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Autumn Report from the University of Oxford FOP Research Team

Research News

This summer we had the pleasure to welcome a Masters student, Miss Elise Riesebos, to the University of Oxford FOP Research Team for a 6 month internship (Figure 1). Elise's visit was funded through the Erasmus scheme and generously arranged by Professor Gerard Pals, a member of the European FOP consortium at the VU University Amsterdam.

Figure 1. Our visiting student Elise Riesebos.

Elise worked under the supervision of our postdoctoral researcher Ellie to study the proteins that the body makes naturally to regulate bone formation. The DNA of the FOP-causative gene *ACVR1* comprises 1527 nucleotide units ("letters A/T/G/C") that encode for the ACVR1 protein, also known as ALK2. In FOP, the letter "G" at position 617 out of 1527 is typically replaced by the letter "A" creating a faulty code for making the ACVR1 protein. This single mistake is sufficient to yield an ACVR1 protein that doesn't switch itself off properly. Instead,

it continuously sends out weak signals for the body to make more unwanted bone. We have previously drawn an analogy to a “Jack in the Box” that doesn’t close properly (Figure 2A, right). There are, however, mechanisms to counter this effect to force the box closed. The first way is to place a large weight on the lid to stop it from opening (Figure 2A, left). In fact, the human body uses the FKBP12 protein for this strategy. FKBP12 sits atop the catalytic part of the ACVR1 protein and stops it from functioning. Interestingly, FKBP12 is just one of a number of FKBP family proteins in humans. Therefore, we wondered whether other FKBP family members might also provide the perfect shape match to sit atop ACVR1. Elise’s investigations revealed that the close relative FKBP12.6 could indeed bind ACVR1 and Ellie was able to solve the 3D structure of this ACVR1/FKBP12.6 complex (Figure 2B).

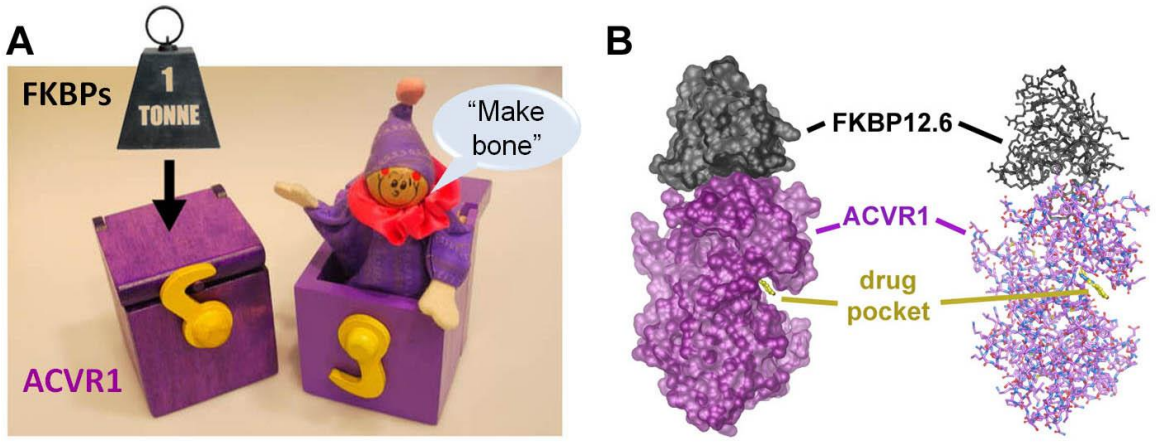

Figure 2. Mechanisms to control leaky ACVR1 activation in FOP. (A) ACVR1 has on and off states similar to a Jack in the Box. Some FKBP12 family proteins sit on top of the ACVR1 “lid” to stop it opening inappropriately. (B) Ellie’s structure of the ACVR1/FKBP12.6 complex. The prototype drug molecule “dorsomorphin” was included in the drug pocket. A solid surface representation is shown on the left and an all atom representation on the right.

Unfortunately, the binding of FKBP12 family proteins to the faulty ACVR1 protein is weakened and insufficient to stop the ectopic bone formation found in FOP. We therefore hope to intervene using a second approach aimed at blocking the activity mechanism itself (similar to forcing the closure of the yellow latch on the front of the Jack in the Box, Figure 2A). To do this, we aim to find highly specific drug molecules that will plug the mouth of the ACVR1 protein (the drug pocket, Figure 2B) and stop its messages to make bone.

We have previously mapped precisely how prototype drug molecules like dorsomorphin bind to ACVR1 and described a more selective molecule K02288. In collaboration with Paul Yu (Harvard) and Greg Cuny (Texas) we are continuing to explore how these molecules may be modified to make them more “drug-like”. We must aim for highly selective small molecule inhibitors that can be applied without signs of toxicity. We hope to provide an update on this work in our next report.

Other team news

We have two other happy items of news. Firstly, we would like to congratulate our team member George on the birth of her baby boy “Donnie”. Secondly, we would like to congratulate our student Caroline on the submission of her doctoral thesis (Figure 3).

Figure 3. Our student Caroline pictured submitting her doctoral thesis.

Final words

We must express our gratitude to everyone at FOP Action as well as FOP France for their continued support. We must also thank the University of Oxford and especially the SGC for hosting us in their superb laboratories. These facilities have now expanded with the opening of the new Li Ka Shing Centre for Health Information and Discovery (Figure 4A). This is a new initiative supported by the Li Ka Shing Foundation to advance drug discovery for novel diseases. The opening was attended by the Prime Minister David Cameron and other dignitaries who also had the opportunity to visit our own laboratory at the neighbouring SGC (Figure 4B). Finally, we wish everyone a safe and pleasant Christmas and look forward to meeting you all next year at the FOP Family Gathering in Manchester.

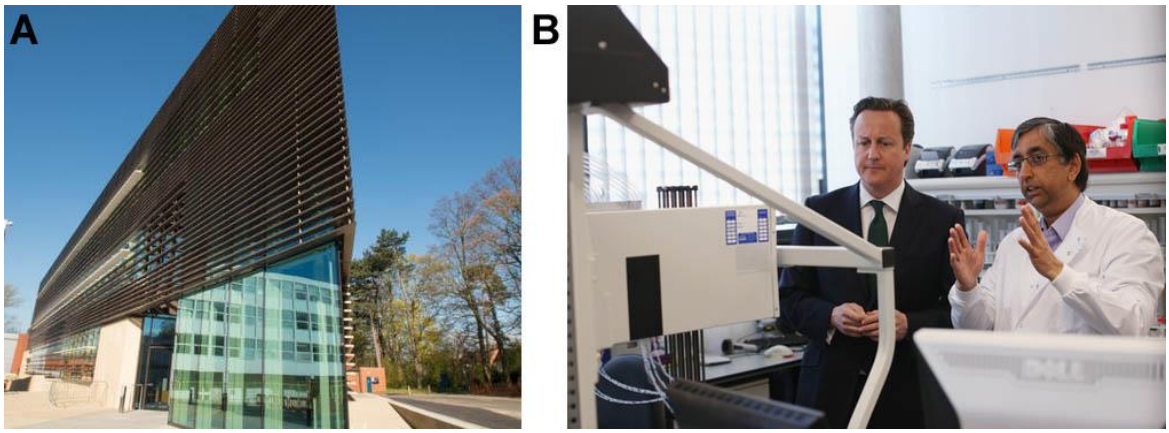

Figure 4. The Oxford laboratories. (A) The new Li Ka Shing Centre. (B) David Cameron tours the laboratories of the SGC.

Sincerely

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University of Oxford FOP Research Team

(From left to right): Dr Alex Bullock (SGC), Miss Caroline Sanvitale (University of Oxford FOP Research Fund DPhil student), Dr Ellie Williams (Roemex postdoctoral fellow), Dr George Kerr (Roemex postdoctoral fellow), Prof Jim Triffitt (Botnar Research Centre).