GoPI3Ks Family Weekend – Scientific summary

**Disclaimer**

*This summary was written by Koen Nijbroek and is not scientifically verified. It contains the highlights of the scientific part and may contain personal views and interpretations.*

**10.30 – 11.00 Professor Rob Semple, overview of PROS**

\* In Mandy’s case; H1047L in her leg (heterozygous/mosaic).

\* Mosaicism is a common thing, around in nature everywhere.

\* We don’t know:

* What explains the selective pattern of abnormal growth
* Which cells are affected
* When growth is changed and when it is harmful
* Whether/how affected cells influence neighbors
* Which problems are reversible
* The best way to design drug trial

\* Sirolimus does a little bit of good (trials), but mild/significant side effects may occur.

\* Taselisib hits the PIK3CA gene itself, but study had to be stopped due to nasty side effects caused by a related gene causing problems in the immune system.

\* In 2023 results published by Dr. Canaud and can now be used in the US. Follow-up study is underway.

**11.30 – 11.50 Dr Ralitsa Madsen – PI3K Research Update**

\* Researchers community; PIK3CA Roundtable (share before it’s out in the public domain).

\* 8-11-23; preliminary results of European multicentric phase III (sirolimus) slow-flow VMs.

\* 16-11-23; FDA approves capivasertib with fulvestrant for breast cancer (not yet PROS – could be?).

\* You need to tweak the PI3K pathway, you cannot turn it off completely because of all the good things it does, too.

\* Madsen lab; focuses on the signals of the PI3K pathway with the goal ‘to turn it back to normal’.

* PIK3CA variant causes signal misinterpretation, like a ‘blurred vision’.
* Systematic mapping of the PI3K code across contexts (work to be started).
  + Different cell types
  + More signals
  + Different mutations (now: H1047R)
* Predictive computational models.

\* Wilms Tumor only found in kidney related PROS. No higher chances of cancer (Rob Semple).

\* The PIK3ca affected tissues are usually not prone to cancer compared to PTEN eg.

**12.00 – 12.30 Zubyda Azzam from Rare Minds – Mental Health and living with PROS**

\* Service Provision

\* Training & Support

\* Research & Awareness

\* There is no health without your mental health. You cannot pull them apart.

\* Notice feelings, don’t push them away (they will come back).

\* You can control how you behave; not how other people behave.

**14:30 – 14:50 Professor Pierre Vabres – The management of PROS**

\* PROS is like the ‘Blind man and the elephant’ story, in various aspects.

\* Due to the overlap in cancers, there is a variety of drugs out there applicable for PROS.

\* It is not that straightforward to move drugs developed for cancers to PROS (e.g.) as primary outcome, secondary outcome et cetera are completely different. Treatment times and drug dosages are also completely different.

\* From the phase II sirolimus study; definite improvement in pain.

\* From the PERFORMUS trial: volume not much changed, improvement in pain reduction / QoL.

\* Quite a high number of adverse events observed in their own studies.

\* Few results (not trial) from patients treated with Alpelisib:

* Patient 1: small decrease of lesion, after 3-6 months: no further improvement.
* Patient 2: no response in terms of volume, no real improvement.

\* TOTEM: Trial of Taselisib in Overgrowth: assess safety of the drug (30 patients).

* The trial stopped after only 16 patients, due to severe adverse side effects.

\* SESAM? Trial: Alpelisib in MCAP.

\* General issue: risk of cancer in PROS. Theoretically it could be a predisposition.

* Retro perspective study: low risk in PROS throughout life.
* In study of literature: cases of Wilms tumor (although in PROS very low, <5%).
* Other individual cases observed, unclear if related to PROS, no evidence.

\* Re-analysis of patients with PROS, half of them were PIK3CA+, half PIK3CA- (PIK3R1+ mutations observed in 15 patients). PIK3R1 may cause KTS-type overgrowth.

**15:30 – 16:00 Doctors’ discussion panel (on the spot audience questions not noted down)**

**Question about the occurrence of double mutations.**

\* Pierre: In a large panel of various diseases; extremely low frequency observed. Their effect is not yet known whatsoever – as well as how they occur. Rob comments on that as well, also observed in a very low frequency. It seems that it’s not shared among the whole area. Also, Sahar reacts that they observed a few.

**Question about occurrence in prevalence of twins.**

\* The general consensus is that no correlation has been observed.

**Drug trials for children with segmental overgrowth syndromes?**

\* This was covered in the talks.

**Pulled application of Alpelisib in Europe – and resubmission. Any further information on the long-term outcome?**

\* Rob: No, it’s not completely surprising. It’s a very large trial and they are slightly adjusting it, taking some of the learnings. Manaasa: agrees with Rob’s view. Approval systems differ slightly between UK/US. There is no extra information.

**Sahar mentions that there’s already options available that does something already – we shouldn’t forget about that as well.**

**16:00 – 16:20 Doctor Maanasa Polubothu – RDCN Improving the patient pathway for PROS**

\* Genetic diagnosis of 600 patients.

\* Overarching aims;

* To increase knowledge and understanding of mosaic disorders.
* To progress research.
* To improve patient experience.

\* Specific aims;

* To reduce the mean time to first seeing a specialist.
* To reduce the number of trips to the specialist centre.
* To improve access to accurate clinical and genetic diagnosis.
* To improve the transition from pediatric to adult services, and to provide new adult access to specialist opinion.
* To improve coordination of care between the RDCN and local hospitals.

\* Opened an adult clinic, reduce mean referral age.

\* They’re seeing skin diseases + vascular conditions.

* Improve speed of access to MDT specialist care in childhood which includes clinical and genetic diagnosis.
* Improve access to MDT specialist care in adulthood for clinical and genetic diagnosis and management of new problems.
* Improve the transition between the two.