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Dear all,

As many of you would know, there was a meeting in Buxton 10 days ago focussing on the so-called "PI3K/PTEN pathway". In academic circles, this term used to describe a molecular circuitry that is present in all our cells. PIK3CA, which you are all familiar with, is the gene that tells the cell how to make the PI3K component of this circuit, and it is critical for growth and survival in humans. In an individual with PROS, some (not all!) cells will have an altered PIK3CA gene, which leads to the production of a more active PI3K and therefore excessive growth. Think about it like the accelerator of a car that is stuck down most of the time in cells with an altered PIK3CA gene.

There is another molecule in our cells, known as PTEN. This is the brake in the PI3K pathway. In individuals with an altered version of the PTEN gene, the brake is broken and leads to disorders with similarities to PROS. Nevertheless, PTEN-associated disorders are distinct from PROS in key respects – for instance, they come with a high risk of cancer which is not the case in PROS; they are also passed on from parent to child. PTEN disorders are collectively referred to as the PTEN Hamartoma Tumour Syndrome (PHTS).

Both PIK3CA and PTEN are often altered in adult cancers. There is therefore enormous interest in the development of therapeutics that target PIK3CA and PTEN, particularly in oncology. These efforts are starting to benefit individuals suffering from PHTS and PROS. Some of you may have taken part in a sirolimus drug trial run by Professor Semple and colleagues in France and the U.S. The results of this trial have been published (Parker *et al.* 2018 Genetics in Medicine) and were discussed at the PI3K/PTEN meeting by Dr Pierre Vabres. The conclusion of this trial was that a low dose of sirolimus led to modest improvements in overgrowth in some patients but not in others.

Sirolimus is not necessarily the best option for PROS, however, because it does not switch off the PI3K enzyme itself. The hope is that a more targeted approach may yield better results. This has led to another registered trial (TOTEM) in France; this time of a drug known as Taselisib (or GDC-0032) which acts by switching the PI3K enzyme off. Unfortunately, Dr Vabres reported that the trial had to be discontinued due to severe adverse effects of the drug in some participants. Recently, at a hospital in France, some patients with PROS were given a low dose of a third drug, known as Alpelisib (or BYL719), which led to remarkable improvements in several individuals (Venot *et al.* 2019 Nature). While this is encouraging, Dr Vabres emphasised need for caution at this stage. Alpelisib was given on compassionate basis and has yet to be assessed in a formal clinical trial to ensure that the drug is indeed safe to take. This is critical for a disorder like PROS which is likely to require life-long drug administration. Dr Vabres shared some of his experience with Alpelisib in his own clinic – he cautioned that overgrowth reduction is only modest in some patients, which suggests that more research and testing is needed before Alpelisib can be considered standard-of-care for PROS. The drug is imminently expected to undergo formal testing in PROS patients as part of a registered clinical trial. The trial will be driven by the drug company (Novartis) which makes Alpelisib and will involve many hospitals across several countries, likely including the UK.

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Why is it so difficult to find a good treatment solution for PROS? You may know that the change in the PIK3CA gene arises by chance at some point during early development (most likely during the first 3 months following conception). Therefore, the disease path depends on exactly when and in which cell type/tissue this alteration took place. Some individuals with PROS may only have one enlarged finger, whereas others experience brain enlargement or malformed blood vessels. This presents clinicians with a substantial challenge – every patient is different, particularly so when it comes to PROS, and treatment may have to be tailored according to the specific type of overgrowth. This is all work in progress, and it will take some time before scientists and doctors know enough to say with some certainty what the optimal treatment may be.

Beyond drug development and nitty-gritty academic talks, the PI3K/PTEN meeting in Buxton was the first Biochemical Society meeting that featured presentations from patients. James Vincent, a PROS patient, gave a touching account of his life with PROS, allowing scientists to really feel the need for continued progress in this area. It was very inspiring. Kristin Anthony, a PHTS patient and founder of the PTEN Foundation in the U.S. told us about the Foundation's support for new scientific initiatives that are aimed at improving life for patients with PHTS. I would encourage the PROS patient support group to exchange experiences with the PTEN networks – in the States (<https://ptenfoundation.org/>) as well as in the UK (<https://ptenuki.org/>) – when it comes to organisation of new initiatives, be it away-days or the establishment of a formal PROS network.

The take-home message from all this is that there are reasons for optimism and hope, yet patience and caution are necessary, too. The PI3K/PTEN meeting featured a lot of excellent science, and there is no doubt that all the hard work will eventually pay off. Until then, it is important for patients, scientists and clinicians to remain in close dialogue. We all learn from one-another, and it is both an inspiration and an honour for scientists to meet the people they want to help through their research.