Biochemistry in Bristol – Research on Nucleic Acids

As noted elsewhere in this record, many of the founding figures of Biochemistry in Bristol came from Cambridge and one of these was present at the birth of nucleic acid biochemistry. The picture below shows Freddie Gutfreund (centre), walking through Cambridge in the company of his close friends Francis Crick (right) and Jim Watson (left). It dates from 1952 and one year later Watson and Crick published the DNA double helix.

Freddie moved to Bristol when the Department began and continued here his very successful research career. His field was protein biophysics, though Francis noted this as “Freddie’s red herring” on the ground that the instructions for the protein were already laid down in the DNA! The original Watson-Crick model was later found languishing in the basement of Cambridge Physics and, as also noted in this record, was brought to Bristol by another émigré from Cambridge, Herman Watson.

Nucleic acid research in Bristol started shortly after Biochemistry was founded, with the arrival of John Hindley in 1968 from Fred Sanger’s laboratory in Cambridge. At that time, Sanger was between his two Nobel-winning projects, protein and DNA sequencing and was trying to sequence RNA. Perhaps John’s most famous research came shortly after moving to Bristol, in a collaboration with Charlie Weissmann in Zurich on a virus with an RNA chromosome. John advanced Sanger’s methods sufficiently to obtain a sequence of 175 bases from the viral RNA, a massive achievement at the time (1970). Meanwhile, Weissmann determined the amino acid sequence of the corresponding protein and when lined up their two sequences revealed one of the first validations of the genetic code in real life.

University expansion in the 1970s allowed for two more appointments in nucleic acid biochemistry in 1976: Nigel Brown and Steve Halford, shown below (left and right respectively, at work and at play). Nigel, like John Hindley, came from Sanger’s group, but in a later era when DNA sequencing had become practicable. With Sanger, Nigel contributed to the first genome sequence, a viral chromosome 5375 bases long. Nigel’s first objective in Bristol was to sequence a transposable DNA element that conferred resistance to mercury, an element also being studied at that time by John Grinsted and Mark Richmond in what was then the Department of Bacteriology. Nigel went on to cover the general processing of toxic metals in bacteria, though he moved in 1989 to the Chair in Microbiology at the University of Birmingham. Nigel’s later career followed administrative pathways, as Director of Science at the BBSRC and as Head of Science and Engineering and then Senior Vice Principal at the University of Edinburgh. He was awarded an OBE for services to science in the 2014 New Year’s Honours.

Conversely, Steve Halford stayed here throughout his career: as an undergraduate in the second set of students to do Biochemistry in Bristol (1964-67); as a post-graduate with Freddie Gutfreund (1967-70); as a post-doc with Freddie and Mark Richmond (1972-76); and then staff appointments as Lecturer (1976), Reader (1989), Professor (1995) through to an Emeritus post on his retirement in 2011. Steve’s research as a PI focussed primarily on restriction enzymes, where he deployed what he had learnt about enzymes from Freddie and whatever he needed to know about DNA from Nigel and John Grinsted. Some years later, John and Steve set up the Molecular Genetics II course that is now embedded in our year II Biochemistry programme. Steve’s research made significant contributions to our knowledge of the reactions of proteins on DNA: how they find their target sites on DNA; how they can catalyse reactions at one sequence whilst excluding all others;
how in many instances they trap loops by binding two sites on the same DNA. Numerous colleagues participated here, and the photograph below, from Steve’s retirement, shows almost all of his post-graduate and post-doctoral associates. Steve’s work was recognised with the Novartis Medal from the Biochemical Society (2011) and election to the Royal Society (2004).

In 1983, the University of Bristol strengthened its research on nucleic acids by forming the inter-departmental Unit of Molecular Genetics, with several new appointments across the life sciences. Two of these were in Biochemistry: Bill Chia and Len Hall. Bill was primarily interested in developmental genetics but while in Bristol was waylaid by Tony Clarke and Dale Wigley into using his expertise in molecular genetics to enable John Holbrook’s team to carry out their pioneering studies in protein engineering. Bill moved on to a research institute in Singapore in 1991 to work uninterruptedly on development where he advanced that field considerably. Len’s research area was in the fertilisation of mammalian eggs by sperm but he was to take on progressively more demanding administrative roles: as Head of the Department in 2000, Faculty Dean in 2004 and Pro-VC in 2008.

The Halford and Brown groups were initially located in the Inner Court Laboratories off Woodland Road, previously the home of the Molecular Enzymology Laboratory. However, they moved in 1985 to a suite of old laboratories in the D.40-50 corridor of the Medical School, to bring them closer to Bacteriology. The space left by Nigel’s departure was later occupied, from 1995, by Kevin Gaston. Kevin’s appointment, together with Sheela Jayaraman’s MRC Fellowship (1996-2006), brought new advances into this area, expanding it from its previous focus on prokaryotic systems to the eukaryotic world. His research projects included analyses of gene control in papilloma virus and in leukaemia and cancer. The old-style laboratories in D.40-50, small rooms with wooden benches separated by an empty corridor, were thankfully swept away when the corridor was completely refurbished in 1999 as an open-plan laboratory to house the DNA-protein interactions unit. The old and new laboratories can be seen in the backgrounds to these photos of Kevin’s group in 1997 (left) and 2007 (right).

The three most recent appointments in nucleic acid biochemistry were all connected in some way to Steve Halford. Firstly, Mark Szczelkun had been a post-doc with Steve from 1994, where he had done ground-breaking work in DNA looping by restriction enzymes. He then obtained from the Wellcome Trust a Career Development Award (1998) followed by a Senior Fellowship (2002) before his current staff appointments as Reader (2007) and Professor (2010). Nigel Savery came here by a different route, initially as a temporary Lecturer to fulfil Halford’s teaching and admin duties whilst Steve held a Research Leave Fellowship. But it soon became apparent that Nigel was fulfilling these roles far better than Halford ever did, so the post was quickly made permanent, which in turn allowed Nigel to further his research on transcription. That post recently evolved into a Chair (2014). Mark Dillingham had even earlier connections. While he was an undergraduate here (1993-96), Halford was his personal tutor responsible for his first year tutorials. At this year’s 50th anniversary of the Biochemical Society Colworth Medals (which Dillingham had been awarded in 2010), Mark commented that his “first year tutorials had introduced him to the wonders of DNA-protein interactions but pretty much at the expense of all other aspects of the course”. This may explain why Dillingham went on to a summer studentship with Szczelkun and his final-year project with Gaston. After his PhD and post-doctoral research with, among others, Dale Wigley and Martin Webb (both Bristol alumni), Dillingham returned to Bristol, initially as a Royal Society URF (2005-12)
before transferring to the permanent staff. The Colworth medal is for the top biochemist aged below 35 and Dillingham’s award was the appropriate recognition for his work on DNA helicases.

Szczelkun, Savery and Dillingham, shown here, form together a cohesive unit in DNA-protein interactions as all three are presently studying related systems: DNA motor proteins that utilise ATP energy to translocate along DNA prior to mediating key reactions in the interrelated fields of DNA repair, replication, restriction and transcription. Illustrated here is one such protein, the AddAB helicase/nuclease, which first binds to one end of a DNA and then moves along it, separating the strands and cleaving both before leaving the DNA ready for recombination. The techniques used nowadays to analyse DNA translocation include single-molecule methods so also shown here is an image of individual molecules of DNA by atomic force microscopy (with Massimo Antognozzi, Physics)

The recent studies thus extend the work on ATP-dependent enzymes that has been a focus of Bristol Biochemistry for the past 50 years. Indeed, how proteins utilise ATP energy was in large part elucidated here by David Trentham, working with Freddie Gutfreund in the early 1970s.