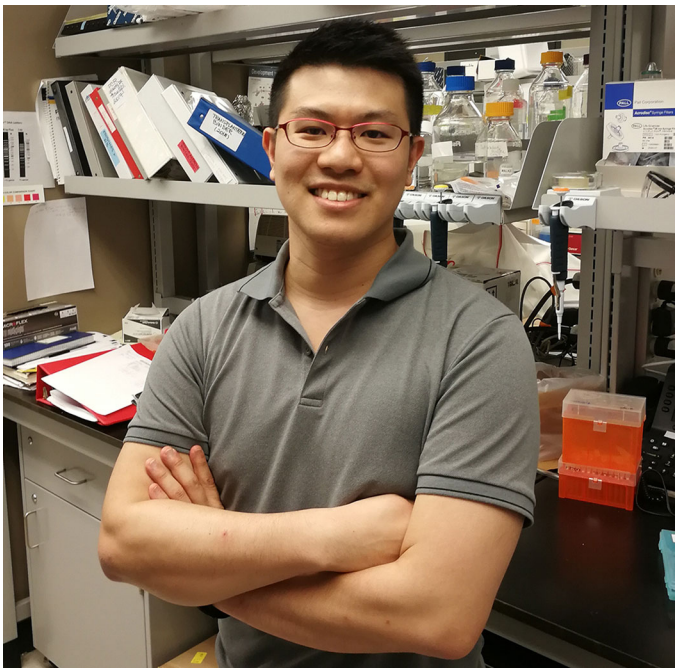
FIRST PERSON

First person – Nobuhiko Tachibana

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping early-career researchers promote themselves alongside their papers. Nobuhiko Tachibana is first author on 'Hamartoma-like lesions in the mouse retina: an animal model of *Pten* hamartoma tumour syndrome', published in DMM. Nobuhiko was a PhD student in the lab of Carol Schuurmans at the Sunnybrook Health Science Centre, Toronto, Canada, while conducting the research described in this article. He is now a postdoctoral fellow in Valerie Wallace's lab at the Donald K. Johnson Eye Institute, Toronto, Canada, investigating the initiation and progression of tumour formation.



Nobuhiko Tachibana

How would you explain the main findings of your paper to non-scientific family and friends?

PTEN hamartoma tumour syndrome (PHTS) is a type of disorder associated with the formation of benign tumours called 'hamartomas'. This disorder is associated with mutations in a gene called *PTEN*. Currently there is only one type of therapy in clinical trials for patients with PHTS (rapamycin), but it is not very effective. Mouse models are a tool used to develop, test and validate therapies for existing diseases, but unfortunately, we currently lack a good mouse model for PHTS. Therefore, our research team wanted to generate a new mouse model that represents PHTS. With our newly generated mouse model, we were able to reliably generate hamartomas in the eye, particularly in the region called the retina. With this animal model, we could analyse how hamartoma form and how they responded to rapamycin to test the utility of the existing treatment. We noted that while rapamycin reduced the size of the hamartomas if given prior to hamartoma formation, the drug was not effective if the hamartomas had already formed. Moreover, drug treatment had other adverse effects on retinal morphology. In addition to obtaining new information on the effects of rapamycin, having an animal model of this disease means we are now in a position to test new treatments.

"With this new model, we aim to provide a better understanding of the etiology of hamartoma formation, and to test new targets for therapeutics."

What are the potential implications of these results for your field of research?

Even though the tumours in individuals with PHTS are predisposed to malignancy, many patients indicate that their greatest suffering comes from their so-called benign disease; soft tissue hamartomas that start growing in early childhood and lead to disfigurement and painful debilitation, which often cannot be successfully treated with surgery or drugs. The underlying mechanism of how hamartomas form in individuals with PHTS still remains to be studied, partially due to the lack of robust and reliable animal models. Our goal was to design and develop a new mouse model that would allow us to study and understand the mechanisms that regulate the formation of PHTS hamartomas. With this new model, we aim to provide a better understanding of the etiology of hamartoma formation, and to test new targets for therapeutics. If well-characterized pathways are causally identified, existing targeted drugs could be potentially fast-tracked into open label trials to arrest or minimize the PHTS disease burden.

What are the main advantages and drawbacks of the model system you have used as it relates to the disease you are investigating?

The main advantage of our animal model system is that we do not have to recruit PHTS patients to test therapeutics. Before our mouse model was developed, one choice was to administer treatments to PHTS patients, which involved risks to the patients. Alternatively, hamartoma cells were extracted from the patients and grown in the lab, but these cell lines did not completely recapitulate the disease. Our animal model recapitulates the complete three-dimensional formation of a hamartoma in the context of 'normal' host tissue. The drawback of our model system is that it can only be used to study hamartoma formed in the retina.

What has surprised you the most while conducting your research?

The greatest surprise was that in order to generate a PHTS animal model, it was necessary to create a mosaic tissue comprised of wild-type and *Pten* mutant cells. Prior efforts to model hamartomas were

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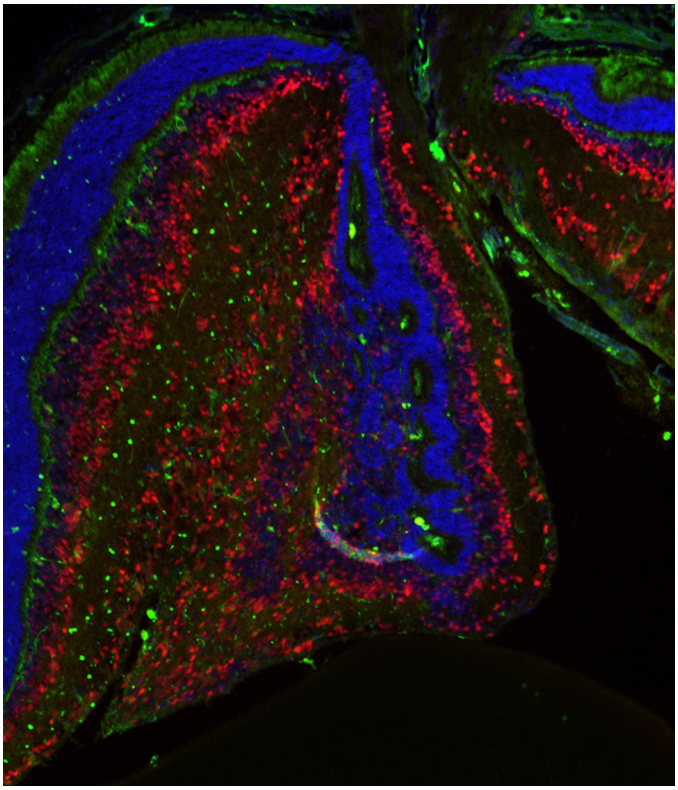

Hamartoma formation on the surface of the retina.

probably unsuccessful because hamartomas form in tissues where there is a mosaic of *Pten* mutant and wild-type cells. Indeed, hamartomas associated with *TSC1*/*TSC2* genes in humans have been phenocopied in zebrafish by the generation of mosaic embryos that carry wild-type and *tsc1/tsc2* mutant cells. In my project, I developed a *Pten* conditional knock-out (cKO) in the murine retina that faithfully recapitulates PHTS in patients. In this model, I also found that hamartomas form in the central retina, which is a mosaic of wild-type and *Pten* mutant tissue.

“Being a scientist means facing lots of failures, as our job is to decipher unknown and unsolved mysteries. Perseverance is a very important attribute of any successful scientist.”

What do you think is important for the professional lives of early-career scientists?

I think that there are two important factors that affect the early careers of scientists: mentorship and persistence. In my opinion, supervisors provide the strongest influence on their students. The styles and approaches that a young scientist takes toward their own research are often originally defined by their supervisors. It is thus crucial to have a supervisor who is accessible to supervise, knowledgeable to mentor, and creative in their science. Another point is to never give up and stay persistent. Being a scientist means facing lots of failures, as our job is to decipher unknown and unsolved mysteries. Perseverance is a very important attribute of any successful scientist.

Reference

Tachibana, N., Touahri, Y., Dixit, R., David, L. A., Adnani, L., Cantrup, R., Aavani, T., Wong, R. O., Logan, C., Kurek, K. C. and Schuurmans, C. (2018). Hamartoma-like lesions in the mouse retina: an animal model of *Pten* hamartoma tumour syndrome. *Dis. Model. Mech.* **11**: dmm031005.