

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 in 2000, election to the Fellowship of the Australian Academy of Science (FAA) in 2002, the NSW Premier's Award for Outstanding Cancer Researcher in 2010 and Honorary Fellowship of the Royal Australasian College of Surgeons (RACS) in 2012. He was awarded a Centenary of Federation Medal for service to Australian society and science in molecular and cellular biology in 2003 and became an Officer of the Order of Australia (AO) in 2010, in recognition of his distinguished service to medicine as an international contributor to cancer research, the development of Australia's research capacity and through leadership roles on advisory bodies.



Early Life and Education

Robert Lyndsay Sutherland (known as Rob) was born on 18 July 1947 in Gore, in the heart of New Zealand's South Island. His parents, Jesse Manson Sutherland and Doris Sutherland (née Baxter), were schoolteachers, born of Scottish emigrants, who passed on the Scottish characteristics of fierce independence, loyalty and strength of character to Rob. They also instilled strong beliefs in the value of education, fair play, hard work and integrity.

Most of Rob's memories of growing up centred on Ashburton, on the Canterbury plains south of Christchurch. The Sutherlands (including Rob's younger brother Alistair) moved there during the 1950s, to a family home that provided

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 BAgSci in May 1969, but continued to study at Lincoln with support from a NZ Wool Board Scholarship (1969–70), and was awarded a MAgSci (Hons I) in March 1971. These degrees included a strong grounding in biological science, particularly animal physiology and reproduction, and had an emphasis on the practical—summers spent working on various farms across New Zealand were part of the course requirements.

Rob formed lifelong friendships at Lincoln, and many of his interests can be traced back to this time. He was delighted to be awarded a DSc *honoris causa* by Lincoln University in 1994. The importance to Rob of the practical application of his research, a recurring theme throughout his scientific career, may have stemmed from principles embedded in his courses at Lincoln, and was certainly fostered by his time there. His MAgSci thesis work on 'Measurement of Total Thyroxine Levels in Bovine, Equine, Ovine and Porcine Plasma' set the foundation for a career-long interest in hormone action, and brought him into contact with his friend and mentor Cliff Irvine, at the time a lecturer in veterinary science at Lincoln. Irvine was internationally recognized for his academic work on equine endocrinology and reproduction, and was also a successful and well known racehorse trainer. In later years, Rob's love of horses and horseracing led to part-ownership of several horses. Of these his favourite was Ticklish, a mare whose

talents as a sprinter were a source of enormous pride and enjoyment.

Hormone Binding Studies

In 1972, Rob moved to Australia to enrol in a PhD in the Department of Experimental Pathology at the John Curtin School of Medical Research, Australian National University (ANU), Canberra, under the supervision of Max Simpson-Morgan, a collaborator of his Lincoln mentor Cliff Irvine. Rob thrived in this environment, surrounded by intelligent and critical colleagues and mentors who would stimulate and encourage his ideas, as well as challenging them. Key amongst these were Mal Brandon, with whom Rob worked closely after Max Simpson-Morgan took up a position at the University of Queensland; Bede Morris, the newly appointed Head of the Department of Immunology at the JCSMR; and Frank Courtice, Rob's Head of Department, who took a keen interest in Rob's work.

Rob's PhD thesis, 'Studies on Plasma Thyroxine-binding Proteins', focused on thyroid metabolism and the transport of thyroid hormones. Radioligand binding assays for thyroxine are both technically exacting and analytically challenging, but Rob eventually developed a robust and reproducible ^{125}I -labelled thyroxine competitive binding assay, a task that took two of the three years allowed for the PhD degree at ANU, and required all of his considerable skills at the laboratory bench for success. He was able to demonstrate that there were three thyroxine-binding proteins in sheep serum, and quantify their thyroxine-binding properties. Mal Brandon was his surgical partner, and together they undertook numerous complex surgeries such as the cannulation of fetal sheep *in utero*, unimpaired by their habit of putting the world to rights over Friday lunch at the ANU Staff Club in University House.

Bede Morris had pioneered techniques for long-term lymph collection from both adult and fetal sheep and he became a trusted mentor and friend to Rob. Both shared deep-seated agricultural roots, an enthusiastic zeal for both science and life in general (exemplified by a 'deep and sincere love of France...especially its wine', and the pursuit of excellence as a gardener, particularly as a vegetable grower) and 'forceful and fearless defence of what he believed to be right'.² Morris was influential in securing

Rob a postdoctoral position with Etienne-Emile Baulieu in Paris, although this did entail the loss of Morris's secretary, Dianne Summerhayes, who married Rob in 1973.

In 1974, Rob joined the Department de Chimie Biologique, Faculte de Medecine de Paris-Sud, as a Searle Travelling Fellow in Endocrinology and CSIRO Post-Doctoral Fellow. By the mid-1970s evidence was emerging that tamoxifen was effective in advanced breast cancer and this pioneering targeted therapy eventually became a mainstay of breast cancer treatment for several decades, prolonging the lives of millions of women.³ Addressing the question of how tamoxifen's anti-oestrogenic and anti-cancer activity were mediated became a major theme throughout Rob's career, beginning with receptor-binding studies in Paris. With Ján Mešter, he provided evidence that the ligand plays an important role in determining the final activity of the ligand–nuclear receptor complex. This conclusion was at odds with the prevailing theory that oestrogen antagonism was due to inhibition of cytoplasmic receptor replenishment, but was subsequently found to be correct.

Antioestrogen Binding Sites

Rob returned to Australia after three years in Paris. After a brief but productive period in the CSIRO Division of Wildlife Research in Canberra studying the reproductive endocrinology of the Tammar wallaby, he moved to Sydney in late 1977 with his young family, including his son Andrew, who was born earlier that year. The new Human Cancer Therapy Unit of the Ludwig Institute of Cancer Research at Sydney University had advertised for group leaders, including a biochemist 'to establish a laboratory to measure steroid receptor proteins in human tumour specimens'. This was tailor-made for Rob, and allowed him to build on his experience in steroid hormone receptor binding in a setting where his commitment to making what is done *in vitro* relevant to the situation *in vivo* could be applied to human health. He rapidly established a strong laboratory that focused on unravelling the determinants of the anticancer activity of antioestrogens. Key questions were how antioestrogens worked at the level of receptor binding and subsequent biochemical steps and what factors determined their potency.

Tamoxifen and other triphenylethylene antioestrogens can act as either oestrogen agonists or antagonists, depending on the species, organ or tissue examined. It was difficult to account for this complex pharmacology in terms of binding to the oestrogen receptor alone, and in the early 1980s the molecular basis of oestrogen antagonism was a topic of considerable debate. One of the first discoveries of Rob's laboratory was that tamoxifen interacts with a high affinity, intracellular antioestrogen binding site that is distinct from the oestrogen receptor,⁴ raising the possibility that some of its activity was not oestrogen receptor-mediated. Leigh Murphy and C. K. W. (Charlie) Watts continued the work by characterizing the structural requirements for antioestrogen binding to both the oestrogen receptor and antioestrogen binding site. Over the next 5–10 years it became increasingly clear that the antioestrogen binding site was not directly involved in mediating antioestrogenic activity, but the series of definitive studies begun by Rob in Paris and continued in Sydney made a major contribution to understanding the mechanisms of action of steroid hormones and their antagonists at the receptor. In turn this contributed to the successful identification and clinical development of the progestin antagonist, RU486, by Baulieu and colleagues⁵ and shaped the design of clinical trials to determine the optimal use of tamoxifen in the treatment of breast cancer.

Control of Proliferation

Steroid hormones promote striking proliferative responses *in vivo* but progress in understanding the mechanisms for these responses was initially limited by the cumbersome and labour intensive techniques for analysis of cell cycle progression, and by the lack of corresponding *in vitro* experimental models. This changed during the 1970s, when the first oestrogen-responsive breast cancer cell line, MCF-7, was established, and the development of flow cytometry and DNA staining techniques allowed rapid assessment of cell cycle phase distribution in large populations of cells.⁶

Antioestrogens

Rob's laboratory at the Ludwig Institute was ideally placed to investigate the effects of antioestrogens on proliferation. One of the other newly

recruited group leaders, Ian Taylor, had expertise in cell cycle kinetics and flow cytometry, and was using Ludwig's flow cytometry facility—one of the first in Australia—to refine methods for DNA staining and the analysis of the resulting DNA histograms. The exceptional quality of the data that could be produced with this methodology led to a collaboration between Ian and Rob that established the cell cycle kinetic basis of tamoxifen inhibition of proliferation. They undertook a detailed and comprehensive investigation of the effects of tamoxifen on both asynchronous and synchronised cultures of MCF-7 breast cancer cells.⁷ Something of the nature of the experimentation can be deduced from time courses in these publications, which typically involve data collected every 3–4 h over at least 24–36 h and in many cases used cells synchronised by mitotic selection, where 20 large flasks were necessary to provide enough cells for an individual data point. This somewhat heroic set of experiments was subsequently extended by Roger Reddel and others in the laboratory. Collectively these studies led to several important conclusions. First, they demonstrated that tamoxifen and other structurally related antioestrogens were cytostatic rather than cytotoxic. This was at odds with the prevailing view at the time—that all effective anticancer drugs are cytotoxic—but consistent with the clinical observation that extending the duration of tamoxifen treatment improves patient survival. They also showed that the anti-proliferative potency of antioestrogens correlated with their affinity for the oestrogen receptor, consistent with the idea that their anti-cancer effects were mediated via the oestrogen receptor. Finally, they demonstrated that sensitivity to tamoxifen was restricted to a limited window of the cell cycle: early-to-mid G₁ phase. Later experiments showed that steroidal antioestrogens also shared this window of sensitivity.

Progestins

In 1986, Rob moved his laboratory to the Garvan Institute at St Vincent's Hospital, Sydney, and soon after recruited Christine Clarke, a research fellow interested in progesterone action. Understanding the control of breast cancer cell proliferation remained a major research focus for the laboratory, but the techniques used to study antioestrogens

were adapted and extended to other growth-stimulatory and -inhibitory factors including progesterone. The laboratory's initial work in this area showed that progestin treatment of breast cancer cells resulted in arrest in G₁ phase.⁸ However, although response was related to progesterone receptor status, neither the relative sensitivity nor the magnitude of the response were related to receptor concentration. One challenge in interpreting these results was the presence in the culture medium of an undefined mixture of steroids and growth factors. At that time much effort worldwide was devoted to testing the concept that the effects of steroids such as oestrogen and progesterone on cell proliferation were mediated indirectly, via modulation of growth factor expression, rather than by direct actions on the cell cycle, and Masafumi Koga's experiments showing that the presence of peptide growth factors could modulate responsiveness to both antioestrogens and progestins were underway in the laboratory. Rob decided that before molecular mechanisms could be addressed, it would be necessary to characterize the actions of different steroids, steroid antagonists and growth factors on the cell cycle in defined culture conditions. This task was assigned to Liz Musgrove, who had developed an interest in the cell cycle while working with Ian Taylor and had subsequently joined Rob's laboratory at Garvan. Once appropriate methods had been established, studies of the effects of progestins led to the discovery that they both stimulated and inhibited cell cycle progression in the same cells.⁹ Progestin treatment promoted transient stimulation of the rate of cell cycle progression but once the stimulated cells completed the cell cycle and divided, they became arrested in G₁ of the next cell cycle, so that the previously described inhibition of proliferation predominated in the longer term. This effectively resolved a major conflict at the time, that is whether progestins stimulated or inhibited proliferation in breast cancer cells, and the potential clinical implications received a great deal of attention.

Steroid and Growth Factor Receptor Regulation

The relocation of Rob's laboratory to the Garvan Institute provided an opportunity for the initiation of some new research directions and a

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 underpinned the core funding for the department, initially as part of the NHMRC Block Grant to the Garvan Institute, and subsequently through programmatic grants from NHMRC, The Cancer Council NSW, and the Cancer Institute NSW. The relatively stable funding provided a platform that enabled the department as a whole to take a longer-term view of its research goals, and hence undertake projects that would have been intractable within the constraints of a three-year (or less) funding cycle.

From the beginning of his time at Garvan, Rob established a daily ritual of taking coffee at Bar Coluzzi, a renowned local coffee shop. Except in the worst of weathers, he could be found at lunchtime perched on a stool on the pavement amidst the passing parade of Darlinghurst street life, deep in discussion with a cross-section of his colleagues. This provided a regular venue for informal updates on ongoing and planned projects and the exchange of opinions on the philosophy and practice of science (among other less weighty topics), and ensured that he remained accessible through what was a particularly busy period of his life. Rob had married his second wife, Cheryl Frewin, in 1982, and their children Sarah, Rebecca and Charles were born over the following seven years. With three young children at home and a department that increased in size from four members in 1986 to around 30 in the mid-1990s, he was also a Director (1983–7) and President (1987) of the Australian Society of Medical Research and served on the National Health and Medical Research Council as Chair of the Grants Committee (1988–90) (having previously served on Regional Grants Interview and Program Grant Review Committees), and as Member (1988–90) and Deputy Chair (1991–3) of the Medical Research Committee.

Although it was increasingly accepted that steroid receptor expression identified breast cancers that might potentially respond to therapeutic administration of antioestrogens and progestins, not all receptor-positive breast cancers responded to these treatments. The need to better define different phenotypes in breast cancer, particularly the steroid-insensitive phenotype, prompted Rob to embark on studies aimed at assessing patterns of receptor expression, understanding how receptor expression was regulated, and determining the degree to which responsiveness was related to receptor expression. The technology of the day for measurement of receptor levels was Northern blotting—PCR was still some time in the future, and sensitive antibodies against steroid hormone receptors were still being characterized. A panel of breast cancer cell lines encompassing most of those available at the time was assembled, and used to show that the oestrogen, progesterone and androgen receptor mRNAs were co-expressed, and inversely expressed with the epidermal growth factor receptor (EGFR) mRNA. Further studies showed that the expression of the EGFR was under the control of steroid hormones, and that EGFR regulation and control of proliferation were markedly different in oestrogen receptor-positive and oestrogen receptor-negative cell lines. This suggested that there might be a causal relationship between the loss of steroid hormone responsiveness and the acquisition of a more aggressive, hormone-independent phenotype. Perhaps more importantly, these were amongst the first studies to define breast cancer subtypes according to their pattern of gene expression, and to relate these patterns of expression to cellular behaviour in response to compounds with therapeutic potential, predating an extensive literature addressing these questions after the advent of large-scale genomic technologies.

Steroid Hormones and the Cell Cycle Machinery

Steroid hormone receptors are ligand-activated transcription factors and therefore were amongst the first systems in which the path from hormone signalling to changes in gene expression and subsequent alterations in cellular behaviour could be delineated in any detail. As early as 1983 Rob

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 G₁ 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 G₁ 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 G₁ 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 over-expressed 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 Research Program through the late 1990s and beyond. A series of publications from the laboratory identified both *MYC* and cyclin D1 as critical early targets of oestrogen action on the cell cycle, with each gene individually capable of mimicking oestrogen by promoting cell cycle progression. The CDK inhibitor p21 (CDKN1A) provided a link between these two pathways. Antioestrogens, conversely, rapidly decreased *MYC* and cyclin D1 expression. By itself this was sufficient to inhibit cell cycle progression, but again was reinforced by regulation of p21. Decreased expression of *MYC* and cyclin D1

was also an early response to progesterin inhibition of proliferation, but in this case p27 (CDKN1B) and members of the INK4 family of endogenous inhibitors such as p18 (INK4C/CDKN2C) reinforced the downstream effects on cyclin-CDK activity. These later studies pointed to redistribution of CDK inhibitors between different CDKs

as an important mechanism of cell cycle regulation. Collectively this body of work led the way in establishing the links between steroid hormone action and cell proliferation control, and underpinned a detailed understanding of how these compounds regulate cell proliferation at the molecular level. It also had implications for the role of these hormones in the development of breast cancer, since MYC and cyclin D1 are both oncogenes as well as cell cycle regulators.

This work on the cell cycle effects of steroids and their antagonists was predominantly undertaken by a succession of PhD students, ably supported by two research assistants (Christine Lee and Marcelo Sergio), both of whom worked closely with Rob and Liz Musgrove for decades. The enthusiasm and collegiate spirit of this group of researchers was a significant factor in the success of the work, as was Rob's commitment to developing the next generation of researchers. In his view one of the measures of success of a scientist was the number of former students and postdocs who went on to build successful careers as independent researchers. Rob was exemplary in this regard, and alumni of his laboratory currently include three institute directors, a FAA, sixteen professors or associate professors and sixteen or more independent group leaders, based at laboratories worldwide. Through them, Rob's maxims—advice such as 'do not confuse activity with progress'—are being passed on to a further generation of researchers.

Biomarkers of Cancer Phenotype, Clinical Outcome and Therapeutic Response

Throughout his career the directions of Rob's laboratory research were shaped by important clinical questions. In the early 1990s this led him to complement the increasingly well-established laboratory research groups within the Cancer Research Program with an explicitly translational research group. The goal of this strategic decision was a characteristically practical one: to

investigate how increased knowledge of cell and molecular biology might be applied to the development of new diagnostic, prognostic and therapeutic strategies that could be used to improve the clinical management of breast and other cancers. This was well before translational research became fashionable, and the idea was not universally embraced, nor was it well supported by funding agencies. Despite the challenges faced in the early years of this initiative, it became very successful and was a major focus for Rob in the later stages of his career.

Investigating the relationship between known markers of breast cancer phenotype and prognosis, and the cell cycle and signalling molecules that were the focus of basic research within the department, necessitated access to clinically well annotated breast cancer specimens. Initially this was achieved through national and international collaborations, including a long-term collaboration with Rob Nicholson in Cardiff, who hosted the joint effort of extracting RNA from several hundred breast cancers collected by a team of surgeons in Nottingham. This was no small task since the samples needed to be processed individually and then analysed by Northern blotting. In a series of publications that preceded a vast literature on the role of cell cycle regulatory proteins in breast cancer development and their potential role as biomarkers, the laboratory showed that cyclin D1 overexpression in breast cancer was much more common than amplification of the CCND1 gene, was apparent in early pre-malignant disease, and predicted early relapse and shorter patient survival.¹⁴ Over the next decade material from these studies and from collaborations with local surgeons and pathologists was also employed for biomarker studies on a large number of genes in developmental pathways and signalling networks, as well as cell cycle, DNA damage and cell death pathways. These showed that aberrant expression of oestrogen target genes involved in cell proliferation and cell death is characteristic of different subtypes of breast cancer, an important insight into the context of understanding mammary oncogenesis.

Among the lessons Rob learned from these studies was the truly multidisciplinary nature of translational research, and the necessity of involving surgeons, oncologists, pathologists and other clinical specialists from the very

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 pancreatic cancer. Smaller collections of both fresh and archival material from other cancers were also established. The group identified zinc- α 2-glycoprotein (AZGP1) as the first molecular biomarker of prostate cancer metastasis¹⁵ and undertook definitive examinations of cell cycle gene expression in pancreatic cancer and squamous cancers of the head and neck as well as prostate and breast cancer.

The quality and depth of the clinicopathological data assembled in the prostate and pancreatic cancer databases also led to their use in the development of clinical staging and predictive models, validation of nomograms, and assessment of the relative merits of different treatment approaches. These studies directly evaluated ongoing clinical practice, and underpinned such changes as the routine use of the Kattan nomogram in prostate cancer management and the inclusion of measurement of

Gleason grade at positive surgical margins into routine pathological reporting of prostate cancer. Highlights in pancreatic cancer included the prospective testing of S100A2 as a marker of likely benefit from surgical resection, and demonstrating the importance of surgical margin clearance in disease progression and patient stratification for adjuvant treatment trials. In breast cancer, the utility of assessing intrinsic molecular subtype using an immunohistochemical panel was compared with traditional pathological indices in early breast cancer, suggesting that tumour subtyping complemented existing practices but had less predictive value on its own. Rob's ability to engage both scientists and clinicians was central to his success in this area, as was his appreciation of the necessity for building infrastructure to not only collect samples, but also ensure their ongoing comprehensive clinical annotation. The systems established within his department exemplified internationally recognized best practice in prospective tissue collection.

Discrimination between patients who will or will not benefit from particular therapies remains amongst the most pressing global clinical problems in breast and other cancers, so the identification of molecular markers of therapeutic response and understanding the mechanisms underlying resistance to therapy became an increasingly prominent theme within the department. The laboratory's early studies on cyclin D1 expression in breast cancer had pointed to an apparent association between high cyclin D1 expression and shorter duration of response in women treated with tamoxifen, although the data were hypothesis-generating rather than conclusive.¹⁴ A series of complementary *in vitro* studies showed that overexpression of cell cycle genes such as cyclin D1 was sufficient to attenuate sensitivity to antioestrogen treatment. This work identified deregulation of specific cell cycle regulators as a novel mechanism of therapeutic resistance, and this mechanism was also shown to extend to other therapies. In February 2015 palbociclib, a specific inhibitor of cyclin D1-associated CDKs, was granted accelerated approval by the FDA, for treatment of advanced breast cancer in combination with the aromatase inhibitor letrozole following striking results in initial clinical trials. This not only indicated that augmenting endocrine therapies by targeting the

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 priority informs basic science questions, was of importance equal to the more popular bench-to-bedside approach, led to his early application of genomic technologies to clinical material. As the then-novel technology of genome-wide expression profiling began to emerge, Rob established a collaboration with Eos Biotechnology (subsequently acquired by Protein Design Laboratories) that allowed access to their pro oligonucleotide arrays and analysis tools, several years before this technology was widely available. These were used in one of the first attempts to use genome-wide expression profiling to identify novel biomarkers that co-segregate with patient outcome. Because of its use of cutting-edge technology and new statistical techniques, this was able to identify individual genes that predicted outcome in prostate cancer.¹⁶

Following Andrew Biankin's return from postdoctoral work at Johns Hopkins in Baltimore in 2005, pancreatic cancer research became an increasing priority within the department. This is a particularly deadly and intractable form of cancer—although the last 50 years have seen significant improvements in diagnosis and treatment for many other cancers, there has been essentially no change in the five-year survival rate for pancreatic cancer. When NHMRC called for expressions of interest to undertake Australia's contribution to the International Cancer Genome Consortium (ICGC) the group joined the Brisbane-based genomics team from the Institute of Molecular Bioscience in a collaboration that became the Australian Pancreatic Cancer Genome Initiative (APGI), led by Andrew Biankin and Sean Grimmond. The APGI undertook an in-depth genomic analysis of ~375 pancreatic cancer patients. From the outset the goal was to use the best clinical material available, with well characterised and accurately annotated clinico-pathological,

treatment and outcome data acquired prospectively. Pancreatic cancer tissue collection was already well established in the department, but the conceptual, logistic and technical challenges presented by the ICGC pancreas project were substantial and Rob was an enthusiastic and active participant in many discussions on how these challenges could be overcome. Within six years of its inception the APGI had contributed sequence data from almost 500 unique donors to the public ICGC database. The first major analysis of the APGI pancreatic cancer samples was documented in a publication in *Nature*, dedicated to Rob and accepted for publication five weeks before his death.¹⁷ This sequencing effort provided an unprecedented depth of knowledge of the mutational landscape and other genomic abnormalities in pancreatic cancer, emphasizing the significant heterogeneity in this disease. The data provide a foundation for ongoing efforts aimed at providing genomic information in a clinically relevant timeframe, allowing informed allocation of targeted therapies to those patients most likely to respond.

Throughout his career Rob contributed to the development of strategic research initiatives aimed at increasing research capacity, and fostering both basic and translational research. He served on the Boards of The Cancer Council NSW (from 2009 until his death) and Cancer Institute NSW (from its foundation in 2003 until 2008), and was Chair of the Research Committees of both organizations. He was awarded Life Membership of the Australian Cancer Research Foundation in recognition of his involvement with the Foundation over many years. The Cancer Institute NSW commemorates Rob with an annual 'Professor Rob Sutherland AO Make a Difference Award', which recognizes a researcher whose work has resulted in a significant and sustained shift in cancer care or research practice, reflecting Rob's career-long commitment to patient benefit as a central goal of medical research. One of the more tangible outcomes of that commitment was the establishment of The Kinghorn Cancer Centre. Rob was the inaugural Director and a driving force behind this initiative, which had as its core principle the integration of research and health care delivery in a collaborative relationship within a single centre. Rob's vision for the Centre was patient-centred, and aimed at allowing clinical challenges to

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 both St Vincent's and Mater Health Sydney and the Garvan Institute of Medical Research, and culminated in the opening of the Centre building in August 2012.

Rob's comprehensive contributions to cancer research and the integration of research findings into improved patient care spanned four decades of amazing worldwide progress in our understanding of the pathophysiology of cancer. His work elucidating the molecular basis of steroid control of proliferation was at the forefront of our progress in improving treatment of hormone dependent cancers. As a basic scientist his commitment and insight into 'clinical priorities informing basic science questions' was well ahead of its time and a model for modern medical research. Perhaps more importantly, Rob profoundly influenced his worldwide circle of friends and colleagues through his scientific vision and intellectual acuity, his support as a supervisor and mentor, and his passion for life.

Bibliography

A full bibliography of scientific publications by Robert Lyndsay Sutherland is available online as Supplementary Material to this paper.

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Endnotes

1. Photograph taken by Penelope Clay in Rob Sutherland's laboratory at Garvan, courtesy of Garvan Institute of Medical Research.

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