







Neil J. Bulleid (1960–2023), a virtuoso of protein folding and redox biology

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Neil John Bulleid, 5th October 1960 to 22nd March 2023.

Image courtesy of Susan Bulleid, used with permission.

His many friends, colleagues and collaborators were shocked and saddened by Neil Bulleid's sudden and untimely death on 22nd March 2023. Neil was an outstanding biochemist and a prominent and widely respected member of the global protein folding and ER-redox research communities.

After studying Biochemistry at the University of Liverpool, where he graduated in 1982, Neil did his PhD at the Glasgow College of Technology (now Glasgow Caledonian University). Neil's first stay in Glasgow had two profound effects on the rest of his life. Firstly, it was here he met and married his wife Susan. Secondly, he exploited endoplasmic reticulum (ER)-derived microsomal membranes to study the metabolism of xenobiotics.

In 1986, Neil joined Robert Freedman's group at the University of Kent to study protein disulphide isomerase (PDI), an enzyme thought to assist oxidative protein folding. Neil set out to test this hypothesis by combining *in vitro* protein synthesis with his detailed knowledge of ER microsomes. By carefully opening these vesicles to remove their contents and then resealing them in the presence or absence of the purified enzyme, he showed that PDI promotes the formation of native disulphide bonds in newly synthesised secretory proteins. This ground-breaking work set the scene for his future research on ER luminal chaperones. After a stay in Mary-Jane Gething's laboratory in Dallas, Neil established his own research group at the University of Manchester, holding a Royal Society University Research Fellowship from 1990 to 2000. Neil was a founding member of the membrane trafficking group in Manchester and made several key discoveries during his time there. Building on his earlier work, he played a key role in the identification of ERp57, an ER oxido-reductase that partners with calnexin and calreticulin to assist glycoprotein folding. Intrigued by the dozens of other PDI-like enzymes in the ER, Neil went on to systematically explore their functions in living cells. He also made seminal discoveries in the field of matrix biology, identifying the molecular recognition sequence that determines the type-specific assembly of procollagen trimers.

Since the mid-1970s, ER membranes were typically obtained from canine pancreas. However, procollagen biogenesis

requires specialised ER components, and Neil did not hesitate to explore alternative models. Digitonin-treated "semi-permeabilised" mammalian cells proved to be an optimal solution. Neil mastered their use, teaching courses and inviting colleagues to visit his laboratory for training. This discovery paid huge dividends when combined with the genetic depletion/removal of specific components, allowing the function of many ER enzymes and chaperones to be deciphered. In 1999, these achievements resulted in Neil's appointment as a Professor of Biochemistry. Towards the end of his time in Manchester, Neil co-organised the successful 63rd Harden conference, bringing together scientists studying protein folding *in vitro* and *in vivo*.

It was with the new millennium that relationships between cellular stress responses, ER redox conditions and protein homeostasis began to interest pathophysiologists. Neil was quick to spot this newly emerging field and, as ever, his curiosity was matched by his generosity. Bringing together a group of European laboratories with similar interests, Neil was central to the development of the *ER Redox club*. This group now meets every other year to provide a fertile environment for young scientists who aspire to become international research leaders. Neil and his group were regulars at these conferences and attended the most recent meeting in Italy last year.

Although this group was frustrated by their failure to obtain EU-network funding, their resulting collaborations were extremely productive. Neil's contributions opened new

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research fields and included the discovery of the H₂O₂-Peroxiredoxin 4 pathway operating in parallel to the Ero1-PDI electron transfer relay. Neil's work freed ER-redox from its organellar isolation and demonstrated its connections with metabolism and redox regulation in the cytosol. He would fearlessly embark on such novel and challenging research questions, using the best and most elegant techniques. He was also famous in the *ER Redox Club* for always asking for another control experiment.

In 2009, Neil moved to the University of Glasgow, a new challenge after his successful time in Manchester. Unsurprisingly, Neil quickly established a competitive research group, recruiting ambitious and talented co-workers and continuing to drive the field forward. As Director of the Institute of

Molecular, Cell and Systems Biology from 2014, his efficiency and talent for identifying the right people for the right role had a huge and lasting impact.

Neil was always very supportive of young researchers, and this ethos was reflected at all levels of his activity. Likewise, he was instrumental in recruiting excellent female scientists to key positions and empowering them towards leadership careers. After almost 10 years of leadership in Glasgow, Neil stepped down as Institute Director, passing on the baton to Helen Walden, one of the recruits he had mentored. Seeing junior colleagues thrive gave Neil an enormous sense of fulfilment, and he was always keen to help support and develop their careers in any way he could.

Neil typically carried out his research with a small group of trusted co-workers,

some of whom worked with him for many years, further testifying to his mentoring skills. In the last year, Neil had even put his laboratory coat back on and was enjoying working at the bench alongside his group, who revelled having him in the laboratory. Because he was so well organised, Neil always found time to chat and share ideas and suggestions over a coffee or a beer. While Neil's research was flamboyant, his personality was archetypically British: understatement and a sweet smile made the enormously high-quality work in science and leadership that he achieved appear an easy task. Such modesty belies his huge contributions to the fields of protein folding and redox biology and to the Universities of Manchester and Glasgow. Neil is survived by his wife Susan and their son Nick.