

The yin and yang of rheumatoid arthritis

In an effort to spread recognition, the major prizes awarded each year for biomedical research are often given to two or three scientists who have contributed to the development of a field, usually at different stages and from different laboratories. But sometimes an award acknowledges teamwork — a partnership that changes the course of medical science. This year's Albert Lasker Award for Clinical Medical Research is a classic example.

Friends and colleagues for 20 years, Sir Ravinder Maini and Marc Feldmann won the 2003 prize for translational research, which started with identification of a molecular cause of rheumatoid arthritis (RA) in animal models, moved through its validation in human tissue, and culminated in the development of a new class of drugs for the disease.

Feldmann began his career as a doctor in Australia, where he found that “the realities of medical practice served only to reveal how much we didn't understand about mechanisms of disease.” He switched to basic research, earned a PhD, and in 1972 went to London to work as a postdoc at a new department of immunology at University College. Sir Ravinder was also a physician with a keen interest in research. As a fellow in the relatively new subject of clinical immunology, he published his first paper in *Nature* in 1968, on a lymphocyte extract in RA patients.

Their collaboration began in the mid-1980s when Sir Ravinder, as head of the Kennedy Institute of Rheumatology at Imperial College, recruited Feldmann. Their *in vitro* studies showed that blocking TNF- α with antibodies prevented IL-1 production, revealing TNF- α to be a master regulator of cytokine activity. In 1989, they demonstrated that biopsies of human synovium showed TNF- α receptors to be upregulated in RA at the height of disease. And by 1992, clinical trials with a TNF- α monoclonal antibody — performed against a backdrop of skepticism from both industry and academia — yielded powerful results that led to the development of three anti-TNF

drugs, infliximab, etanercept, and adalimumab, which are effective in most RA patients and can protect joints from further destruction.

“We grew with that field,” Sir Ravinder told the *JCI*. “We were on the ground floor when cytokine cDNAs were cloned by industry, and we had access to these probes to find out which cytokines were expressed in joints and so on. So we were children of circumstance.”

Feldmann and Sir Ravinder talk about each other's contributions as much as each does his own. Feldmann calls Sir Ravinder “an excellent clinician and good administrator” and describes himself as “strong on science and finding commercial partners for ventures,” while Sir Ravinder explains that the partnership works because “our knowledge base and expertise is overlapping and in different areas. We have found that with Marc being more deeply engrossed as a full-time laboratory researcher in the lab

side of things, and me with one foot in the lab and one in the clinic, there has been an overarching continuum of expertise which we needed to take things from bench to the bedside. At the personal level, we like and complement each other in our character.”

Although Sir Ravinder retired last year, their collaboration seems unbreakable. Last October, Feldmann succeeded him to become director of the Kennedy Institute. They are now keen to recruit young blood. “The demographics of the British academic system are quite old,” Feldmann says. “People don't have the chance to work independently at an early age. So we're currently recruiting four lecturers to work as team leaders.” Sir Ravinder has an emeritus position and still comes

into the institute. He says, “We will still probably discuss things that will allow the next generation of investigators to take this work further.”

Among other endeavors, Sir Ravinder and Feldmann plan to resolve issues regarding anti-TNF therapy. For example, why do 30% of patients not respond to treatment? Sir Ravinder offers an answer. “One of the interesting things about RA is that it's a disease characterized by periodic exacerbation and relative quietness. I think there is some kind of underlying trigger, which we

don't understand, acting in a pulsatile fashion and recurrently exhibiting itself. I suspect what's happening in the 70% that respond is that you're catching them in a stage when it's been triggered again, and the other 30% could be in a stasis phase which is independent of TNF. So I think there's a dynamic to this process that we haven't fully understood. I want to discuss these crazy ideas

with younger people and encourage them to think of ways of investigating this kind of thing. Marc's group is now very interested in looking at whether T cells are playing such a role.”

What does winning the Lasker Award mean to them? “It's too early to say what effect it will have on our work,” says Feldmann. “The nice thing for me,” says Sir Ravinder, “is that it's come at a stage in my career when I don't feel I need to gain any Brownie points. So I hope it allows me to encourage this field of research, especially the transitional area where you need to make sure that young people who are clinically qualified and scientifically well trained realize that this is a very rewarding thing to be doing.”



Marc Feldmann (left) and **Sir Maini Ravinder** (right) receive the Albert Lasker Award for Clinical Medical Research

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