NEWSLETTER

Genetic Overgrowth PI3K Support

www.gopi3ks.com

December 2019

Welcome to the newsletter for GoPI3Ks – Genetic Overgrowth PI3K Support. Here we will keep you informed of the current research, fundraising and stories from overgrowth patients.

Research update:

Firstly from By Dr Ralitsa Madsen (UCL Cancer Institute, London, UK)

Dear GoPI3Ks community,

Somehow – and somewhat too fast for my taste – another year has passed, and the time has once again come for my annual contribution to the GoPI3Ks Christmas Newsletter. This is also the first time that this Newsletter will be shared with the CLOVES community in the U.S., and I hope it will be informative for all parties.

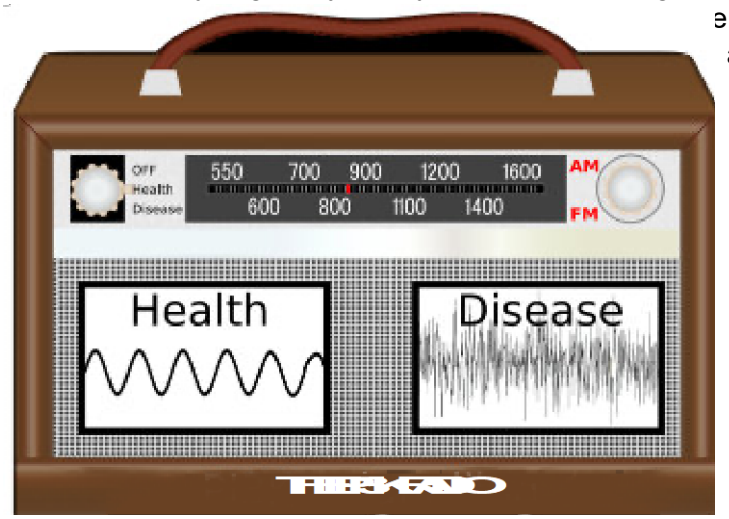
To start with some generic news, I have now joined the research group of Prof Bart Vanhaesebroeck at University College London. This is a natural move for someone at my career stage – transitioning from being a PhD student to becoming a so-called postdoc. That said, I still retain a close connection to Prof Robert Semple, and my future work will almost certainly feature his input in one way or another.

A few words about Prof Bart Vanhaesebroeck (next to me in the photo on the right) and his group before I get into the details of my upcoming research and how it relates to PROS. Bart is a world-renowned expert in cancer research, with a specific focus on the so-called PI3K signalling pathway. This is the molecular circuit that becomes dysfunctional in PROS and in a lot of human cancers due to a 'spelling mistake' (or mutation) in a gene known as PIK3CA. By genetically engineering laboratory mice, Bart's group has contributed several key disease model systems of both cancer and PROS. With a strong focus on drug development, the group's work has also resulted in the development of pharmacological therapies for specific cancers.

By joining Bart's group, I am in the fortunate position to tap into the wide range of resources and knowledge that his team has established over the years – an ideal combination for my 4-year PI3K research vision. I am personally very excited at this opportunity because it will allow me to pursue novel research questions, some of which are of particular relevance to PROS. Indeed, I remain firmly committed to understanding molecular aspects of PROS diseases; only when we understand these mechanisms can we be certain that effective therapies will eventually become the norm for all patients.

From 'white noise' to music: repairing the broken PI3K radio

While typing away on my computer on a flight back home earlier this year, the person e got interested in my work and asked about my research area (the disease terms on my screen gave my discipline away!). As it happened, I ended up telling him about my future research vision instead. To explain it in lay terms, I showed him the picture of my so-called 'PI3K radio'. I told him that there are individuals in whom the radio doesn't play music – instead, all you hear is 'white' noise. In other words, the radio is out of tune. This analogy can be used to describe the state of cells in a patient with a PIK3CA flaw. A functional PIK3CA is required for the cells to execute their normal functions, yet in PROS patients, a defective PIK3CA is bringing the system out of balance. Similar to a broken radio, the cells are out of tune with their environment and misinterpret the signals they receive. For example, whereas a normal cell would stop growing in the absence of nutrients, cells with defective PIK3CA grow unabated, giving rise to the characteristic overgrowth in individuals with PROS.



So far so good. I then told my neighbour that many pharmaceutical companies and academics are keen on fixing the broken radio, especially because of its importance in cancer. What has their 'fixing' strategy been so far? To simply switch PIK3CA off. BYL719 or Alpelisib, which many of you would know about, works like that. It enters the cell and switches both its normal and its defective PIK3CA off. Supported by recent clinical reports, this approach is not necessarily wrong – at least when it comes to PROS, it has proven effective in a small number of patients treated on a compassionate basis. However, we also know that in cancer, simply switching PIK3CA off does not confer long-term disease stabilisation, i.e. it is not a cure. In PROS, a question that remains unanswered is whether simply switching PIK3CA off will be sufficient to reverse developmental abnormalities such vascular malformations which affect a substantial proportion of patients. This, I said to my neighbour, is where my future research comes in.

To me, simply switching PIK3CA off corresponds to turning the radio off – while the annoying 'white noise' may have stopped, the radio still does not play the music I want to hear. To learn how to fix it, I propose to take a different approach inspired by the question: what would an engineer do? Rather than studying each component of the radio separately, as most conventional biologists do when they study cells, the engineer would study *the system of components* and how they are *wired* to one another. Analogously, my research on PI3K in the next four years will focus on the system – all the different cell components that are linked to PIK3CA – and how it functions as a unit. To achieve this, I will collaborate with mathematicians and computational scientists who will teach me how to analyse new types of experimental data that can be used to predict optimal therapeutic strategies for cells with PIK3CA defects.

This is **not** a trivial task. Biological systems feature a bewildering complexity. Although many PROS patients share the same type of PIK3CA defect, they do not necessarily share its location. Different tissues – and therefore different cells – may be affected. Each one of these represents a slightly different radio design, with slightly different

wiring. Each one will play a slightly different tune. Eventually, I want to understand them all to be able to predict optimal treatment strategies that are tailored to a patient's specific disease. For a start, however, I will have to restrict myself to two particular cell types – one of which corresponds to the cells that line the blood vessels in PROS patients with vascular malformations.

Even with two cell types to study, this research will take time and cost a lot of money. Thus, my Christmas wish this year is to obtain the funding that I am currently applying for to support my work. Beyond money, the remaining success ingredients are patience and perseverance. With those in place, I am confident that the *systems* approach will eventually get us to a point where each PROS individual's PIK3CA radio plays the right tune again.

By Dr Ralitsa Madsen (UCL Cancer Institute, London, UK)

Update on PROS Treatment from Professor Semple:

8 years ago we had no idea what the cause of the range of types of overgrowth we now call PROS was, and no-one had clearly linked them all together. So the fact that we now know the underlying gene change, the fact that people are increasingly linked together, the fact that the scientific world now has name for these problems and something to research (see the exciting plans that Ralitsa now has to pursue this in Bart Vanhaesebroeck's lab, one of the leading PIK3CA labs in the world), and the fact that new medical treatments are now on the doorstep is fantastic progress. Having said that, I know how frustrating the delays involved in actually having treatments available to doctors to prescribe can be. These delays are well meaning, and are what produce safe and effective medicines in the end, but I thought it would be useful to give my view of where we are at present.

First of all, it remains very important that everyone who might have PROS gets a proper diagnosis, including a gene test if they wish. We have now moved on from these being done in a research study, because testing in the NHS is available, and should be findable by specialists (I'm happy to help point them the right way if not). It is also important that affected people and their doctors are able to find out about new treatments or new trials that might be available to consider. Receiving this newsletter means that you are already in a network, but we should all think about any other ways we can to get the word out when opportunity arises. On my side, I'll send word out through our contacts from the former Cambridge study, and via the RUDY study as it grows. We are still aiming to set up RUDY to be much more tailored to PROS, but as usual, this involves money that we are trying to find.

Second, some people may benefit from a trial of medical treatment. Already available to doctors who are happy to take responsibility for prescribing is sirolimus, which several will be on or have tried. No trials have yet been done of sirolimus compared to a placebo, which would be the strongest evidence for it use, but our own study, and stories we hear from doctors around the world, suggest that it can sometimes be of benefit. This seems very variable, however, and while some report useful changes in their condition, many others don't. In our study we also observed some side effects of sirolimus. So, all in all, it is

something to consider with your doctor, but not something to rush into. Anyone who starts sirolimus should have agreed with their doctor in advance exactly how they will decide if the medicine is working, should have discussed the possible side effects, which are well known, and should stop after a reasonable period of there is no sign of benefit.

Most exciting is a medicine called alpelisib, made by the company Novartis, which directly targets the PIK3CA gene. This caused a lot of excitement in France where its use in an unregistered study was reported to show benefits in a range of people with PROS, especially those most severely affected. This was not a formal clinical trial, and everyone agrees that such trials are now urgently required to allow us properly to weigh up the risks and benefits of treatment. However because the preliminary results were so encouraging Novartis has set up a process which means that doctors can apply to them on behalf of their patients as part of a so-called "Managed Access" programme to try the medicine. Details aimed at doctors can be found at https://clinicaltrials.gov/ct2/show/NCT04085653. This scheme is intended to help people with the most severe problems, and the latest information I have is that around 70 patients around the world have received the medicine through this route. We don't yet have information about the outcomes, but reports I have heard from individual doctors suggests that it does at least sometimes have useful effects. It is not free of side effects (for example it may cause or worsen diabetes), but these have not been very common or severe to my knowledge to date (but this is based only on individual small scale discussions and is NOT the same as having a formal assessment). Anyone who is severely affected may wish to make sure that their doctor is aware of the possibility of gaining access to alpelisib, and should discuss whether this might be appropriate.

Novartis are also working towards designing an international clinical trial so the benefits and risks of alpelisib can properly be assessed. This is a major, complex and expensive project, and so really needs to be led by an interested company, so I'm delighted that this is being done. We in the medical research community are eagerly waiting to hear more about how exactly the trial will be run, who will be eligible, and where the study centres will be. I shall of course pass this information on as soon as available.

Alpelisib is not the "only show in town" as a possible new treatment, as other companies are also interested. One company is ArQule in the USA, who make a different medicine - miransertib - which targets growth in PROS. In fact some may have heard Brian Schwartz from ArQule talk about this in 2018 at the PROS gathering at Heathrow co-organised by Mandy. Some press details about an ongoing clinical trial of miransertib in PROS and Proteus syndrome can be found here:

http://investors.arqule.com/news-releases/news-release-details/arqule-announces-first-patient-dosed-registrational-mosiac-trial. Having different companies trying to develop different medicines to target PROS is very good news for patients – competition between them will help produce the best medicines as quickly as possible. Again, we shall pass on any important new information as soon as we hear it.

So, there is lots of energy being invested, and signs of major encouragement for the (hopefully near) future, but lots of effort is still needed to make sure only safe and effective medicines eventually become widely available. On that note of optimism, I wish everyone a happy festive season and a great 2020!

FUNDRAISING & AWEARENESS

As always a big **THANK YOU** to everyone who has helped, whether this be by running fundraisers, donating & raising awareness of GoPI3Ks & PROS. You continued help & support really makes a difference.

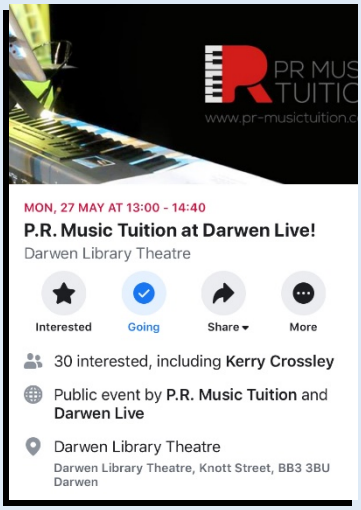
In February 2019 I (Mandy) decided to run a fundraiser for my birthday. So instead of receiving gifts, I raffled two £20 Vue cinema vouchers & asked people to donate to GoPI3Ks the charity. This was done via social media & word of mouth. A fabulous amount of **£720** was raised & 2 happy people enjoyed their cinema visit.

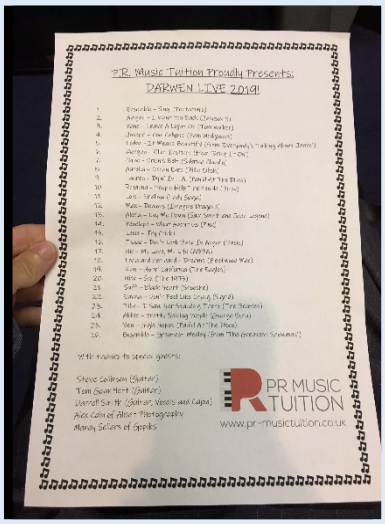
Also in February we received an extremely generous donation of **£450** from Sue Rowlands

"As far as we're concerned, *dis*ability means *possibility*."

In May I was lucky enough to be invited by my friend Rachel Toner who runs P.R Music Tuition to attend the Darwen Live music festival. Here her students spent an afternoon performing various songs. I was able to have the chance to address the audience to tell them about PROS & GoPI3Ks, also to be able to hand out GoPI3Ks leaflets.

We were also able to raise a wonderful **£136.11** for GoPI3Ks.

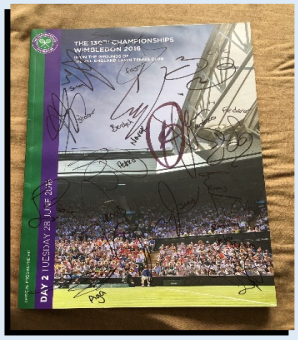


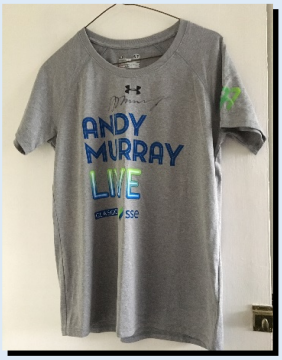


In May we ran an online auction to sell some items that had been kindly donated from one of Madonna's tours. We had a tour hoodie & a tour cap. We raised **£51.99** for these two items.

Following a grant application to St James' Place (thanks to Kerry Hockaday for the introduction) GoPI3Ks were given a grant for **£1,000**. Here is Kerry & Amelia with Our cheque.

An online auction in July raised **£122** by auctioning two kindly donated tennis items. We had an official Wimbledon program signed by such tennis stars as Federer, Novak, Venus Williams & more. We also had a t-shirt signed by Andy Murray from his appearance at the SSE in Glasgow.





FUNDRAISING HOW YOU CAN HELP

You can help raise funds for GoPI3Ks by simply shopping online with Go Raise. Click on the link: www.goraise.co.uk/gopi3ks-genetic-overgrowth-pi3k-support & follow the instructions provided. Thank you ☺

SHOP AND EARN DONATIONS FOR FREE

Join GoRaise

Click on Join to add a few details and start supporting us

Go shopping!

Search on GoRaise for the retailer or product that you want, and click out. It's that easy.

Raise money for free

Shop as normal and the retailer donates a portion of your spend to us. You don't pay a penny extra.

Join

HOW GoPI3Ks HAS HELPED

We were also able to help one of our members with purchasing footwear, shoes & socks from the USA as they are unable to get the size they need in the UK to fit their overgrowth.

In February we were contacted by our member Margaret who had been struggling with her old electric wheelchair that wasn't working well at all. We were happy to be able to supply her with a brand new electric wheelchair, Margaret was happy to for us to share photos of her using her new chair.

As 2019 draws to a close, the GoPI3Ks team would like to wish you all a very MERRY CHRISTMAS & wonderful New Year. xx

NEXT YEAR

As always we will continue to spread the word about PROS & GoPI3Ks.

To raise funds & help our PROS members with items / equipment that will improve the quality of their life.

Also as we hear anything more about PROS research and drug trials we will pass this on to you.

Hopefully 2020 will be a good year for us all & we will get closer to finding medication that works to improve the lives of those of us living with PROS.