Name	VIVIAN LI
Position	Group Leader (2nd 6)
Year joined *(Crick or founder institute)*	2013

Career History

2001-2003: BSc (Hons) in Molecular Biotechnology, the Chinese University of Hong Kong
2003-2008: PhD in Pathology, Faculty of Medicine, the University of Hong Kong (Outstanding, Top 5%; Gold Medal Prize)
2008-2013: Postdoctoral Fellow, Hubrecht Institute, Utrecht, the Netherlands
2013-present: Group Leader, the Francis Crick Institute, UK

Major Awards, Honours and Prizes

2008: Dr KP Stephen Chang Gold Medal (best PhD thesis), the University of Hong Kong, LKS Faculty of Medicine
2008: Outstanding Research Postgraduate Student Award, the University of Hong Kong
2009: Poster Prize, The Second Norwegian Cancer Symposium, “Frontier in Cancer Stem Cell Research”
2008-2010: Croucher Fellowship, The Croucher Foundation
2012: Women In Cancer Research Scholar Award, AACR Annual Meeting
2018: CRUK Future Leaders in Cancer Research Prize

Membership of external committees, editorial boards, review panels, SABs etc

Membership:
2014-present: F1000Prime Faculty Member – Developmental Biology
2014-present: British Association for Cancer Research (BACR)
2014-present: European Association for Cancer Research (EACR)
2019-present: International Society for Stem Cell Research (ISSCR)

Editorial board:
2014-present: Editorial Advisory Board of American Journal of Physiology – Cell Physiology

Review panels:
2015: Wellcome Trust Clinical PhD Programme
2018-2019: UK Nutrition Partnership Collaborative Awards Expert Review Panel,

Lab Name	***Stem Cell and Cancer Biology Laboratory***

Research programme and achievements

The overarching aim of our research is to investigate the signalling regulation in intestinal stem cell (ISC), cancer and damage-induced regeneration, and to exploit their therapeutic potential in intestinal diseases. We focus on investigating Wnt signalling, one of the major pathways contributing to virtually every developmental decision in the lifetime of an organism. We use mouse models and organoids as powerful tools to dissect Wnt signal regulation in intestinal development and cancer. We also explore intestinal tissue engineering strategies using patient-derived organoids (PDOs) for regenerative medicine and disease modelling. The three specific and inter-related research objectives in the lab are:

1. Spatio-temporal regulation of Wnt signalling in ISC homeostasis
Precise control of the Wnt signal strength is crucial to drive stemness and prevent tumorigenesis in the intestine. Our lab investigates how precision Wnt signalling is achieved spatially and temporally in the crypt under ISC homeostasis, and what happens when it goes wrong. We have recently uncovered a number of new Wnt inhibitors that contribute to the fine-tuning of the Wnt signal strength for ISC maintenance and tumorigenesis, including SH3BP4, NEDD4/4L, MTG8 and MTG16. Mtg8 and Mtg16 regulates niche exit and fate decision at the early progenitors via Wnt and Notch regulation, while the underlying expression dynamics of the transcriptional network remains unclear. Given the importance of transcriptional dynamics in regulating other stem cell systems (e.g. embryo and neural progenitors), we will continue to explore the spatio-temporal regulation of the transcriptional network and the related signalling under ISC homeostasis in the next six years.

2. Wnt activating mechanism in colorectal cancer (CRC)
Although Wnt activation is one of the major drivers for CRC, there are significant challenges in targeting the Wnt pathway due to its pivotal role in stem cell function and tissue homeostasis of many body systems. One key objective of our lab is to uncover new druggable targets against Wnt signalling. We have recent discovered the deubiquitinating enzyme USP7 as a tumour-specific drug target for 80% of CRC with *APC*-mutation. Apart from targeting Wnt signalling directly, we are also exploring the link between Wnt activation and immunosuppression in CRC and the therapeutic potential. Our recent results demonstrate that Wnt activation in cancer cells decreases tumour-infiltrating lymphocytes. In the next six years, we will uncover the mechanism underlying Wnt-mediated immune evasion and explore new therapeutic approaches via combination of Wnt inhibition and immunotherapies. Since Wnt activation is the first step for tumour initiation, we will further explore Wnt-induced extracellular biomarkers for non-invasive CRC early detection.

3. Intestinal tissue engineering for regenerative medicine and disease modelling
Our lab is also involved in a EU-funded consortium project of intestinal tissue engineering, aiming to apply organoid technology to reconstruct small intestine to treat intestinal failure, a chronic debilitating disorder without a cure. We have generated proof-of-concept data to engineer patient-specific functional and transplantable jejunal grafts, which could offer a safe and longer-lasting alternative to traditional donor transplants. We will continue and extend the work to engineer CRC with tumour microenvironments to develop improved strategies for disease modelling and drug screening as compared to PDOs.

Research outputs

Meran L, Massie I, Campinoti S, Weston A, Gaifulina R, Tullie L, Faull P, Orford M, Kucharska A, Baulies A, Novellasdemunt L, Angelis N, Hirst E, Konig J, Tedeschi A, Pellegata AF, Eli S, Ambrosius AP, Collison L, Thapar N, Thomas G, Eaton S, Bonfanti P, De Coppi P, Li VS. (2020) ***Engineering transplantable jejunal mucosal grafts using patient-derived organoids from children with intestinal failure*****. Nature Medicine 26,1593-1601. DOI: 10.1038/s41591-020-1024-z**

Children with intestinal failure cannot absorb the nutrients that are essential to be healthy. In the most severe cases, patients may require transplantation. However, there is a shortage of donor organs and complications can arise after surgery. We have shown how intestinal stem cells and intestinal tissues taken from patients can be used to grow functioning intestinal grafts in the laboratory, which could offer a safe and longer-lasting alternative to traditional donor transplants.

Baulies A, Angelis N, Danielson T, Foglizzo V, Patel H, Kucharska A, Novellasdemunt L, De Coppi P, Li VS. (2020) ***The transcriptional co-repressors Mtg8 and Mtg16 regulate exit of intestinal stem cells from their niche and differentiation into enterocyte vs secretory lineages.*** **Gastroenterology S0016-5085(20)34764-8. DOI: 10.1053/j.gastro.2020.06.012**

Despite decades of research, it remains unclear what defines the intestinal stem cell position, and how the binary fate decision between the secretory and absorptive lineages is controlled in the early progenitors. In this study, we uncovered two important transcription regulators, Mtg8 and Mtg16, regulating the intestinal stem cell identities via Notch signalling. The data provide important insights about how intestinal stem cells regenerate, and the role of these genes in tumorigenesis.

Novellasdemunt L, Kucharska A, Jamieson C, Prange-Barczynska M, Baulies A, Antas P, van der Vaart J, Gehart H, Maurice MM, Li VS. (2020) ***Nedd4 and Nedd4l regulate Wnt signaling and intestinal stem cell numbers by degrading Lgr5 receptor*****. EMBO J. 39(3):e102771. DOI: 10.15252/embj.2019102771**

The bona fide intestinal stem cell marker Lgr5 has been extensively studied in the past, mostly focussed on its transcriptional control. However, how the protein level of Lgr5 is regulated remains unknown. In this paper, we showed that the E3 ligase Nedd4 and Nedd4l target the Lgr5 protein for ubiquitination and degradation, and prevent intestinal tumour development and progression. The results may shed light on therapeutic development for CRC.

Antas P, Novellasdemunt L, Kucharska A, Massie I, Carvalho J, Oukrif D, Nye E, Novelli M, Li VS. (2019) ***SH3BP4 regulates intestinal stem cells and tumourigenesis by modulating β-catenin nuclear localisation*****. Cell Reports 26(9):2266-2273.e4. DOI: 10.1016/j.celrep.2019.01.110**

Fine-tuning of the Wnt signal activity along the intestinal crypt to the “just-right” level is crucial to maintain stemness and prevent tumour transformation. In this study, we uncover a novel tumour-suppressive role of SH3BP4 that functions as a negative feedback regulator of Wnt signalling by restricting nuclear localisation of β-catenin. The results provide not only new regulatory mechanism of Wnt signalling, but also the link between Wnt negative feedback mechanism and tumour development.

Novellasdemunt L, Foglizzo V, Cuadrado L, Antas P, Kucharska A, Encheva V, Snijders AP, Li VS. (2017) ***USP7 is a tumour-specific WNT activator for APC-mutated colorectal cancer*****. Cell Reports 21(3):612-627. DOI: 10.1016/j.celrep.2017.09.072**

APC truncating mutation is the hallmark of CRC, leading to hyperactivation of Wnt signalling. Despite of decades of research, targeting Wnt signalling remains challenging due to its essential role in normal stem cell maintenance. There is an urgent unmet need to develop new generation of Wnt inhibitors focusing on tumour-specificity. In this study, we discover that USP7 is responsible for Wnt activation specifically in APC-mutated colon cancer, suggesting that USP7 is a tumour-specific drug target. This is a major discovery in the field of therapeutic intervention of Wnt signalling in cancer.