

## **Mapping the Frontier: Cutting-edge conference ponders future research directions**

By: Dennis Jeanes

Top clinical investigators, basic scientists of virtually every stripe and consumer/activists from a variety of arthritis organizations came together for the "Frontiers in Inflammatory Joint Diseases" conference, held in Toronto from May 7–9. A collaborative undertaking by The Arthritis Society, the Institute for Musculoskeletal Health and Arthritis, and the Canadian Arthritis Network, the conference's ultimate goal was to set the Canadian research agenda for such chronic inflammatory diseases as rheumatoid arthritis, ankylosing spondylitis and juvenile arthritis.

Prior to the two-day scientific forum, the conference hosts held a one-day consumer program, featuring presentations on Canada's arthritis research infrastructure, current trends in research, the evolving role of ethics in clinical trials, and best practices in developing informed patient advocacy. Highlights of the day included: Dr. Ed Keystone's compelling overview of how TNF-alpha inhibitors have transformed treatment of RA and how new targets (such as inflammatory mediator p38 and activated B cells) are emerging from a much more complete understanding of the molecular events involved in inflammation; advocate Debra Lappin's account of how the unethical behaviour associated with US business practices (think Enron, Tyco, Martha Stewart and many more) has seeped into American academic research, prompting a consumer revolution in the ethical treatment of clinical-trial participants; and later, the dinner address by Ipsos-Reid Senior VP John Wright who painted a striking portrait of Canadian attitudes and beliefs, and advised the arthritis community to invest in strategic communications so that its voice stands out amid all its competitors.

On Day Two of the conference, the programme was divided into four sessions: biomedical perspectives, clinical interventions, challenges in clinical and population health studies and health-services research. After each session, participants were asked to debate in small-group roundtable discussions what were the strengths and weaknesses in each particular area of research. The discussions were recorded and then submitted to the conference facilitators for synthesis the following day.

In the biomedical session, presenters reviewed current understanding of inflammation from a molecular and genetic perspective, as well as what can be learned from animal models. Dr. Michael Brenner of Harvard Medical School noted that, at the molecular level, researchers are starting to distinguish between the body's innate inflammatory response and localized tissue response. The major molecular events of inflammation take place in the synovium's sub-lining, which lies between a fine web of blood vessels and the actual synovial membrane. Tissue response takes place when the synovium thickens and becomes pannus. Dr. Wim van den Berg from the Netherlands noted that animal models have shown that pro-inflammatory TNF-alpha, by itself, isn't terribly destructive but that interleukin-1(IL-1) is, and appears to dominate the scene in later stages of tissue response. Genetically bred mice that are deficient in IL-1 have no erosive arthritis.

Interpreting clinical trials, the prospects of gene therapy, non-pharmaceutical interventions and scientific analysis of synovial samples were the main areas covered in the day's second session. Clinical investigator Dr. James O'Dell of the University of Nebraska Medical Center reviewed recent clinical-trial data to sketch out current trends in RA chemotherapy. Among the findings: The earlier DMARD therapy is started, the better; combination therapy appears more effective than methotrexate alone, and triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) seems much more effective than DMARD monotherapy. In short-term trials of methotrexate versus etanercept in early RA, outcomes were fairly similar, but response was much faster with biologic therapy. For all of this, clinicians are still finding it difficult to match the appropriate therapy with the individual patient. That's probably because the pathogenesis of RA follows many different pathways toward a common clinical outcome, according to Dr. Paul Peter Tak of the Netherlands, who has examined hundreds and hundreds of synovial samples under a

microscope. Eventually the different sub-types of RA will be distinguished by subtle differences in gene-expression profiles.

The topics for the population-health session ranged from challenges in pediatric rheumatology to the value of early intervention to the impact of arthritis in the workplace. Pediatric rheumatologist Dr. Brian Feldman of Toronto's Hospital for Sick Children noted that childhood inflammatory joint disease was comparatively rare and, thus, it made sense to create a nation-wide registry that could coordinate clinical research in larger patient populations through multi-centre research. Dr. Edward Yelin, a professor of medicine and health policy at San Francisco's University of California, examined the costs and benefits of early intervention in RA — especially with the advent of biologics, which can be highly effective but raise the cost of treating inflammatory joint disease. The case can be made that, by keeping people with RA productive with biologics, the indirect costs of lost productivity (which are much greater than the direct costs of treatment) could be lowered substantially. Rheumatologist Diane Lacaille from Vancouver's Arthritis Research Centre of Canada presented data showing that 18% of workers with RA are work-disabled five years after onset of symptoms. Her research also indicates that the earlier the initiation of DMARD therapy, the longer a worker with inflammatory arthritis stays on the job.

The health-services research session was essentially a debate about the safety and efficacy of TNF-alpha inhibitors, as well as the issues about their inclusion on provincial drug formularies. Rheumatologist/epidemiologist Dr. Kimme Hyrich, an Arthritis Society-funded research fellow presently working at the University of Manchester, presented findings from a biologics registry that tracks everyone receiving anti-TNF therapy in Great Britain and Northern Ireland. The safety profile for biologic therapies were excellent in the controlled populations of clinical trials, however as they became available to the wider population, rare but serious adverse events (including tuberculosis and other infections, aplastic anemia and congestive heart failure) began popping up. Dr. Kimme noted that there were still many questions about long-term risk of toxicity or adverse events, and whether any increased risk was due to dose or duration of biologic therapy. She also raised the intriguing question whether biologic combination therapy increased risk of side effects.

The last day of the research forum began with two contrasting presentations on strategic opportunities for Canadian arthritis research: Peter Lipsky, Scientific Director, NIH - Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), summarized what's known about the pathogenesis of RA and noted that current outcome measures, such as the benchmark ACR20 (which denoted a global 20% improvement in symptoms), weren't sensitive enough to distinguish the varying effects of different drugs. Then he launched into a series of provocative questions for clinical researchers: Should future clinical trials of new drugs be measured against biologics? Should there be head-to-head comparisons of current and new arthritis drugs (as opposed to placebo)? Do current outcome measurements underestimate the degree of benefit from biologics? Dr. Lipsky called for all people receiving biologics to be recruited into a national registry that then could be used to extract safety and efficacy data from large populations.

Dr. John Frank of the CIHR's Institute of Population and Public Health examined the prospects of primary prevention of RA. Noting that rheumatoid arthritis was the result of interaction between genetic and environmental factors, he stated that the determinants of disease severity depended more on psychosocial status in early stages and more on genetic profile in later disease. He, too, echoed the call for more sensitive outcome measures. However, his approach was to study identical twins (who have exactly the same genes) or large, stable populations of migrants (whose shared gene pool is responding to a changed environment). Such genetic studies could identify biological markers of risk to disease and predictors of disease severity.

After these two presentations, forum participants broke into discussion groups to debate strategic research themes and potential research questions. Notes from the discussions were written down on flip charts for analysis. At the concluding plenary session, the process was outlined for further

refining the participants' collected wisdom into funding programs offered by the three conference hosts.

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