



Interview with Dr Sim Yirong & Dr Su Xinyi -The Cambridge MD-PhD Journey

By Dr Tan Wu Meng, Editorial Board Member

Dr Sim Yirong and Dr Su Xinyi are MB/PhD graduates from the University of Cambridge. They have recently started House Officer postings in Changi General Hospital and National University Hospital respectively. With the upcoming change in postgraduate medical education, Dr Tan Wu Meng takes the opportunity to interview Dr Sim and Dr Su over their path of choice towards their clinician-scientist careers.

TWM: The journey to a MB-PhD is long and less travelled. What made you choose this path over the usual MBBS route?

SXY: My mother once told me that as a child, my favourite question was “Why?” Rarely content with a simple explanation, I had always insisted that my parents give me more details about the way things worked. While this inquisitiveness was at times the subject of affectionate jokes, I was always encouraged to value the explorative process as much as any answer found. During my college years, I avidly pursued any opportunity to gain experience and insight into the world of research.

Through the Science and Research Programme (SRP) during my ‘A’ Levels, I was introduced to the world of molecular biology. Under the guidance of Dr Lai Poh San (Department of Paediatrics, NUH), I characterised a single nucleotide polymorphism (SNPs) in the retinoblastoma gene (RB1) which contributed to the development of a molecular toolkit that predicts

a child’s inherited susceptibility to retinoblastoma. Being awarded the National Science Talent Search, Merit Award, an overseas scholarship from the Agency of Science Technology and Research, Singapore (A*STAR), I was given the opportunity to pursue the MB-PhD course in Cambridge.

Essentially at the tender age of 17, arguably in a naïve fashion, I set my sights on being a clinician-scientist, as it is a career which allows me to embrace both my passions – the pursuit of scientific research and to practice medicine.

SYR: In Cambridge, all medical students get the opportunity to spend their third year in research, which counts towards our BA. I had the honour of completing my research project with Professor Robin F. Irvine, FRS, who inspired me with the intellectual stimulation and excitement of research. I really enjoyed my project (which lasted three months) and was delighted with the lovely opportunity to pursue a PhD, as well as to spend another three years to conduct further research with my project.

TWM: Tell us about your PhD. What was your research about, and how do you see it making a difference to human health?

SXY: For my PhD, I was privileged to work with Prof Ashok Venkitaraman (Ursula Zoellner Professor of Cancer Research) at the Hutchinson MRC Cancer Centre in Cambridge. The laboratory’s main interest is in understanding the vast network of cellular machinery that functions to preserve the integrity of the human genome (particularly during the cell cycle), failure of which results in chromosomal instability – a hallmark of most cancers. The focus of our work is on understanding and defining the events that lead to carcinogenesis, and translating these molecular insights into clinical practice.

My PhD research involved the development of novel cell-biology methods to rapidly, reversibly and conditionally ablate protein functions *in vivo*, and its application to gain hitherto unattainable information of biological processes within a single cell-cycle. Very briefly in the next paragraph,

I shall attempt to explain the premise and significance of my research.

In modern biology, the functional characterisation of any gene relies on the inactivation of its protein product, followed by the assessment of its consequences. Although well-established methods such as siRNA exist to allow the regulation of gene function at the transcriptional level, there is a paucity of biological tools which possess sufficient spatial-temporal resolution to dissect cell-cycle specific functions of protein. Motivated by the excitement through which a plethora of biological questions could be interrogated if such a technological advancement were to occur, I devoted the first half of my PhD to the establishment of a temperature-sensitive N-end rule degenon for conditional genetics in vertebrate cells. In the latter half of my PhD, I applied this method to the uncoupling of DNA replication from homologous DNA recombination (HDR) within a single cell cycle. This work led to the description of a new model for the vertebrate cell cycle, in which HDR is temporally segregated in G2, from replicative DNA synthesis in the S phase. This is consistent with observations in radio-resistant cancer cell lines, whereby an increased DNA repair activity is observed during radiation-induced G2 delay, suggesting a mechanism whereby the G2 phase is utilised by cancer cells to undergo additional DNA repair. This has implications for the development of novel cancer therapeutic drugs. One such application is the use of specific HDR protein inhibitors to sensitise radio-resistant cancers to existing radiotherapy or chemotherapeutic regimes.

SYR: My PhD thesis is titled *An Investigation of the Protein Associations and Phospholipid Interactions of GAP1IP4BP and GAP1m*. Ha, I know it's a mouthful. I suppose most medics are familiar with the inositol trisphosphate (InsP3) signalling pathway (for example, in insulin signalling).

For my PhD, I was interested in these GTPase-activating Proteins (GAPs)

which bind to InsP4, a downstream product of InsP3. InsP4 has been proposed to be involved in calcium regulation, B lymphocyte development and neutrophil chemotaxis, to name a few. I wanted to understand the role of InsP4, and hence was interested in the proteins and phospholipids that bind to these GAPs, their dynamic interactions intracellularly, and when membrane-bound. So, it was three exciting years spent learning and applying a lot of techniques in molecular biology, cell biology and molecular biophysics.

What are the clinical implications? Well, I think it's still early days before this basic science research can be translated clinically. I look forward to the day when all these findings, built on the hard work of predecessors, can pave the way for further research.

TWN: What were your most memorable experiences in Cambridge:

(a) **As a clinical student?**

SXY: As part of the MB-PhD programme, I was able to take part in a fully sponsored two-month exchange programme, as part of my final year in clinical school, at Yale University, New Haven US. It was an eye-opening experience. In comparison with the NHS system I have become so accustomed to, medicine in the US was a lot more reliant on investigations and modern technology, rather than the good old bedside clinical examination. Yet, the rigour with which every patient was worked-up during their hospital admission by the US doctors, scouring through every abnormal blood results, leaving no stone unturned was admirable (arguably this is the result of the high incidence of medical litigation in the US).

The Yale School of Medicine also has a fine tradition of transforming world-class fundamental biology research into the clinical setting. One reason for their success is the close partnership and interaction fostered

between basic researchers and clinical investigators. I was able to experience this first-hand, whilst working as an intern in the Klatskin firm (named after Dr Gerald Klatskin, the founding father of modern hepatology).

SYR: Because of the collegiate system (the university comprising 31 colleges), I enjoyed the ease in interaction with other non-medical students and fellows in my college. Dinners in hall were usually spiced with the flavours of history, engineering, science, law and political sciences.

In the hospitals, I also appreciated the emphasis on evidence-based medicine in the clinics and wards. Ward-rounds and lectures are often peppered with the latest research findings and clinical trial data and I found it inspirational to be amongst the Regius Professor of Medicine and many other prominent clinicians from various fields (and to also put a face to the authors of my textbooks!).

(b) **As a researcher?**

SXY: Apart from the surprisingly enjoyable late-night time-course experiments (during which I wait dutifully for my cells to replicate in their petri-dishes) which often ended up as movie-marathon nights, my entire PhD experience has been one of self-discovery; a process of identifying my strengths and overcoming my weaknesses. Importantly, the intellectual rigour obtained from carrying out an independent scientific research project and the ability to critically analyse new information, are invaluable skills that have made a significant impact on the way I approach problems.

(c) **Outside of studies?**

SXY: Beyond clinical medicine and research, I am actively involved in the Christian Graduate Society in

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Yirong punting with some friends



Christ's College Medical Society 2000

Cambridge. Being Co-Chairperson (2007-2008), together with fellow MB-PhD student Yirong Sim, we were involved in organising welcome activities for international graduate students arriving in Cambridge, as well as events for the Christian Graduate Society, such as Society Squash, garden parties, graduate forums, weekend retreats and Bible study leadership training events.

During my final year in Cambridge, I also felt passionate about setting up *Veritas Forum at Cambridge University*. Together with a committee of like-minded graduate students, we spear-headed the inaugural forum (March 2008), themed "Faith in the Public Sphere". The Veritas Forums were first started at Harvard University in 1995, and are typically university-wide events aimed to engage both students and faculty in open discussions about important intellectual, social and moral questions of present day in relation to Christianity. Prior to this, there were few opportunities at the University of Cambridge to do so. It is hoped that the inaugural Cambridge Veritas Forum 2008 themes will encourage university graduates to engage in such dialogue and also lay the groundwork for such forums in the future. (<http://www.veritasforum.eu/cambridge.html>)

SYR: Despite the busy schedule of medical school and PhD research, I enjoyed the flexibility in our schedules to relax and to participate in various sports like rowing, netball and badminton. One of the most memorable experiences in Cambridge is the joy of being a Co-Chairperson with Xinyi (another Singaporean MB-PhD student) for the International Student Welcome. Knowing the joys as well as the struggles of being an international student in Cambridge, we enjoyed welcoming new international graduate students to Cambridge through organising events for them during their first few weeks and throughout the year, as well as offering them home visits.

TWM: Tell us about your experience of the Cambridge MB-PhD course structure. What efforts are made to keep students current with clinical medicine, even as they devote a significant part of their time to research?

SXY: Each MB-PhD student is attached to a clinical supervisor, one whom we should ideally meet with on a weekly basis for clinical bed-side teachings. Also, we are required to fulfill two weeks' worth of clinical attachments per year (during our PhD) to ensure that we're keeping in touch with clinical medicine. In the ideal scenario, we should not turn "rusty" with our clinical acumen

during our PhD years, but realistically the transition to clinical medicine from PhD was rather daunting initially (not to mention we had to take our MB finals within nine months of returning to clinical medicine!). Fortunately we made it through.

SYR: After four and a half years of medical school, I took three years out to complete my PhD, before returning to finish my final year of MB BChir. We had clinical supervisions which lasted about two hours a week during the period of our PhD to keep us in touch with medicine. Other efforts included a monthly clinical seminar as well as a two-week clinical attachment each year during our PhD. There was a fair bit of catching up to do when I returned to medical school, because medicine had progressed rather quickly. I was thrilled to see what was perceived as clinical trials during my pre-PhD years become accepted clinical practice by the time I reached my final year of medical school (i.e. post-PhD)!

TWM: What have your MB-PhD seniors in the UK gone on to do after graduating? Are there any special career structures (in the NHS and Cambridge) targetted at MB-PhDs? For example, Clinician-Researcher or Clinician-Scientist or Clinician-Educator (AKA Clinical Lecturer) programmes?

SXY: As far as I am aware they do make provisions for MB-PhD students to do

research during their ST years; I am not sure if they have a fixed structure.

TWM: Having just returned from Cambridge to start work in Singapore, what are your impressions of Singapore healthcare and life as a House Officer?

SXY: It's definitely more physically and mentally demanding being a HO here in the UK compared to being a HO in the UK, simply because of the workload. Fortunately, everyone is very helpful and keen to help us settle in, which is always a plus point.

There is quite a steep learning curve, as medicine is practiced differently here, compared to the UK. In Singapore, it is closer to the US system, with more access to (and hence more reliant) laboratory results and investigations. Singapore doctors also call their mobile computers COWs (short for "computer on wheels"!) which I previously thought was specific to Yale.

I also appreciate the highly efficient healthcare system here in Singapore! CT scans are done on the same day – which is a luxury in the UK! ☺

Lots of acronyms are being used in the hospitals in Singapore. For the first week I was left wondering what "hypocount" was, until I realised that it is the Singapore version of capillary glucose level/blood glucose level, because the machine that reads BGL is called hypocount!

SYR: Although I'm Singaporean, I did spend nine years (a third of my life) in Cambridge. As such, there was a bit of re-acclimatising to the Singapore culture, the faster pace of life, the various languages (and dialects) and the hot humid weather! Nonetheless, I am very thankful to my lovely and helpful colleagues who have helped me settle into my job, which I enjoy.

My impressions of Singapore healthcare? I think we're doing fine as we are well-funded and well-equipped with the latest technology and medical equipment. However, I do notice that many of the patients whom I have come across do not seem to have as

good an understanding of their health conditions or the medications that they take, as compared to their British counterparts. Also, I have noticed that in most cases, the families of the patients are also quite involved in their healthcare (lots of family updating!), and this is rather different from the individualism and patient confidentiality in the UK.

TWM: What did you miss most about Singapore, during your years away?

SXY: Family and friends, as well as food.

an effective clinician-scientist – firstly the need to be a clinically-competent physician and secondly, the need to concurrently achieve cutting-edge world-class research. But I am hopeful that Singapore is steering in the right direction to help nurture a future generation of clinician-scientists.

SYR: I enjoy clinical work and interacting with patients, so I would definitely like to continue with clinical practice. Personally speaking, I think keeping active in clinical work will give



Yirong, Xinyi and fellow medics from Christ's College

SYR: My family, of course, and mummy's good home cooking! =) But with modern telecommunication, it is not too expensive to make regular phone calls to keep in contact with each other.

TWM: What do you see yourself doing in 10 years' time? Do you foresee a future in laboratory, translational and/or clinical work?

SXY: Having had an appreciation of basic molecular biology research, it is my hope to explore translational research in the future as a specialist trainee. I would imagine that many aspiring clinician-scientists like myself in the foreseeable future struggle to strike the delicate balance between the two competing factors of being

me an added focus and motivation in the event I get the opportunity to pursue laboratory or translation research alongside my clinical practice.

TWM: What are your hobbies? What do you do to chill out?

SXY: Catching up on sleep and preparing for my wedding in December! ☺

SYR: In my free time (of which there is hardly any as a House Officer) I enjoy playing board games with my friends as I find it relaxing and fun to use the other part of my brain for strategic planning. Also, I enjoy playing the piano and listening to music. But for now, I just appreciate catching up with my sleep. **SMA**