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Colin Wesley Ward 1943–2017

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Colin Wesley Ward's professional life played out at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) laboratory on Royal Parade, Parkville, Victoria, where he was a scientist, leader, raconteur, colleague and friend to several generations of staff who worked there. Ward's scientific legacy encompasses large bodies of work on antigenic variation in influenza viruses, the taxonomy of plant viruses, veterinary vaccines and the structure and function of several growth factor receptors. On retirement from CSIRO he continued work on the insulin receptor with colleagues at the Walter and Eliza Hall Institute of Medical Research, conceived of and founded *CSIROpedia* and compiled his family history.

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Early Years

Colin Ward was the fourth of five children born to Alan and Olive (née Gardiner) on 3 January 1943 at Cootamundra, New South Wales (NSW). Alan was a grazier, the great-grandson of Samuel Ward who settled in the Cootamundra district in 1865. Olive was a highly educated woman who taught English and Latin at the Cootamundra Intermediate High School. In the 1940s, fourteen Ward descendants of Samuel were on the land around Cootamundra; in 2016 only three of those properties remained in family hands.

All five of Alan and Olive's children were talented. The eldest child, Phyllis, became an educator. She was deputy principal at Frensham, an independent non-denominational secondary school in Mittagong and she wrote four text books on the English language. Colin's brother, Bruce, worked the family property. He served on the Cootamundra Shire Council for sixteen years from 1987, six of them as mayor/president, was awarded an OAM in 2013 for 'service to local government and to the community of Cootamundra', and passed away in 2016. The third child, David, took first class honours in applied science at the University of New South Wales (UNSW), worked briefly at the CSIRO Division of Textile Physics and in 1965 joined the Australian Wool Testing Authority. His career in the wool industry included roles in the Australian Wool Corporation and the International Wool Textile Organisation, and he was awarded an OAM in 1999 'for services to the Australian Wool Industry'. Margaret, Colin's younger sister, has lived most of her adult life in the UK where she pursued a teaching career. Colin was the only one of the five children who did not become captain of Cootamundra High School. However, he was also the only one later to win the University Medal and a University Blue (in Rugby Union) at UNSW, both in 1964.

While at university, Colin retained a deep affiliation with the land and saw himself making his livelihood from it. The family purchased a property in Cootamundra to give effect to his dreams, but drought 1964–5 frustrated these plans. With no intention of making a career in teaching, he took a position as a trainee teacher in the NSW technical education system. In mid-1965, he became aware that the registrar of UNSW was wondering why the university medallist was not pursuing a higher degree. He exercised all the bargaining power at his disposal and embarked on a well remunerated PhD project of his own choosing. His topic, 'The Biochemistry of Parasitic Worms' now seems a good compromise for a frustrated, scholarly farmer.

Colin prepared for his research career in the library of the CSIRO's Animal Health McMaster laboratories at the University of Sydney, married Christchurch-born Lynette Elizabeth Wilson in January 1966, and submitted his thesis late in 1967. Five publications resulted from his thesis, describing comparative studies on the citric acid cycle and glycolysis in the parasitic worm *Haemonchus contortus* and in the rat liver. A full list of Ward's publications is included in the Bibliography (see Supplementary Material). In 1968–9 Colin was a postdoctoral fellow with Donald Fairbairn at the University of Massachusetts in Amherst, Massachusetts, USA. Continuing his high productivity from his PhD studies, he published another five papers with Fairbairn on different aspects of fatty acid metabolism in parasitic nematodes. Colin and Lyn's first child, Nicholas Colin, was born on 3 October 1969 in Northhampton, Massachusetts. Their daughter, Juliette Fay, was born on 9 May 1972 after their return to Melbourne.

With his farming background and early success in biochemistry research, Colin now saw a new future for himself, not on the land but at the CSIRO's Division of Animal Health where he believed future work on parasite biochemistry would suggest ways for controlling parasitic diseases in livestock. His approach to that division was turned down, but the Division of Protein Chemistry in Parkville was more receptive. They did have a vacancy, albeit for an organic chemist. But there would be something useful for Colin to do, and his appointment was just one of many shrewd decisions taken by the foundation chief of that division, Gordon Lennox.[1] Another had been Lennox's arguing that the division should bear the name 'Protein Chemistry' rather than 'Textile Chemistry', which was favoured by the Australian Wool Corporation, a major funder of the division at that time.

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Moth Larvae Enzymes

Being housed in the Division of Protein Chemistry rather than the Division of Animal Health shifted Colin's immediate research from the sheep's gut to the sheep's back. Even more significantly, it

later provided opportunities for him to impact the diverse fields of influenza and plant virology and, later again, mammalian cell surface receptors important to human health.

Colin's first project in wool research concerned moth larvae. The keratin proteins of wool are notoriously insoluble, but are digestible by moth larvae and Colin's task was to identify the larval enzymes responsible. With a characteristic sense of not doing the job by halves, he identified and studied over two dozen of these enzymes. In a summary article of this work, Colin noted that the larval digestive tract contained serine proteases, metalloproteases, aminopeptidases and carboxypeptidases with an array of specificity requirements.[2] Unfortunately, there was no single target that might be attacked with a moth-proofing agent. Always quick to have a good laugh at himself, Colin recorded in *CSIROpedia*

> The highlight for me was the note from the Editor of BBActa, who on accepting my paper on 'The amino peptidases of intermediate electrophoretic mobility' felt I had exhausted the world's interest in the enzymes of that insect. I had already published papers on 'The amino peptidases of low electrophoretic mobility' and 'The amino peptidases of high electrophoretic mobility'. It was time to move on!

He didn't so much move on as move out of wool research.

Influenza Antigens

Gordon Crewther succeeded Lennox as Chief of Protein Chemistry in 1973. At that time wool funding for the division was declining, but Crewther was convinced that Australian industries needed protein chemistry expertise, and he initiated a collaboration between the division and the influenza researcher Stephen Fazekas de St Groth of the Division of Animal Genetics in North Ryde, NSW. Fazekas had proposed a model for antigenic variation in influenza which, were it correct, would enable one to predict future strains of the virus and thereby better control periodic but devastating outbreaks of influenza in poultry sheds. No overt case was made for dealing with human influenza, although the viruses involved are extremely similar. The test of the Fazekas model would rely on a full chemical characterization of the two major influenza antigens, the haemagglutinin and neuraminidase proteins. Crewther tapped Colin on the shoulder to take on the task of determining the amino acid sequence of the haemagglutinin, a glycoprotein of some five hundred residues and a major challenge in 1973.

Together with Theo Dopheide, Colin set about learning from Graeme Laver (Australian National University) how to culture influenza virus in embryonated chicken eggs, a technique pioneered in Australia by Macfarlane Burnet at the Walter and Eliza Hall Institute of Medical Research (WEHI). Colin's first publication on influenza, with Theo Dopheide, made clear the size of the problem.[3] The sequencing effort required harvesting virus from some 150,000 eggs and was completed in 1981 (Figs 1 and 2). Colin and Theo's sequencing data established an evolutionary relationship between an avian influenza virus and the Hong Kong strains of human influenza virus.[4] A series of publications with Laver and others built up a picture of variation in the haemagglutinin protein sequence among the Hong Kong (H3) viruses.[5] In 1981, that picture graduated from one-dimension to three-dimensions when the crystal structure of the protein was described,[6] indicating regions of the protein to which neutralizing antibodies would bind.[7] During the sequencing work,

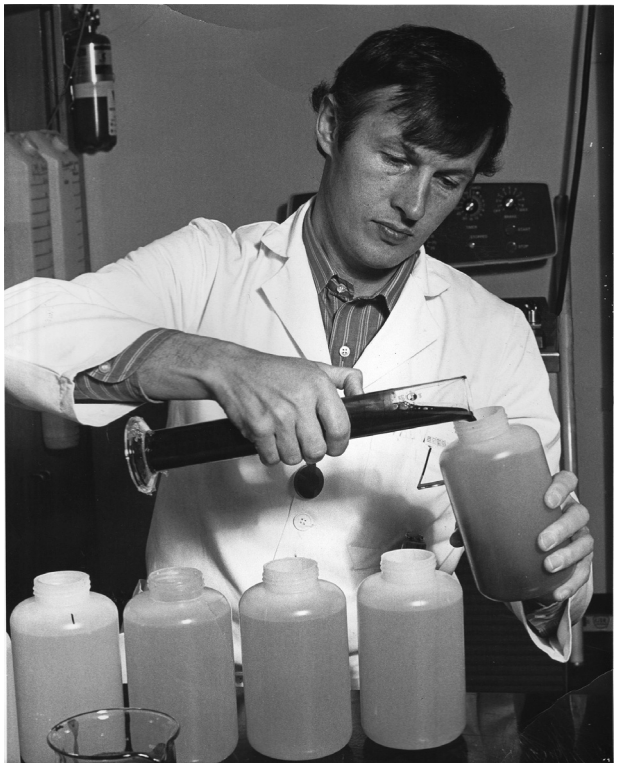

Figure 1. Colin in the influenza laboratory.

Colin noticed a particular amino acid sequence signature in the haemagglutinin that was very similar to that found in fibrous proteins, such as the α-keratins of the wool fibre.[8] His prediction that a long helical segment would be found in the three-dimensional structure of the haemagglutinin was subsequently confirmed, twice. When the crystal structure of the protein as found on the virus particle was described, Colin's prediction appeared only partly correct. The long helical segment described in his paper turned out to be divided into two helices separated by a hairpin turn. Sadly, this discrepancy was dismissed as a limitation of the predictive power of amino acid sequences up against the primacy of crystallography as a structural technique. However, the influenza haemagglutinin is one of nature's marvels; it is able to transform its shape from the one found on nascent viruses, allowing it to attach to cells the virus will infect, to a structure that is able to fuse the viral membrane with the target cell membrane, gaining the virus entry to the infected cell. When the crystal structure of this form of the molecule was determined, Colin's long helix was found largely as he had predicted.[9] The crystallographic studies of the haemagglutinin by Wiley and Skehel revealed not only how membrane fusion occurs in influenza infection, but also a widely used molecular principle for membrane fusion in biology.[10]

Meanwhile, one of us (PMC) was working away on the crystal structure of the other influenza antigen, the neuraminidase. The interpretation of the X-ray derived image of the neuraminidase was greatly aided by information about the amino acid sequence and Colin, having now shifted his attention to the neuraminidase sequence, shared every piece of his data as it became available.[11]

Figure 2. Colin (centre) holding forth on the influenza haemagglutinin, under the approving eye of Gordon Crewther (far left).

With the influenza antigen sequences done, and with gene sequencing having taken the challenge out of it, Colin moved on from influenza. The Fazekas model of antigenic variation had not passed the molecular test and no great insight into strain prediction had emerged. It was certainly not the case that influenza was then scientifically barren, but the CSIRO had other challenges in store and, as Colin had before, he took them on.

Plant Virus Taxonomy

Even while the influenza work was in full swing, Colin had begun helping a new recruit to the division, Dharma Shukla, a plant virologist. Gordon Crewther believed that protein chemistry techniques would yield better methods of detecting and classifying plant viruses, thus complementing biological studies aimed at crop protection. Almost as soon as this work began in 1977, a CSIRO review committee recommended it cease. Due largely to Crewther's determination, it continued until 1992, by which time Ward, Shukla and colleagues had solved the complex problem of the taxonomy of the economically important group of viruses known as potyviruses.[12] In 1994, Ward and Shukla were awarded the CSIRO Chairman's Medal for this work, and the following year they won the Australian Medal of Agricultural Science. Colin's interest in classification extended to the taxonomy of animal and plant viruses and his recommendations were influential in decisions of the International Committee on Taxonomy of Viruses. He served as an executive committee member of this International Committee from 1996 to 2002. Right up to the last weeks of his life he remained engaged with virus taxonomy.[13]

Colin published some forty papers on plant viruses, including work on the use of plant virus particles as scaffolds for vaccines.[14] His impact was more like that of a scientist with few interests outside of plant virology, but it was just one of many strands in his scientific fabric.

Veterinary Vaccines

In 1982, when Colin had finished with sequencing influenza antigens, he established a program of work on veterinary vaccines. During 1983–4, he took a sabbatical in Bill Rutter's laboratory at the University of California San Francisco. Recombinant DNA technology was transforming molecular biology and allowing the study of protein molecules whose natural abundance was otherwise too low, such as the antigens from various pathogens. Colin brought these technologies to the veterinary vaccine program. His projects targeted the causative agents of ovine footrot (*Dichelobacter nodosus*),[15] of bursal disease in poultry (a *Birnavirus*, infectious bursal disease virus—IBDV)[16] and of worm infestation in sheep and cattle (*Trichostrongylus colubriformis*).[17] All were undertaken in collaboration with colleagues at the CSIRO's Division of Animal Health. The most successful of these was the IBDV work. The recombinant vaccine based on the VP2 protein of the virus was developed in partnership with the vaccine manufacturer Arthur Webster's Vaccines.[18] As a result of their development of the IBDV vaccine Colin, Ahmed Azad and Kevin Fahey (Division of Animal Health) were awarded the CSIRO Chairman's Medal in 1997 for their leadership of the team involved.

Medical Research

In the midst of Colin's research program on veterinary vaccines, the Division of Protein Chemistry was torn by competing visions of its future. The wool industry had been the traditional industry partner of the division but new opportunities were emerging in the biotechnology sector. The CSIRO Executive thought that relocating the entire laboratory to Clayton would allow consolidation of its work. Several senior staff at the time voiced opposition to this move, arguing that Parkville was a more suitable home for those activities

Figure 3. Colin (centre) setting out with determination on the annual two-miler around Princes Park.

with human health relevance. Colin was a passionate and influential advocate of this new focus for the division, and the proposal to relocate to Clayton was set aside. Scientists engaged in work on the wool fibre and on hides, skins and leather were redeployed to the Division of Wool Technology. For the remainder, a merger with the Division of Molecular Biology in North Ryde occurred in 1988, and the new entity was rebadged as the Division of Biomolecular Engineering at the end of 1989. Its charter was to support a research-based pharmaceutical industry, thus acknowledging that CSIRO had a role in medical research, and Peter Colman was appointed division chief. The pharmaceutical industry in Australia at that time was largely involved in manufacturing and distribution, not research, thus posing a challenge for the new division to partner its work with commercial interests.

The shift in focus in 1990 might have been an opportunity for Colin to re-connect with his interests and international networks in influenza research. But the path of least resistance was not for him (Fig. 3). Instead he proposed, and won support for, determining the three-dimensional structure of the human insulin receptor and its complex with insulin, thus opening the chapter on what were to be his crowning achievements. In particular, he aimed to understand how blood sugar levels are regulated and whether better treatments for diabetics might ensue.

The Insulin Receptor

The hormone insulin is essential for controlling blood sugar levels but to do so it must first partner with its receptor, a protein of more than 1300 amino acids located on the surface of various cell types. Just over 900 of these amino acids are on the outside of the cell, the remainder traversing the cell membrane and forming an intracellular kinase domain. The receptor is synthesized as a single polypeptide that is cleaved post-translationally and the resulting α and β chains are covalently attached to each other through disulphide bonds. On the cell surface the receptor occurs as a covalent $(\alpha\beta)_2$ dimer. When bound to insulin the receptor sends a signal across the cell membrane to the cellular interior where chemical reactions combine to move a transporter protein to the cell membrane through which glucose can pass, thus lowering the concentration of glucose in the circulation. The immediate goals of the project were to determine three-dimensional structures of the extra-cellular part of the receptor, both before and after it had encountered insulin. To do so would require large scale production of the receptor of sufficient purity to allow it to crystallize, after which X-ray crystallography could be used to image the structure. The 917 amino acids of the extracellular region of the receptor include at least eighteen sites at which carbohydrates are attached and multiple intra- and inter-chain disulphide bonds. It would be no trivial exercise to express this molecule correctly folded and capable of binding insulin, let alone to crystallize it.

Over the following seventeen years, Colin led a team of molecular biologists, cell biologists, protein chemists and structural biologists focussed on these goals.

Because the extra-cellular part of the receptor is heavily and variably glycosylated, a feature that frustrates the goal of purity for crystallization, special mammalian cell lines were deployed to manufacture the receptor in a minimally glycosylated form,[19] and to ensure correct folding of the cystine-rich structural modules and other disulphide-bonded cross-links.[20] Large scale production of the receptor required the handling of (literally) thousands of litres

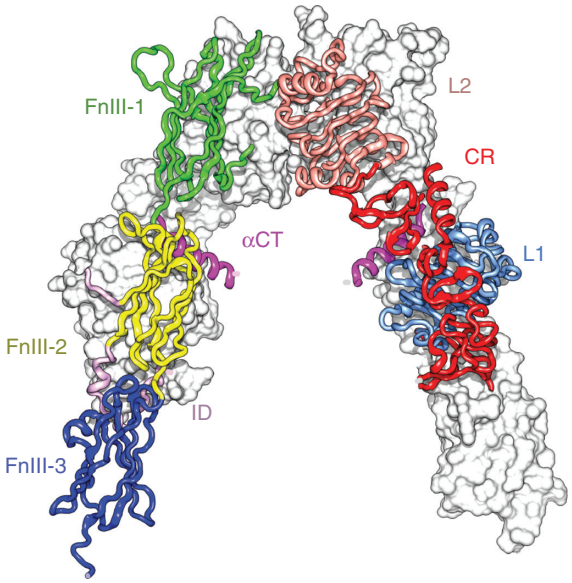

Figure 4. The insulin receptor structure.[23] One half of the dimer is shown as a grey surface (rear) and the other as a coloured 'worm' on which the structural modules are labelled and coloured distinctly. The cell membrane would be at the base of the picture.

of mammalian cell culture fluid and multiple purification steps to obtain material for crystallization trials, trials which remain largely a black art to this day.

Success came in stages because the insulin receptor, like most large proteins, is modular. The extracellular region of the receptor contains seven such structural modules and some of these modules could be crystallized and studied by themselves. In fact their first successes with this approach came with a protein closely related to the insulin receptor, namely IGF-1R, the type I insulin-like growth factor receptor (see below),[21] and only later with the insulin receptor.[22] In 2005, the team finally determined the three-dimensional structure of the entire extra-cellular domain of the receptor, and their results were published in *Nature* the following year.[23] The picture of the molecule (Fig. 4) hinted at likely places where insulin would bind, but a companion picture of the complex would be required to illuminate how the signal propagated across the cell membrane. All twenty-three of the authors posted their address as CSIRO, 343 Royal Parade, Parkville. First among them was Neil McKern to whom had fallen the task of purifying countless different preparations of receptor constructs. The corresponding authors were Mike Lawrence, who had met the considerable crystallographic challenge of the project, and Colin.

Colin has recounted among his scientific high-points the 2006 Keystone Symposium in Cambridge UK on 'Multi-protein complexes involved in cell regulation'. Tom Blundell, who in 1969 with Dorothy Hodgkin and others had determined the insulin structure, was among the organizers. Colin's *Nature* paper was not yet published so this was a very high-profile announcement of a long-awaited result. Colin even recalled his journey to the insulin receptor structure in the family history beginning with: 'Here was the son of a red dirt farmer from Cootamundra….'.[24]

As this scientific triumph was slowly unfolding, the scientific staff at CSIRO's Division of Biomolecular Engineering were enduring multiple chiefs, name changes, and mergers. Countless administrative reviews questioned the wisdom of the insulin receptor program within an organization placing heavy demands on commercial partnerships with industry. Patience ran out just as the structure was finally unveiled. Colin and many of the team were made redundant, but not before they collected Colin's third CSIRO Chairman's Medal in 2006 for their success. What had begun in an organization that David Rivett might still have recognized, finished in an altogether different one. Rivett's over-riding aim in establishing the Council for Scientific and Industrial Research was (in the words of his biographer, Rohan Rivett):

> to find the best possible man in a given field and then clear the way for him at all costs to develop his own team, workplace and methods with the minimum of interference or hindrance for administrative or financial reasons.[25]

Before recounting the final stanzas in the insulin receptor story that played out after Colin had left the CSIRO, it is important to record his contributions to two other cell surface receptors. These receptors are of critical importance in the biology of many cancers. He was drawn to them because it was expected that their three-dimensional structures would be similar to that of the insulin receptor, and because the riskiness of the entire program could be reduced. Tackling the insulin receptor meant competing with some of the most accomplished and best funded structural biology laboratories in the world. One way to mitigate the risk was to study closely related molecules, because even small differences between two proteins can have a dramatic, if unpredictable, effect on their propensity to crystallise. In Colin's case this could have suggested trying to crystallise, for example, the insulin receptor from a mouse. He took a different tack that expanded his biological horizons.

The Type-1 Insulin-like Growth Factor Receptor (IGF-1R)

As its name suggests, this receptor is very closely related to the insulin receptor, so much so that the receptors can recognize each other's primary ligands, the insulin-like growth factors (IGF) and insulin, respectively. So similar are their amino acid sequences that it was predicted that the same structural modules would be found in both receptors, and it was a good bet that much could be learned about the extracellular region of the insulin receptor from a companion study of the IGF-1R. Despite these similarities, the biological consequences of signalling through the two receptors are quite different. Dysregulated signalling through the IGF1-R is associated with uncontrolled cell growth, making this receptor an interesting target for anti-cancer therapies.

As noted above, the first significant success of the insulin receptor program came from a crystal structure of the first three structural modules of the IGF-1R. The work was reported in *Nature* in 1998 with Tom Garrett, who had determined the crystal structure, and Colin as the corresponding authors.[26] This first glimpse of the structure, albeit only a fragment of the receptor that did not bind ligand, contained regions that were known to be essential for ligand to bind. The hypothesis from that study about where insulin and insulin-like growth factors might bind their receptors has since been substantiated.

The Epidermal Growth Factor Receptor (EGFR)

Colin also recognized the opportunity and importance of embracing studies of another cancer-related receptor, the epidermal growth factor receptor (EGFR). The EGFR is more distantly related to the insulin receptor than is the IGF-1R, but the amino acid sequence of the EGFR's extracellular portion pointed to it containing structural modules similar to the insulin receptor, though arranged in different order along the length of the protein chain.[27] Accordingly, constructs containing various modules of the EGFR were prepared and crystallized by the Ward team.[28]

The EGFR is associated with certain epithelial tumours, and one of us (AWB, then at the Melbourne Branch of the Ludwig Institute for Cancer Research) had a long-standing interest in how EGFR signalled cells to grow after it encountered its partner, epidermal growth factor (EGF). The structure of a truncated form of the extracellular portion of the EGFR bound to one of its ligands, transforming growth factor α (TGFα), was resolved and published in *Cell* in 2002.[29] Tom Garrett (by then working at at WEHI) led the structural studies in a three-way collaboration with the Ludwig Institute and Colin's team at the CSIRO. The three-dimensional arrangement of the dimer of receptor molecules was unlike anything seen before for a cell surface receptor and explained how EGFR could associate with different ligands, such as TGFα and EGF. Correct interpretation of the structure relied on a battery of biological data from the Ludwig Institute collaborators. The following year the team published their structure of a closely related family member ErbB2, which engages with no partner ligands but which associates with EGFR in a heterodimer competent for signalling to the cell's interior.[30]

Around the time that these structures were revealed, monoclonal antibodies were being evaluated as a means of shutting down EGFR-dependent cell proliferation. In 1998, the first of these antibodies, trastuzumab (Herceptin) was approved for clinical use, followed later by cetuximab (Erbitux) in 2004. These antibodies do not distinguish between their targets (ErbB2 and EGFR respectively) on healthy and diseased tissues. However, on certain cancer cells, the EGFR is expressed in a mutated variant form that lacks some of the structural modules. The Ludwig Institute raised a monoclonal antibody (mAb806) against the EGFR expressed on cancer cells. The mAb806 does not bind native EGFR expressed at physiological levels, but it does bind to activated and unfolded EGFR expressed on some cancer cells. The antibody shows anti-tumour activity against many cancers that express mutant forms of the EGFR or that overexpress the EGFR. The structural studies of EGFR bound to TGFα from Colin's team at CSIRO and complementary work from Daniel Leahy in the USA,[31] provided a basis for understanding why this anti-EGFR antibody, unlike others being used clinically, was so selective for tumour cells.[32] At the time of writing, this antibody (licensed to Abbvie and known as ABT-806) is in late-stage clinical trials for glioblastoma and other cancers that overexpress the EGFR.

The publication of the EGFR structure created enormous excitement around the 'receptor biology' world. Consequently, Colin and AWB invited leaders in the EGFR field from the USA, Japan and Europe to a meeting in March, 2003, at Lorne, Victoria. With apologies to Neville Shute the meeting was called 'ErbBs on the Beach' and it was an enormous success (Fig. 5). The disclosure of the three-dimensional structures of EGFR with and without ligand stimulated a new era in EGFR biology, biochemistry and medicine.

Figure 5. Colin with Tom Garrett at 'ErbBs on the beach'.

The Walter and Eliza Hall Institute of Medical Research (WEHI)

When the CSIRO closed down the insulin receptor program (Fig. 6) the outstanding task was to determine the structure of the receptor bound to insulin. Suzanne Cory, then director of WEHI, offered Mike Lawrence a position on the Institute's faculty in order that the work might continue. Colin also joined WEHI as a part-time fellow. The CSIRO facilitated the transition by making available countless reagents and cell lines and, fresh from the 2006 *Nature* paper, Mike and Colin were able to secure NHMRC support for the work. The project was heavily scaled back but based on seventeen years of experiences (both good and bad) could now be more focussed.

In 2013, Mike, Colin and their WEHI team published in *Nature* the first image of insulin bound to the receptor, not the whole extracellular domain but a smaller fragment that contained all the primary elements required to engage insulin.[33] The structure revealed that insulin itself partially unfolds in order to make the complex with the receptor. In contrast to the 'solely-CSIRO' authorship of the 2006 paper, this work brought together data and authors from two US universities (Case Western Reserve and Chicago), two European laboratories (University of York and the Academy of Sciences of the Czech Republic) and Australia's La Trobe University to underpin the essential structural findings (Fig. 7).

Legacies

Beyond his scientific legacy, Colin bequeathed two important CSIRO-based centres of scientific infrastructure to Australia. To the CSIRO he gifted *CSIROpedia*.

Science and Honours

Colin Ward's scientific legacy is unusually broad and deep. His scientific fingerprints are still evident in influenza virology and plant virology, whilst the vast field of receptor biology, to which

Figure 6. Colin and Lyn at his retirement dinner from CSIRO, 2006.

Figure 7. Colin with Mike Lawrence, proofing a manuscript at WEHI.

he was committed for over two decades, owes much to his leadership and discoveries.[34] He set himself ambitious goals and led large teams of scientists in his pursuits. His encyclopaedic knowledge of the subject, his personal commitment to the goals he set and his comradeship with his various colleagues (whose creativity and intellect he was first to acknowledge) were important ingredients in his success.

In addition to his honours mentioned above, he was the 2008 Keith Harrison Memorial Lecturer (the Endocrine Society of Australia), the 2007 Lemberg Lecturer and Medallist (the Australian Society for Biochemistry and Molecular Biology) and the 2001 Leach Lecturer and Medallist (Lorne Protein Conference). In 2000, he received a Lifetime Achievement Award from UNSW where he had graduated in 1967 and, in 2003, the Commonwealth of Australia awarded him a Centenary Medal. Colin was elected a fellow of the Australian Institute of Agricultural Science (1995), the Australian Academy of Technological Sciences and Engineering (1998) and the Australian Academy of Science (2011).

Colin's research into the manner in which ligands bind to the extracellular domains of the human insulin receptor and human IGF-1R continues under Mike Lawrence's leadership within his laboratory at WEHI. In August 2017, Mike's laboratory presented the structure of the intact IGF-1R extracellular domain in both ligand-free and ligand-bound form at the 24th Congress of the International Union of Crystallography in Hyderabad, India. Employed in this study were precisely the protein-producing cell lines and the crystallization centre that Colin had established at the CSIRO more than a decade before. The insulin receptor successes of Colin and Mike are now being expanded further to capture avenues of new therapeutic insulin design.[35]

The Recombinant Protein Production and Purification Facility

The CSIRO's partnership in the Cooperative Research Centre for Cellular Growth Factors (1991–2004) contributed expertise in large scale cell culture techniques for producing and purifying biological materials. The capability was developed during the insulin receptor project. Following the closure of that CRC Colin, George Lovrecz and Tim Adams were instrumental in establishing the National Biologics Facility (NBF)—funded under the National Collaborative Research Instructure Strategy (NCRIS)—with the University of Queensland based Australian Institute of Bioengineering and Nanotechnology. This facility is providing quality recombinant proteins in large-scale to enable further research including structural studies, high-throughput screening, animal, preclinical and Phase-I testing. The CSIRO node of the NBF has delivered proteins for over 70 partners including Australian universities, medical research institutes (including WEHI's insulin receptor program), Cooperative Research Centres and industry. Colin was also supportive of training and educational initiatives and he encouraged Lovrecz to establish the (now popular) annual Protein Expression Workshop.

Collaborative Crystallisation Centre

In the 1990s, the art of crystallizing biological macromolecules was confronted by robotic technologies. On one level, with no way of knowing at the outset under what conditions a protein might crystallize, using robotics to try simply every known recipe for crystallizing any protein might be seen as taking the science out of it. In fact, the deployment of robotics to tackle this problem has become increasingly scientific. Colin saw an opportunity to establish a robotic crystallization facility at CSIRO in 2004 when the Victorian Government's initiative known as Bio21 called for collaborative projects around the Parkville precinct. Together with Mike Lawrence and Neil McKern, Colin mounted a successful proposal that led to the establishment of the Collaborative Crystallisation Centre (C3) in 2006, the first of its type in Australia. Janet Newman was recruited to develop and operate the C3. At the time of writing C3 has had over 400 users, set up some 3.5 million crystallization 'drops', recorded over 90,000 crystal hits and seen 160 papers published on the strength of those crystals. CSIRO continues to this day to re-invest heavily in C3, recognizing its importance to the CSIRO and the wider structural biology community.

CSIROpedia

It might strike some as odd that the CSIRO's summary termination of the insulin receptor project did not alienate Colin in retirement. Instead, he threw himself into the creation of a living archive of the CSIRO's achievements, *CSIROpedia*. For a publicly funded research organization, constantly under the government microscope for budget savings and 'continuous improvement', such a record of its performance is invaluable. Reading the CSIRO's stories should inform policy makers about the scientific environment in which big discoveries were made, and give them pause to consider how hard to push the organization towards becoming a fee for service enterprise. The genesis of *CSIROpedia* may have been the 1996 publication the *Lennox Legacy* that Colin had co-authored with four of his CSIRO colleagues and that recounted the life of the CSIRO laboratory at 343 Royal Parade (since 1950) and its precursors in the 1940s.[36]

Personal Life

Colin took a keen interest in his children's school and community sporting activities, and spent many years manning a stopwatch, setting up hurdles and raking long jump pits at Kew Little Athletics Club, where his children Nick and Juliette were keen competitors, and Colin served as president for several years in the early 1980s. His children believe this eventually inspired him to acquire his own running shoes and join his workmates for lunchtime runs around Parkville and Royal Park, including the Annual CSIRO Parkville Two Mile Handicap (see Fig. 3).

Nick married Anna Lee, an obstetrician/gynaecologist, and they have three children Joshua (b. 2003), Samuel (b. 2005) and Heidi (b. 2010). Juliette married Adam Balchin, a lawyer, and they have two children, Joely (b. 2003) and Zac (b. 2006). Colin was devoted to his grandchildren and delighted in spending time with them and following their interests, becoming a well known fixture on the sidelines at Fitzroy Junior Football and Edinburgh Cricket Club, and taking them to the MCG to watch the Hawthorn Football Club in action.

Colin and Lyn also loved indulging their passion for horseracing, regularly attending Flemington as members of the Victoria Racing Club (VRC), and developing many friendships there.

With Lyn's illness and death on 24 March 2015 Colin lost his life's partner. Nick spoke for the family at her funeral, a moving memorial laced with Colin's sense of humour and timing, but one

he could not deliver himself. Colin's memorial to Lyn was self-published in 2015. On learning of his own illness in the spring of 2016, he busied himself with finishing the Ward family history.[37] His penchant for the past, whether personal or scientific, was always about the present and the future.

Colin kept his illness relatively private until it was clear that treatment would fail him. He saw the humour in the chemotherapy clearing up a basal cell carcinoma on his scalp, but not the metastasized gall bladder tumour inside him. When asked what he thought about one last party in his honour he said 'I think I'm up for that'. And so he was. Nine days before his death, one hundred of his colleagues took the trip down memory lane, back to 343 Royal Parade, back to the keratins—the soft ones in the wool fibre and the hard ones in the kookaburra beak, back to influenza viruses being transported in the back of Colin's car from Commonwealth Serum Laboratories (CSL) to CSIRO, back to his leadership—ahead of his time—in appointing women in senior scientific roles, back to the technology platforms he established—the C3 crystallization facility and the recombinant protein production facility, back to the well researched and humorous farewell speeches he gave, back to CSIRO's various attempts to move us somewhere we really did not want to go or to stop things we really wanted to do, back to Christmas parties and all other parties for that matter, and finally to the name we should have given him long ago—the Cootamundra colt. The alliteration and the imagery both appealed to him. Messages of respect were sent by John Skehel, Pierre De Meyts and Tom Blundell. Nick delivered his father's thanks. All one hundred present had a last opportunity for one-on-one time with Colin.

Shortly before he died in Melbourne, two years to the day after Lyn, he declared himself content with the thought that his bones would lie beside those of his ancestors in Cootamundra.

Conflict of Interest

The authors declare no conflict of interest.

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