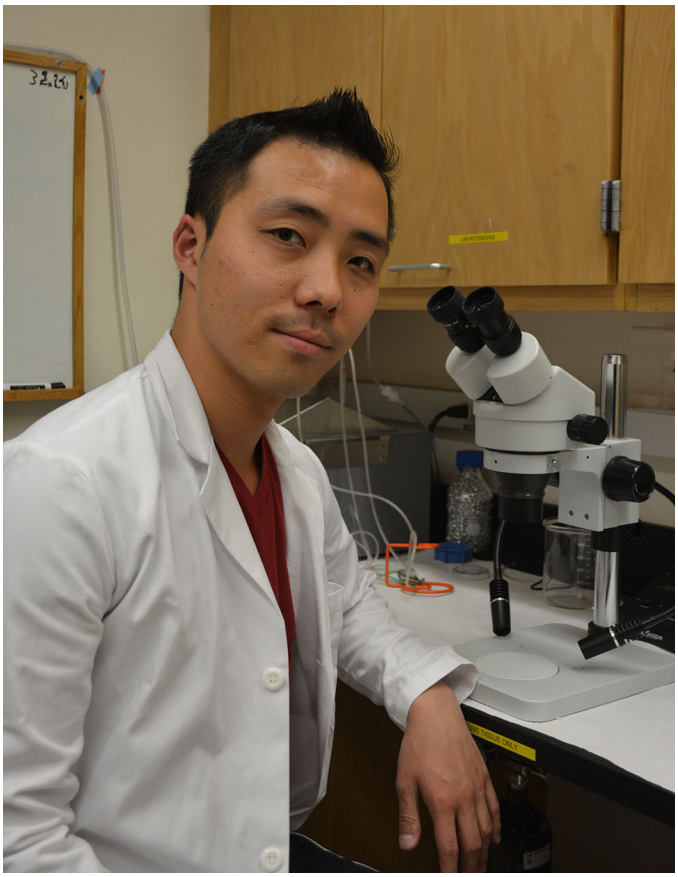
FIRST PERSON

First person – Genki Hayashi

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. Genki Hayashi is first author on 'Use of 4-phenylbutyrate to define therapeutic parameters for reducing intracerebral hemorrhage and myopathy in *Col4a1* mutant mice', published in DMM. Genki is a Postdoctoral Fellow in the lab of Douglas B. Gould at University of California San Francisco, USA, using genetic and pharmacological approaches to understand the pathology and molecular mechanism of *COL4A1*-mediated vascular defects leading to cerebral small vessel disease and stroke.



Genki Hayashi

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

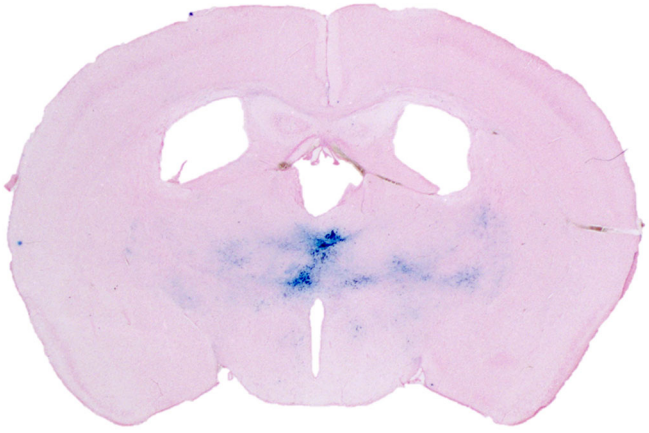
Mutations in the gene *COL4A1*, encoding a collagen protein, cause a multisystem disorder that includes cerebral hemorrhage and muscle disorders for which there is no treatment. The disease is caused when the mutant collagen protein is not secreted from cells properly. We used a mouse model with a mutation in this gene to test the therapeutic potential of a drug that promotes protein secretion. We found that even by starting the treatment after birth, we were able to reduce the severity of cerebral hemorrhages in mice with the mutation.

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

There is currently no treatment for *COL4A1*-related multisystem disorder. Here, we show a potential therapeutic avenue that can ameliorate both cerebral hemorrhage and myopathy and determined that treatments can be effective even when they are started postnatally.

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

There is extraordinary conservation for *COL4A1* between mice and humans and the phenotype of *Col4a1* mutant mice recapitulates what is observed in human patients. However, we only tested a single mutation in this report and we know that different mutations behave differently. Additionally, we used inbred, genetically identical mice and we know that genetic context is important and that humans are genetically heterogeneous, which could influence if and how this intervention translates to clinical care.



Hemosiderin staining of *Col4a1* mutant mouse brain section.

What has surprised you the most while conducting your research?

The variability of drug effect and how some therapeutic paradigms resulted in phenotypes that were worse than untreated cohorts.

Describe what you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

A significant challenge is to better understand the post-translational regulation of type 4 collagen to improve secretion of mutant protein. This will allow a new class of drugs to specifically promote type 4 collagen heterotrimer secretion rather than all misfolded protein, which may have unintended effects. One way is to annotate the changes in post-translational modifications in mutant cells and identify drugs that bypass the checkpoint so that even mutant heterotrimers can be secreted.

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“As a scientist, great communication skills, both in written and spoken form, are instrumental when applying for grants, promoting your work or publishing articles.”

What changes do you think could improve the professional lives of early-career scientists?

It is beneficial for early-career scientists to have a mentor who can teach them how to organize their research project so that a clear and concise message can be communicated to the readers. As a scientist, great communication skills, both in written and spoken form, are instrumental when applying for grants, promoting your work or publishing articles.

What's next for you?

My next step is to use this mouse model to discover the pathomechanism of *COL4A1*-related multisystem disorder. Understanding how mutations manifest as a multisystem disorder can uncover new therapeutic opportunities.

Reference

Hayashi, G., Labelle-Dumais, C. and Gould, D. B. (2018). Use of 4-phenylbutyrate to define therapeutic parameters for reducing intracerebral hemorrhage and myopathy in *Col4a1* mutant mice. *Dis. Model. Mech.* **11**: dmm034157.