

## *Meeting Report*

### European Masterclass on Rheumatology

Thursday and Friday, 7–8 May 2009  
Royal College of Physicians of Ireland  
No. 6 Kildare St, Dublin 2



# Introduction

Dr John Donohoe, *President, RCPI*



The series of Masterclass educational workshops currently being organized by the Royal College of Physicians of Ireland are aimed at highlighting advances in those areas of medicine which are most significant and the most rapidly evolving.

When the College was approached by Bristol-Myers Squibb with an offer to continue their support of superior quality educational programmes, via way of a European Masterclass on Rheumatology, the opportunity was enthusiastically accepted.

Rheumatological conditions represent a substantial health burden facing society in this country. They are of increasing importance to the health of both the individual and the community and carry significant financial and social implications. Efforts directed towards an understanding of basic and novel aspects of these conditions are particularly appropriate.

A Faculty of College Fellows, Prof Michael Molloy, Prof Doug Veale and Dr Paul O'Connell, was convened and nominations were made for topics and speakers. It was gratifying to see that those invited

to speak and to chair – all leaders in the world of rheumatology – immediately accepted and I thank them for their enthusiastic support of the meeting. As a result, a strong programme, delivered in a focused manner by internationally recognised speakers, was put in place, and designed as an intense day-long session. Each presentation was of the highest scientific standard.

The College was pleased that many specialists and trainees were represented in the large attendance. This booklet contains summaries from those presentations and will serve as a useful review of novel insights into the topics covered, for trainee and specialist alike.

Finally, I wish to extend the College's gratitude to Bristol-Myers Squibb for their unstinting and continued support of educational activities such as this Masterclass.

Thank you and congratulations.

Yours sincerely,

Dr John Donohoe  
President, RCPI

## Do national registries add value to randomised trials?

**Prof Ronald van Vollenhoven,**  
Karolinska University Hospital, Stockholm, Sweden



Ronald F van Vollenhoven received his MD and PhD degrees from the University of Leiden in The Netherlands. After graduating in 1984 he pursued immunology research at Cornell Medical College in New York, followed by residency (specialty training) in internal medicine at the State University of New York at Stony Brook, and a fellowship in rheumatology at Stanford University in Palo Alto following which he received American Board of Internal Medicine certification in both internal medicine and rheumatology.

From 1993 to 1998 Prof van Vollenhoven held a faculty appointment as Assistant Professor of Medicine in the Division of Immunology and Rheumatology at Stanford University, and from 1995 he was the Medical Services Chief and Fellowship Director in that division.

In 1998 Prof van Vollenhoven moved to Stockholm, Sweden, where he is a Senior Physician and Chief of the Clinical Research Unit in the Department of Rheumatology at the Karolinska University Hospital and Associate Professor of Rheumatology at the Karolinska Institute.

Prof van Vollenhoven's research interests focus around the development and systematic evaluation of biological and

immunomodulatory treatments for the rheumatic diseases. With his co-workers, he has established the Stockholm registry for biological therapies (the STURE database) for this purpose, which has supported a number of research projects relating to clinical efficacy, pharmacology, outcomes and pharmacoeconomics. He has been principal investigator in many clinical trials of novel therapies in rheumatic diseases, including recent trials with adalimumab, rituximab, abatacept, tocilizumab and other biologicals, and has published over 100 original papers, book chapters and reviews. In 2004, Prof van Vollenhoven was awarded the Scandinavian Research Foundation Prize for excellence in clinical research in rheumatology. He also served as the scientific secretary of the Swedish Rheumatological Society for four years.

In the opening presentation of the day, Prof van Vollenhoven outlined the structure of the Swedish Rheumatology Registries, which he believes complement randomised trials by providing not only long-term safety data, but also valuable information on the real-life efficacy of biologics.

Prof van Vollenhoven explained that between 1990 and 1998, a number of inception-cohort registries were initiated in rheumatology departments across Sweden under the auspices of the Swedish Rheumatology Society<sup>1,2,3</sup>. Starting in 1999, registers such as SSATG<sup>4</sup> and STURE<sup>5</sup> began to follow patients on biologic therapies, using the same follow-up as the inception cohorts and utilizing the same I.T. platform.

"We decided to use the same system as we had established to follow-up newly diagnosed patients. There were thus two streams of patients, those that were newly diagnosed and then those that were being treated with biologics," said Prof van Vollenhoven.

As the registries are internet-based, once logged in, it is possible for the treating physician to see his or her patient's inclusion data. It is then possible to see the development of disease parameters after follow-up, and provide "personalised" treatment.

"We like to think this helps us provide better care, and make rheumatology more a quantitative specialty, working a little bit more with numbers," he commented.

The SSR saw a total of 169,000 visits in 2009 - an approximate increase of 25 per cent on the previous year - involving more than 50,000 patients. Several different registries operate in parallel, explained Prof van Vollenhoven - the STURE and SSATG registries each compose 25 per cent of the national registry ARTIS (Anti Rheumatic Therapies in Sweden).

He also explained that possibly the biggest strength of registry-based studies in Sweden is the existence of a "unique identifier" for each patient, meaning that, for example, a patient who is included in the hospital's inpatient registry can be cross-linked to the ARTIS registry. The same applies to the RA outpatient registry and the early RA registry, he added.

These registries can also be linked to other registries such as: The Cancer Register; Cause of Death Register; Medical Birth Register; and Tuberculosis Register.

Prof van Vollenhoven then detailed some of the long-term safety aspects of biologic therapy, as deduced from ARTIS data. These research efforts naturally involve much collaboration.

"As biologic therapy suppresses the immune system in such a specific way, there have obviously been questions as to whether suppression of tumour necrosis factor may engender a greater risk from certain diseases. Data from clinical trials

cannot answer that, so we need registries," Prof van Vollenhoven stated.

A 2009 study<sup>6</sup>, with which Prof van Vollenhoven was involved, investigated the incidence of malignancies within the ARTIS register, looking at the incidence of cancer in patients who had been treated with anti-TNF therapy versus those who were anti-TNF naïve.

It was found that the relative risk was 1.00, so it "could not be better", stated Prof van Vollenhoven.

"With time, there does not appear to be an increased risk from exposure to anti-TNF so this goes a long way to allay fears."

The ARTIS registry was also used to provide data on the risk of infections<sup>7</sup> explained Prof van Vollenhoven.

"Studies from clinical trials have shown that there is an increased risk of infection with virtually all the biologic medications but not all of these reached statistical significance in the individual trials; however a meta analysis showed the risk to be just a little bit higher when the trial data were pooled. This is exactly what was seen in our registry-based study. Compared to patients who were not treated with anti-TNFs those patients that were anti-TNF treated were shown to have a relative risk of 1.3. There is thus a 30 per cent increase in the risk of acquiring an infection serious enough to require hospital admission. However, this risk disappears with increasing treatment duration."

Tuberculosis (TB) has emerged as a specific infectious concern with TNF-antagonists, although for Swedish rheumatologists the practical issue is not overwhelming because the background prevalence in Sweden is very low, the professor explained. Nonetheless, another study from the ARTIS registry provided information on the relative risk by year of treatment.

## Do national registries add value to randomised trials? (Cont.)

“If you look at the first year of anti-TNF treatment, there is clearly a very significantly increased risk of tuberculosis (RR=12) and this is most likely related to latent TB. But this is only in the first year as subsequent years of follow up show a reduced relative risk of 7.7 after two years and 7.8 after three or more years.”

Having presented examples of safety data provided by the national registry ARTIS, Prof van Vollenhoven then presented efficacy data obtained from some of the regional Swedish registries that are included in ARTIS.

One 2004 study<sup>8</sup>, using data from the STURE registry, looked at the presence of anti-cardiolipin (aCL) antibodies in patients treated with infliximab and etanercept. It was seen that the development of aCL during treatment with infliximab, but not etanercept, is associated with worse clinical results and more frequent serious infusion reactions.

Prof van Vollenhoven then outlined a 2003 registry-based study<sup>9</sup> of which he was the lead author, comparing treatment with etanercept and methotrexate with treatment with etanercept alone.

In this study, comparison of DAS28 scores between the two regimes showed a rather modest difference but it was seen that a significantly greater number of patients achieved remission in the group taking both etanercept and methotrexate.

“While the differences in the lower-level outcomes were small, with the high-level, excellent responses there was a big difference,” stated Prof van Vollenhoven, adding that the “exact same thing” was seen in the TEMPO trial<sup>10</sup>, confirming, as it were, the validity of the registry-based efficacy data.

This very large trial, comparing methotrexate given by itself; etanercept given by itself; or both agents in

combination, found that ACR20 responses did not differ very much (albeit significantly) between groups but ACR70 scores were much higher in the group receiving etanercept plus methotrexate.

Prof van Vollenhoven also discussed an observational trial<sup>11</sup> that suggested that dose increases of infliximab had little, if any effect on disease activity. The same was suggested by a randomised trial<sup>12</sup> published earlier this year.

Further evidence for the value of national registries is their role in carrying out health economic assessments, stated Prof van Vollenhoven.

“We can use national registries to inform health economics. An example of this is an analysis<sup>13</sup>, based on the STURE Registry, which showed increases in work force participation from patients treated with anti-TNFs. The average number of hours worked each week increased during the first four years on such treatment. This demonstrates the indirect health benefit as well as the benefit to society.”

In conclusion, Prof van Vollenhoven looked at evidence, provided by national registry data, on the success of anti-TNFs in RA patients.

“The majority of patients achieve moderate disease activity but only 20 per cent achieve remission. The glass is half full and half empty – we recognise that there is a very significant need for other therapies and other options.”

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**Prof Michael Weinblatt,**

Harvard Medical School/Brigham and Women's Hospital, Boston, USA



Michael E. Weinblatt, MD, is Co-director of Clinical Rheumatology at the Brigham and Women's Hospital and the John R. and Eileen K. Professor of Medicine at Harvard Medical School, both in Boston, Massachusetts. He is the Associate Director of the Center for Arthritis and Joint Diseases, of the Division of Rheumatology, Immunology & Allergy at Brigham and Women's Hospital.

His major research interest is in therapeutics for rheumatoid arthritis. His work on the development of methotrexate therapy for rheumatoid arthritis garnered him the Carol Nachman Prize for Rheumatology and the Arthritis Foundation Virginia P. Engalitcheff Award for Impact on Quality of Life. He has also received the American College of Rheumatology Distinguished Clinical Investigator Award.

Author of *The Arthritis Action Program: An Integrated Plan of Traditional and Complementary Therapies*, Prof Weinblatt has authored or co-authored more than 180 published papers, reviews, and book chapters on rheumatology. He is the co-editor of *Treatment of Rheumatic Diseases* and an editor of the textbook *Rheumatology* 3rd and 4th editions

and currently sits on multiple editorial boards for journals including *Journal of Rheumatology*. He also served as an Associate Editor of *Arthritis & Rheumatism*.

Prof Weinblatt was a member of the Rheumatology Subspecialty Board of the American Board of Internal Medicine and served as the President of the American College of Rheumatology (ACR) in 2001.

Prof Weinblatt earned his medical degree at the University of Maryland School of Medicine in Baltimore, where he also completed his internship and residency. He also completed a fellowship in rheumatology at the Robert B. Brigham Hospital in Boston, Massachusetts.

Prof Weinblatt outlined various new approaches to the treatment of rheumatoid arthritis in his presentation. Mentioning abatacept, rituximab and certolizumab, he also stated that there were “small molecules, some that will never be approved because the developments have been stopped due to a lack of efficacy”.

Regarding anti-TNF therapeutics, Prof Weinblatt advised that “these drugs work, and they work reasonably well.”

“These drugs are approved for multiple rheumatological diseases, including rheumatoid arthritis, juvenile inflammatory arthritis, ankylosing spondylitis and psoriatic arthritis. These agents are also approved for psoriasis and inflammatory bowel disease and I think everyone in the audience would agree anti-TNF therapy has been a significant advance in treatment and it is one of the most important examples of bench to bedside therapeutics. Many of the drugs we have used in rheumatology have been developed for other diseases and we have stumbled across their efficacy in RA – anti-TNFs are one of the first classes of drugs

that were actually based on a lot of pre-clinical data and animal models,” stated Prof Weinblatt.

There are two other anti-TNF therapies that are approved or are soon to be approved – certolizumab is under review by the FDA and an approval is anticipated shortly, and also golimumab, which was approved recently by the FDA for treatment of RA.

“Certolizumab, already approved in the US for Crohn's disease, is the only PEGylated molecule that we are using in RA and there are a number of randomised trials that have been published. The bottom line is that the response rates are very similar to what we see with the other agents. Given as a subcutaneous injection every two weeks it has a similar safety profile and as anticipated it has a positive effect on the radiograph<sup>1</sup>.”

Golimumab which is essentially in the same class as infliximab, is given as a subcutaneous therapy, generally on a monthly basis, and there is also an IV preparation. Again it has very similar response rates to the other agents and a very similar safety profile.<sup>2</sup>

Prof Weinblatt then discussed the questions surrounding the switching of patients from one anti-TNF to another.

“Would one anticipate a satisfactory clinical response with switching?” he asked, explaining that there is as yet no centrally controlled blinded study that addresses the concept of switching.

“Clinicians still switch because of their “comfort level” with anti-TNF molecules and their rapid action, and also because we know the beneficial effects seen on X-rays are so great that we want to change from one molecule to another in the same class because we want to achieve the radiographic improvement that it is essential.”

A UK registry study<sup>3</sup> showed that 75 per cent of patients who switched to a second anti-TNF remained on therapy for at least six months but those whose discontinuation was due to lack of efficacy was associated with a higher rate of lack of efficacy with the second drug, explained Prof Weinblatt.

“The registry data was disappointing. The vast majority of patients who failed one anti-TNF due to lack of efficacy were not maintained on the second anti-TNF.”

The GO-AFTER (Golimumab After Former anti-TNF Therapy Evaluated in RA) trial<sup>4</sup>, involving solely patients that had been on a prior anti-TNF therapy, showed a “modest response rate”, said the professor.

“About 40 per cent of patients responded on the anti-TNF, compared to about 20 per cent in the placebo group. There is a 20 per cent delta but the clinical response rates are much lower than one would see with initiation of the first anti-TNF. Based on this data, there is some suggestion that there may be a modest response with anti-TNF when you switch.”

Prof Weinblatt then discussed co-stimulation blockade and the molecule CTLA4-Ig, more commonly known as abatacept. Initially developed for the treatment of psoriasis, it is now ten years since the first clinical trial was published<sup>5</sup>.

Prof Weinblatt highlighted some of the key studies involving abatacept and its unique mechanism of action.

“This drug is given intravenously for thirty minute intervals. When looked at in patients who were non-responders to anti-TNF therapy, the response rates were in the fifty percent range with abatacept plus a DMARD versus 20 per cent with placebo plus a DMARD<sup>6</sup>. The ASSURE trial<sup>7</sup> involved 1441 patients on DMARDs and randomised to receive either abatacept or placebo. ASSURE demonstrated that

the rate of adverse events with DMARD plus abatacept were essentially the same as with DMARD plus placebo, which was “reassuring and important information”, according to Prof Weinblatt.

He added that the trial confirmed the earlier observation that combining abatacept with another biologic delivered no greater clinical effect than the biologic by itself and there was again a four times greater risk of serious infection.

A comparative trial<sup>8</sup> was mandated by European authorities for the registration of abatacept in Europe. A dose of 10 mg/kg of abatacept was compared with 3mg/kg of infliximab in patients on methotrexate. Although local screening was carried out, two patients developed tuberculosis, with one subsequently dying, and Prof Weinblatt cautioned those in attendance to be particularly aggressive in using the appropriate screening techniques

to exclude patients at risk of latent tuberculosis.

“All of us that have used this molecule have really been impressed by the safety profile. Infusional reactions are distinctly uncommon. There is a modest increase in bacterial infections above placebo and in patients that already had chronic lung disease, there was a slightly higher risk of developing infections when on biologics. The risk of tuberculosis is quite low actually. The risk of lung cancer is no greater than with placebo and is about the same as one would see in rheumatoid arthritis for which there is a higher risk of TB to begin with.”

An animal model<sup>9</sup>, involving mice with latent TB given either abatacept, anti-murine TNF antibody or vehicle, demonstrated that abatacept did not impair host resistance to *Mycobacterium tuberculosis* – **Figure 1**.

Abatacept is currently being investigated in systemic lupus and also psoriatic arthritis.

“Rituximab is an approved therapy in both non-Hodgkin’s lymphoma, as well as rheumatoid arthritis,” continued the professor as he began to speak about B cell depletion strategies in the treatment of RA.

“The REFLEX trial<sup>10</sup> was carried out in patients who had failed a previous anti-TNF therapy. It was given in doses of 1000mg two weeks apart. After 24 weeks, 51 per cent of rituximab patients had achieved an ACR20 compared to 18 per cent of placebo-treated patients, a result almost identical to that seen in the abatacept studies,” said Prof Weinblatt.

Additional clinical data on rituximab has now become available, a fact that is important because when the drug was first launched there was very little guidance for the rheumatology community on what to do after the first dose was given, explained the professor.

“There has been controversy about if you are auto-antibody negative whether you will respond to rituximab therapy. You will get a response if you are rheumatoid factor (RF) and CCP negative, but the response rates are not in the same range as those patients who are positive with one of those autoantibodies, with a difference of 30 per cent between groups”. In my mind I would reserve rituximab as probably the last treatment for those patients that are double negative because the response rates are much lower in this setting”

Results of the Phase III IMAGE study will be presented at EULAR this year, where it was shown that ACR endpoints exceeded expectations, added Prof Weinblatt.

“This looked at patients who were anti-TNF blockade naïve with early rheumatoid

arthritis. Patients were randomised to placebo or 500mg or 1000 mg of rituximab, plus methotrexate. If you look at the ACR20 clinical responses at 24 weeks they are absolutely identical for 1000mg, 500 mg and placebo, respectively. The two doses of rituximab are more effective than methotrexate alone and the results for ACR50 and ACR70 are very similar.

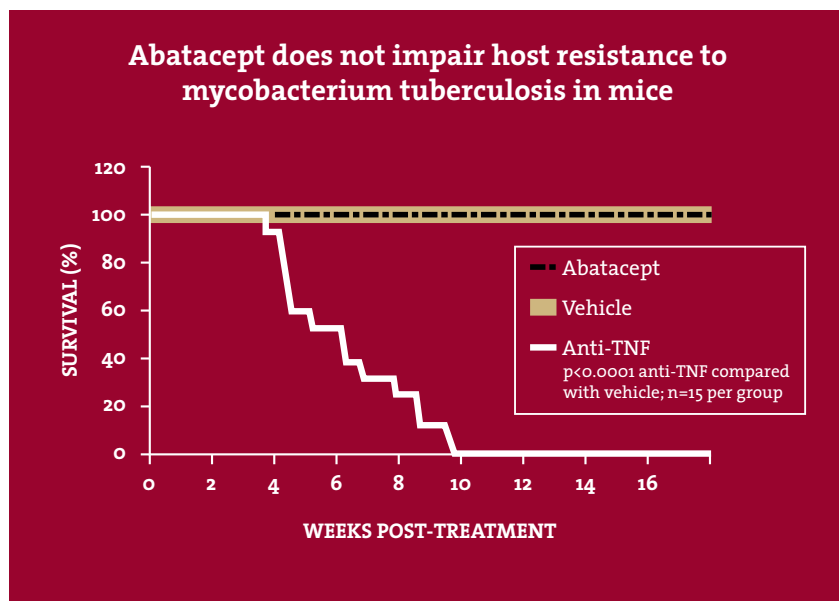
Prof Weinblatt discussed the safety profile of rituximab, stating: “Infusion reactions are seen in three to five per cent of patients, and the greatest risk is with the first and second infusion and there is a lot of discussion now whether you need to continue to pre-treat these people with corticosteroids. There are rare cases of serum sickness seen, rates of bacterial infection are similar to what is observed with all the biologics and none of the biologics should be used in a patient who is Hepatitis B positive. There have been rare reports of fatal brain infection i.e. PML syndrome. There have also been reports of new onset psoriasis or flares, as well as rare reports of interstitial lung disease. A decreased level of immunoglobulin has also been observed but to date do not correlate with infection.”

Rituximab has been investigated in lupus but has unfortunately failed in all the major trials, to “everyone’s great surprise”, although some positive open studies have taken place with vasculitis and myositis, as well as a positive randomised controlled trial in multiple sclerosis (MS), added Prof Weinblatt.

He then went on to describe some other molecules that are under development, such as tocilizumab, which is a humanized anti-IL6 receptor monoclonal antibody.

“High levels of IL-6 are seen in RA and lupus to name just two. It is approved for use in Japan and Europe but not

Figure 1



in the United States, as the FDA has delayed approval for this molecule. The randomised trials<sup>12,13</sup> for tocilizumab report similar efficacy to what has been observed with the other biologics, as are rates of bacterial infections. There have however been cases in the randomized and long term extension studies of bowel perforations, with the 8mg dose. There have also been reports of lipid abnormalities, with some patients requiring statin therapy. Tocilizumab also works in Still's disease and juvenile inflammatory arthritis and there are trials ongoing in lupus.

Denosumab is a molecule that is currently being studied in the treatment of post-menopausal osteoporosis but there is a very exciting study being carried out in RA, Prof Weinblatt told the delegates.

"It has been shown to reduce erosions in animal models and it has shown these remarkable effects in its first clinical trial<sup>14</sup>. However it had no anti-inflammatory effects and it did not affect joint narrowing at the dose that was used. It is hoped that this molecule could be combined with a synthetic DMARD therapy to confer an added radiographic advantage to the synthetic therapy by itself."

Other small molecules studied for RA include: TACE inhibitors, which worked in animal models but failed in clinical trials; chemokine antagonists, which have also failed in RA trials; P38 MAP kinases of which at least 10 types have been under development in recent years but development on some have been stopped due to disappointing efficacy results; and the first trial of spleen tyrosine kinase (SYK) inhibitors reported promising results<sup>16</sup>, Prof Weinblatt explained.

JAK inhibitors have shown promise and one molecule (CP-690,550) is the furthest along, currently in Phase III development, with a 50-61 per cent response rate when

used in combination with methotrexate, compared with 38 per cent for placebo<sup>15</sup>.

Prof Weinblatt concluded by discussing the RA therapy in 2009, and also made predictions for the future.

"Earlier introduction of methotrexate with rapid dose escalation after two months (is appropriate). I believe that patients should get a dose of 20-25 mg and if they are not responding orally should move to subcutaneous treatment. In 2015 we are going to have more biologics available, with pharmaceutical companies moving into biosimilar molecules. There may also be small molecules that would substitute for the biologics or added to biologics plus methotrexate. I am also hopeful that by 2015 with pharmogenomic studies we will be able to sit at our desks and develop rationale treatment approaches by identifying those patients that will or will not have a great clinical response to a prospective drug."

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## The Impact of New Data on Management of Patients with Undifferentiated RA

Dr Elena Massarotti, Brigham and Women's Hospital, Boston, USA



Elena Massarotti is an Associate Professor of Medicine at Harvard Medical School and Co-Director of the Center for Clinical Therapeutics in the Division of Rheumatology at Brigham and Women's Hospital in Boston, MA where she is the principal investigator of therapeutic trials for rheumatoid arthritis and lupus. She divides her professional time between patient care, education, and clinical research and has authored numerous articles in peer reviewed journals and has been an invited speaker for many years at the American College of Rheumatology and at the American College of Physicians.

The post-TNF era poses different questions for the management of rheumatoid arthritis (RA), explained Dr Massarotti, as she commenced her presentation.

"It actually provides us with the opportunity to ask some very good questions about the therapies we use in RA," she stated.

According to Dr Massarotti, these questions include:

- Asking what are the predictors of response, such as phenotypic and genotypic correlates and biomarkers;

- Asking is the disease actually more heterogeneous than is already thought;
- What the optimal treatment is in early RA;
- Is it possible to prevent RA;
- What the appropriate approach is to treating undifferentiated arthritis

Dr Massarotti defined undifferentiated arthritis (UA) as "an inflammatory arthritis in which a specific diagnosis cannot be made"<sup>1</sup>.

She then made a typical case presentation that she explained would have relevance for the attending rheumatologists:

*The patient was a 43 year old woman, presenting with recurrent joint swelling. Four months previously, she had noted that her right wrist was painful and swollen, lasting for a few days with rapid resolution. This was followed by a similar painful episode affecting the left PIP joint, again lasting a few days. These recurrent episodes were associated with at least one hour of morning stiffness. ROS was negative and a physical examination showed no psoriasis, oral ulcers, injected conjunctivae or sclerodactyly. Patient also had a swollen, tender left second MCP and right third PIP joints.*

Dr Massarotti continued by noting the marked differences between the 1958 ACR criteria for RA<sup>2</sup> and the 1987 criteria<sup>3</sup>. The 1958 Criteria allowed for identification/diagnosis of "possible RA", seeking two symptoms of: morning stiffness; tenderness or joint pain on motion; and/or history or observation of joint swelling, for at least three weeks.

Discussing biomarkers as predictors of response, Dr Massarotti explained that while rheumatoid factor (RF) positivity remains part of the diagnostic criteria, its testing sensitivity is 66.9 per cent and its specificity is 83.6 per cent, compared with 70 per cent and 95.4 per cent for the sensitivity/specificity of anti-CCP<sup>4</sup>.

She then discussed anti-mutated citrullinated vimentin (MCV), which is the "new anti-CCP on the block", according to Dr Massarotti.

"It's possible that the addition of this test might improve the sensitivity of the diagnosis a little" she stated.

Dr Massarotti then presented the evidence for the role anti-CCP antibodies play, if any, in assessing patients with UA.

She outlined a 2004 study<sup>5</sup> that attempted to answer this question. In that study, the presence of anti-CCP antibody and its role in predicting RA at one year, two years and three years was examined. All the patients had to fulfil the classic ACR criteria for RA.

At one and two years, patients who tested positive for anti-CCP had a much greater chance of developing RA compared to patients who tested negative (83% vs. 18% at 1 yr; 90% vs. 24% at 2yr). At three years 93 per cent of positive patients had developed RA and the odds ratio was shown to be 37.8.

"This clearly demonstrated that the presence of anti-CCP antibodies is a good predictor of developing RA as the years go on," stated Dr Massarotti.

Dr Massarotti also described a study carried out at the Leiden Early Arthritis Clinics<sup>6</sup>, which examined the outcome of UA for 330 patients compared with patients initially diagnosed with RA. The one year outcome showed that 41 per cent had arthritis of an unknown cause; 28 per cent developed RA; 12 per cent had probable RA; and 20 per cent had other RA causes.

"It was seen that for those who developed RA, disease severity after four years was similar as for those patients initially diagnosed with RA. This would suggest that defining UA in patients is important in predicting RA."

Dr Massarotti then proceeded to present the evidence for the possible prevention of progression of UA to RA, by intervening earlier in the disease.

The PROMPT (Probable Rheumatoid Arthritis: Methotrexate Versus Placebo Treatment) study<sup>7</sup> looked at the use of methotrexate as a preventative medication in RA, she explained.

"The study involved 110 patients who fulfilled the 1958 ACR criteria for probable RA. Patients were randomised to receive 15mg methotrexate versus placebo and then they were evaluated at three, six and nine months. At each evaluation, patients whose DAS score was less than or equal to 2.4, their medication was unchanged. For those who had a score greater than 2.4, their dose of methotrexate was increased by 5mg. At 12 months, their medications were tapered and then discontinued."

The results, Dr Massarotti explained, showed that at 30 months, 40 per cent of the patients in the methotrexate group had developed RA, compared with 53 per cent in the placebo group.

"This study suggested that using methotrexate in patients with an undifferentiated form of RA meant they did not go on to develop RA."

The effects were more pronounced in patients that were anti-CCP positive, added Dr Massarotti.

"Only two out of 12 anti-CCP positive patients achieved remission, suggesting that methotrexate did not induce remission but delayed the onset of RA," she stated.

Dr Massarotti then outlined a 2008 study<sup>8</sup>, which looked at the role of anti-TNF therapy for undifferentiated arthritis. This study recruited a small number of DMARD naïve patients (n=17) with UA, defined as more than one swollen joint

## The Impact of New Data on Management of Patients with Undifferentiated RA (Cont.)

plus 12 months of symptoms. Patients were randomised to placebo or infliximab, and methotrexate for persistent clinical inflammation was allowed after week 14.

The primary outcome of this study was the number of patients in clinical remission, defined as CRP < 10 mg/L and no clinical synovitis, at 26 weeks. Secondary outcomes were changes in clinical, laboratory and quality of life measurements.

“This study found that one of seven patients in the placebo group and two out of 10 patients in the infliximab group achieved remission and there seemed to be no significant changes between the groups for any of the secondary outcomes. All patients in the infliximab group and five patients in the placebo group had developed RA by week 56. This is suggesting that short course of anti-TNF therapy provides short-term relief but does not have a significant effect in preventing the development of RA in patients with poor prognosis UA.”

Dr Massarotti then discussed the role of co-stimulatory blockade in UA, outlining a study<sup>9</sup> that compared the proportion of patients with UA who develop RA at one year, after six months treatment with abatacept or placebo – **Figure 2**.

“These were patients who were greater than or equal to 18 years of age and had a UA diagnosis defined as symptomatic clinical synovitis of two or more joints and at least one but not more than three of the criteria under the 1987 ARA classification of RA. All patients had to be anti-CCP positive. 58 patients were randomised to either abatacept or placebo with treatment stopped after six months, although assessment continued to 24 months. The results showed that while 79 per cent of patients has oligoarthritis, only 56 per cent had erosions, which I found to be remarkable.”

Evaluation of the primary endpoint showed that 46.2 per cent of patients developed RA at year one, compared with 66.7 per cent of the placebo group.

“Abatacept is associated with a delay in progression to definite RA in some patients with UA. The delay in RA onset was mirrored by delayed radiographic progression and the effect of abatacept was maintained even after therapy was stopped,” commented Dr Massarotti.

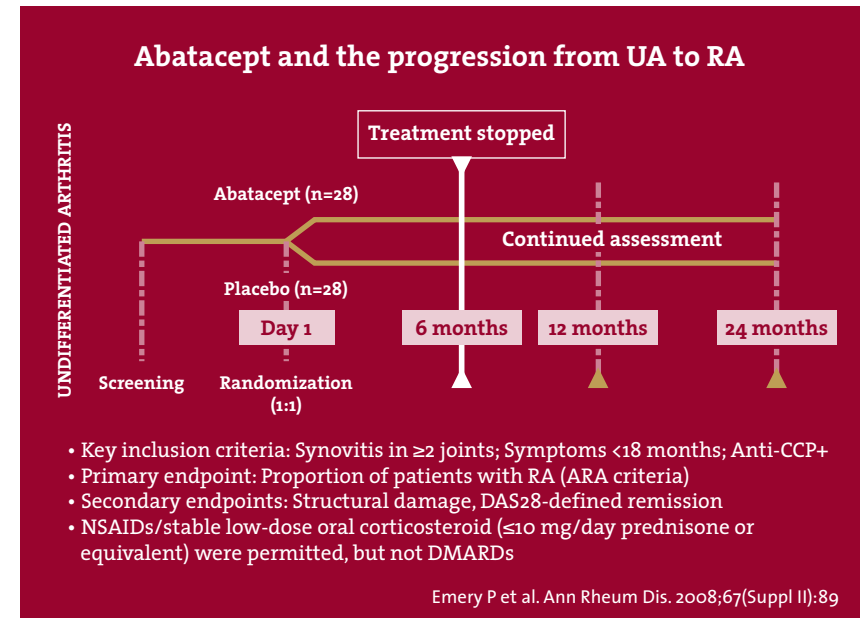
Dr Massarotti then concluded by summarising what could be taken from the answers these studies provided to her original questions.

“Anti-CCP antibodies may distinguish forms of UA that progress to classic RA. Secondly, methotrexate appears to delay progression from UA to RA. We also learned that infliximab therapy for UA was associated with a modest short-term benefit in a small, placebo-controlled study, which had some limitations. We know that abatacept may be of benefit in anti-CCP positive UA patients. The optimal treatment for UA has yet to be defined but genetic profiling information may eventually provide this. As of 2009, it is not yet possible to prevent RA.”

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**FIGURE 2**



4. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assays in rheumatoid arthritis. Visser et al., *Ann Rheum Dis*, 1996; 55: 157-161.
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## Future Therapies for Early Aggressive Rheumatoid Arthritis

Professor Michael McDermott,

NIHR-Leeds Musculoskeletal Biomedical Research Unit



Michael McDermott received his primary medical degree and a postgraduate DMed from the National University of Ireland. He is Professor of Experimental Rheumatology in the Leeds Musculoskeletal Biomedical Research Unit (LMBRU) at the University of Leeds.

Among the current research themes of his group include the pathogenesis of autosomal dominant periodic fevers, as well as the molecular and cellular basis of therapeutic responses to biologic therapies in patients with rheumatoid arthritis (RA), with an emphasis on innate immunity and mechanisms of non-response to anti-TNF. Different components of the NALP3 inflammasome and how anti-TNF blockade impacts on this system are investigated.

“What we are trying to prevent is not that easy to prevent,” admitted Prof McDermott as he began his presentation.

“Genetics is rarely used to test the patient and I notice the shared epitope hasn’t been mentioned at this point. This is probably because this is considered as a susceptibility gene for CCP, which is a tremendous biomarker for disease, response to therapy and possibly for severity as well and this has developed in the last 10 years or so.”

Prof McDermott discussed what a heterogeneous disease RA is, explaining that many different genes are involved in its pathogenesis and susceptibility.

“In the coming years, the advances in genotyping will allow us to tailor therapy far more pharmacogenetically.”

In the normal synovial lining there are two types of cell: macrophages and fibroblasts – **Figure 3**, explained the professor.

“In RA, however, there is a massive cellular infusion, including T and B lymphocytes, and something else which is now receiving a lot of attention is the formation of new blood vessels. This is a major feature of the disease and is also the target of some therapies.”

Mapping of the genome has shown that even with a so-called simple monogenic hereditary disease such as Muckle-Wells syndrome (MWS), there is heterogeneity, he added.

“MWS is associated with periodic fever and amyloidosis. We found a gene for this, which turned out to be a mutation coding for the NALP3 protein, which has been subsequently renamed as NLRP3. Because it is involved in interleukin-1 beta (IL-1 $\beta$ ) production, we decided to try anakinra [IL-1 receptor antagonist] in a single individual with the syndrome”. It was seen that the anakinra worked dramatically – **Figure 4**. This was an example of where you have a single target, possibly even a single cell, and by blocking that we achieved complete remission in these patients. With this you can control the disease and it won’t recur while there is IL-1 $\beta$  blockade.”

This is “rarely” the case in RA, stated Prof McDermott.

“It is a mystery that anti-TNFs work so well in RA yet anti-IL-1 $\beta$  therapy hardly works at all in RA. These factors are not really understood just yet.”

Figure 3

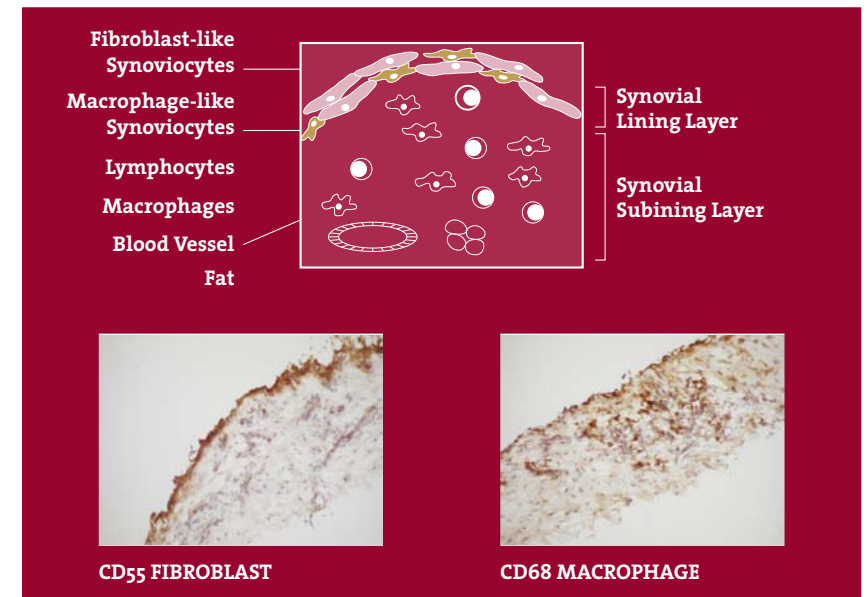
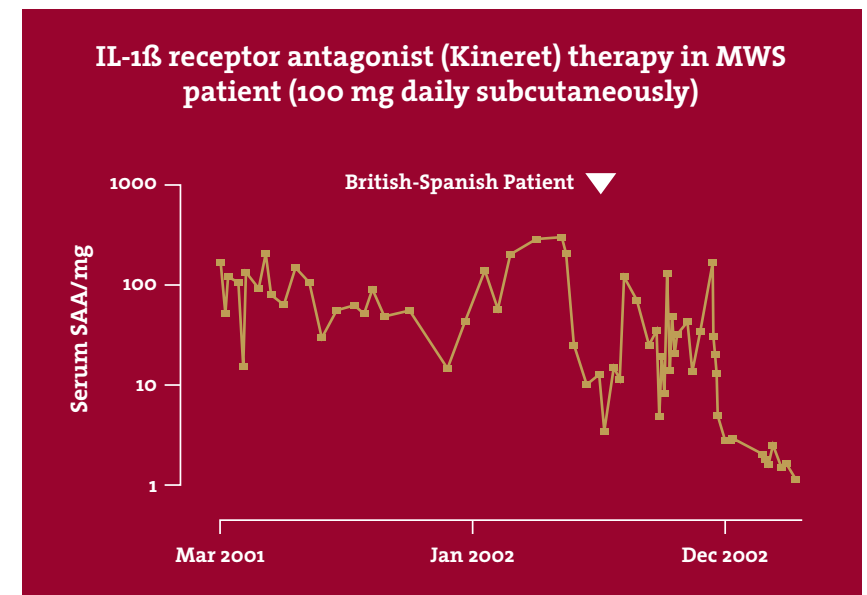


Figure 4



## Future Therapies for Early Aggressive Rheumatoid Arthritis (Cont.)

Prof McDermott explained that the current paradigm of treatment is “heavily influenced” by a small study<sup>2</sup> that looked at the effects of methotrexate plus infliximab versus methotrexate alone.

“The CRP response was much better in the infliximab treated group, and even when infliximab was stopped, after a year, it did not return to previous levels. The message of this study is that controlling inflammation is crucial.”

Prof McDermott then summarised the fundamental concept and core principles of contemporary RA management, as detailed in a recently published paper<sup>3</sup>.

The fundamental concept remains controlling inflammation by minimising cumulative inflammation, which improves signs and symptoms, increases functional performance and reduces risk of non-articular complications. The core principles include: 1. Referring patients immediately, even if diagnosis is uncertain; 2. Treating RA immediately; 3. Tight control of inflammation, which requires structured protocols and regular review; 4. Consideration of the risk-benefit ratio and treatment tailored to each patient.

There are also four simple and effective criteria to be included in shared care protocols, in order to encourage referral by GPs, as set out by the paper, said Prof McDermott.

These are: Three or more objectively swollen joints on examination; Morning stiffness greater than 30 minutes; Involvement of the metacarpal-phalangeal or metatarsal-phalangeal joints, or both; and no more than 12 months of onset before referral.

Prof McDermott also discussed the Leiden Predictive Rule<sup>4</sup>, based on nine different clinical and laboratory features that might predict disease progression.

“Basically you are trying to prevent the

patient from getting to a disease stage where you can’t control it or reverse the resulting pathology.”

Prof McDermott also outlined a Norwegian study<sup>5</sup> that attempted to predict radiographic progression.

This study found that seropositivity for rheumatoid factor and anti-CCP were independent predictors of radiographic progression and may aid prognostic information.

He also outlined a study published earlier this year<sup>6</sup>, which produced an algorithm for the diagnosis of inflammatory arthritis in a very early cohort, incorporating both pre and post-test probabilities.

An investigation of the role of NLRP3 in treatment response<sup>7</sup> showed that patients with low levels of the protein responded well to infliximab while those with high levels did not.

“This tells us more about why some patients respond to infliximab and some don’t.”

The COMET trial<sup>8</sup> had remission, defined as a DAS score of less than 2.8, as one of its endpoints, said Prof McDermott.

“For patients on etanercept plus methotrexate there was a significant difference in the DAS28 remission rate, with 50 per cent achieving remission versus 24 per cent of those on methotrexate alone after two years.

As promised, Prof McDermott then discussed some “very novel, controversial and untested” therapies for RA.

“There are many cells involved in the synovium of active RA,” he reiterated, citing a study published in 2007<sup>9</sup> that looked at many possible targets in the treatment of RA, including the IL-17 receptor and several kinases, such as JAK and MEK.

Prof McDermott also outlined an example of a patient receiving allogeneic stem cells transplantation.

“You can see just by looking that the patient responded remarkably well. This is a very controversial way to treat severe RA but the people who support it say there is five per cent of rheumatoid that we cannot control, maybe less. It is something worth considering.”

He also presented data on autologous stem cell transplants<sup>10</sup>.

“This shows you that disease usually recurs after autologous stem cell transplants, in RA in particular, but it does have a role in juvenile rheumatoid and possibly in scleroderma, but it isn’t effective in the control of RA.”

Gene therapy is another approach showing potential<sup>11</sup>, although RA is quite difficult as it is a polygenic disease, stated Prof McDermott.

“Gene therapy has had a few setbacks, with at least one mortality about ten years ago.” The biggest study currently ongoing is one that is attempting to deliver etanercept (Enbrel) via an adeno-associated virus (AAV) vector, he added.

The professor also outlined a vaccine pilot study that is currently taking place in Newcastle, England, which is utilising tolerogenic dendritic cells.

The experimental approach, developed by Prof John Isaacs, aims to induce a tolerogenic state by adding steroids, lipopolysaccharides (LPS) and vitamin D to the patient’s white blood cells. These are then re-injected into the patient’s knee as a vaccine. While mature dendritic cells are responsible for activating the immune system, tolerogenic dendritic cells suppress immune activity, explained Prof McDermott.

This approach has proved promising in animal models but this may not translate to the human patient, he stated, adding that tolerogenic dendritic cells may eventually be used as an adjuvant therapy.

Angiogenesis, or new vasculature formation, is also garnering a lot of interest<sup>12</sup>, said Prof McDermott.

“There is a whole ‘orchestra’ of molecules involved in angiogenesis in the synovium, of which VEGF has the most importance. This is already being targeted in cancer with some success, with the VEGF antibody known as Avastin (bevacizumab). I know there are plans to use it in the rheumatoid synovium as well.”

Other anti-VEGF therapies include pegaptanib sodium, and ranibizumab, he added.

Epigenetic changes in rheumatoid arthritis are reversible and are therefore viable treatment targets, Prof McDermott continued.

“Gene transcription of inflammatory mediators is regulated by the tight balance between histone acetylases (HATs) and histone deacetylases (HDACs). This balance is shifted to hyperacetylation in RA. Therefore specific HDAC inhibitors may help control the synovitis of RA. This approach is highly experimental at this stage but I think it will have a role in the future.

MicroRNAs are the “hot topic” in immunology at the moment, Prof McDermott said. He explained that a study last year<sup>13</sup> showed that miR-155 may be involved in modulation of the destructive properties of synovial fibroblasts.

“This is still at the test tube stage and remains very much in the future.”

Prof McDermott concluded by making predictions about the treatment of RA in the year 2032.

“Whole genome sequencing of newborns will be possible by 2020, and the whole proteome will be available by 2030. Systems biology and a network model of the disease will allow earlier diagnosis, treatment and ultimately

## Future Therapies for Early Aggressive Rheumatoid Arthritis (Cont.)

prevention of RA. Molecular imaging will allow visualisation of specific cellular functions and follow-up. Developments in pharmacogenomics will allow the diagnosis and management of early undifferentiated inflammatory arthritis. Improved understanding of the regulatory role of different cells, including B cells and monocytes, as well as epigenetics in rheumatic diseases will facilitate gene therapy.”

Prof McDermott also predicted that there would be no biologics in use at that point and he stated that he hoped the pathogenesis of RA may also finally be understood.

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## Outcomes in Osteoarthritis: Update 2009

**Prof Marc C Hochberg,**

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*Marc C. Hochberg, MD, MPH, received his undergraduate degree (A.B. cum laude in Chemistry) from Franklin & Marshall College in Lancaster, Pennsylvania. He received his M.D. from The Johns Hopkins University School of Medicine and M.P.H. from The Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland. He completed residency training in internal medicine and fellowship training in rheumatology at The Johns Hopkins Hospital in Baltimore, Maryland. He was a member of the full-time faculty of The Johns Hopkins University School of Medicine from 1977 to 1991. Since 1991, Prof Hochberg has been Professor of Medicine and Epidemiology & Preventive Medicine at the University of Maryland School of Medicine. Since 1995, he has been the Head of the Division of Rheumatology and Clinical Immunology in the Department of Medicine at the University of Maryland School of Medicine.*

*Prof Hochberg's research focuses on the clinical epidemiology of musculoskeletal disorders, particularly osteoarthritis and osteoporosis. He is the Principal Investigator of the Baltimore Clinical Centers of the Osteoarthritis Initiative and the Study of Osteoporotic Fractures, and Co-Principal Investigator of the Baltimore Hip Studies.*

Prof Hochberg explained that as there is so much to discuss when it comes to osteoarthritis (OA), his presentation would focus on various outcomes in OA.

The most common form of arthritis, osteoarthritis (OA) accounts for more functional limitation, work loss and physical disability than any other chronic disease, stated the professor.

The economic cost of OA runs at 1-3 per cent of the gross national product (GNP) of developed countries worldwide, he added.

“In providing an update on outcomes, it is worthwhile mentioning that OA was referred to as degenerative joint disease and thought to simply be a degenerative disorder of the articular cartilage and it [is] now recognised that [this] is in fact no longer true. It is now known that OA is a dynamic process that represents the biochemical reaction to a biomechanical insult on the joint.”

The disease has a complex etiopathogenesis, with changes in bone and cartilage integral components of the OA process, as is inflammation, which plays an important role in the production of symptoms and signs, as well as the progression of the disease, said Prof Hochberg.

“This role is being increasingly recognised and we are only a small way now from utilising some of the agents that have been shown to be effective in RA for patients with OA.”

Future treatment goals include the development of drugs to prevent structural progression, but currently total joint arthroplasty is a cost-effective intervention for patients with end-stage hip or knee OA, stated the professor.

Prof Hochberg then outlined some of the facets of osteoarthritis, using a diagram taken from a 2005 paper <sup>1</sup>.

## Outcomes in Osteoarthritis: Update 2009 (Cont.)

“The primary reason that people come to you with osteoarthritis is pain so when we talk about outcomes to assess, the major outcome we will be looking at will be related to an improvement in pain. The occurrence of pain leads to a reduction in joint function. So an improvement in joint function is sought, usually measured by self-reported functional ability.”

Other facets of the condition include disability, depression and reduced quality of life, he added.

With no known cure, current treatment goals are focused on reducing pain, maintaining or improving joint mobility, limiting functional impairment and improving health-related quality of life, stated the professor.

“The clinically relevant outcomes I am discussing are those which you can utilise in the individual management of your patient, to determine whether they have improved, and also those that have been used in clinical trials of patients with OA. Rather than looking at mean changes

in pain scores or functional scores of a group of people, we are looking at how an individual has improved and whether patients improved on drug A compared to placebo. Therefore we wanted to develop scales that were similar to the ACR20 and also parameters that are similar to remission and low disease activity too, so that we can advance the field of OA the way that the field of RA has been advanced over the last 20 years.”

Prof Hochberg explained that the Osteoarthritis Research Society International (OARSI) Response Criteria were initially derived from a study that analysed data from 14 clinical trials of 1886 patients with either hip or knee OA<sup>2</sup>.

“These involved a variety of interventions, including oral NSAIDs and oral and intra-articular OA specific drugs. There were six sets of criteria, which were developed and labelled Propositions A-F. Each proposition dealt with a different joint group, three for the hip and three for the knee, and each was for a different intervention. This, however, was too complicated for

anyone to use and had various limitations including questionable precision and not being validated in other datasets.”

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT)-OARSI Responder Index<sup>3</sup> was an initiative of the Society that then attempted to develop a simplified, dichotomous response criteria to be used in trials of patients with OA, explained Prof Hochberg.

“These criteria have to be simple and feasible so the OARSI propositions had to be made acceptable for use in practice and in studies,” he said.

The performance of the six different scenarios was compared using two different databases – the original database and also the Revisit database. The expert opinion approach was then applied to the results at the OMERACT 6 meeting.”

Prof Hochberg explained that the resultant index – **Figure 5** was simple and acceptable for use in analysing data from clinical trials by identifying responders and non-responders.

While he explained it had not yet been accepted for use yet as a primary outcome measure for registration of compounds for the treatment of osteoarthritis, Prof Hochberg illustrated its validity by showing examples of its correlation with various measures such as the Health Assessment Questionnaire and the Short Form (SF)-36.

“When I consult with companies developing OA trials, I recommend that it be included as a secondary outcome, although it cannot be used as a primary outcome as of yet.”

Prof Hochberg then outlined the MCII<sup>4</sup>, or minimal clinically important improvement.

“This is the smallest change in a measurement that signifies an important

improvement in a patient’s symptoms. It quantifies just how much better they are on a pain scale or global assessment scale. The study by Tubach et al identified the MCII as the 75<sup>th</sup> percentile of distribution of change score among those who had good or excellent improvement with therapy.”

Prof Hochberg also outlined the Patient Acceptable Symptom State (PASS), which is the value in the measurement of a patient’s symptom beyond which the patient considers herself well.

Tubach et al defined PASS<sup>5</sup> as the 75<sup>th</sup> percentile of distribution of absolute score among those who are satisfied with their current state after therapy.

“This is where you ask a patient whether they are satisfied with how they are doing,” explained Prof Hochberg, adding that the PASS can also be used in both practice and clinical trials.

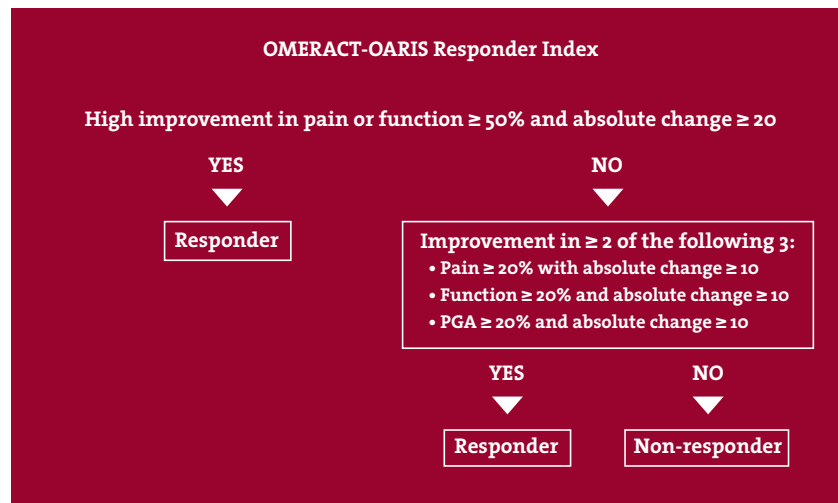
Prof Hochberg then explained that, currently, an indication for total joint arthroplasty (TJA) depends on the level of pain, functional impairment and disability in the presence of radiographic OA. It is also influenced by the patient’s willingness to consider/undergo TJA, the surgeon’s willingness to operate and also issues related to the healthcare system<sup>6</sup>.

It was sought to define a set of criteria for considering total hip replacement or total knee replacement for use in clinical trials evaluating potential disease modifying osteoarthritis drugs (DMOADs).

A scale that measured pain was developed by OMERACT/OARSI<sup>7</sup>.

“A new 11-item scale was developed that separated constant pain from intermittent pain, as it was seen from focus groups that OA patients experienced these two types of pain. This scale was then incorporated into a 48 month follow up visit.”

Figure 5



Another study<sup>8</sup> developed criteria for measuring function in the knee, looking at 2145 patients with knee OA from five countries.

“The Rasch analysis identified seven items to be included in a shortened instrument, which increased in difficulty: rising from a bed; putting on socks; rising from sitting; bending to the floor; twisting/pivoting on painful knee; kneeling and squatting.”

In developing criteria for measure of function of the hip<sup>9</sup>, 2991 patients with hip OA from seven countries took part. The Rasch analysis here identified five items to be included in a shortened instrument: sitting; descending stairs; getting in/out of bath/shower; twisting/pivoting on loaded leg; running.

Prof Hochberg also explained that OMERACT/OARSI definitions for radiologic progression<sup>10</sup>, relevant radiologic progression have also been outlined, while a definition for OA progression based on MRI has yet to be defined.

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**Prof Frank Barry,**

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*Frank Barry is Professor of Cellular Therapy at the National University of Ireland, Galway, and Scientific Director of the University's Regenerative Medicine Institute (REMEDI). Here he directs a large group of researchers who focus on the development of new repair strategies in stem cell therapy and gene therapy in orthopaedics and spinal cord injury. REMEDI includes a GMP stem cell manufacturing facility for the preparation of stem cells for use in human clinical studies.*

*Prof Barry has contributed to the fields of tissue engineering and regenerative medicine by developing an innovative and successful cellular therapy for the treatment of acute joint injury and arthritic disease. This has included the generation of a large body of new data in groundbreaking preclinical studies, and has led to a phase of clinical testing of mesenchymal stem cells in human trials. In addition he has developed new techniques for the isolation, characterization and commitment of bone marrow stem cells. He has also explored the phenotype of bone marrow-derived stem cells in patients with advanced osteoarthritis. These studies indicated that patients have functionally depleted reservoirs of stem cells in the marrow. These data suggest that stem cells may be a component of the diseases*

*process and at the least will influence future strategies in cell-based repair for these patients. “Stem cells are unspecialised cells, lacking any tissue-specific structure. They are capable of dividing and renewing themselves for long periods and can give rise to specialised cells, in a process called differentiation,” explained Professor Barry as he began the final presentation of the day.*

For many decades adult stem cells evaded detection because of this unspecialisation, added Prof Barry.

“They carry none of the characteristics of the tissue in which they are found,” he explained.

Prof Barry presented the evidence for whether stem cells can play an effective role in treating human disease and outlined how the injured host responds in a variety of animal models of human disease.

Although they lack any specific tissue characteristics, when stem cells are exposed to appropriate signals they differentiate and they become highly specialised – this is a “remarkable” ability of stem cells, he stated.

“Embryonic stem cells are totipotent and can differentiate into any one of the 200 or so cell types that make up the human body. Adult stem cells have a much more restricted differentiation potential and we usually think of adult stem cells as having a very small number of differentiation pathways that they can embark upon.

Explaining his research interests at REMEDI, Prof Barry explained that he and his colleagues at the institute are particularly interested in adult stem cells.

**Figure 6** – “The adult bone marrow is a very rich reservoir of stem cells. There are two very distinct populations of stem cells that reside in the bone marrow.

Figure 6

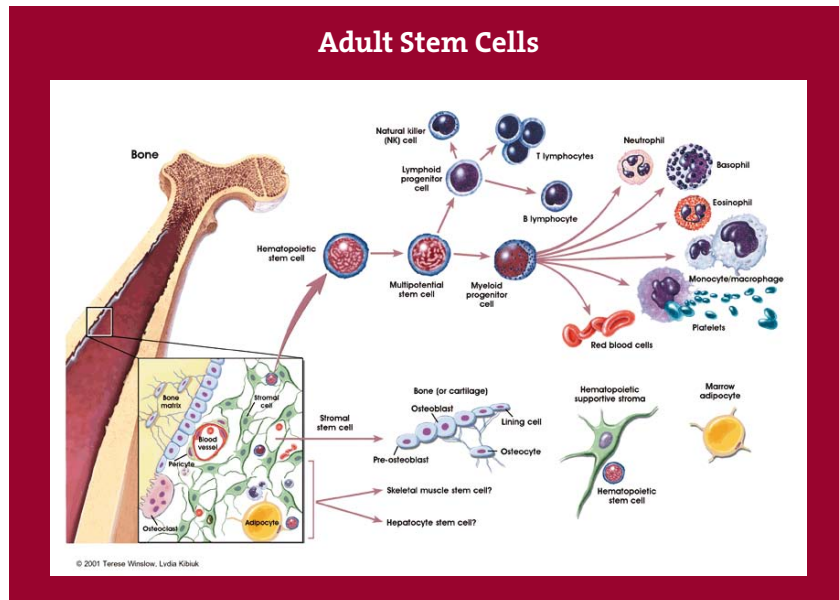
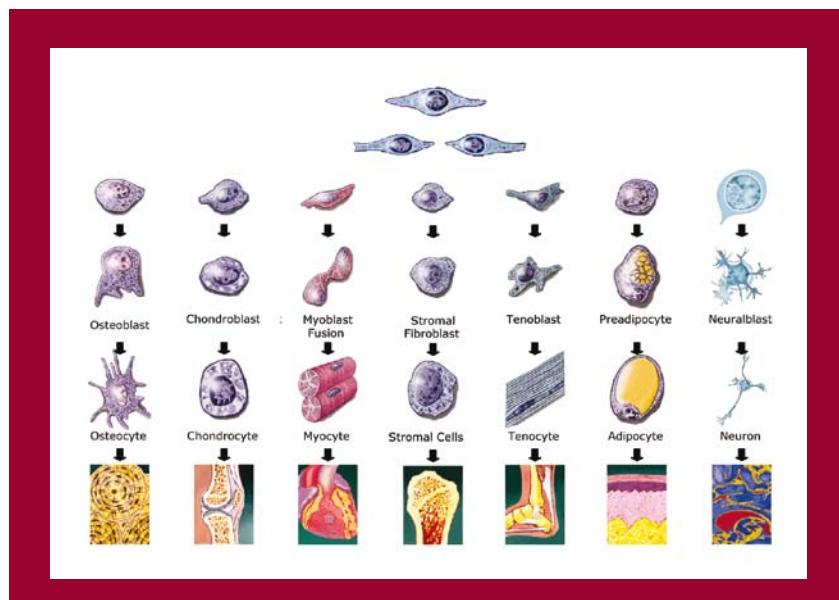


Figure 7



Haematopoietic stem cells can give rise to all of the cells of the blood system such as white cells and red blood cells. They have been characterised for a very long time and of course stem cell transplantation is now widely carried out to treat leukaemias.”

**Figure 7** A second population of stem cells was identified more recently, and are known as stromal cells or mesenchymal stem cells, stated the professor.

“Although these also reside in the bone marrow compartment and are closely related, haemopoietic and mesenchymal stem cells are also quite distinct from each other.”

The undifferentiated cell can be grown very easily in the laboratory and then when exposed to particular signals can be induced to become various cell types e.g. osteoblasts, chondroblasts etc.

According to Prof Barry: “You can see the therapeutic interest because we have cells that we can take from a human bone marrow biopsy, we can culture these cells in the laboratory, preparing very large numbers of them and depending on how we treat those cells we can make them into specialised tissues.”

There is thus an interest in using these flexible cells therapeutically for tissue repair applications, he explained.

“Because this particular population of stem cells make connective tissue-type cells, there is a great deal of interest in using these cells for orthopaedic conditions and treating arthritic disease.

Prof Barry explained that the focus of his research is using these cells to stimulate either a repair response or to repair tissues that are damaged in degenerative arthritis.

**Figure 8** The professor then presented slides depicting microscopic images of human bone marrow stem cells, showing an undifferentiated cell population and

then the same preparation of cells after they have differentiated into different cell types, with huge differences in morphology very apparent.

Three elements of the cell are important in terms of how they behave in vitro. They must adhere to the tissue culture surface; they move very readily across that surface; and they must divide very readily so that exponential growth of the cell quantity occurs.

Prof Barry then went on to describe how these cells are delivered in various animal models of human disease, including myocardial infarction, osteoarthritis, breast cancer and rheumatoid arthritis.

**Figure 9** Regeneration of damaged heart muscle has been shown to be possible, either by injection of stem cells directly into the infarcted myocardium or simply into the vasculature, where they make their way to the site of injury, he explained.

“There is a tissue-specific migration of cells through the circulation to the infarcted heart. This engraftment does not happen in healthy tissue, as this was not observed in healthy animals. The suggestion from these studies is that there is a series of signals derived from the injured tissue to which these stem cells respond.”

Prof Barry continued by explaining that the majority of his research group's interests lie in the use of stem cells in the treatment of osteoarthritis and they have developed a number of animal models for use in experimentation.

These involve the surgical ablation of instability in the knee joint, typically either by a combination of total medial meniscectomy (MMX) and resection of the anterior cruciate ligament (ACL), or MMX alone, or a partial MMX.

Figure 8

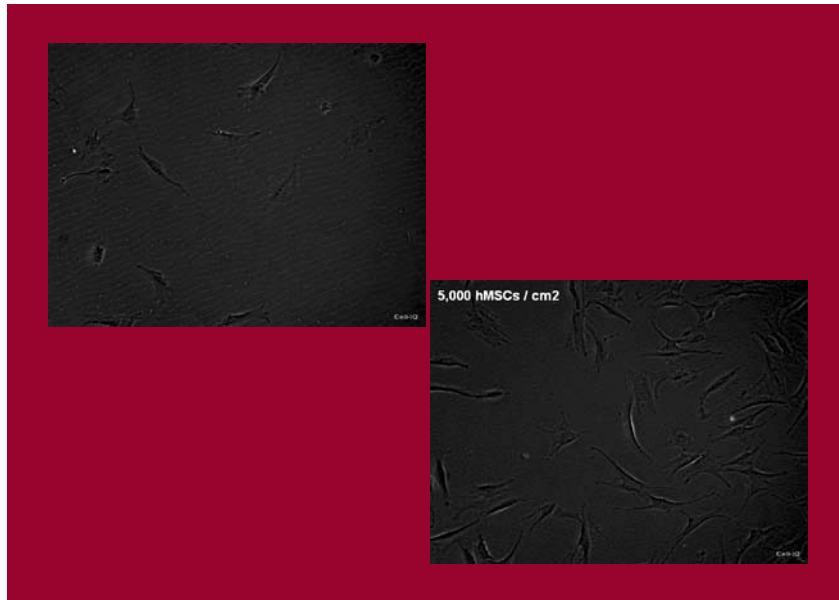


Figure 10

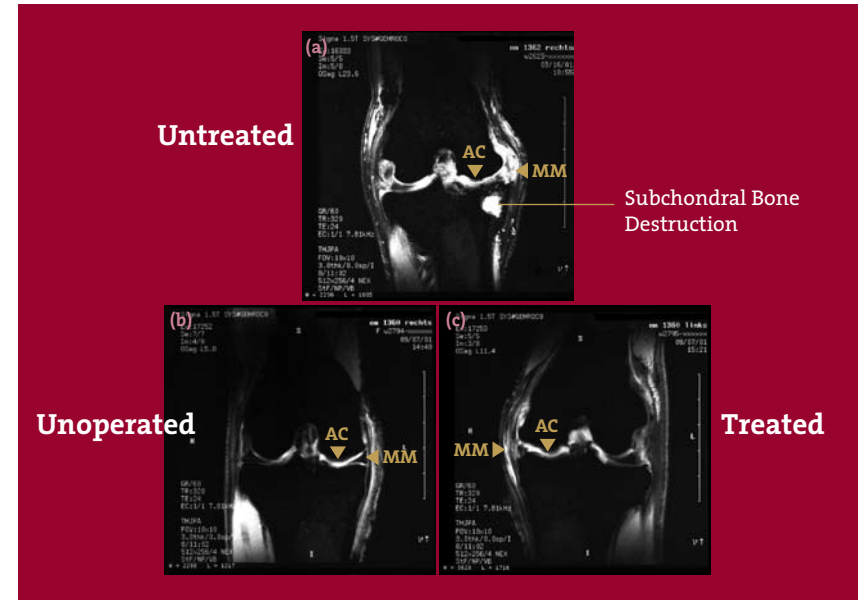


Figure 9

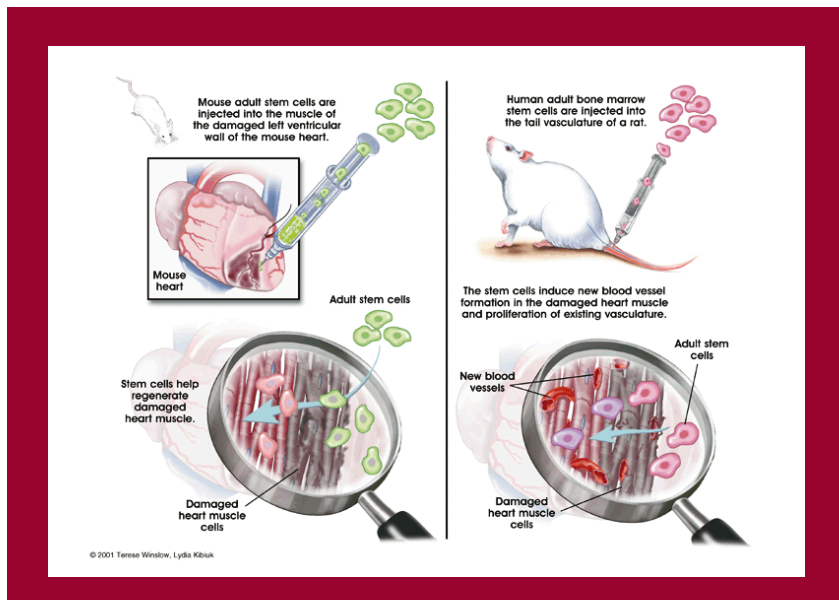
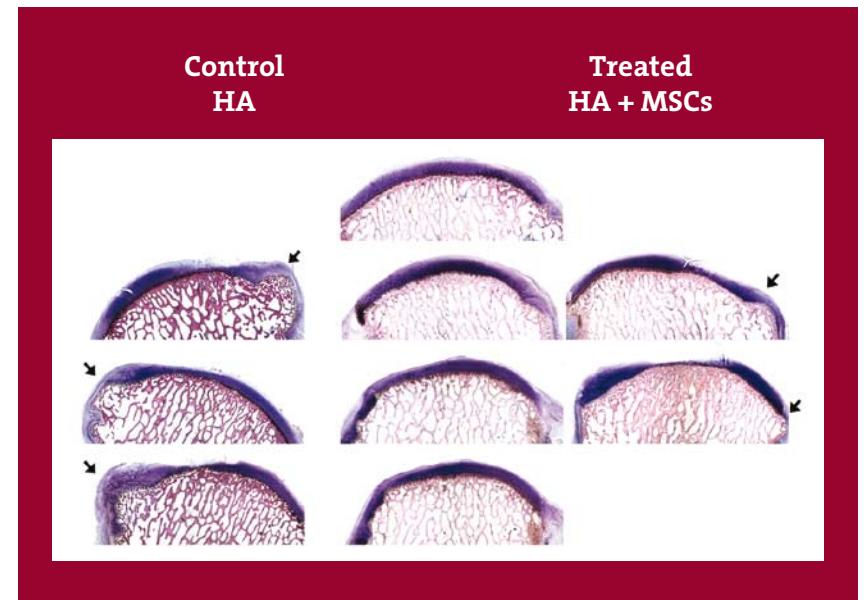


Figure 11



“We have found in a number of experiments that we have done over a number of years, that depending on which of these surgical approaches that you use, the severity of the lesions varies with the combination of MMX and resection of the ACL resulting in much more severe lesions than the partial MMX. When you carry out this surgical procedure after a period of 12 weeks you have severe lesions in the joints of these animals.”

Experimentation is then very straightforward, explained Prof Barry.

“We allow the animals recover from surgery then we initiate a daily exercise regime. After a period of time, we then deliver stem cells into these knee joints.”

A suspension of stem cells is given by simple intra-articular injection into the joint space, the objective of the experiment being to determine if the presence of the stem cells will impact the development of degenerative arthritis in these knee joints.

According to Prof Barry, when these experiments were first carried out, he and his colleagues were surprised to see a dramatic repair response, associated with the delivery of the stem cells. He showed a number of MRI scans that clearly illustrated the differences in untreated and treated knee joints in goats – **Figure 10**

“You can see there is no evidence of sub-chondral destruction or bone cyst formation and it is also clear that there is what appears to be a newly-generated meniscus, which we call the neomeniscus as a result of the therapy. The nature of the repair response in these meniscectomised knee joints, after they have received this injection of stem cells, is clear magnascope tissue formation, which occurs only as a result of the stem cell delivery.”

The effect of this neo-meniscal tissue formation, Prof Barry explained, is to

alter the mechanical environment of the knee joint so that it much more closely resembles “normality” than untreated joints.

Cross-sectional views – **Figure 11** of control knee joints treated with hyaluronic acid (HA) compared with those of knees treated with both HA and mesenchymal stem cells (MSCs) showed that stem cell delivery resulted in limited articular damage and there was no evidence of osteocyte formation or sub-chondral sclerosis.

“All this suggests that the chemical signals which these joints are experiencing are much closer to normality than those which did not receive stem cells,” said Prof Barry.

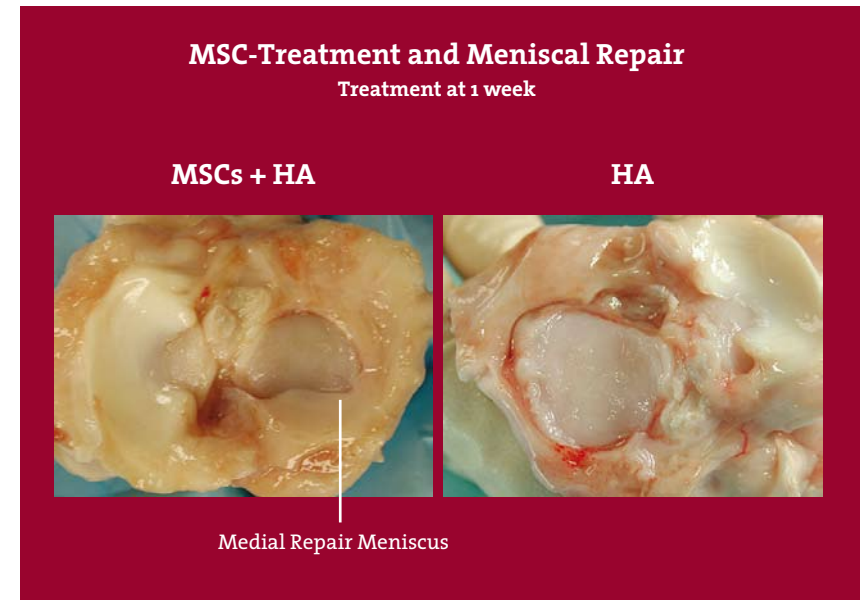
A macroscopic view of the tibial surfaces – **Figure 12** clearly shows the lack of neo-meniscus formation in control joints, whereas in HA+MSC treated joints this is evident after just one week of treatment.

“The area of unprotected medial tibial plateau in MSC-treated joints is much, much smaller than that in untreated joints, with the damage to the articular surface much less than in these joints also. There is chondral protection conferred on these stem cell-treated knee joints but this is secondary to the formation of the regenerative tissue.”

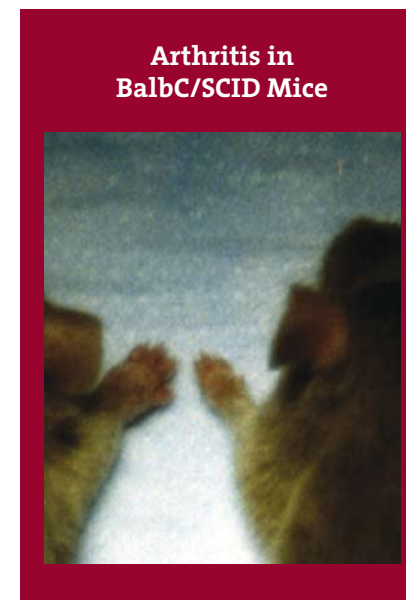
Prof Barry then described similar experiments involving fluorescently-labelled stem cells, (expressing GFP) delivered into meniscectomised knee joints.

“Having seen the tissue repair response, we assume that the stem cells were responsible for making this repair tissue, so we started tracking the stem cells. We found that there was a reasonable level of engraftment of the delivered stem cells within these injured knee joints, however, within the repair meniscus itself there was

**Figure 12**



**Figure 13**



very little engraftment. In other words, the transplanted stem cells contributed only a very small proportion of the cells that made up this repair tissue - one per cent - with the remainder derived from the host.”

Stem cells therefore stimulate the host to make new tissue but the host cannot achieve this without the presence of the stem cells, the professor explained.

“The stem cells contribute to a dynamic signalling network whereby stem cells secrete factors to which the host responds. It is not that the stem cells differentiate or make new tissue, it is that they provide soluble factors that the host was missing.”

Prof Barry and his colleagues at REMEDI also investigate the role of stem cells in treating antibody-induced arthritis in BalbC/SCID mice.

**Figure 13** – These experiments involved both unmodified hMSCs and also

genetically-modified hMSCs that were transduced with a viral vector to express soluble tumour necrosis factor receptor II (sTNFRII). The mice were first injected intramuscularly with one of the two stem cell suspensions and then rheumatoid arthritis was induced using the antibody a week later. The course of the inflammation was then monitored by measuring paw volume throughout the course of the experiment (up to three weeks).

Prof Barry admitted that his team were “surprised” by the results of the experiment.

“Based on previous observations we assumed that we would see some ability of the stem cells to modify the disease but in fact it had no effect. The unmodified stem cells had no effect on the inflammatory phase of the disease but the genetically-modified stem cells had a dramatic effect however. Indeed there was no difference between naïve mice and those treated with the genetically modified stem cells.”

This illustrated another principle of stem cell therapy, Prof Barry explained, that there are some diseases where the stem cells are not effective themselves but can instead be used as vehicles to carry therapeutic genes of interest.

Prof Barry explained some of the principles of stem cell therapy that he and his colleagues have deduced over the course of their experiments.

“In the case of cell-based repair, where we deliver stem cells to the injured host, it doesn’t matter which kind of model of human disease we are dealing with, we are always delivering these cells to an injured tissue and trying to discover whether there is a repair response or not.”

He explained that within cell-based repair, it is now known that the therapeutic

effect observed is associated with limited engraftment, with the vast majority of stem cells not reaching the injury site. “It is also clear to me that the differentiation of transplanted stem cells is uncertain.”

Prof Barry concluded by summarising what his team has surmised from the available evidence for how the stem cell interacts with the cells of its host environment:

- Modulation of the host phenotype involves activities such as: engraftment; trophic effects; immune suppression; mobilisation of host cells; tissue formation and tumour engraftment.
- Modulation of the stem cell phenotype involves: migration; proliferation; differentiation; and cell death.

Further information on stem cell mechanisms can be found at:  
<http://www.nuigalway.ie/remedi/>

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