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Editorial

The Crafoord Prize in polyarthritis 2013

Why is this prize important in the field of RA?

While everyone knows about the Nobel Prizes, the almost equally exclusive Crafoord Prize is almost anonymous. The award was initiated in 1980 when the Swedish industrialist, Holger Crafoord, and his wife, Anna-Greta Crafoord, donated money for an annual Crafoord Prize to the Royal Swedish Academy of Sciences. This prize is meant to be awarded in areas not covered by the Nobel Prizes, namely mathematics and astronomy, bioscience and geoscience. The first Crafoord Prize was awarded in 1982. Since Holger Crafoord suffered from severe RA, the bylaws stipulate that the prize can also be awarded for major advances in polyarthritis. However, the committee of the academy has to be convinced that prize-worthy work has been done.

Similar to the Nobel Prize, the academy solicits nominations from scientists around the world. The prize can be shared by up to three winners. However, the hurdles were high and it took 18 years before the first Crafoord Prize in polyarthritis was awarded, because the academy requires a real breakthrough that is equivalent to a Nobel Prize. In 2000, Ravinder Maini and Marc Feldmann shared the prize for their definition of TNF-α as a therapeutic target in RA. In 2013 the prize was given to Peter Gregersen, Lars Klareskog and Robert Winchester for their discoveries of the roles of different genetic factors and their interactions with environmental factors in the pathogenesis, diagnosis and clinical management of RA. The awardees this year shared no less than 4 million Swedish crowns between them. The prizes were handed out at a ceremony on 2 May by his Majesty the King of Sweden (Fig. 1).

Holger Crafoord (1908–82) retired as CEO of one of the world's largest packaging companies in Lund, Sweden, in 1972. Ten years earlier he met a professor of nephrology in Lund, Nils Alwall, who had developed the haemodialysis technique. Crafoord realized that for the lifesaving technique to be widely available, the procedure needed to be streamlined. He then founded the company Gambro to develop easy-to-use machines and disposable filters. Haemodialysis then became a worldwide standard. After some initial difficulties, the company became a world leader in its field.

Holger Crafoord came from a simple background and recovered from life-threatening tuberculosis at 20 years of age; he then developed severe RA in 1970. However, Holger and Anna-Greta felt that since life had been good to them, they wanted to give something back to society. Their interest in science and Holger's painful joint disease resulted in the very substantial donation for the prize. The Crafoord family is not keen about the publicity that this prize truly deserves.

Fig. 1 His Majesty the King of Sweden and the Crafoord Prize winners Peter Gregersen, Robert Winchester and Lars Klareskog.

The awardees each gave a lecture about their prize-wining topic on 3 May, the day after the award ceremony. Dr Winchester acknowledged his teacher Henry Kunkel and especially Kunkel's important post-doctoral year in Nobel Laureate Arne Tiselius's laboratory in Uppsala in 1950. He gave a splendid lecture about the history of the initial observations with suppressed mixed lymphocyte reaction between patients with RA [1], the MHC and Ia antigens, and the discovery of the DR4 and later DR1 associations with RA, including the intellectual ground work that lead to the conclusion that both DR4 and DR1 must be heterogeneous and thus could have common susceptibility features for RA. He then acknowledged the sequencing skills of Jack Silver [2] and the important role of Peter Gregersen in the discovery of the shared epitope [3].

Robert Winchester's intriguing title 'RA and autoimmunity: good genes, elegant mechanisms and bad results' alluded to the fact that hopes that the binding features of the shared epitope would lead to the discovery of the cause of RA had not yet materialized [4]. However, recently it was shown that only citrullinated peptides presented from cells with the shared epitope trigger T cells to produce proinflammatory cytokines [5]. He reminded

everyone of the timeline of discoveries: in 1978 the susceptibility to RA among HLA-DR4-positive patients was discovered and in 1987 the shared epitope was described. Genome-wide association study (GWAS) genomic techniques exploded around 2000, resulting in the complete human genome sequence in 2001. With a nostalgic smile, Gregersen then mentioned that it was possible to define the shared epitope story using $<$50 patients' sera, whereas proving the association with *PTPN22* in 2004 required 2000 patients [6]. These data obviously require large international collaboration, of which Gregersen is a master. Although now some 40 susceptibility genes have been confirmed, they only explain 20% of the genetics of RA. Despite the progress, this work is only in its infancy and he predicted big surprises in the future, which are likely to include gene–gene as well as gene–environment interactions.

Lars Klareskog was the first Swedish Crafoord Prize winner in part for his PhD work back in 1978, defined as the Ia, later renamed as DR class II structures [7]. In the past decade, Klareskog's goal has been to understand how genetic and environmental factors interact in the pathogenesis of RA. His prize-winning contribution relates to the interaction of smoking and the presence of shared epitopes, *PTPN22* mutation and ACPA positivity [8, 9]. The worst combination increases the risk of susceptibility by $>$40 times! Had Sweden been a non-smoking country, 20% of RA cases would not have occurred.

Klareskog hypothesises that smoking increases citrullination in the lungs, which in turn triggers the autoimmune disease. But then we should not forget that our gastrointestinal tract may also play a role [10].

The work of these three awardees has enlightened us about how several genetic factors, along with the immune system and triggered by environmental factors, can lead to the crippling chronic disease called RA. Altogether, this new understanding will not only facilitate prognostication, but may also help in prevention.

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