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Robert Lyndsay Sutherland 1947–2012

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Professor Rob Sutherland, AO, FAA was an internationally recognized pioneer in the application of molecular and cellular biology approaches to the translation of research discoveries into more effective prevention and treatment of cancer. Over his career he made significant contributions to the understanding of the pathophysiology and molecular basis of breast, prostate, pancreatic and other cancers and applied this knowledge to the discovery, validation and development of new biomarkers of disease phenotype, prognosis and response to therapy.

Introduction

Professor Rob Sutherland AO, FAA (pictured here in 2011)[1] was Director of the Cancer Research Program, Garvan Institute of Medical Research, Sydney, and the inaugural Director of the Kinghorn Cancer Centre, Garvan Institute of Medical Research, St Vincent's Hospital, Sydney until his death from pancreatic cancer on 10 October 2012. He was an NHMRC Senior Principal Research Fellow for more than 20 years, and Conjoint Professor in the Department of Medicine, St Vincent's Hospital Clinical School, University of New South Wales. His research on the role of steroid hormones in the pathophysiology of breast and prostate cancer and the development of biomarkers and therapeutic targets to aid clinical management of several common cancers (breast, prostate and pancreas) was at the forefront of these fields internationally. Rob's achievements were recognized by the award of the Ramaciotti Medal for Excellence in Biomedical Research

ample room for two boys passionate about cricket and rugby to amuse themselves, notwithstanding the disrespect of the local cows for their cricket pitch. It also provided ample room for a flourishing vegetable patch that Rob strove to replicate later in life. As well as placing first in general science and chemistry in his final years at Ashburton High School, Rob was a member of the first rugby XV and first cricket XI and already displayed his characteristic 'happy knack of being able to mix with all types'. He remained a passionate supporter of All Black and Canterbury rugby, and an enthusiastic cricket follower, throughout his life.

When the time came to go to university, Rob was awarded the John Bell Memorial Scholarship (1965–8) and enrolled in the agriculture course at Lincoln College near Christchurch (then part of the University of Canterbury, and now Lincoln University). He graduated with a BAgrSci in May 1969, b>>BDC 0ioaoaoQ4u (i)-2 (t)4.6 emorial Scholar
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broader base for existing interests. His mandate was to strengthen Garvan's research capabilities in the areas of cancer and cell biology. Rob had a very clear vision for the department that he led for more than 27 years (initially the Cancer Biology Division, and later the Cancer Research Program) as one that addressed areas of major clinical importance through an integrated program of research, rather than being a 'research hotel' and so he began to establish a cohesive structure of complementary research groups under his overall leadership. This structure

had speculated that tamoxifen (and by extension, other steroid receptor ligands) might directly regulate the cell cycle machinery,[7] and subsequent detailed cell cycle kinetic experiments within the laboratory had added further weight to this idea. Although the obvious next step was to identify steroid-responsive genes that might have a role in controlling the cell cycle, very little was known about the molecular mechanisms that governed progress from one cell cycle stage to the next in mammalian cells, and few steroid target genes had been identified since the available methods for doing so were cumbersome and labour-intensive. The proto-oncogene *MYC* was an exception in that it was known to be steroid responsive and to have a role in controlling the cell cycle. In 1991, the laboratory showed that *MYC* was regulated by progestins within 1–2 h, one of the earliest detectable transcriptional responses to progestin treatment known at the time and a potential mechanism connecting progestin action to the cell cycle. However, a revolution was underway in the cell cycle field, and over the next few years many of the key components of the cell cycle machinery were identified.

The cyclin-dependent kinases (CDKs) and the cyclins that activate them were initially identified in yeast, sea urchins and frogs and subsequently shown to be functionally equivalent throughout evolution.[10] The idea that cell cycle control mechanisms were conserved at that level of molecular detail was ground breaking and opened the way for much more rapid progress in understanding the mammalian cell cycle. When the news of the discovery of the first mammalian G_1 cyclins reached the laboratory in 1991, it was clear to Liz Musgrove and Rob that if these genes had roles that paralleled the functions of the homologous yeast genes, they were potential mediators of steroid effects on the cell cycle. The detailed understanding of how steroids and steroid antagonists regulated cell cycle progression that the laboratory had gained over the previous decade provided the launching pad for experiments which showed that G_1 cyclins such as cyclin D1 were indeed steroid regulated, and that this preceded detectable effects on cell cycle progression after progestin or antioestrogen treatment, meaning that they were not simply a consequence of changes in cell cycle position.[11] Using a zinc-inducible vector brought to the laboratory by Roger Daly, a new recruit who went on to lead the Signal Transduction Group within the Cancer Research Program for the next two decades, Liz and her colleagues showed that cyclin D1 was rate-limiting for cell cycle progression in G_1 phase in breast cancer cells, establishing cyclin D1 as a cell cycle regulator in epithelial cells.[12] They also showed that it was sufficient to re-initiate cell cycle progression in mitogen-depleted breast cancer cells, with the implication that deregulation of cyclin D1 could contribute to the loss of growth control during oncogenesis.[12] Complementary translational studies within the laboratory showed that cyclin D1 is one of the most commonly overexpressed oncogenes in breast cancer.[13] These papers were amongst the first to characterize mammalian cyclin expression, regulation and function, and they established Rob's laboratory at the forefront of cell cycle research in breast cancer, with the translational study recognized internationally as amongst the 20 most significant breast cancer publications of the decade 1990–2000.

Over the next five years or so an intensive research effort worldwide mapped out the main features of the mammalian cell cycle machinery. Because of the multiplicity of possible cyclin-CDK complexes, the presence of two families of small molecular weight endogenous CDK inhibitors, and the regulation of CDK activity by multiple phosphorylation/dephosphorylation events it is not a simple matter to predict the consequences of regulating the abundance of any of the cyclins or CDK inhibitors. Dissecting how steroids and steroid antagonists regulated these interdependent CDK complexes and identifying which elements of the response were causative occupied the cell cycle team within the Cancer

earliest stages of the project. During 1994 he and John Grygiel, a medical oncologist based at St Vincent's Hospital, began discussions that led to a translational prostate cancer group being established within the Cancer Research Program. Having agreed to differ on the relative merits of All Black and Wallaby rugby, Rob and John continued their discussions over daily coffee at Bar Coluzzi for the next two decades. Links were established with the Departments of Urology and Anatomical Pathology at St Vincent's Hospital so that the collection of both archival tissue specimens and prospective fresh–frozen specimens could begin, and a postdoctoral scientist (Susan Henshall) and PhD student (David Quinn, a medical oncologist) were recruited to undertake the task of tissue acquisition. Susan Henshall went on to coordinate translational research within the department for more than a decade, while the tissue bank became one of the world's largest and best-annotated prostate cancer tissue collections: fresh–frozen radical prostatectomy specimens from >2000 men and >1200 archival tissue blocks, with long-term clinical follow-up documented in a purpose-built database.

The growing reputation of the prostate cancer tissue bank and databases and their potential value for translational research led Andrew Biankin, an upper GI surgeon, to join the Cancer Research Program in 1999 with the intention of developing a similar resource for pancre-

kinases activated by cyclin D1 could be successful therapeutically, but it was also a clear demonstration that insights from studying basic cancer biology can lead to improvements in patient outcome and disease management, concepts that underpinned Rob's research career.

Molecular Oncology

Rob's conviction that a bedside-to-bench approach, where clinical observations [illegible]

directly drive laboratory research and maximizing the rapid translation of research findings into improvements in diagnosis and treatment outcome. Strategic development of this initiative began in 2006 with support from the Boards of