patients. The evaluation of benefit and harm continues to be investigated in the post-marketing era. In 2002, the National Institute for Health and Clinical Excellence approved the use of anti-TNF drugs for the treatment of RA not responding to two disease modifying drugs. Today, anti-TNF therapy, most frequently added to prior MTX, is a well-established option for aggressive RA. Over one million patients with RA have been exposed to anti-TNF biological drugs worldwide, with long-term benefit in 50–60%. Excellent responses are seen especially in patients with intervention early in the disease course. Treatment indications have extended to psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease. However, the high cost of treatment limits access and there remains an unmet need.

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Human leukocyte antigen B27

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The year 1973 was quite an eventful one with key important milestones occurring in the political and scientific domains. It was the year when American troops finally withdrew from Vietnam, Pink Floyd released *Dark side of the moon*, and the UK joined the European Economic Community. The first US space station, Skylab, was launched and thalidomide victims finally won compensation from the Distillers drug company.

I was working as a research registrar in rheumatology with Frank Dudley Hart at the Westminster Hospital and, largely due to his encouragement, had developed a clinical and research interest in ankylosing spondylitis (AS) – a specialist area in rheumatic diseases for which Dudley Hart had an international reputation.

At that time there was a burgeoning interest in the major human histocompatibility system (HLA) and the possibility of HLA-linked diseases. The equivalent H2 system in the mouse had already been shown to be linked with immune response genes and reports had appeared in the literature linking autoimmune diseases, such as myasthenia gravis, with specific HLA antigens.[1,2] These reports had interested David James who was working as a consultant haematologist in the blood transfusion laboratories at St Mary Abbott's Hospital. He had a chance conversation with Derrick Brewerton, a consultant in rheumatology and rehabilitation at the Westminster Hospital, and asked him if there were any rheumatic diseases that had a strong familial tendency. Brewerton had the remarkable intuition to reply 'ankylosing spondylitis' and from this serendipitous encounter an exciting research project was born.

I was then running a dedicated AS clinic at the Westminster Hospital and was approached to collaborate in a research project to explore any possible HLA association with the disease. Together with Maeve Caffrey, David James' technician, blood samples were taken from 75 AS patients and 60 first-degree relatives of 25 of them. At that time, the blood samples had to be defibrinated by hand using orange sticks prior to being sent to the lab for HLA analysis.

The results were astonishing in that 96% of patients, but only 4% of the controls, were positive for the HLA-B27 antigen. Moreover, 50% of the patients first-degree relatives

were HLA-B27 positive.[3,4] Our paper was accompanied by a Lancet editorial that was less than enthusiastic:

> *Nowadays the suggestion of yet another association between a genetic marker and a human disease does not generate much enthusiasm – in fact, as far as the HL-A system is concerned, it tends to lead to cerebral switch-off.*[5]

In the same month as the *Lancet* publication, Schlosstein and colleagues independently published similar findings in the *New England Journal of Medicine*.[6]

Despite the *Lancet* editorial, the findings created great excitement in the world of rheumatology and in quick succession HLA-B27 associations were found with reactive arthritis and acute anterior uveitis.[7,8] Family studies in AS also confirmed the strong link with the disease.[9] HLA class 2 antigen associations have subsequently been found to predispose to both disease and disease severity in RA and to be important in other autoimmune diseases such as systemic lupus erythematosis.[10] Genetic studies arising from the ability to undertake genome-wide scans in patients and families suffering from AS have also created exciting new data in the last five years indicating that genes linked to HLA-B27 may begin to explain the pathophysiology of the condition.[11]

An exciting original observation in 1973 was the catalyst for many other research groups to explore the immunogenetic aspects of rheumatic diseases over the ensuing 35 years and may now, at last, lead to identifying potentially exciting therapeutic targets in AS. As Titus Maccius Plautus once said, '*Nemo solus satis sapet*' (Nobody knows enough alone).

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