Where do new clinical treatments come from? Translating knowledge into practice

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According to the Australian Institute of Health and Welfare, we gained over 25 years of extra life expectancy during the 20th century. These extra years have resulted largely from development of public health measures, vaccines and antibiotics that have reduced the impact of infectious diseases on a global basis. These interventions are the tangible result of medical research conducted by health care professionals and scientists worldwide. Over the last 100 years, there has been a slow but steady revolution in the way that medical research is conducted. What was once the province of hobby scientists, working alone in spare time and using their own funds, in lab space hidden away in hospitals and medical schools, has become a multi-million dollar business, conducted in large biomedical research institutes by professionally trained government and industry funded scientists and clinician scientists. Why has this change come about, and where is this leading?

The early drivers of medical research were the desire of the health care professions to ensure better health outcomes for their patients, and the curiosity of scientists about human physiology and pathophysiology, and these remain relevant today. However, as the technologies available for research have become more sophisticated, and the existing knowledge base more extensive, research has required more prior education, more sophisticated facilities, more collaboration, and more money. Further, the funding model for universities, the traditional trainers of researchers, has changed to one driven by quantity of throughput in addition to quality of output. In consequence, further drivers have emerged which have encouraged a more commercial and managed approach to research. These include desire of universities to maximise student numbers and research grants, government desire to see outcomes from research at affordable prices, and a growing "for profit" pharmaceutical industry hungry for the next blockbuster product, that might be expected to sell over $1billion per annum in the first years of launch. These drivers have increasingly led to focusing of research into institutes that can compete on a world playing field for resources and talent, and can afford the increasingly sophisticated infrastructure of the large scale "hypothesis free" approach to biology currently being practiced.

These drivers will likely continue to influence the conduct of medical research in the first decades of the 21st century, though some new ones have recently emerged. The supply of blockbuster drugs has largely dried up, at a time when many of the major successes of recent years are about to come off patent. This appears in part to be due to the pharmaceutical industry becoming a victim of its own success. Many of the commoner chronic diseases that require ongoing therapy already have a choice of successful drugs available: the space in the market for new ones is correspondingly limited. The future successes will likely be niche market high value products and, if current trends continue, the majority of these will be biopharmaceuticals, naturally occurring protein or peptide signalling molecules and biomimetics of these, including antibodies, and soluble receptor molecules, rather than small molecules screened from synthetic libraries for biological activity in *in vitro* assays.

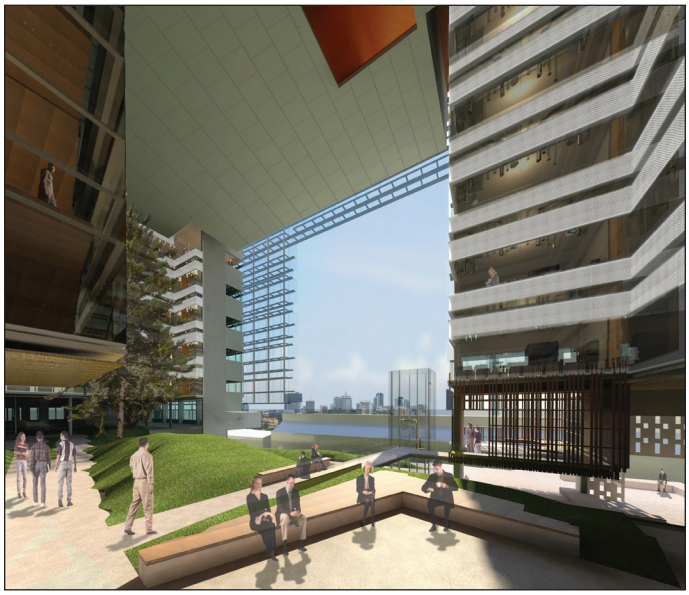

Figure 1. *The Outdoor Room – a focus for collaborative activity (© Wilson Architects and Donovan Hill. Reproduced with permission).*

As we understand more of the genetic determinants of risk of chronic disease, the significance of genetically engineered animal models of these diseases for successful research will increase. These models will become a key component not only of the understanding of pathophysiology of chronic disease, but also of testing of interventions to manage, and increasingly to prevent, these diseases. A further driver of change will be the perhaps belated realisation by "big pharma" that while they are now well experienced in the manufacture and global distribution of drugs, their in-house research programs are now generally less productive and more expensive than those of universities and research institutes. Outsourcing of research from industry to academia, already widely practiced, will likely become the preferred model.

A successful future for biomedical research will likely require a partnership between government and industry to meet the costs of development of the new products required for prevention and amelioration of the common chronic diseases of an ageing population; indeed, one estimate is that more than a third of these costs are already met from the public purse, one way or another. The challenges we face with an ageing population seeking not just a long life but a long and healthy one will include dementia, mental illness, cancer, arthritis and other musculoskeletal degenerative disease, metabolic disease (type two diabetes and other consequences of obesity) and cardiovascular disease.

So what will the research institute of the near future look like, if designed to address these multiple drivers? Probably, it will resemble the new Translational Research Institute (TRI) currently being constructed in Brisbane. Institutes will likely be located in the

grounds of a major government funded teaching hospital with a strong track record in clinical research and innovation, such as the Princess Alexandra Hospital or the Mater Hospital in Brisbane, to ensure close contact with the clinical world. They will be an active part of an Academic Health sciences centre, like the newly created Diamantina Health Partners, which will bring together ten agencies responsible for health delivery on the south side of the Brisbane River, so that the institute can contribute to selection and training of key staff with teaching, research and clinical service responsibilities across several hospitals and clinics, covering the spectrum of clinical care.

Figure 2. *The North East Corner of the Translational Research Institute Facility (© Wilson Architects and Donovan Hill. Reproduced with permission).*

These "super-institutes" will bring together researchers from several different disciplines and technologies, possibly combining existing successful institutes, to share the necessary but expensive and short lived state of the art infrastructure, and to make efficient use of talent and promote scientific interactions. The Translational Research Institute, which is not so much a new building under construction as an alliance of research groups, will bring together the University of Queensland Diamantina Institute, the Mater Medical Research Institute, the Princess Alexandra Hospital Centres of Research Excellence, and the Queensland University of Technology Institute of Health and Biomedical Innovation. These partners will work in state of the art premises on two campuses, where the latest technologies for biomedical research – high speed nucleotide sequencing, proteomics, flow cytometry, animal and cell imaging, animal models of disease – will interface with clinical research facilities.

The institute of the future will likely incorporate the necessary facilities for making and testing new drugs, to facilitate their translation into clinical practice. TRI will, for example, have a facility, Biopharmaceuticals Australia, which can manufacture biopharmaceuticals to Good Manufacturing Practice standards and to a large enough scale to enable clinical trials to be conducted with locally made materials. This facility, which will be operated by a world leader in biopharmaceuticals manufacture, DSM biologics, will be available not only to the researchers from the Translational Research Institute but also more widely to the Australian Research community to facilitate conduct of clinical trials in Australia, of products arising from Australian research.

However, these technical details of what the research institute of the future will need for success do not really convey the philosophy of what I believe will be necessary for the Translational Research Institute to be successful in its ambition of sharply increasing the rate of translation of research knowledge into clinical practice. Rather, success will require bringing together people from diverse backgrounds and training, with a common passion to contribute not only to their own research programs but also to those of others, and to the training of the next generation of scientists and health care professionals.

The research focus will be on clinical problems, rather than scientific disciplines, hardly a new idea but one more often paid lip service to than put into practice, and the research standard will need to be competitive on a world stage to justify the considerable ongoing investment in the work of the institute by government and industry. These two requirements will mandate that the number and focus of the research programs undertaken will necessarily be limited: while a broad focus on cancer, metabolic medicine, infection and inflammation will be apparent, teams will be established which will focus on more specific aspects of these broad pathophysiological problems – for example, prostate and skin cancers, the metabolic syndrome associated with liver disease, autoimmune diabetes, and genetically determined inflammatory arthritic disease. Inevitably these diseases of particular interest will be the ones in which clinical expertise in the associated hospitals matches with local availability of realistic animal models of these diseases, and strong researcher interest in their underlying pathophysiology. These characteristics are the most likely to ensure that new insights from the research program will more easily cross the "valley of death" from the research bench to the clinic, leading eventually to new treatments.

The major driver of research innovation has been, and will continue to be, interactions between researchers across boundaries – interactions between scientific disciplines (mathematics, engineering, chemistry, biology); those that cross technologies (protein analysis, animal modelling) and those that cross the age boundaries (students with risky new ideas interacting with researchers who are more experienced but more conservative). The Translational Research Institute has been designed to encourage these interactions – meeting places abound, and traditional boundaries between craft disciplines will be discouraged in the layout of the facilities, and in the planning of meetings and other professional interactions.

As always, the most useful meetings will be casual conversations over coffee, and these will also be catered to. One interaction that TRI is particularly designed to encourage is to bring together the clinicians that trial new treatments with the product engineers that will produce them and the scientists that design them – an early reality check on the feasibility of a particular approach to solving a clinical problem will be the goal. Another interaction to be encouraged will be between the next generation of scientists and the current generation – SPARQ(Ed), a joint initiative of the Institute and the Queensland Government Department of Education, is a program that brings young scientists from school years 10-12 into working labs in the Institute where, mentored by active researchers, they will conduct research as part of the program of their mentors, and in the company of their school science teachers. This exposure is designed to encourage these up and

Figure 3. *Construction of the Translational Research Institute Facility.*

coming scientists to realise that their contribution to knowledge will be valuable at all stages of their careers. A further significant interaction to be encouraged across boundaries is geographical. Research students within the institute already come from every continent of the world (except Antarctica) and each brings a different perspective on the value of particular research objectives for their country, and a different approach to the appropriate methods for developing new knowledge in research.

Creation of the Translational Research Institute is, like the conduct of all medical research, an experiment. As with all experiments, there is risk, and uncertainty of outcome, but the potential benefits are considerable, and strategies are in place to mitigate the risks, which seem small in comparison with the risks of continuing to run clinically focused research as a small scale activity when the rest of the world is moving towards a different scale of activity. I was delighted to be offered the opportunity to be the first CEO and research director of the TRI, but would be the first to acknowledge that while my position comes with the responsibility of making the experiment a successful one, the major determinants of success will be the commitment of the partner institutions, and the scientists and clinicians who drive the research. The institute will succeed to the extent that they make TRI, when it opens in 2012, a world leading research institute and a model of how partnerships between government, industry and the research community can ensure a continued healthy future for the people of Australia and elsewhere. I hope that many of those of you reading this article will become a part of that success story!