

Alan Wolffe (1959-2001)

Alan Wolffe, who died at the age of 41 on 26th May 2001 in a road accident in Rio de Janeiro, was a leading cell biologist interested in the structure and function of chromatin. He was renowned for his pioneering demonstration that the chromosomal organisation of genes is a dynamic phenomenon determining their expression, cell division and differentiation. He was a prolific writer, an engaging speaker and the leader of a large research group.

Alan was born on 21st June 1959 in England in the Staffordshire town of Burton-on-Trent, where he lived up until finishing school at the age of 18. He was already attracted by biology and was awarded the Biological Council Prize upon leaving Pingle School. Having obtained entrance to Oxford University, he graduated with a first class B.A. degree in 1981. Under the influence of his tutor at university, the late Dr Ian Walker, he became interested in DNA-histone interactions, which must have sown the seeds in Alan's mind as to how genes are organised within the nuclear structure, an area of research that he was to pursue with great passion throughout his postdoctoral research career.

I first met Alan when he was 20 and had come to spend a few weeks as a summer student in my laboratory in the then Division of Developmental Biochemistry at the National Institute for Medical Research (NIMR) in London. This was a great success, since he returned the following summer before continuing as a PhD student with me. Summer students are usually given trivial jobs, usually to plug holes in the work of postdocs or PhD students writing up their thesis. Alan was not one to be satisfied with such 'boring' activities and insisted on participating in the ongoing work of the group on the hormonal regulation of egg protein genes in the frog *Xenopus laevis*, an organism of choice for the rest of his life. His first PhD project was to refine the preparation of primary hepatocyte

cultures in order to activate with estrogen the silent vitellogenin genes in male *Xenopus* hepatocytes. A simple 'trick' that allowed the cells to recover from heat-shock proteins produced in the initial period of 'culture shock' enabled him to optimise the vitellogenin gene induction system in vitro. Seven full publications in major journals resulting from his PhD thesis work made certain that Alan would have no difficulty in finding a prestigious American lab to embark on his postdoctoral training.



The award of an EMBO long-term postdoctoral fellowship in 1984 led Alan to the laboratory of Donald D. Brown at the Department of Embryology, Carnegie Institution of Washington in Baltimore. At that time Brown's group had been exploiting the differential expression of 5S RNA genes in *Xenopus* oocytes and somatic cells, a system that lent itself exquisitely to identifying the structural elements underlying the developmental switch for selective expression within the same family of genes. In a series of papers with Brown, Alan established the relationship

between a number of important structural features and the transcription of 5S RNA genes, such as negative supercoiling, their interaction with transcription factors and nucleosomal organisation. At the end of this fellowship, he moved a few miles away to the NIH in Bethesda to work with Gary Felsenfeld in the Laboratory of Molecular Biology (National Institute of Arthritis, Diabetes and Metabolic Diseases), whose work on chromatin structure is well renowned. Enjoying the

freedom and resources offered by the NIH, Alan focused his efforts on the role of histones in the functional organisation of nucleosomes, in particular the importance of histone acetylation in the activation and silencing of transcription. His interests in gene expression during development led him to Igor Dawid's lab at the National Institute of Child Health and Development. This move was in fact a stepping stone towards his appointment in 1990, at the age of only 30, as Chief of the newly founded Laboratory of Molecular Embryology (LME), a position he held for the next 10 years.

During this period, when the LME grew to nearly 45 members, there followed a most extraordinary outpouring of research and new ideas, a period that also established Alan as a leader in the area of chromatin research. Rather than list all his publications chronologically, he preferred to group them into three major areas of his research. The most substantial of these was the work on the dynamic nature of the roles played by histones and nucleosomes in transcription. Starting with his work on the *Xenopus* 5S RNA genes, his group extended their studies on nucleosome assembly and transcription factors to a number of other genes, which, interestingly, included the transcriptional activation by estrogen of one of the *Xenopus* vitellogenin genes, a system he had worked on as a PhD student. During the 1990s the Wolffe lab became increasingly aware of the

importance of histone H1 acetylation for the incorporation of transcription factors during chromatin assembly and how this affects the processes of transcription and replication. This period also coincided with the rapidly growing recognition throughout the chromatin community of the central position occupied by histone acetylases and deacetylases in the concept of co-activators and co-repressors, particularly for zinc-finger transcription factors.

In many of their studies on nucleosome and chromatin assembly, the Wolffe lab very judiciously exploited frog egg extracts, which also proved to be particularly valuable for his work on his other two areas of interest, namely gene expression and nuclear organisation of transcription. It is impossible to mention all their contributions in these areas, but worth noting are their papers on histone phosphorylation, remodelling of sperm chromatin in *Xenopus* egg extracts, a recognition element within the structure of the nucleosome for the thyroid hormone receptor (a zinc-finger protein) and how histones are assembled into the chromatin of early *Xenopus* embryos. Towards the end of this most fruitful period at the NIH Alan was becoming increasingly involved with transcription factors, such as Y-box factors, in the context of the higher-order organisation of the cell nucleus.

Alan's departure from the NIH last year to take up the position of Senior Vice President and Chief Scientific Officer at Sangamo Biosciences, Inc. came as a surprise to many of us. He wrote to me recently to explain his move simply as 'having run a department for a decade... 40 seemed a good time to move on.' Sangamo is a California biotech company with major interests in novel transcription factors for the regulation of gene expression. Only a few weeks ago he also wrote to me enthusiastically about his future plans for working on zinc-finger proteins and chromatin and said that he was actively building up a new group around him for just that purpose. Sadly, his dreams will remain unrealised.

Most remarkably, Alan had authored 260 publications, most of them original research papers in 'high impact' journals

but also many reviews and two books on chromatin. Being such a prolific writer was one facet of his being a great communicator. He enjoyed attending meetings and loved debates, where his encyclopaedic knowledge would soon become evident to all. No wonder he was in great demand to attend national and international conferences. Unfortunately, this imposed an enormous amount of travelling. It is therefore even more remarkable that he was always 'on the ball' about what was going on in his large lab. With the reputation that he had acquired, Alan continued to receive a stream of job offers from the most prestigious of universities and research institutions. He was also invited to join the editorial boards of several cell and molecular biology journals, scientific societies, grant committees and governing bodies of research foundations. He was an active member of the Editorial Board of the Journal of Cell Science. Few have accomplished in a long lifetime what Alan did in barely 20 years.

Ever since his days as a PhD student in my lab I don't recall Alan saying that any problem would be too difficult to solve or wasting any time getting moving with a new project. Even as a busy PhD student, he was always ready to help others around him, especially those having difficulties with their research, and always with that wonderful smile of his. No wonder he made innumerable friends - friendships that he nurtured throughout his life. Alan was a frequent visitor to the UK, when he would make every effort to visit his old lab at the NIMR, even though the last 16 years were spent in the United States. In 1997 I spent a few months in Alan's lab at the NIH, a valuable experience when your ex-graduate student is your boss. This period gave me a unique insight into his tremendous productivity, capacity for hard work and leadership. For those who did not know him well, his extraordinary pace of work and travels may have masked an endearing side of Alan's life as a caring family man who adored his two young children.

The cell science community has not only lost a leader but for many of us a dear friend. We know that Alan would not have achieved his success and reputation

without the support and affection that he received from his wife Elizabeth, also a cell biologist at the NIH and later at Sangamo. He is survived by her and their children, Max and Katherine.

Jamshed Tata

National Institute for Medical Research,
UK

The post-doc's view

Those of us who worked as post-docs in Alan's lab gained further insight into his unique approach to science and life. First and foremost, in all aspects, Alan possessed a quickness of mind that allowed him to grasp ideas, both good and bad, with ease. He could also be counted on to provide assistance or constructive feedback on any issue - a draft of a manuscript or support with a letter of recommendation. He was not one to keep you waiting and, in fact, had to make efforts to pace himself. These qualities were instrumental in promoting an exciting lab atmosphere, in which his enthusiasm and motivation were examples to be emulated. He loved to challenge people, and many of our most enjoyable discussions were in the form of arguments. Sometimes extreme in his opinion, he forced one to be knowledgeable to defend one's point of view.

The number of post-docs who worked with Alan and have now successfully established themselves in the many areas of nuclear organization/function attests to the success of his active approach to science, and the experiences gained during our tenure with him will be invaluable as we continue our research. More importantly, Alan cared for people, his friends and most of all his family. Of the many images of Alan that reside in my memory, one common feature stands out: his smile and laugh, revealing how much he loved and enjoyed life at all times.

For those of us who knew Alan, we can only regret his loss and be thankful for having had the opportunity to include him among our friends.

Geneviève Almouzni

Institut Curie, Paris, France