

Profile

Marc Feldmann: a trailblazer of modern immunology

Marc Feldmann, Emeritus Professor at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford, UK, retired from directing the Kennedy Institute of Rheumatology 2 years ago, and is enjoying a new lease of life, dividing his time between Oxford and New York City's Mount Sinai Medical School. Research for Feldmann now means a focus on translational science with potential clinical impact, mainly done by mentoring younger researchers.

Born to Jewish immigrant parents, Feldmann's family moved to Australia when he was a child. After graduating from the University of Melbourne Medical School in 1967, he gained a PhD in Immunology from the Walter and Eliza Hall Institute of Medical Research, working with Erwin Diener and Gustav Nossal investigating the immune response of mouse cells *in vitro*. He developed new techniques to study cell interactions, soluble mediators, and autoimmunity, and learnt the power of effective collaboration, interests, and skills vital for subsequent success in his career. In 1972, he joined the Tumour Immunology Unit at London's then Imperial Cancer Research Fund, led by the pioneering immunologist Avron Mitchison. During the 1980s the big research question for Feldmann was how autoimmune diseases were induced. Collaborators analysing the immunohistology of thyroid and diabetic disease tissue provided an important clue, noting augmented expression of HLA antigens in active autoimmune sites. He connected this to the antigen-presenting function of human leucocyte antigens and proposed a new mechanism of inducing autoimmunity, with autoantigens presented locally to T cells, activating them. "This linked my autoimmune knowledge and my work on cells and their mediators involved in immune activation", he says. This concept was published as a Hypothesis in *The Lancet* in 1983, and became the blueprint for subsequent discoveries in autoimmune disease.

Feldmann began his long collaboration with the rheumatologist Ravinder Maini in the mid-1980s, analysing the mechanism of rheumatoid arthritis (RA). "The next piece in the immunological puzzle was to understand which molecular mediators were important during active disease, and hence potential therapeutic targets, and RA with accessible active disease tissue was a perfect model", he says. Feldmann and Maini identified many pro-inflammatory molecules in inflamed joints using molecular biology techniques. By culturing human tissue from rheumatoid joints, they found that blocking tumour necrosis factor (TNF) inhibited the production of other pro-inflammatory cytokines, thereby finding a candidate for the elusive therapeutic target. "The end of the 1980s was a key time for immunology in understanding the therapeutic potential of monoclonal antibodies", he recalls.

The next decade was game changing. Helped by his ex-student Jim Woody at the US biotech company Centocor, in 1992 Maini and Feldmann began clinical research on anti-TNF therapy in patients with RA. The results were dramatic, and kick-started competition in the field. Two *Lancet* papers published in 1994 heralded the start of the anti-TNF therapy revolution, showing this therapy was safe, effective, and sustainable. By the end of the decade, longer-term studies provided evidence for anti-TNF therapy to be even more effective in combination with methotrexate. "The 1999 phase 3 ATTRACT study was a milestone, being the first drug therapy that could halt joint destruction", Feldmann says.

Feldmann succeeded Maini as Director of the Kennedy Institute of Rheumatology in 2002, and he led the institute for 12 years, including its move from Imperial College London to Oxford. His tenure was a time of consolidation, deepening and widening the research base. Today he still helps companies develop therapeutics, and promotes academic-industrial collaborations, notably with an annual translational conference "From the Laboratory to the Clinic". Awards aplenty have been bestowed on Feldmann, including European inventor of the year in 2007, a knighthood, and a Companion of the Order of Australia, and, with Maini, the Crafoord Prize, Albert Lasker Clinical Medical Research Award, and the Canada Gairdner International Award. Sir Ravinder Maini, Emeritus Professor of Rheumatology at Imperial College London, comments: "Marc brought so much to our 'bench to bedside' translation of anti-TNF therapy over 25 years. Key in the success of this complex project was access via his extensive contacts to enabling molecular and cellular technologies, his intellectual drive, endless energy, fostering of and loyalty to younger colleagues, and, in our collaboration, enduring trust and friendship."

Feldmann remains passionate about the future of his field: "Can we get closer to a cure for RA? As anti-TNF is the world's best-selling drug class, with over \$30 billion sales annually, and with many biosimilars becoming available, I am optimistic that the impetus of my work will continue with further combination treatment added to anti-TNF and methotrexate." When looking back at his career, he is struck by its continuity, from the topics of his PhD work facilitating discovering the mechanisms of autoimmunity, to successful clinical trials and new approaches to RA treatment, and to treating related diseases such as inflammatory bowel disease and psoriasis. "It gives me great satisfaction to have played a part in improving the lives of millions of patients. None of this could have happened without Ravinder Maini's collaboration. But much remains to be done which can only happen through effective academic-industrial partnerships", he says.

Richard Lane



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