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Professor Ashok Venkitaraman introduces his work in Singapore, coordinating and catalysing research on the causes of cancer in Asia, and translating this research to clinical impact through improved detection, treatment and prevention. Professor Venkitaraman also outlines how the Singaporean research ecosystem compares to that of his former base in Cambridge, UK, and the global challenges that still need to be overcome in cancer drug discovery and development.

How has your past helped shape your goals today?

I began my career as a physician working on infectious diseases before undertaking a PhD in London with Sir Marc Feldmann, and then moving to Cambridge to work in the Medical Research

Council Laboratory of Molecular Biology (LMB) first with Prof. Michael Neuberger, and later, in my own laboratory there. At the LMB, my lab investigated the control of DNA rearrangement in the immune system, when the cloning of the breast cancer gene BRCA2 by groups in the US and UK prompted us to consider its potential role in this process. We soon discovered that BRCA2 maintains genome stability through functions in DNA repair by recombination. This led us to propose that BRCA2 mutation carriers become highly predisposed to cancer through loss of these functions. Since then, my research for the last 25 years has used BRCA2 deficiency as a lens through which to explore how genome instability leads to cancer development, as well as to find better ways to detect, treat and prevent cancer.

This second aspect of my work is probably the most relevant to PharmaBoardroom and has centred around creating disruptive technologies to facilitate the discovery and development of new therapeutics and diagnostics. We have focused on three questions.

How to develop new genetic technologies that can parse complex biological pathways to efficiently identify and validate first-in-class therapeutic targets?

How to utilize structure-guided drug discovery approaches to assess the ligandability of previously 'undrugged' first-in-class targets?

And lastly, how to better understand the mechanism of action of first-in-class agents using new approaches in microscopy, in order to find precise biomarkers for patient stratification?

What are your current roles in Singapore?

I have three roles. I direct the Cancer Science Institute of Singapore at the National University of Singapore (NUS), which is the largest of five Research Centres of Excellence established by the Singapore government. I recently took over from David Lane at A*STAR to lead the Disease Intervention Technology Laboratory, where I will continue my work on developing and deploying new technologies for drug discovery. Finally, I direct the NUS Center for Cancer Research, which aims to create a seamless environment at NUS and associated hospitals for bench-to-bedside cancer research.

What brought you to Singapore and what do you see as your mission there?

I am excited to move here from [Cambridge](#), because I think that Singapore has reached an inflection point from which the pace and extent of progress in translating biomedical research to clinical application could rapidly accelerate.

Singapore has already built world-class infrastructure and facilities for biomedical research. Many talented researchers work in the institutions here, and the environment has also attracted a number of internationally recognized experts from other countries. There is improving access for translational research to the healthcare systems within the major university hospitals through initiatives like the Singapore Translational Cancer Consortium. Singapore represents a gateway to Asia in several respects. It shares the ethnic and genetic diversity of larger neighbours. Its well-regulated systems are similar to those in the UK and other countries, and its excellent infrastructure makes it easy to undertake research.

I see my mission here as helping to coordinate and catalyse research on the causes of cancer in Asia, and in translating this research to clinical impact through improved detection, treatment and prevention.

When I directed the MRC Cancer Unit in Cambridge, I developed its distinctive research focus on early intervention in cancer, and plan to nucleate this area through my own research at the Cancer Science Institute of Singapore. I will also continue my work on developing technology platforms for first-in-class drug discovery at A*STAR.

What challenges must be overcome to develop better treatments for cancer?

Cancer drug discovery and development has moved at an explosive pace in recent years, propelled by our rapidly improved understanding of cancer genomics, but fundamental challenges still remain, which are common to all therapeutic areas. For example, I referred before to challenges in identifying and validating new therapeutic targets, in extending the repertoire of 'druggable' targets, and in improving ways to match patients to the right drugs through better understanding of therapeutic mechanisms of action.

I'll refer to my own work in one of these areas as an example. The genomic instability that drives carcinogenesis leads to profound changes in the genome of cancer cells, which rewires in complex ways how genes are expressed and how biochemical pathways operate. How to penetrate this complexity to identify and validate first-in-class therapeutic targets remains a major challenge.

My lab recently devised a technology platform that we call 'Protein interference' or 'Protein-i', in which evolutionarily diverse protein fragments are used in phenotypic screens to parse disease pathways to identify first-in-class therapeutic targets. Cambridge University spun this technology out into a start-up company, PhoreMost. Reflecting the importance of overcoming current challenges in target identification, PhoreMost has grown rapidly, and has been able to enter deals with major pharma companies including Novartis, Plexxicon, Boehringer-Ingelheim and Otsuka. Of course, target identification is only the first step, and so my lab has also developed approaches for structure-guided lead discovery, which have enabled us to assess the ligandability of previously 'undrugged' target classes like protein-protein interactions. Assets from this work have already been licensed to industry by Cambridge University, with some in late stages of preclinical development poised to enter clinical trials.

Looking beyond current advances in personalized or stratified cancer therapy, I think that early intervention – before the disease becomes advanced – will be the future goal of cancer treatment. But to accomplish this we still have a long way to go. We lack fundamental understanding of what drives cancer progression, of what turns pre-malignant cells into rapidly progressing cancers. Without this knowledge, it is difficult to know when a cancer will become clinically significant, or how to develop new approaches to therapy that are safe and can be administered at these early stages. My own research focuses on some of these problems.

How do you translate world-class research in Singapore to commercial success?

As I said before, Singapore has a lot going for it in this area, but it will be very important to play to existing strengths and plan strategically to address weaknesses. I think that one focus here should in future be on developing disruptive technologies that address unmet needs in drug discovery and development, and not simply on building portfolios of assets, which may be inherently risky. New companies that are technology-driven have a better chance to become durable commercial successes. Of course, this is easier said than done, and I think that it will be important in future to build an ecosystem here that encourages technological innovation of this kind.

There are several challenges. One is to encourage a greater appetite for measured risk, along with the view that failures are sometimes the beginning of the journey, rather than the end of it. A second is to encourage entrepreneurship, particularly amongst younger researchers. Training younger researchers to harness their entrepreneurial mindset will help to create a pool of talent from which to identify the next CEO's or CSO's of budding companies. A third is to develop local

networks to attract the funding required for the leap from initial start-up to larger commercial enterprise. I am heartened that these issues are recognized by government agencies and senior researchers in Singapore, and if there is the will to find ways to address them, Singapore has the potential to grow rapidly as a technology and science hub in the future.

What are your goals in the near future?

I have two main goals over the next three years. Foremost, I aim to leverage my triad of roles to help build a robust framework that allows innovative cancer research to go from the lab to the clinic, and vice-versa. Fostering new partnerships with global industry will be vital in this framework. In addition, I'm excited about new directions in my own research, and aim to bring them to fruition!

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