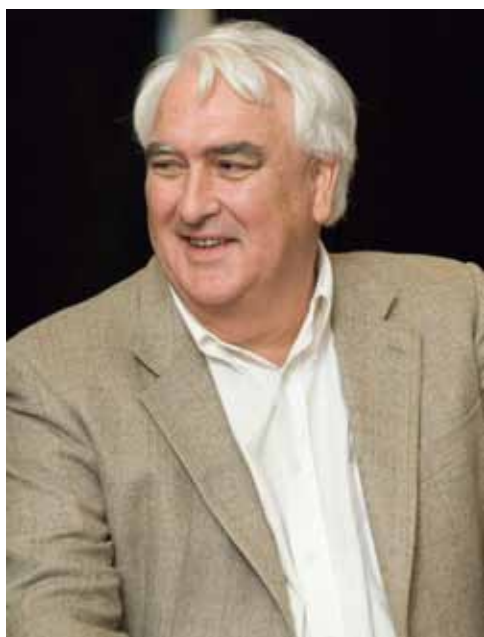


GREAT EXPECTATIONS



Michael Berndt.

Michael Berndt describes his professional path from platelet research in Australia to university administration in Ireland.

The Clot Thickens

Another PhD student finishing at that time had arranged to do a postdoc with David Phillips in the Biochemistry Department at St Jude Children's Research Hospital in Memphis, Tennessee, but had withdrawn to further a career as a concert pianist. I wrote proffering myself as an alternate, on the basis of similar training, and was offered the position to work on and purify a potential thrombin receptor on human platelets, platelet membrane glycoprotein (GP)V. My knowledge of platelets and cell biology at that time was essentially nonexistent, but I did have an understanding of protease biology and tackled the issue from that angle. During the next two years, I succeeded in purifying the protein and confirmed it as a direct thrombin substrate, although to this day, its pathophysiological role remains unclear.

This was an exciting time to become involved in platelet biology, a research area still in its infancy, with only a handful of prominent research laboratories in the field internationally. In the mid-70s, it was known that platelets prevented blood loss by adhering to the subendothelial matrix to initiate the formation of a platelet aggregate or plug. The activated platelets facilitated activation of the coagulation cascade, leading to thrombin generation and thus the stabilisation of the platelet plug by fibrin. It was also known that a number of agonists, such as collagen, epinephrine, ADP and thrombin, could activate platelets and promote platelet aggregation, but the surface receptors involved in platelet adhesion, agonist activation and platelet aggregation were completely unknown. This changed in 1975 with the publication in *Nature* of a seminal paper by Nurden and Caen based in Paris. Using tube SDS-polyacrylamide gels and periodic acid-Schiff staining, they analysed the surface glycoproteins of platelets from patients with two rare genetic disorders: Bernard-Soulier syndrome, in which the platelets have a defect in vessel wall adhesion, and Glanzmann's thrombasthenia, in which the platelets have a defect preventing platelet aggregation. They showed missing, but different, major surface glycoproteins in both disorders. Subsequent studies by Clemetson in Berne and Phillips in Memphis in the late 70s, using better surface labelling techniques and more sophisticated gel analyses, defined the loss of a surface glycoprotein, GPIb, in Bernard-Soulier syndrome and a complex, GPIIb-IIIa, in Glanzmann's thrombasthenia. The latter finding prefaced the discovery of integrins, a large superfamily of heterodimeric adhesion receptors involved in cell-matrix and cell-cell interactions, with GPIIb-IIIa, now termed $\alpha_{IIb}\beta_3$, now known to be a platelet-specific member of this superfamily. Phillips, exploiting this platelet-specific expression, later went on to establish a company, Cor Therapeutics, which developed one of the GPIIb-IIIa receptor antagonists now widely used to prevent thrombosis post-coronary artery stenting.

One of the inevitable questions asked at interview is where one sees oneself in five years' time, with the usual response targeted to the situation and what one hopes is expected. In reality, it is a question that is essentially unanswerable. Five years ago, I would not have predicted that after a research career spanning nearly thirty years in Australia, I would, in my mid-fifties, move halfway around the world to Ireland to take up an Executive Dean role as Head of the College of Medicine and Health at University College Cork, Ireland. In hindsight, it was even less obvious in my early career, but I am sure like many others, the focus of my PhD and postdoctoral periods set the direction of my career.

I completed my undergraduate BSc degree at age 19 at the University of Queensland in 1973 with a major in both organic chemistry and biochemistry, unclear still on any career path. Honours was the clear default choice, but isolating alkaloids from marine coral did not inspire, so I shifted to the Biochemistry Department and then to a PhD under the supervision of Burt Zerner, designing, synthesising and testing transition state analogue inhibitors of chicken liver carboxylesterase. This resulted in two publications in the *Journal of the American Chemical Society*, studies which, to this day, remain personal highlights of my career. This was a dynamic research environment that also included prominent researchers such as Bob Blakeley and John de Jersey. Other PhD students at this time were Sue Hamilton, Nick Dixon, Hugh Campbell and Peter Riddles, all of whom have had successful research and/or academic careers. Supervision centred on understanding the research method and was delivered very much using the 'rough end of the pineapple' approach. In retrospect, we were given enormous freedom to do our own research, but still graduated as fully trained researchers.

It was at this time that chance events first shaped my future research career. In the last year of my PhD, I had decided to continue my research career and was looking to do a postdoc overseas, but I had little idea how to proceed and where.

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In China in 1984, where Michael and his wife, Cheryl, ran a workshop on platelet biology. They are photographed with Professor Changgeng Ruan and his wife. Changgeng was the first person from China after the cultural revolution to complete a PhD in a foreign country.

Most of the effort in the Phillips' group while I was there was on GPIIb-IIIa, which they purified whilst I was in Memphis. On returning to Australia in 1981 to take up a research appointment with Peter Castaldi at the University of Sydney, Westmead Hospital, I therefore decided to focus on GPIb. Research by Margaret Howard and Barry Firkin in Melbourne in the 1970s had shown that a failed antibiotic, ristocetin, agglutinated platelets in platelet-rich plasma, except the platelets of patients with Bernard-Soulier syndrome or von Willebrand's disease, suggesting a relationship between GPIb and the plasma and matrix protein, von Willebrand Factor. Other studies by Baumgartner in Switzerland, Sixma in the Netherlands and Weiss in the USA had shown a profound platelet adhesion defect under arterial shear flow rates to subendothelial matrix in both these disorders, again consistent with a receptor/ligand relationship. The initial attempts to purify GPIb at Westmead were frustratingly unsuccessful. Again a chance event provided the breakthrough. In 1982, I met Heddy Zola at a poster presentation at an ASMR meeting in Canberra. Heddy had not only raised a large number of monoclonal antibodies against T-cells, but also against platelets, which were contaminating his T-cell preparations. One of these, FMC25, proved to be directed against a component of the GPIb receptor complex, allowing our production at Westmead of additional monoclonal antibodies. One of these monoclonal antibodies, WM23, proved suitable for purifying the GPIb receptor under mild, non-denaturing conditions. In 1983, we reported additional glycoprotein defects, namely GPV and GPIX, in Bernard-Soulier platelets and showed that GPIb and GPIX were non-covalently associated. This was followed by the purification of the GPIb-IX complex in 1985 and subsequent direct confirmation of its role as the von Willebrand Factor receptor by reconstitution with the purified components.

My research career at this time was greatly facilitated by the award in 1986 of a Wellcome Australian Senior Research Fellowship. This allowed me to consolidate my career as an independent researcher and, more importantly at that time, the potential to apply for NHMRC grants as chief investigator and initiate collaborations in other areas. With Peter Newman in Milwaukee, we cloned and defined the role of PECAM-1 in mediating endothelial cell/endothelial cell interactions.

Studies with Mathew Vadas and Jenny Gamble in Adelaide defined the role of P-selectin in mediating platelet/leukocyte and endothelial/leukocyte interactions in inflammatory responses. More recently, collaborations with Steve Watson in Birmingham and Mark Kahn in Philadelphia have contributed to understanding the role and signalling function of platelet GPVI as the platelet collagen receptor. Nevertheless, the biology of the platelet GPIb-IX-V complex has remained the primary focus of my research for over thirty years.

In 1987, my long-term colleague, Robert Andrews, joined the laboratory and we both have led the research team since that time. Robert had also done his PhD with Burt Zerner, but on jack bean urease. Robert's initial efforts resulted in two *Biochemistry* papers in 1979: one paper defined the interaction domains in GPIb and von Willebrand Factor that mediated their interaction; the other, the purification of botrocetin, a C-type lectin from *Bothrops jararaca*, the South American pit viper, that modulated the binding of von Willebrand Factor to GPIb. In subsequent years, snake venoms proved to be a rich source of very specific platelet receptor agonists and antagonists, including the identification of mocarhagin, a metalloproteinase disintegrin, from *Naja mocambique mocambique*, the Mozambican spitting cobra, which helped us define the ligand binding functions of both GPIb and PSGL-1, the neutrophil P-selectin receptor.



Christmas 1987 in the Blue Mountains with daughter Jessica, Robert Andrews and PhD student, Xiaoping Du. Xiaoping is now Professor of Pharmacology at the University of Chicago.

In the late 80s, I was becoming increasingly frustrated about the career opportunities at that time in an academic medicine department. The Wellcome Fellowship had not translated into an academic or research appointment and so I shifted into a somewhat dispiriting Hospital Scientist appointment in the Coagulation Department at Westmead Hospital. The consequence of this was my move to the Baker Medical Research Institute in Melbourne in October 1991 to establish and head the Hazel and Pip Appel Vascular Biology Laboratory. Shortly thereafter, I was joined by Robert Andrews on his return after two years with Joan Fox in San Francisco, where he had defined at a molecular level how GPIb interacted with the platelet cytoskeleton. Here I spent the next ten years. The critical mass associated with a larger cohort of researchers with similar broad interests was invaluable and many close friendships and collaborations were developed, in

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particular with Ian Smith and his research team. Ian's interest in protein chemistry and later, proteomics, nicely dovetailed our own interests. Many experiments were planned on the back of a beer coaster at the College Lawn! In the 90s, other long-term researchers joined the group, including Elizabeth Gardiner and Yang Shen. This period was interspersed with two sabbaticals. One with Glenn Begley at the Bone Marrow Laboratories at the Walter and Eliza Hall Institute helped demystify molecular biology for an organic chemist, although I never mastered a Northern blot. It was however an inspiring experience to be associated with one of the best haematological research teams in the world with Don Metcalf, Nic Nicola and Doug Hilton. The second sabbatical was with Jose Lopez at Baylor College of Medicine in Houston, resulting in two *Journal of Experimental Medicine* papers identifying Mac-1 and P-selectin as novel GPIb counter-receptors.

Increasingly, I found institute structures to be too restrictive and thus in 2001, I moved to Monash University as an NHMRC Senior Principal Research Fellow in the Department of Biochemistry under the leadership of Christina Mitchell. Jane Arthur and Fi-tien Mu also joined the team at that time and remain still with the group under Robert Andrews. Monash also allowed me to satisfy my increasing interest in senior leadership roles. In 2002, I took on the half-time role of Deputy Dean Research in the Faculty of Medicine, Nursing and Health Sciences and, in 2006, Headship of Immunology charged with its restructuring. This progression in part explains the evolutionary path by which I now find myself based in Cork. What have I learnt in this thirty-year

journey? Firstly, that one should move in one's research career every five to ten years and in leadership roles every three to five years. This refreshes the spirit and always the opportunities. Second, that an open laboratory policy ultimately is the best and most rewarding approach to research. I have always shared reagents and ideas with all, regardless of whether they were competitors or not. The joy of research is in the discovery, not the attribution. Third, that research provides the opportunity to collaborate widely and travel the world to countries as diverse as the USA, China, Japan, France and Russia. Finally, I have most enjoyed the mentorship role and fostering the career development of the many PhD students and postdoctoral fellows with whom I have been associated. In a long career, this remains the most satisfying.



The Main Quad at University College Cork.

