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IN SHORT

REFLECTION ON THE QUEENSLAND BRAIN INSTITUTE'S GROWTH AND DIRECTION

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The article details how Professor Bartlett realised his vision of creating a unique scientific environment in which to discover the fundamental mechanisms that regulate brain functions like learning and memory through the formation of the Queensland Brain Institute (QBI). The establishment of the QBI came about through the prescient support of philanthropist Chuck Feeney, Queensland Premiers Beattie and Bligh and The University of Queensland Vice Chancellor John Hay. This underpinned the ability to recruit a team of outstanding neuroscientists from around the world and around Australia and ensured the QBI was equipped with state of the art technologies. Although, the QBI has been in its new building for three years, the success of the venture already is evident by its peerless grant and fellowship success, and its output of highly cited publications positioning it as a pre-eminent neuroscience research institute within the Asia-Pacific region.

As the founding Director of the Queensland Brain Institute (QBI), my vision was to create a unique environment in which outstanding neuroscientists working across a range of sub-disciplines and animal models could interact and collaborate to discover the fundamental mechanisms regulating brain function in health (learning, memory, attention) and disease (developmental and neurodegenerative disorders, mental illness). My *raison d'être* for this was the belief that a deeper understanding of these mechanisms would create the opportunity to develop novel therapeutic approaches to address the tidal wave of neurological and mental illness in our community. Furthermore, I was convinced that the application of discoveries about learning, memory, and attention would provide the basis for radically improved outcomes in academic and occupational education, from childhood to old age, through the development of a new discipline, the 'science of learning.' In addition, understanding of sensory and motor systems provided the potential to develop a variety of rehabilitation strategies, robotic sensors and even in-flight guidance systems for unmanned vehicles.

However all of the above advances would rely on elucidating how nerve cells in the central nervous system were able to respond and adapt to changes in external stimulation by changing their pattern of connections (synapses)—a process known as brain plasticity. Thus brain plasticity in its many forms became the centrepiece of our research endeavours, being both the primary determinant of brain function as well as offering the malleability to promote repair following disease, injury or even the effects of normal ageing.

Recruitment of researchers to QBI was based on this concept, beginning with a cohort of neuroscientists interested in the cellular plasticity generated by new neuronal production. These included members of my own group and those of Dr. Elizabeth Coulson and Dr. Rodney Rietze, who transferred from the Walter and Eliza Hall Institute (WEHI) in Melbourne, as well as Professor Brent Reynolds,

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the co-discoverer, with my research group, of neuronal stem cells in the adult brain, who joined us from Canada. The drive to understand synaptic plasticity was initially spearheaded by Professor Pankaj Sah's group from the John Curtin School of Medical Research at the Australian National University (ANU) in Canberra. However this cohort has since been expanded by the inclusion of a number of outstanding UQ neuroscientists (Professors Joseph Lynch and David Adams and Associate Professor Frederic Meunier), as well as Associate Professor Stephen Williams, who has recently joined us from the University of Cambridge. Linking electrophysiology-based research with cellular- and molecular-based studies has proven a major success, most notably leading to discoveries about how learning and memory are regulated in two key regions of the brain, the hippocampus and the amygdala. This work was driven in part by a major five year NHMRC Programme Grant to myself and Pankaj Sah, the only such grant to be funded to investigate basic neuroscience. This work is now continuing with our second NHMRC Programme Grant, which commenced in 2009.

Axonal guidance was another key area of plasticity research, spearheaded by the recruitment of Professors Linda Richards and Geoffrey Goodhill from the USA, together with Associate Professor Helen Cooper from WEHI More recently, Dr. Massimo Hilliard from Rockefeller University has established a laboratory using the nematode *C. elegans* as a model. Together, these scientists have made major discoveries regarding the molecular guidance of axons, a process that is essential for the correct wiring of the nervous system. In a related line of investigation, work from my own laboratory has identified the importance of the molecule EphA4 in preventing the regrowth of injured axons, with therapeutics designed to block its deleterious effects nearing clinical trial for the treatment of spinal cord injury.

Having established this nucleus of researchers, the next phase of recruitment centred on developing a system-wide understanding of these regulatory processes by focusing on the whole animal. In this regard, we have taken an eclectic approach in our choice of animal models, which range from the fruit fly *Drosophila* and the honeybee through *C. elegans*, to rodents and ultimately humans, in the belief that each offers particular but complementary advantages. We have recruited a very high profile group of scientists to lead these studies: Associate Professor Bruno van Swinderen from the Neurosciences Institute in San Diego, Professor Mandyam Srinivasan and Drs. Judith Reinhard and Charles Claudianos from the Research School of Biological Sciences at ANU, and neuropsychologists Professor Jason Mattingley and Associate Professors Ross Cunnington and Mark Bellgrove from the University of Melbourne. Collaboration between these groups has flourished since we relocated to the new QBI building, with joint programmes being developed based on common behavioural assays that can be applied in organisms as diverse as *Drosophila* through to humans. Discoveries from these groups are providing new insights into the mechanisms regulating how attention is directed during learning. Meanwhile the Srinivasan group is revolutionising our concepts of optic flow during flight, navigation and distance measurement based on knowledge obtained from the visual-motor system in honeybees. Similarly, work on the visual system from Professors David Vaney and Justin Marshall's laboratories are revealing the fundamental retinal pathways that mediate vision in a variety of animal models.

Another key area we identified as integral to our success is computational neuroscience. Driven by Professor Goodhill, our ability to construct testable computational models of plasticity is beginning to complement much of our research. The awarding of one of only three multi-million dollar ARC/NHMRC five year special research initiative Thinking Systems grants has allowed us to expand our capabilities in this area and foster numerous productive collaborations with computational scientists. This exciting development is already providing new insights into hippocampal and amygdala learning at the neuronal and systems levels.

Another large five year ARC grant with Professor Max Lu from the Australian Institute of Bioengineering and Nanotechnology and Professor Dongyuan Zhau from Fudan University has seen us establish one of the first groups in the area of Nano-Neuroscience, with Associate Professor Helen Cooper as the lead biologist. Already this has led to the development of nanoparticles to deliver drugs across the blood-brain barrier, a key advance that has both therapeutic and research applications. We are also investigating nanotechnology-inspired approaches to molecular magnetic resonance imaging (MRI) and brain recording and stimulation, the latter opening up the exciting possibility of developing nanoelectrodes to stimulate and record from large numbers of synapses at the one time, thereby creating a more complete picture of how networks influence behaviour.

More recently, we have expanded our research capacity by fostering the experimental programmes of a number of outstanding basic and clinical neuroscientists exploring the genetic basis of disease susceptibility. These include Professors Bryan Mowry, and John McGrath, Dr. Darryl Eyles and Dr. Tom Burne (schizophrenia), Dr. Tim Bredy (epigenetic basis of anxiety-related disorders), Associate Professor Mark Bellgrove (autism and ADHD), Dr. Robyn Wallace (MND and epilepsy), Professor David Reutens (epilepsy and stroke) and Professor Linda Richards (developmental brain disorders). The addition of psychiatrists and neurologists to the faculty has also enhanced the potential for clinical translation. In this regard I am particularly pleased that two of our early discoveries are nearing the clinical phase for treatment of spinal cord injury and multiple sclerosis, and that we hold many patents related to other neurodegenerative conditions, including ageing dementia and Alzheimer's disease.

To give us a competitive edge in this field we have also recently formed an alliance with the Second Military Medical University to establish a Neurogenetics laboratory in Shanghai, which will allow us to recruit large cohorts of patients for genotyping and possible future clinical trials. To facilitate this initiative we have appointed the Clinical Director in the Changzheng Hospital, Professor Huji Xu, to the faculty of QBI. This development also coincides with major advances in gene sequencing technology which now enable us to perform gene-sequencing including epigenetic sequencing, very rapidly and in fine detail. In order to ensure we are able to advance as quickly as possible in this competitive area, we are currently installing an Illumina next generation sequencer. As an example of how the animal models are complementing this research, we are now using *Drosophila* to explore the function of genes identified in these human screens, as the powerful genetics of this model allows us to rapidly link genes to behaviour and disease. Our capabilities in this area have been expanded by the forging of strong collaborative links with the Chinese Academy of Science's Institute of Biophysics (IBP) in Beijing, which hosts a world- renowned *Drosophila* group headed by Professors Aike Guo and Li Liu. We recently received three million dollars in an NIRAP grant to facilitate the establishment of a joint laboratory with the IBP, which we believe places us and Queensland at the forefront of the burgeoning Chinese research endeavour in biological sciences.

However, one undeniable truth of modern neuroscience is that maintaining a leading research profile requires a significant investment in providing the best technology available. In addition to our recruitment strategy we therefore also acknowledged the importance of infrastructure support, beginning with the establishment of the world's largest and best neuroscience-dedicated flow cytometry facility, an advanced microscopy suite, and a behavioural facility. However, of primacy in this regard was our belief that QBI would have to establish advanced imaging technologies such as MRI and positron emission tomography (PET) if we were to be able to translate our findings and test hypothesis directly. This has taken considerable effort, but has ultimately resulted in the creation of a Centre for Advanced Imaging to be housed in a new purpose-built $50,000,000 building in the same precinct as QBI. We are also delighted to have recruited as the Centre's inaugural Director Professor David Reutens, previously Director of Neurology and Professor of Neurosciences at Monash University, and through intensive grant applications have successfully obtained funding for a suite of imaging technology second to none, which includes 16.4T and 9.4T MRI scanners and a PET/MRI system for animal studies, as well as 7T, 4T, and 3T MRI scanners for human research.

In summary, the recruitment of a highly talented and well-resourced team of neuroscientists has underpinned our success, exemplified by our peerless grant and fellowship success. However, this level of achievement could not have been attained without the generous and farsighted support I have received from many parties since arriving from Melbourne in 2002. A confluence of foresight by three major Queensland figures, Premier Peter Beattie, Vice-Chancellor Professor John Hay and philanthropist extraordinaire Mr. Chuck Feeney delivered the $65,000,000 required to build the QBI. Wonderfully designed by the gifted architect John Wardle, it was opened by Premier Anna Bligh in October 2007 who announced a further $25,000,000 to support our operations. The current Vice-Chancellor, Professor Paul Greenfield, has continued with visionary support and the QBI has been enormously lucky to have the support of several high-profile community figures such as David Merson, Sallyanne Atkinson, and Jeff Maclean, and philanthropists Peter Goodenough and Ross Maclean, amongst many others. I hope and believe these investments and support have already returned significant economic benefit to the people of Queensland, but that this return pales beside the contribution that our scientific discoveries will make to health and education of the people of Queensland over the coming years.