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UN PEU D’HISTOIRE

Professor Jean Roudier hosted this workshop in Marseilles (fig 1) on the 27 February to 2 March 2003. The European Workshop for Rheumatology Research (EWRR) series of annual meetings was started in 1981 at Guy’s hospital in London, UK, by Gabriel Panayi and Peter M Johnson as a forum for scientific exchange between active investigators. In part it was intended as an alternative to the big, expensive, and industry dependent international congresses. Not least, it was a reaction to the style of the EULAR congresses of the time. The lecture hall in building 4 at Guy’s hospital was filled with about 75 participants, the registration fee was £5, and the abstracts were probably only distributed among the attendees.

The success led to a second meeting which was arranged in 1982 by Arnold Cats outside Leiden, followed by the third in 1983, organised by Jochen Kalden in Mainz. Later convenors have included a large number of the scientific leaders in Europe. A scientific poster is the admission ticket to these workshops, the number of posters is 150 at most, and it is the privilege of the convenor(s) to invite a number of speakers of their own choice. The country and convenor changes every year. This has proved very fruitful and a particularly stimulating concept for the younger investigators.

EULAR now supports the meeting with a number of bursaries and the standing committees of EULAR have meetings in connection with the workshop. Some highlights from the most recent meetings are presented below. They are meant to give the readership a flavour of these open, but not heavily protected, discussions and the standing committees of EULAR have meetings in connection with the workshop. Some highlights from the most recent meetings are presented below. They are meant to give the readership a flavour of these open, but not heavily protected, discussions.

STEM CELLS AND OSTEOARTHRITIS (OA)

Martin Lotz, La Jolla, CA, USA, dealt with differences between aging and OA in cartilage and the general problem of chondrocyte abnormality in OA. He reminded us of the apparent paradox that advancing OA is characterised by decreased chondrocyte response to anabolic transforming growth factor \( \beta \) (TGF\( \beta \)) and yet signs of increased matrix remodelling. Using cartilage explants from patients with OA, he stained for CD105 or endoglin, also named TGF\( \beta \) receptor, and for CD166 and was able to identify double positive cells in OA cartilage in considerable amounts, 10–15% of all cells in some specimens. Such cells are abundant in bone marrow and have been associated with stem cell features. As was brought out in the discussion, they can, however, not be considered identical with mesenchymal stem cells, but rather should be called progenitor cells. The chondrocyte clusters may be enriched in double positive cells. Interleukin 1 may have a key regulatory role. It not only suppresses the growth factor Sox 9 and inhibits transformation of mesenchymal stem cells to chondrocytes but also up regulates some 800 genes including matrix metalloproteinases and ADAMTs. This interesting talk provoked a lively discussion. I was not too clear as to how OA and aging could be separated by the techniques used. The session showed that knowledge about the pathogenesis of OA is still rather fragmentary.

THE LUBRICIN STORY

Camptodactyly-arthropathy-coxa vara-pericarditis (CACP) is an autosomal recessive defect, which is characterised by synovial cell proliferation, joint swelling, contractions, deformities and destruction of joints, and pericarditis in a fraction of affected subjects. “Campto” means bent and camptodactyly means bent fingers and toes. CACP is a differential diagnosis in patients presenting with claw hands. Matthew Warman entertained the meeting with a brilliant presentation, making it perfectly clear why this rare syndrome deserves our close attention. In 1981 Swann et al isolated a glycoprotein with a molecular weight of around 200 kDa from bovine synovial fluid which had as strong lubricating potency as the whole fluid from which it was purified and which they named lubricin in 1985. Later it was shown that lubricin could also be identified in human knee joint fluid. More recently it was shown that lubricin, in contrast with different hyaluronan preparations, possessed as much boundary lubricating ability as whole normal synovial fluid. The role—if any—of synovial fluid hyaluronan in lowering friction or lubrication of joints remains unclear. Then in the year 2000 it was shown that lubricin is synthesised by human synovial cells and is a gene product of the megakaryocyte stimulating factor (MSF) gene on the first chromosome. This protein in turn had previously been shown to be identical to the superficial zone protein, identified in 1994 by Barbara Schumacher and later named proteoglycan 4 (PG4). This protein is now better characterised and has a size of 345 kDa. It is a secreted protein that in contrast with several other matrix components is not retained in cartilage matrix.

Examining families with CACP, Matthew Warman identified at least eight mutations in the CACP/SZP/MSF/PG4/lubricin gene, causing frame shifts and truncated lubricin in affected subjects. At present mutations have been identified in 27 families. All mutations have been in the C-terminal 6th exon, which codes the mucin part of the molecule. Because only homozygous subjects are affected, it was concluded that CACP is caused by the absence of lubricin, and not by damage of an abnormal gene product. Lubricin is expressed where tissue surfaces are in motion. Thus it can be seen in the superficial but not in the deep layer of cartilage. One effect of lubricin is to inhibit hypertrophy of synovial tissue. In order to reduce friction, lubricin must bind to the tissue surface, much as Teflon to a frying pan. Lubricin also coats tendon sheets and pericardium. It is now possible to investigate whether lubricin abnormalities—perhaps accelerated breakdown by proteases in inflamed joints—contribute to the pathogenesis of rheumatoid arthritis (RA) or OA. The lubricin story which started more than a quarter of a century ago, although not

Figure 1  Marseilles.
nearly complete as yet, demonstrates the power of molecular biology. It raises hopes that in the end a new insight will result in better remedies, not only for patients with CACP.

CITRULLINATION IN THE DIAGNOSIS AND PATHOGENESIS OF RA

In 1964 the Dutch investigators Nichius and Mandema described the antiperinuclear factor and in 1979 Young et al described antikeratin antibodies in the serum of patients with RA using indirect immunofluorescence and rat oesophagus epithelium.12 In 1993 Guy Serre demonstrated that the common antigen for these antibodies was filagrin.13 The quantitative testing for these antibodies was hampered by difficulties in preparation of the antigens. In the late 1990s both the Nijmegen and Toulouse groups identified citrulline as the amino acid to which the antibodies were reactive, and imidination, or conversion of arginine into citrulline, as the biological event leading up to the antibody formation.11,12 It was a scientific highlight of the meeting to hear Professor Serre review the development and illustrate the strong impact that the diagnostic tests have already had on clinical research in RA. Several varieties of tests are now available, but the best seems to be an enzyme linked immunosorbent assay (ELISA) directed against deaminated fibrin, which tests 76% of all patients with RA positive, 97% rheumatoid factor positive, and is an aid to early diagnosis. Interestingly, citrullination may reveal an important element in the pathogenesis of RA. The success of the deaminated fibrin test may point to essential and long neglected disease mechanisms, and reminds me of Danish observations dating back to the 1960s which demonstrated prominent fibrin deposits in the rheumatoid joint.14 Similarly, another early paper, by van de Putte et al, had good electron microscope illustrations of fibrin deposits, correlating the deposits with lack of fibrinolytic activity and pointing to a pathological role of the deposits.15

THE POSTER SESSIONS

A most important part of the meeting was the poster session, featuring 116 titles covering subjects such as autoantibodies and antigens, cytokines, major histocompatibility complex, and other topics related to cell biology. The abstracts have been published as supplement 1 in volume 5, 2003 of Arthritis Research and Therapy (http://arthritis-research.com). The posters were manned for periods during the meeting, and it was rewarding to witness the enthusiastic young presenters interacting with visitors, both younger and more experienced. The former were in the majority. This makes me feel optimistic about the future of the EWRR.

I will not attempt to review the many interesting posters, but let me end by listing the five winners of the EULAR bursaries. The lucky torch bearers of the emerging new generation were Johan Rönnelid, Stockholm, Sweden, who had compared anti-type II collagen and anticitrulline antibodies in patients with RA (abstr 21); J Zwerna, Vienna, Austria, who had studied a model of transgenic tumour necrosis factor driven arthritis in mice (abstr 65); D Baeten, Ghent, Belgium, who presented results for histopathology in RA and the HC gp-39 epitope presentation (abstr 67, 68); U Ungethüm, Berlin, Germany, who had studied expression profiles of candidate genes in RA (abstr 81); and J Törner, Regensburg, Germany, who had studied cell migration in the collagen induced arthritis model, using T cell hybridomas and dendritic cells transfected with luciferin (abstr 116). The winners were selected during the meeting by the chairmen of the poster sessions, and the prize covered the meeting costs of the winners.

LA GRAND FINALE

The meeting ended with a splendid banquet in the best of French traditions in the Palais du Pharo close to the harbour entrance. Professor Roudier reminded us of the fact that Marseille is the oldest French city. It was founded by the Phoenicians some 2600 years ago, based on its natural harbour. It offers today’s visitors great Mediterranean charm, culture, and food. Jean Roudier is to be congratulated for achieving a very stimulating and well organised workshop.

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REFERENCES