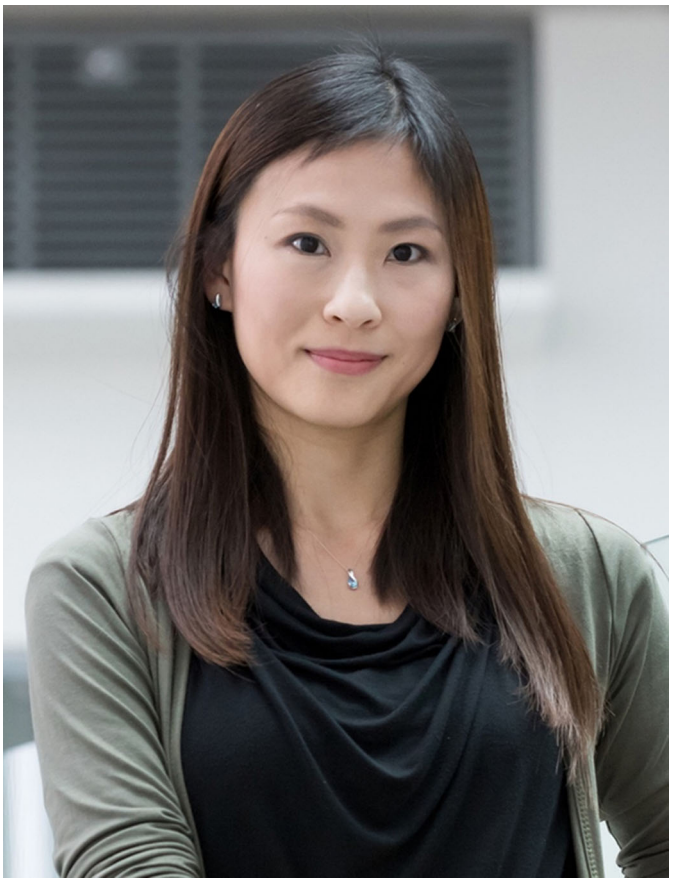
© 2021. Published by The Company of Biologists Ltd | Journal of Cell Science (2021) 134, jcs259245. doi:10.1242/jcs.259245

CELL SCIENTISTS TO WATCH

Cell scientist to watch – Vivian Li

Vivian Li obtained her PhD from the University of Hong Kong in 2008, where she investigated the molecular mechanisms of human colonic development and tumorigenesis. Funded by a Croucher Foundation Fellowship, she joined the lab of Hans Clevers at the Hubrecht Institute in the Netherlands for her postdoctoral work. There, she identified novel Wnt signalling mechanisms at different subcellular levels and characterised intestinal stem cell genes using newly created transgenic mouse models. Vivian established her group at the MRC National Institute for Medical Research, which is now part of the Francis Crick Institute, London, in February 2013. In her lab she uses genetic mouse models and organoids to investigate the regulation of intestinal homeostasis and cancer with a primary focus on the Wnt signalling pathway. Vivian was awarded a Future Leaders in Cancer Research Prize in 2018 by Cancer Research UK and is the winner of the 2021 Women in Cell Biology Early Career Medal awarded by the British Society for Cell Biology.



Vivian Li

What inspired you to become a scientist?

I was always drawn to biology. When I was deciding whether to study medicine or science for a university degree, the human genome project featured a lot in the news. This was very exciting, and I thought it was a great time to get into science, as knowing the sequence of the entire genome would allow you to learn a lot about human diseases, such as cancer. So I entered a new molecular biotechnology programme in Hong Kong, which specifically trained scientists to do experimental work in a laboratory – although my parents probably would have preferred if I chose medicine, to be on the safe side [smiles].

Following your PhD in Hong Kong, you moved to the Netherlands to join Hans Clevers' lab as a postdoc. What prompted this move?

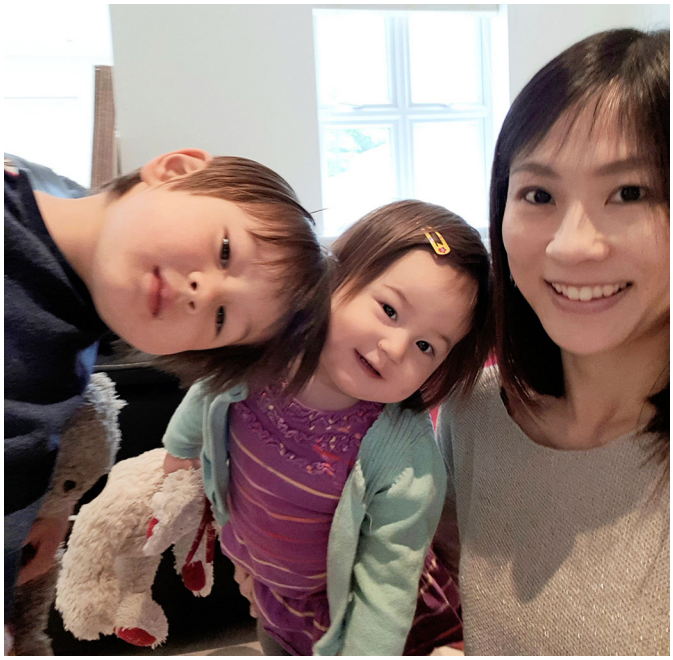
I did my PhD in a clinical lab at a pathology department, working on colorectal cancer. I really liked the topic and wanted to continue working in cancer research, but felt that I needed more advanced training in molecular biology and mouse genetics. I also wanted to experience a different research culture by doing a postdoc abroad. Towards the end of my PhD, the Clevers lab published a major discovery where, using mouse genetics and lineage tracing, they identified Lgr5 as an intestinal stem cell marker. Hans Clevers actually came to Hong Kong and gave a talk, and I was really impressed by the scientific achievements coming from his lab. After finishing my PhD, I was lucky to receive a Croucher Foundation Fellowship, which supports scientists from Hong Kong to do a postdoc overseas, so I joined his lab. This was an incredible working experience that also changed my career plans, because I initially thought I would go back to Hong Kong right afterwards.

Vivian Li's contact details: The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK
E-mail: Vivian.Li@crick.ac.uk

Your mechanistic work on Wnt signalling, a key pathway in intestinal stem cell homeostasis and cancer, has sometimes challenged the textbook views. What are some key issues that we still don't fully understand and that you are hoping to find out?

It's not easy to challenge the textbooks, and it's actually quite difficult to get such a paper published [smiles]. A key question in the field, and one we are particularly interested in, is how to target Wnt signalling safely and effectively in colon cancer. Over 80% of sporadic colon cancers have a truncating mutation in APC, a Wnt pathway component, and this causes Wnt activation and tumour initiation. But even after 30 years of research, there is no approved drug in the clinic to target APC. The major challenge is on-target toxicity, as Wnt signalling is important in many normal tissues, and therefore Wnt inhibitor treatments are highly toxic; so, the pathway is generally considered undruggable. When I started my own lab, I thought this is something we could try to challenge by finding tumour-specific targets, which would avoid the toxicity issue. We identified USP7, a deubiquitylating enzyme, as a tumour-specific target against the APC truncating mutations, and we are exploring the therapeutic potential of targeting this molecule. Another research direction we are going into is understanding the link between Wnt signalling and immunotherapy. The immune checkpoint blockade has been used in the clinic for different

Journal of Cell Science (2021) 134, jcs259245. doi:10.1242/jcs.259245



Vivian with her two children.

tumours, but in colon cancer the response rate is really low, particularly for the types in which APC is mutated. There seems to be a clear association between high Wnt activation and poor response to the immune checkpoint blockade, and we are trying to understand why. So we're developing a project to look into the mechanisms of Wnt-induced immune evasion.

Could you tell us what you aim to achieve by engineering functional intestinal organoids?

Apart from using organoids to study stem cell biology and develop colon cancer models, we've attracted many collaborators across London, including people from Great Ormond Street Hospital, who contacted me when I first set up my lab to apply organoid technology for intestinal tissue engineering. In this project, we want to reconstruct the small bowel with the aim of treating intestinal-failure patients, who can't absorb nutrients, water or electrolytes. These patients rely on intravenous administration of nutrition or, in severe cases, need small bowel transplantation. However, there is a shortage of donor organs, and complications, such as the body rejecting the donor organ, can occur. So, our aim is to grow a piece of the patient's own gut in a dish using the derived organoids, which can then be used for transplantation.

"…our aim is to grow a piece of the patient's own gut in a dish using the derived organoids, which can then be used for transplantation."

What are the greatest challenges in engineering complex tissues such as the small intestine for regenerative medicine?

At the moment, we're able to grow relatively small, one or two square-centimetre pieces of small bowel grafts in a dish using patient-derived organoids. The next challenge is to significantly scale up this process to whole-tissue engineering. While you can easily maintain a small piece of graft in a normal tissue culture dish, growing a thicker and larger piece of organ tissue is difficult, because the nutrients and oxygen cannot penetrate very easily. This is the reason why people are moving into vascular engineering in order to reconstruct and incorporate blood vessels into different engineered organs. Once this works, it will not only help us grow bigger tissues in the dish, but also aid the survival of the grafts following transplantation.

Looking back at the beginning of your independent career, what challenges did you face when starting your lab?

When you start your own lab, you're not only responsible for your scientific project, but also for recruiting and managing people. We all have years of training in doing science experiments, but I didn't receive training during my postdoc in how to be a manager, so dealing with some interpersonal issues was a bit challenging in the beginning. Luckily, the Crick and other institutes have leadership training programmes after you start as a PI, but I think getting such training during your postdoc would be very helpful. It also took time to get projects up and running in the new lab, which is probably expected, but it's still a bit frustrating when you have lots of exciting ideas and are ambitious.

And what advice would you give to someone seeking independence?

To people who are applying or planning to apply for group leader positions, I think what I would say is that your research proposal is more important than your CV. Many applicants will have excellent CVs, so the thing that can make you stand out from others is your research proposal, which should address important research questions using state-of-the-art technology; you'll need to have long-term and short-term visions and, most importantly, you have to identify why you and your research are unique and what you can bring to the institute.

You are this year's Women in Cell Biology Early Career Medal winner. What does this prize mean to you?

First of all, I feel very honoured to be the winner of this prize this year. I think starting your own lab from scratch is really challenging, particularly for women – I also had two kids and took time off, so things sometimes went a bit slower. The award doesn't specifically recognise my own achievement, but rather the six years of hard work by my whole lab. I'm very grateful to have such an amazing team working together, and that they trusted me at the start of my independence as a junior, young female group leader. They are the real stars behind the prize. Receiving this prize is very motivating, because it tells us that we are on the right track in our work.

What do you think is needed to help more women and underrepresented researchers take up leadership positions in science?

I think in the past few years, global initiatives for promoting women in science have been quite successful already. The representation of women at the group leader level has been improving, although it is not equal, and I feel that large parts of the scientific community are supportive towards women in science and women with young families. So, we should continue extending initiatives promoting other underrepresented researchers. Apart from addressing the diversity and equality issue at the higher management level and making organisations aware of biases, we should probably also focus more on encouraging early-career underrepresented researchers to

Journal of Cell Science (2021) 134, jcs259245. doi:10.1242/jcs.259245

apply for leadership positions. And encouraging women to get into science should already start at the high-school level, for example, by organising workshops and finding role models from underrepresented groups to share their experience.

“…encouraging women to get into science should already start at the high-school level, for example, by organising workshops and finding role models from underrepresented groups to share their experience.”

As a mother of two, how do you balance research and parenthood?

Despite the work being demanding, it’s very important to achieve a healthy work–life balance. Having two kids, I try to make sure I prioritise my family as soon as I’m off work. Before, I worked quite a lot at the weekend, which I don’t do much anymore. From time to time I work in the evening after putting my kids to bed; you just need to find your own routine that works for you and your family. I actually think having kids made me work more efficiently during the week – it’s an extra kind of motivation to finish everything and fully be there for my family at the weekend.

Finally, what do you do in your free time?

I mostly spend my free time with my family, as my kids are still young. Since the pandemic lockdown last year, I’ve been doing lots of cooking and baking with them. We have an allotment, where we keep our chickens and grow lots of fruits and vegetables, such as strawberries, rhubarb, courgettes and green beans. The kids love getting their hands dirty. It is very satisfying to harvest your own produce after months of hard work and cook a nice meal out of it. Also, it’s particularly refreshing after spending long hours in front of my computer writing manuscripts and grants. As someone who grew up in high-rise buildings in Hong Kong, I really treasure the green space here in the suburbs of London.

Vivian Li was interviewed by Máté Pálfy, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.