

Alan Barrett: an appreciation (21 August 1937–23 November 2020)



Alan John Barrett was born in Battersea, London, on 21 August 1937, the son of the eminent Cambridge pathologist Dr Max Barrett and his wife Win. Alan was the eldest of five children and brother of Roger 'Syd' Barrett, one of the founder members of the rock band Pink Floyd.

Alan's family moved to Cambridge while he was a child, and Alan spent his life and academic career in the Cambridge area. He studied natural sciences at Pembroke College, University of Cambridge, graduating in 1961. His PhD, awarded in 1964, under the supervision of Don H. Northcote at the University's Biochemistry Department was on the 'Pectic Polysaccharides of Higher Plants'. In 1965 he joined the Strangeways Research Laboratory, where the research was focussed around osteoarthritis. Alan led his own group and eventually became co-deputy director. In 1977, Alan was awarded a Higher Doctorate (Sc.D) from the University of Cambridge. In 1982, Alan was made a member of the external scientific staff of the Medical Research Council. When the retirement of the director in 1994 forced research at Strangeways into new directions, Alan and his team joined the Immunology Department at the Babraham Institute. Eventually, Alan led the Molecular Enzymology group at Babraham. When Alan retired from the Medical Research Council in 2002, he was invited to join Alex Bateman's team at the Sanger Institute and remained as a visiting scientist when the Bateman team moved to the EMBL-European Bioinformatics Institute.

At Strangeways, Alan's interest was in the lysosomal endopeptidases able to digest native collagen. Alan's approach was to devise a purification method, characterize the specificity of the peptidase from its interactions with synthetic substrates and inhibitors and to calculate the kinetics. Initially, Alan worked on the aspartic endopeptidase cathepsin D, then the cysteine endopeptidases cathepsins B, H and L. He and his PhD student, Phyllis Starkey, put forward the 'trap mechanism' for the inhibitory activity of the large plasma protein α_2 -macroglobulin, which inhibits endopeptidases of all catalytic types. Alan's team also characterized the cysteine endopeptidase inhibitors known as cystatins. In collaboration with pharmaceutical companies, Alan's team worked on cysteine endopeptidases from papaya (especially chymopapain) that were used for chemonucleolysis of intervertebral discs, and peptidases from pineapple (bromelain and ananain) and fig (ficain) that were used for debridement of burns. Alan's team also developed a blood test for amoebic dysentery by detecting the cysteine endopeptidase histolysin from the pathogenic protozoan *Entamoeba histolytica*. The discovery of haemoglobinase in the platyhelminth *Schistosoma* prompted Alan to look for a human homologue, leading to the discovery of legumain, a

lysosomal asparagine-specific cysteine endopeptidase previously overlooked. Alan's team also worked on the metallo-oligopeptidases thimet oligopeptidase and neurolysin. It was the action of these oligopeptidases on peptides derived from digestion of proteins by the proteasome that led to the invitation to join the Babraham Institute, where there was an interest in the cell surface presentation of antigenic peptides by the major histocompatibility complex.

Alan had an interest in the classification and naming of peptidases, and in the 1980s he and J. Ken McDonald wrote the two volume *Mammalian Proteases: A Glossary and Bibliography*. When I joined Alan's lab in 1982, eventually becoming his PhD student, we developed a classification of peptidases based on sequence and structural similarities. At Babraham we had better internet access and decided to post our classification online. Eventually, this developed into the *MEROPS* website, dedicated to the classification and nomenclature of peptidases. The classification was quickly adopted by the SwissProt database and became internationally recognized. It was because of our shared interest in classifying protein sequences into families that we joined Alex Bateman's group at the Sanger Institute who were working on the Pfam database. At Sanger, we expanded the *MEROPS* website to include peptidase inhibitors, extended the classification to include all proteolytic enzymes and added small molecule inhibitors and collections of known substrate cleavages and peptidase/inhibitor interactions.

Alan was instrumental in setting up the International Committee on Proteolysis (now the International Proteolysis Society) and chaired an expert committee on peptidases for *Enzyme Nomenclature*. He became the first non-American to organize a Gordon Conference ('Proteolytic Enzymes and Their Inhibitors' in 1990). He was a member of several grant review panels and editorial boards, and held consultancy posts with several pharmaceutical and biotech companies. At Strangeways, Alan was supervisor for eight PhD students. He edited two volumes of *Methods in Enzymology* and he, Fred Woessner and myself were editors of the first two editions of the *Handbook of Proteolytic Enzymes*.

Alan died on 23 November 2020 and is survived by his second wife Dr Jinq-May Chen, his children Mark and Ginny from his first marriage, and grandchildren Max and Annabel. An extended appreciation of Alan's life and work can be read in the online supplementary material 1.

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