From asymmetric stem cell division to tissue engineering

**By**[**KCL's Centre for Stem Cells and Regenerative Medicine**](https://www.regmednet.com/users/7532-kcl-s-centre-for-stem-cells-and-regenerative-medicine)**on 09 Nov, 2015**

Interview with Dr Shukry Habib, Sir Henry Dale Research Fellow at KCL's Centre for Stem Cells and Regenerative Medicine

As part of the Spotlight on KCL's Centre for Stem Cells and Regenerative Medicine, RegMedNet Community Manager Alexandra Thompson speaks to Dr Shukry Habib.



Dr Habib is a Senior Research Fellow and a Principal Investigator at the Centre for Stem Cells and Regenerative Medicine. He carried out his undergraduate degree, Masters and PhD at the Technion (Israel), Tel-Aviv University (Israel) and Ludwig Maximilian University (Germany), respectively. He also carried out postdoctoral research at Stanford University (CA, USA), and was recently awarded a Sir Henry Dale fellowship from the Wellcome Trust and Royal Society, UK. His research interests are the external and internal cues that regulate mammalian stem cell division and cell fate choice during homeostasis, tissue regeneration and tumorigenesis, with a particular emphasis on the role of Wnt signals in asymmetric cell division of both embryonic and adult stem cells. To understand these cues his laboratory utilises principles from organic chemistry, biochemistry, bioengineering and stem cell biology alongside advanced imaging techniques.

### Can you tell us a little about your career to date, and how you came into regenerative medicine?

While studying biochemistry as an undergraduate, I became fascinated by the unique abilities of proteins to interact with each other and drive specific cellular responses. I joined the lab of Professor Abdussalam Azem at Tel-Aviv University for my master’s degree and studied the biochemical and biophysical properties of mitochondrial inner membrane translocase TIM23. To further develop my theoretical knowledge and scientific skills in protein biochemistry, I was very fortunate to obtain a graduate studentship in the lab of the renowned biochemist Professor Walter Neupert at the Ludwig Maximilian University, Munich. In his lab, and under the supervision of Dr Doron Rapaport (now a Professor at the University of Tubingen), I became highly interested in the biogenesis of mitochondrial outer membrane (MOM) proteins.

I have always been interested in different fields of biology. Reading the research literature on stem cells and their therapeutic potential inspired me to pursue a career in this field. It was clear to me that I have a unique opportunity to apply the principles of protein biochemistry and bioengineering into the stem cell field. This idea motivated me to join the lab of Professor Roeland Nusse as a postdoctoral fellow at Stanford University. Professor Nusse discovered Wnt proteins and his lab pioneered the purification of these proteins. Wnt proteins are essential for the maintenance and differentiation of stem cells and therefore they play a crucial role in tissue regeneration. During my postdoc, I developed a novel system that combines protein bioengineering, pluripotent stem cell biology and live imaging to study the fundamental processes of asymmetric cell division. To strengthen my discovery I joined the Howard Hughes Medical Institute Janelia research Campus visitor program and worked with Nobel laureate Dr Eric Betzig’s group to visualise cell division at high resolution by using the newly developed Bessel beam plane illumination microscope.

I was awarded a Wellcome Trust Sir Henry Dale Fellowship and since April 2014, I have been working as a Principal Investigator at the Centre for Stem Cells and Regenerative Medicine at King’s College London. Recently I was also recruited to establish an advanced bioimaging lab at the Francis Crick Institute, which provides me with a unique opportunity to share my expertise with the wider scientific community. Enthusiastically, I continue my research on Wnt-mediated asymmetric stem cell division and develop new bioengineering strategies to deliver purified Wnt proteins to different tissues *in vivo* to assess their effect on the regeneration.

### You have carried out research in Europe and the USA, what are the major differences in approach to stem cell research you encountered?

Europe and the USA are paramount contributors to stem cell research and regenerative medicine, and I feel very fortunate to have the experience of working in both continents. The regulation of stem cell research and the amount of funding dedicated to a specific line of research varies in Europe and USA. I recall very well that during the early period of my postdoctoral studies at Stanford University, there was a major problem in directing government funding for human embryonic stem cell research. Consequently, the research of many labs in this field was severely affected. However, the situation improved with the change of the government administration. Importantly, major American organisations such as the Howard Hughes Medical Institute and the California Stem Cell Agency continue to support stem cell research and specifically help American scientists to share key cell lines and reagents worldwide.

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Among numerous achievements, scientists in the UK were among the first to identify proteins that control the ability of embryonic stem cells to replicate without limitless. Importantly, at the Roslin Institute in Edinburgh, a major breakthrough was achieved in the field of cellular reprogramming. The birth of Dolly the sheep provided the first demonstration that all the programming needed to transform a fertilised egg into a living animal was contained within a somatic cell. I strongly believe that the UK continues to be at the forefront of stem cell research and attracts top scientists. The UK has well-established system for regulating stem cell research. It is among the few places in the world that supports the creation and use of embryos under the Human Fertilisation and Embryology Act of 1990 to advance human embryonic stem cell research. Furthermore, the British government continues to actively invest in stem cell research and among the exciting projects that they fund, the £25 million UK Regenerative Medicine Platform is exemplary. In addition to government support, the Wellcome Trust and other charities continue to support stem cell research and enable scientists to advance this exciting and promising field.

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### What led to your current specialties in cell signaling and stem cell division?

I am fascinated by the unique ability of stem cells to self renew and give rise to differentiated cells that replenish the tissue throughout life. One mechanism to achieve both tasks is asymmetric cell division (ACD). The activities of the stem cells are controlled by the local stem cell microenvironment and signals such as Wnt proteins. Therefore, my transition to the stem cell world started while trying to connect Wnt signaling to ACD in mammalian stem cells.

Before I started my postdoc in the Nusse lab at Stanford University, I conducted the literature mining on Wnt signaling. The first Wnt protein, Wnt3a, was purified and characterised in 2003 by Karl Willert *et al*. at the Nusse lab. Since then researchers using mammalian systems have applied purified Wnt proteins globally to cells in tissue culture or soaked beads with the protein and introduce them to tissues to study the effect of Wnt proteins on biological processes. Importantly, the Wnt is released from the beads and diffuses through the tissue. On the other hand, research mainly conducted in embryos of *Drosophila* and *C. elegans* clearly shows that Wnt proteins are often secreted locally and presented to only one side of the responsive cells. Based on the observations made in these organisms and the hydrophobic nature of the protein, I took the challenge of introducing Wnt proteins locally to mammalian stem cells and observing their effect. I succeeded in covalently immobilising the hydrophobic Wnt to beads, thereby revolutionising the process of specifically targeting the Wnt proteins to any microscopic location on cells and tissues. Using advanced live imaging techniques, I demonstrated that the directed Wnt signal, unlike soluble Wnt, can polarise a mammalian stem cell, orient the plane of mitotic cell division, and induce asymmetric stem cell division. This was the pioneering demonstration of how localised Wnt affect vertebrate stem cells at the single cell level.

### Can you tell us a little about the research projects being undertaken in your lab?

I have previously established that localised Wnt induces asymmetric cell division of an embryonic stem cell. Accordingly, the Wnt-proximal cell remains as an embryonic stem cell whereas the Wnt-distal cell becomes an epiblast stem cell. My lab focuses on the role of Wnt signaling in stem cell division and tissue regeneration. We base our research on the technology of immoblised Wnt and the process of Wnt-mediated asymmetric stem cell division. Specifically we focus on:

1. Analysing the molecular mechanism of Wnt-mediated ACD in stem cells and comparing it to the response of cancer stem cells.
2. Tissue engineering and regeneration based on the modulation of Wnt signalling
3. Integrating and developing advanced super-resolution live imaging microscopy to gain insight into aim 1 and 2.

### How do you hope this research might affect the clinic?

By understanding the basic process of asymmetric stem cell division and tissue formation, we hope to improve our ability to specifically target key molecular pathways to boost the regenerative capacity of tissues upon injuries. It is becoming clear that Wnt signalling plays a central role in the maintenance of stem cells from different types of tissues and contributes to tissue homeostasis and regeneration upon injury. Therefore, targeting this pathway is important to treat different developmental disabilities and degenerative disorders. I believe that the technology of immobilising Wnt proteins will enable scientists to deliver the protein locally to the injury site to boost the regenerative capacity of the tissue.

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Because of its ability to induce asymmetric cell division, immobilised Wnt can be used to engineer artificial tissues. Tissue engineering and cell-based therapies are at the forefront of regenerative medicine. By designing tissues that recapitulate the *in vivo* situation we can mimic human diseases, study the molecular mechanism of the disease and allow for drug screening. Additionally, for degenerative diseases, engineering organised 3D tissues can also be used for transplantations in patients to replace the damaged tissue.

### If you could, how would you go about addressing this?

Multidisciplinary scientific collaboration is the key to achieving the aforementioned goals. Being based within the UK, and specifically in London, means that my science can flourish and the spectrum of my interdisciplinary research will widen. My lab currently collaborates with bioengineers, mathematicians, clinicians and stem cell biologists across the country. We have recently succeeded in generating a new platform of highly stable Wnt that can be used for the purification of stem cells from tissues, maintain the stem cell population and be adapted for tissue engineering. Accordingly, we demonstrated the ability of the new Wnt platform to generate 3D culture conditions where the primary human mesenchymal stem cell population is maintained alongside the formation of differentiated cells in an organised manner and recapitulate the in vivosituation in bone. Our next step is to assess the transplantation of 3D tissue into injured bone. Furthermore, we aim to adapt the Wnt-platform to engineer tissues from other types of stem cells including skin stem cells and neuroprogenitors.

I am very confident that the tools and strategies developed by my lab will contribute to pushing the boundaries of this field as well as facilitating progress within the wider scientific community.

### What are your long-term scientific goals?

I am very passionate about my current research on harnessing the understanding of the molecular mechanism of Wnt-mediated asymmetric stem cell division for tissue engineering. At the molecular level, my long-term scientific goal is to build a comprehensive map of the genes, transcripts, proteins and organelles involved in asymmetric stem cell division. At the cellular and regenerative medicine levels, I see a great potential in 3D tissue engineering and establishing new biomaterials that can tune key signaling pathways during regeneration. We will continue to develop the immobilised Wnt-platform and combine it with biomaterials and other signalling molecules to make it suitable for as many types of stem cell as possible.

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