 2022