The Duke-NUS Graduate Medical School in Singapore is the consequence of Duke University, USA and the National University of Singapore joining forces. Here, Professor Patrick J Casey, Senior Vice Dean, explains how the School came into being and the trials of intercontinental research.

Firstly, could you provide some background on the formation of the Duke-NUS Graduate Medical School (Duke-NUS)?

Duke-NUS was established in 2005. It is the result of a strategic collaboration between Duke University in the US and the National University of Singapore (NUS), two of the world’s top institutions for higher education. The partnership was an integral component of Singapore’s Biomedical Sciences (BMS) initiative, which aims to make the country a leading centre for medical research, innovation and education. The involvement of Singapore Health Services (SingHealth; see p24) medical organisation was also a key element, as the vast majority of clinicians involved in educating the students were affiliated with SingHealth hospitals. The partnership with SingHealth has strengthened dramatically in the past years with the development of the Academic Medicine initiative which integrates educational and research activities across both organisations.

The beginnings of Duke-NUS can be traced back to 2001-02, when blue-ribbon commissions recommended the establishment of a graduate-entry medical school in order to produce highly trained clinician scientists needed to support the emerging BMS initiative and to conduct innovative research in areas of biomedical science that would impact on healthcare and economic development. Particular emphasis was placed on translational and clinical research. The aim was to accelerate the pace at which biomedical discoveries lead to the development of products and services. This will ultimately enhance the quality of healthcare for the population and contribute to the economic growth of Singapore.

Previously you were a senior staff member at the Duke University Medical Centre in the US. Why do you think you were chosen to help set up Singapore’s second medical school in 2005?

While the nature of my personal research programme has been quite basic, I have a longstanding interest in interdisciplinary science, particularly in facilitating the exchange of ideas and fostering collaborations between laboratory-based scientists and clinicians delivering care. This is important as it is clinicians who identify the most important biomedical problems. I have also always been interested in translating discoveries into application and in fostering partnerships with the commercial sector, such as biotechnology and pharmaceutical companies, to facilitate this process.

At Duke University, I founded the Center for Chemical Biology in 1999, which had a primary aim of bringing together investigators in the biological, chemical and physical sciences, all of whom had an interest in seeing their work extended into the study of the basis of disease and therapies. These were the likely reasons that I first came to the attention of the Duke leadership as someone who might be able to play a major role in the venture.

As the Senior Vice Dean of Research at Duke-NUS and also James B Duke Professor of Pharmacology and Cancer Biology at Duke University, what are your main day-to-day responsibilities?

I spend most of my time in Singapore, and am in the US roughly two weeks each quarter. I still have a small laboratory at Duke, and also one at Duke-NUS, where we continue to study cellular signalling processes involved in cancer formation and progression. The majority of my time, however, is spent in developing and overseeing the research programmes underway at Duke-NUS. In the early days of the initiative, my main tasks involved the recruitment of faculty members and establishment of facilities. Now my role involves more administration and strategic planning, although I am still directly involved in faculty recruitment and mentoring.

A current major initiative of Duke-NUS is the creation of a virtual Academic Medical Center on the campus by teaming up with our clinical partner SingHealth. This will integrate research and educational activities across the spectrum of clinical sciences. I also serve on several national working groups that are charged with charting the course of the ever-evolving BMS initiative in Singapore.

Further to this, how do you manage your time commitments between the US and Singapore effectively?

This was much more of an issue in the first few years, when I still had a major lab at Duke and hence spent many early mornings and late evenings engaged in teleconferences and lab meetings. The 12-hour time difference is a killer! These days, I find that I am only on such a call perhaps once a week, and that the quarterly trips to Duke allow me sufficient engagement with both my lab members there as well as the Duke leadership and faculty with regard to developments in Singapore. Of course, email is a daily, if not hourly, means of staying in touch, and there is also a
steady stream of faculty and senior officers moving between the US and Singapore, so I find that many meetings with my Duke colleagues take place at Duke-NUS.

You have stated that, despite holding important administrative roles, conducting research yourself is very important. Why is this?

I am, at my core, a scientist. It has been my passion and calling since I was quite young, and I spent the better part of a decade after college training to do it well. I still derive significant satisfaction from finding something new, from engaging colleagues in discussions and in the training of the next generation of biomedical scientists. I guess you could say that a major portion of my self-image is still directly tied to my own research programme. However, with time this is just as much, or more, tied to the success and contributions of the programmes that I had a part in developing, both here at Duke-NUS and at Duke University.

Can you illustrate the most surprising findings you have unearthed during your research career?

I would have to say that it is the accumulated evidence over the past 20 years as to just how prevalent in biology isoprenoid lipid modification of important regulatory proteins is; and the many ways in which the attached lipid can be employed to modulate key protein activities. This was not anticipated when we and others discovered the process of protein prenylation in the late 1980s.

Regarding your lab, who are your main collaborators and how do they enrich research being conducted by you and your colleagues?

Throughout my career, I have benefited enormously from collaborating on research projects. Biology is a big area, and a single person or laboratory cannot be expected to be proficient in all techniques and approaches that could provide real insight into the problem they are studying.

I would highlight two long-term collaborations at Duke University which had a real impact on our science and the field of protein prenylation. The first was in structural biology with Professor Lorena Beese, a colleague at Duke, where we solved many structures of the two enzymes that catalyse the initial step of attaching the isoprenoid to a protein. We learned a great deal about the precise molecular details of the reaction from these studies. In addition, the information was very useful to colleagues in the pharmaceutical sector who were designing drugs which targeted the enzymes.

The second collaboration was with a molecular geneticist at the University of California, Los Angeles, Professor Steve Young, in which we created mouse models lacking each of the enzymes involved in the entire prenylation pathway. Providing a great deal of information on the biological consequences of impairing particular steps in the pathway, these mice represented the first biological validation that targeting isoprenylcysteine carboxylmethyltransferase (Icmt) could have therapeutic utility. The findings led to the collaboration with my wife, Assistant Professor Mei Wang, and Associate Professor Mei Lin Go here in Singapore, which has brought together a biochemist (myself), a chemist (Go) and a clinician scientist (Wang) to embark on a drug discovery programme around Icmt as a therapeutic target in cancer.

How involved are you in developing partnerships between academia, industry and healthcare in order to realise clinical application and commercialisation of research findings?

These activities are a major focus for me these days, and are a big reason why I am still in Singapore. The research enterprise we have developed here at Duke-NUS, and in our partnership in Academic Medicine with SingHealth, is ideally situated to play a major role in the development and application of biomedical technologies. We can already count over 100 collaborative publications between Duke-NUS and SingHealth investigators, and several of the findings are already impacting medicine in a way that improves the lives of patients. Moreover, we regard partnerships and collaborations with the private sector as a natural pathway to achieve these goals. If we are successful, there should be a tangible positive impact on the health of both patients and the Singapore economy.
Singapore’s world-class medical school

Singapore’s Duke-NUS Graduate Medical School is rapidly becoming the leading School in its field, as well as a prolific producer of world-class scientific research. With five ongoing research programmes and having procured significant funding, this institution promises great scientific and medical advances in the future.

**DUKE-NUS GRADUATE MEDICAL SCHOOL** (Duke-NUS), a result of a partnership between Duke University in the US and the National University of Singapore, was set up with the ambition of not only being the best medical school in Asia, but to become an institution for excellence in health and medical research. Seven years later, it would appear that such an aim has been achieved. In terms of medical education and translational research, Duke-NUS is already world leading. So far, the School can boast over 200 medical (MD) students from more than 20 countries, with many of them studying for the unique PhD in Integrated Biology and Medicine.

However, the impressive education programmes are not the only asset Duke-NUS can be proud of. Indeed, since its establishment, the School has developed five research programmes, published over 700 peer-reviewed journal articles and fostered collaborations with other world-class institutions including Harvard University and Imperial College, as well as several pharmaceutical and biotechnology companies. Needless to say, Duke-NUS has a huge number of strings to its scientific bow and is only likely to continue to grow and produce high-quality research.

**A VAST BODY OF WORK**

There is a vibrant culture of research at Duke-NUS. The School has organised its research activities around what is called ‘Signature Research Programmes’ (SRPs), each extending from fundamental or discovery science into the translational/clinical realm. Four of these SRPs are laboratory-based; Cancer and Stem Cell Biology; Cardiovascular and Metabolic Disorders; Neuroscience and Behavioural Disorders; and Emerging Infectious Diseases. A fifth, Health Services and Systems Research, is more orientated towards public health policy with an emphasis on health economics, decisions sciences and disease prevalence/health burden modelling.

These five areas were chosen as each represents a major health burden for Singapore and the region. There also needed to be good reason, or a competitive edge, for conducting the studies in Singapore – such as access to unique populations, technologies and expertise. Examples include major projects on autism and schizophrenia, gastric cancer, myopia and dengue. Additionally, the nature of the Singapore healthcare system provides unique opportunities to study health sciences, an example being ageing and the impact of a rapidly ageing society on healthcare needs and delivery.

Professor Patrick J Casey, the Senior Vice Dean of Duke-NUS, sums up the School’s research goals: “The School does not want to support research that is second to something done elsewhere – it should be research that leads its field”. Enhancing research conducted at Duke-NUS are important partnerships that are mutually enriching. First, the partnership between NUS and Duke is paramount to all activities. Each of the research areas links back to major programmes at Duke University, and the Duke-NUS graduate-entry four-year MD training programme is based on the unique Duke model of education, with one year dedicated to independent study and research projects on basic science or clinical aspects of research. Second, a major collaboration between Duke-NUS and SingHealth – the largest healthcare group in Singapore – aims to boost the exchange of ideas and research findings among scientists and clinicians at the two institutions, allowing progress to be made at a much faster pace.

A more specific example of the research taking place at Duke-NUS is that carried out by Casey and his colleagues on guanine nucleotide-binding regulatory proteins (G proteins). They have been deciphering the mediatory role of G proteins to transmembrane signalling in cells. The most recent findings in this regard, which will soon be published, involve the processes by which activation of specific G proteins – the G12/13 proteins – is able to elicit the secretion of
particular factors which facilitate the metastasis of cancer cells, and also how the activities of these G12/13 proteins are elevated during the metastatic process.

Furthermore, researchers at the School are close to translating these findings on the enzymes that catalyse G protein prenylation (a type of lipid modification) into effective anti-cancer therapies. The investigation has focused upon the enzyme named isoprenylcysteine carboxymethyltransferase (Icmt), much of it being done by Assistant Professor Mei Wang. Wang is a clinician scientist who has teamed up with a pharmaceutical chemist at NUS, Associate Professor Mei Lin Go, and Casey to develop inhibitors of Icmt that show great promise as anti-cancer agents, both in cancer cells and in mouse tumour models. The challenge now is to complete the pre-clinical development of these compounds and produce just the right form that can be effectively and safely delivered in humans so that clinical trials can be initiated.

FRONTIERS IN TRANSLATIONAL MEDICINE

More than a year ago, Casey was involved in organising a symposium on ‘Frontiers in Translational Science: From Preclinical to Clinical Investigation’. Since then, he has been reflecting on this subject: "The frontiers in medicine and biomedical research are always shifting," explains Casey. "I feel two of the major frontiers right now are the ever-growing appreciation of the critical roles that non-coding RNAs have in controlling gene expression and function of gene products, and the enormous potential of being able to create stem cells from individual patients, both for understanding the molecular basis of their disease but also to hopefully create a tailored therapy for the disease."

Indeed, the advances in genomic technologies over the past few years serve to prove Casey’s point. Duke-NUS therefore puts much attention on computational and analytical technologies with the hope that these can evolve as rapidly as the advances they are making in genomic technology. This way, the School’s researchers have a much better chance of being able to process and understand all of the data they are obtaining. Similar progress is being made at Duke-NUS in the area of imaging, both at molecular, tissue and organism levels, providing unprecedented insight into biology processes and what goes awry in disease. There is renewed hope by scientists at the School that together these advances will lead to a new era in medicine, so-called stratified or personalised medicine, whereby a doctor could rapidly determine the precise cause of an affliction and prescribe the treatment regimen specifically tailored to the patient’s biology and that of their disease.

A BRIGHT FUTURE

A major element of Duke-NUS’ research hopes for the future includes the development of new cancer drugs or therapies. Within five to 10 years, it is expected that new technologies and approaches will allow researchers at the School to more accurately determine the major driving events in a particular cancer, so that oncologists can reach into their arsenal of drugs and pick the right one for that particular patient. Furthermore, if the cancer comes back, the molecular events that drive that recurrence can be rapidly identified, and the right drug can be chosen once again.

Examples of success in this arena are already emerging at Duke-NUS, where collaborations with colleagues in the National Cancer Centre (see p32) of SingHealth have led to the identification of molecular determinants underlying disease progression and response to therapeutics in leukaemia and certain forms of lung, gastric and liver cancers. Through this process, cancer should be transformed from a life-limiting illness into a disease that is managed; similar to the management of diabetes and heart disease: “I am not at all enamoured by statements about ‘curing cancer’,” Case y exclaims. “I feel these statements are misleading, and are doing more harm than good of late in trying to communicate with both the population and the decision makers in government just what progress has been made and what we can expect to achieve with the funding that is provided for research. The term ‘controlling cancer’ is much more appropriate.” Indeed, cancer is a very complex compendium of hundreds of different diseases. However, while a ‘cure’ for all cancers may never be found, it is certain that Duke-NUS, through its multi-faceted research, will be leading the way in providing the very latest breakthroughs in drugs and therapies for years to come.