



Arthritis and Autoimmunity Research Centre

2010 Activity Report



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2010 Activity Report

From the Director

Dear Colleagues,



This 2010 AARC Activity Report once again illustrates that the AARC scientists are international leaders in their respective fields, contributing significantly to advancing knowledge about these debilitating diseases. In 2010 AARC scientists were recognized nationally and internationally with awards for their scholarship and achievements. Following is a brief survey of some of the achievements in 2010 of AARC scientists, illustrating the scope of research and impact on health care.

Evidence that a molecule circulating in the blood of lupus patients may contribute to immune disruption, that lupus is associated with increased risk of heart disease and that antimalarial drugs reduce the risk of hypertension and thromboses in lupus patients are amongst the latest findings from Drs. Fortin, Gladman and Urowitz and their associates studying lupus.

In the context of heritable/genetic factors that are associated with autoimmune diseases, a seminal publication by Dr. Siminovitch reported on 7 genes linked with rheumatoid arthritis. In similar studies, Drs. Tsui, Inman and colleagues identified a new set of related genes, wherein mutations were associated with development of ankylosing spondylitis. Intriguingly, these genes have been linked to blood pressure regulation. In other genetic studies, Drs. Gladman and Inman were involved in a multi-national study that examined genes in patients with ankylosing spondylitis and Crohn's disease and identified a linkage with a gene that is also associated with disease development for rheumatoid arthritis, diabetes and multiple sclerosis. The implications, borne out in therapies that now have widespread application across many autoimmune diseases, is that there are common features to these autoimmune diseases, some genetic, that may be targeted for therapeutic intervention.

Dr. Keystone headed up one of the trial sites leading to the approval of Golimumab for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Dr. Inman's research group identified a population of immune cells that contribute to tissue damage in rheumatoid arthritis, and suggested that gene manipulation in these cells may lead to a potential vaccine against arthritis. Moreover, addressing the challenge of better strategies for patient care, Dr. Keystone reported that within 3 months of onset of a particular treatment, effectiveness is predictable, allowing for continuation, or discontinuation and switching to an alternate therapy. Dr. Inman's research identified that infliximab, a drug used effectively in rheumatoid arthritis, is also effective in the treatment of ankylosing spondylitis.

In the Fall of 2010, Dr. Carette launched the Canadian Vasculitis Network, a national network to improve research and care for vasculitis. AARC researchers, including Drs. Gignac, Davis, Badley and Bombardier, continue their research activities evaluating the impact of arthritis on employment and workplace productivity, on lifestyle, and the impact of accessibility of medical care to disease progression.

In closing, let me acknowledge once again with sincere gratitude the remarkable support of the AARC Foundation Board, the Chair, Trudy Eagan, and ViceChair Marc Milgrom, the Executive Director of the AARC Foundation, David Prowten, and the dedicated staff of the AARC Foundation. Your continued commitment to raising the research funds that will allow us to 'Beat Arthritis, Beat them All,' is shared by all the AARC scientists.

Sincerely,

A handwritten signature in dark ink, appearing to read 'E. Fish', written over a horizontal line.

Eleanor Fish

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Programs and Centres

Since its inception in 1998, the Arthritis & Autoimmunity Research Centre at the University Health Network has combined clinical and applied studies with basic science research to become one of the most comprehensive centres of its kind. The AARC research team includes internationally recognized leaders in genomic medicine, health services research, rheumatology, medical imaging, immunology, and orthopaedics.

Arthritis Centre of Excellence (ACE)

ACE, founded in 1998, is a state-of-the-art facility that performs investigative research into autoimmune rheumatic diseases. Experts in rheumatology, immunology, and orthopaedic surgery collaborate under the direction of Dr. Robert Inman.

Arthritis Community Research and Evaluation Unit (ACREU)

ACREU was established in 1992 to study the impact and management of arthritis. Under the direction of Dr. Elizabeth Badley, the multidisciplinary research team seeks to identify deficiencies in existing treatment and support services, and to assist in the development of new policies and programs. ACREU plays a key role in providing critical information to the provincial and federal governments so as to enhance arthritis care via the health care system. www.acreu.ca

Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS)

Founded in 1995, CaNIOS was initially created to direct a randomized controlled multi-centre study of Methotrexate treatment of Lupus Erythematosus (SMILE). Chaired by Dr. Paul Fortin, CaNIOS links together lupus experts from across the country to conduct additional studies related to the disease. The organization has now received a number of peer-reviewed grants, and published numerous peer-reviewed journal articles and abstracts. www.canios.ca

Canadian Vasculitis Network (CanVasc)

Founded in 2010, the Canadian Vasculitis Network integrates research and clinical groups to address the needs of patients with vasculitis. Presided over by Dr. Simon Carette, CanVasc organizes referral centers for patients with vasculitis, initiates and promotes research programs on vasculitis, develops awareness programs and serves as the premier vasculitis group to identify the needs and directions in the field of vasculitis care and research.

www.canvasc.ca

Rebecca MacDonald Centre for Arthritis & Autoimmune Disease

The Rebecca MacDonald Centre for Arthritis & Autoimmune Disease (RMCAD) at Mount Sinai Hospital integrates clinical patient care with innovative, genetics-based research for rheumatic and autoimmune diseases. Under the direction of Dr. Edward Keystone, RMCAD is home to the Division of Advanced Therapeutics, the largest and most successful clinical trial program in Canada. The Division is devoted to the study of new and innovative therapies for rheumatic diseases with an emphasis on rheumatoid arthritis, osteoarthritis, and psoriatic arthritis.

www.mtsinai.on.ca/care/rmcad

The Centre for Prognosis Studies in Rheumatic Diseases

Since its founding in 1996, the Centre for Prognosis Studies in Rheumatic Diseases has been a unique resource for clinical research in rheumatic diseases. It follows large patient bases with defined rheumatic diseases, including lupus and psoriatic arthritis, in long-term prospective studies. Under the direction of Drs. Murray Urowitz, Dafna Gladman, and Paul Fortin, the Centre's Psoriatic Arthritis Clinic has become the largest of its kind in the world, with 878 patient visits in 2004. The Lupus Clinic has been following a patient group according to standard protocol since 1970, and currently has 1240 patients enrolled in its registry. www.uhnres.utoronto.ca/studies/cpsrd



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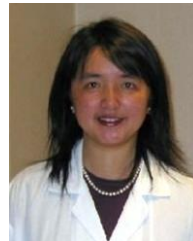
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The AARC Foundation

For over 10 years the AARC Foundation has been working to raise funds to beat arthritis and autoimmune diseases through the unparalleled research taking place at the University Health Network.

In 2010, The Public Health Agency of Canada issued a report titled *Life with Arthritis in Canada: A personal and public health challenge*. This highlighted that over 4.2 million Canadians are battling arthritis and the estimated annual healthcare system cost in 2008 was a staggering \$7.7B. Surprisingly, and not well understood, is the fact that nearly 3 in 5 people with arthritis are under the age of 65; and over 25% of men and women between the ages of 25-44 are out of the labour force due to their condition. With the aging population in Canada, these numbers are expected to dramatically increase. It is therefore vitally important to increase investment in research now to reduce the financial burden of arthritis and help Canadians live better, more productive lives.

The Foundation is meant to be part of the solution. We provide support to all elements of research at UHN – from basic research, to clinical trials, to initiatives to understand how these diseases affect people in their everyday lives.

The Power of Movement Yoga Challenge to Beat Arthritis was staged across Canada, and this year we partnered with the Canadian Arthritis Network. Abbott Laboratories continued to be a generous supporter, and we successfully raised funds for research while also building significant awareness around the message that movement can have a positive impact on the lives of people living with these conditions.

The Foundation is pleased to offer Awards to help scientists further their research. In 2010 the annual Dunlop Challenge Research Grant was awarded to Dr. Stuart Berger for his project titled “Novel Strategy for Boosting Antibody Expression.” It is exploring the possibility of producing a biologic-based therapy more efficiently or cost effectively, thus potentially allowing more patients access to these new treatments. This year the CIBC New Scientist Award will have completed its first three year term with the recipient Dr. Carol Landolt-Marticorena having focused her research on renal disease in patients with Lupus. Over the next year we will be selecting another candidate for these and other Awards.

The T. Robert Beamish Family Convergence Centre continues to grow. In order to continue as leaders, it is critical to evolve, adding new components, fostering new relationships and acquiring new technologies. 2010 saw a number of new initiatives that will ensure that the Convergence Centre continues to be forerunners in the study of disease.

Through the unparalleled relationships amongst and between its basic, translational, clinical, surgical and population health scientists the AARC is not only a national resource but an important partner in international arthritis collaborations. This is an enviable position and one with which the Foundation is honoured to be associated.

Our donors represent patients and their families, visionary philanthropists and corporate partners. We thank each of them for believing that one day we will beat arthritis, and for allowing us to be part of the success.



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Research Developments

Lupus: How the Immune System Attacks the Body's Own Cells

Systemic lupus erythematosus, commonly referred to as lupus or SLE, is a chronic autoimmune disorder characterized by production of “antinuclear antibodies” (ANAs), which are involved in harmful immune responses against the body's own cells. It remains unclear, however, how the immune system loses its “tolerance” to the body's own cells in lupus patients and begins production of ANAs to attack them. A recent study by AARC researcher Dr. Joan Wither and colleagues found that a protein called B cell activating factor (BAFF) acts in concert with the immune system's T cells to trigger an autoimmune response leading to ANA production.

Explains Dr. Wither, “Although increased levels of BAFF in the bloodstream are seen in some lupus patients, many patients have little or no elevation of BAFF levels. However, it is likely that our findings are relevant to the disease, because we found that even modest increases in BAFF levels are sufficient to disrupt regulation of the immune system. Thus, BAFF may represent a key target for therapeutic intervention in lupus.”

PloS ONE 201, 5, e11691

Protective Effects of Antimalarials in Lupus

Patients with systemic lupus erythematosus (SLE) have an increased risk of hypertension and thrombovascular events (TEs). Findings from AARC researcher Dr. Paul Fortin, in collaboration with Drs. Dafna Gladman and Murray Urowitz, confirm that administration of the antimalarial drug hydroxychloroquine to patients with SLE reduces the risk of TEs by 68%.

This group took a closer look at patients diagnosed with SLE between 1970 and 2004 and matched patients according to year of diagnosis and severity of disease. This approach helped to clarify whether exposure to antimalarial drugs was associated with a decrease in TEs and not a product of changing patterns of medication usage. Overall, the use of antimalarials reduced the risk of arterial and venous TEs by 66% and 74%, respectively.

“For patients with SLE, we have identified older age and ever having hypertension as being associated with an increased risk of TEs,” says Dr. Fortin. “Our data support the wide and prolonged use of hydroxychloroquine for the treatment of patients with SLE who do not have any contraindication to treatment with antimalarials. Future studies will help determine what the maximum duration of treatment with antimalarial drugs should be, as well as the side effects of prolonged use.”

Arthritis & Rheumatism. 2010, 62(3), 863-868



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Monitoring Heart Disease Risk in Lupus Patients

New evidence from AARC researcher Dr. Murray Urowitz highlights the variability of cholesterol and blood pressure (BP) in patients with systemic lupus erythematosus (lupus, or SLE)—an autoimmune disease affecting the body's connective tissue resulting in damage to internal organs, joints and skin.

Sampling over 26,000 measurements of total cholesterol (TC), systolic and diastolic BP (SBP and DBP) from greater than 1,200 patients over a nine-year follow-up period, the study determined that over time, 64.7% of patients varied between having normal and elevated cholesterol levels, while 46.4% of patients varied between having normal or abnormally high BP, emphasizing the need for vigilant monitoring of lipid levels during active disease and treatment with corticosteroids.

"This study bears significant clinical importance because patients with SLE are at an increased risk of coronary artery disease (CAD), and understanding how the levels of TC and BP change over time will greatly assist medical teams to better understand risk factors and improve patient care," explains Dr. Urowitz.

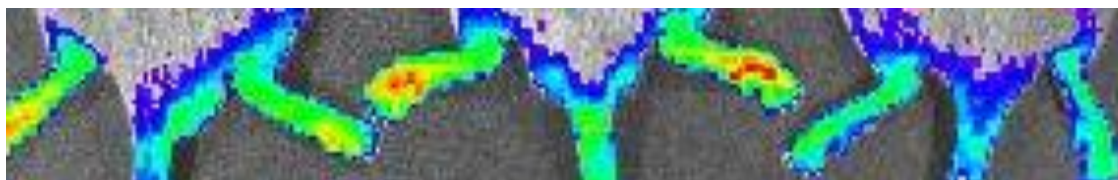
"Other independent factors related to TC and BP were smoking and hormone replacement therapy," says Dr. Urowitz. "We have provided strong evidence showing the important concept of TC and BP variability over time, which makes a strong case for finding summary measure that better capture cumulative exposure to these risk factors over time. Future studies will works towards an even greater in-depth understanding of the complex relationship between various CAD risk factors in SLE."

Arthritis Research & Therapy. 2010, 12(3), R125.

Arthritis: Imaging Inflammation

Ongoing studies in Dr. Eleanor Fish's research group focus on using novel high resolution imaging techniques to identify the earliest tissue damage in joints affected by arthritis. Recently, Dr. Fish's team identified a rare population of stem cells in the blood of patients with arthritis that migrates to joints and contributes to disease onset. Moving between studying blood specimens from patients afflicted with arthritis and mouse models of the disease, Dr. Fish's team discovered that these stem cells move from the blood to joints even before clinical symptoms of arthritis appear. In collaboration with Dr. David Jaffray and the state-of-the-art STTARR facility, Dr. Fish's team are using innovative high resolution imaging of these cells to investigate their relationship to tissue damage and the spread of disease from one affected joint to the next. The novelty of this imaging approach is that these stem cells move to joints and may set up disease even before the first signs of swelling and joint destruction that are traditionally recorded by X-ray, MRI or CT.

"We anticipate that this technology will allow us to image inflammation in the very earliest stages of arthritis – before the disease is established, thereby allowing us to intervene with therapies that will prevent joint destruction," says Dr. Fish. "This imaging technology is transformative."



Mouse with arthritis

Arthritis + Fibrocytes

Healthy mouse

High resolution fluorescent images of circulating stem cells that contribute to disease onset: the red fluorescent cells are located in areas of swelling and joint disability. The LH panel shows the paws of a mouse with arthritis. The middle panel shows the paws of a mouse injected with these stem cells – leading to a more aggravated arthritis.

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Advances in New Therapeutics

In the past 12 years novel therapies have dramatically improved the quality of life of patients with rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis. These therapies have substantially improved symptoms, reducing joint destruction and disability. One of the new therapies evaluated in clinical trials of RA patients, Golimumab, demonstrated similar effectiveness with an ability to reduce the frequency of administration (by injections under the skin from once weekly or every 2 weeks to once per month). The study, by AARC researcher Dr. Ed Keystone, was one of the pivotal trials leading to the approval and availability of Golimumab to all Canadians with RA as well as psoriatic arthritis and ankylosing spondylitis.

Annals of the Rheumatic Diseases. 2010, 69, 1129-1135

New Genetic Risk Factors



Dr. Katherine Siminovitch

The current understanding of the genetic basis of rheumatoid arthritis (RA), an autoimmune disease affecting up to 1% of adults, only explains a small portion of cases. A world-wide collaboration, involving Dr. Katherine Siminovitch, has identified seven new RA-linked genes allowing researchers to better understand the nature of this disease.

They examined genetic risk factors in an initial set of 5,539 cases and in a second set of 6,768 RA cases. Six of the new genetic factors implicated in this study were found to be involved in known immune function. Some of the discovered genetics factors have been previously characterized as components of inflammation, providing further insight into the development of RA. Other genetic factors discovered were previously linked to other autoimmune diseases, including genes involved in systemic lupus erythematosus, Crohn's disease and type I diabetes.

Nature Genetics. 2010. 42(6), 508-514

Rheumatology Information Program

AARC researcher Dr. Claire Bombardier was involved in the establishment of the Electronic Rheumatology (E-Rheum) Program. E-Rheum integrates data collected from computer administered patient questionnaires and clinical data of patients with RA with information from previous visits, resulting in the immediate presentation of a summary report available at the point-of-care. The success of this project will increase the effectiveness and efficiency of rheumatology care across Canada by providing patients and their rheumatologists with an easy tool for monitoring disease activity and response to treatment.

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Boosting Protein Expression for Biological Based Therapies

Treatment of RA through biologics, antibodies and vaccines created through biological process rather than chemical synthesization, is effective in reducing disease symptoms and slowing progression in patients. However the high cost of production and low yield of antibodies are a major limitation in expanding the use of biologics. The work of AARC member Dr. Stuart Berger has focused on new ways of improving production biologics for the treatment of RA.

By modifying antibody-producing cells to over-express ABC50, a gene which is known to be involved in protein production, they were able increase the amount of antibodies produced. "We are currently working on how to apply this strategy to increase antibody production under industrial scale conditions," says Dr. Berger "This discovery may directly benefit patient diagnosis and care by reducing the costs associated with biologic therapy."

Workplace Measures of Impact on Productivity

AARC researchers, including Drs. Monique Gignac and Claire Bombardier, continue to be involved in international efforts to measure the impact of arthritis on employment and to design and evaluate workplace productivity outcomes. Research from this group has evaluated a number of workplace measures, including assessing their ability to measure the personal and economic impact of living with arthritis.

"Arthritis-related disability at work may result in substantial productivity losses that can be two to four times the direct health care costs of managing the disease. It is critical to have comprehensive measures that can assess the impact of arthritis on employment and that can support the development of interventions to help people with arthritis remain working." Dr. Monique Gignac.

Journal of Rheumatology. 2010, 37, 1805-14. Arthritis Care & Research, 2010, 62:28-37

Better Strategies for Patient Care

One of the challenges with new therapies for rheumatoid arthritis is the slow onset of disease and the high cost of therapy (~\$20,000 per year). Knowing how long to continue the medication before determining its effectiveness is important in terms of reducing the duration of suffering but also to the continued cost with no prospect of further improvement. As such, it is essential to establish a time period during which the effectiveness of a given medication will be assessed for its ability to reduce symptoms of the disease. This evaluation will help determine whether a change in medication is required, ultimately leading to this discontinuation of ineffective therapies, a reduction in patient suffering, and an overall decrease in the cost of therapy.

By analyzing the effectiveness of these treatments over a period of three months of a given therapy, Dr. Ed Keystone determined that rheumatologists can predict whether the patient will ultimately have substantial benefit from the treatment. If little improvement is observed within three months of treatment, one could predict with certainty that the medication should be discontinued and a new therapy would be initiated.

"Clearly, this knowledge will reduce prolonged symptoms and decrease direct medical costs of administering a medication that is unlikely to be effective over the long-term." Dr. Ed Keystone.

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Cholesterol Lowering Drugs and Arthritis

In RA the space between joints is invaded with immune cells who recruit another cell type called fibroblast-like synoviocytes (FLS). These FLS cells contribute to joint damage through secretion of cartilage-damaging enzymes. Dr. Stuart Berger has identified that a group of drugs used to lower cholesterol levels (statins) also show an additional effect of modulation FLS cells and reducing their activity.

"We have recently obtained evidence that statins interfere with key intracellular protein degradation pathways that contribute to RA FLS viability. These ongoing studies are therefore providing important insight into the complex web of effects associated with statins in these cells," Dr. Berger.

Establishment of a Vasculitis Network

AARC research, Dr. Simon Carette, launched the Canadian Vasculitis Network (CanVasc) in the fall of 2010. This nationwide network was created to improve research and care for vasculitis, an inflammatory disease affecting blood vessels.

The network established four main objectives: 1. To organize a dedicated health and research network with identification of referral centers across Canada for patients with vasculitis. 2. To initiate, conduct, and promote studies on vasculitides across Canada, using an efficient, established and rapidly mobilisable network. 3. To develop educational and awareness programs for health care providers. 4. To serve as the foremost Canadian referral group to identify needs in vasculitis and consider new drug approvals for vasculitis in Canada.



Gene Involvement in Primary Biliary Cirrhosis



Findings from the laboratory of Dr. Katherine Siminovitch confirm that genes involved in primary biliary cirrhosis (PBC) have genetic overlap in other autoimmune diseases commonly found in patients with PBC and their families.

Building upon a previous study conducted in 2009 and published in the *New England Journal of Medicine*, the team conducted genetic tests on over 1300 individuals with PBC and 1800 non-PBC patients to identify potential risk loci, or genetic areas of disease susceptibility. Specifically, findings show that genetic risk or 'hot spots' for PBC are genes located in an area that is also involved in the development of systemic lupus erythematosus, systemic sclerosis and Sjögrens syndrome. Similarly, a second region of interest shows increased PBC susceptibility and is associated with asthma, Crohn's disease and type 1 diabetes.

"Importantly, our studies have helped to identify three new genetic risk locations, including MMEL1, which has been associated with a risk for the development of rheumatoid arthritis and celiac disease," explains Dr. Siminovitch. "We have provided important new evidence that demonstrates there are several shared autoimmune susceptibility loci that contribute to the frequent appearance of additional autoimmune diseases."

Nature Genetics. 2010, 42(8), 655-7.

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2010 Activity Report

Inflammation and Back Pain

While lower back pain is a common ailment affecting 60-80% of the adult population over a lifetime, the involvement of inflammatory diseases and joint disorders have not been fully examined. AARC member Dr. Robert Inman examined how sacroiliac joint (SI) disease, a condition characterized by inflammation and degeneration of the major joint of the pelvis, contributes to lower back pain. Because lower back pain patients are often seen by chiropractors and physicians, the involvement of inflammation in this condition has not been fully explored.



Dr. Robert Inman

Dr. Inman's group examined images of the lumbar spine and anteroposterior pelvis of 315 patients suffering from lower back pain to determine if their pain coincided with SI disease. They observed that 24% of lower back pain patients suffered from degenerative changes of the SI joint and another 8% had inflammation of the SI joint. The gender of the patient also plays a role in the involvement of SI disease with lower back pain: 68% of cases with SI joint degeneration occurred in women while 63% of inflammation cases were in men.

"Degenerative change of the SI joint is an under-recognized clinical feature that contributed significantly to the findings of back pain," states Dr. Robert Inman.

Arthritis Care & Research. 2010, 62(4), 447-454.

Therapy: Using the Immune System to Treat Arthritis

The use of cells involved in regulating the immune system towards the treatment of autoimmune diseases has gained considerable interest in recent years. Dendritic cells (DCs) serve as a gatekeeper for controlling immunity. In conditions where tissue damage occurs, DCs activate the immune cells (T cells) involved in inflammation. By manipulating DCs to perform their opposite function, Dr. Robert Inman has engineered DCs that suppress the onset of rheumatoid arthritis (RA), an autoimmune disease where the inappropriate activity of T cells contributes to the progression of this condition.

Building on the findings of previous studies, the researchers turned off a number of genes in DCs shown to be involved in immune function (CD40, CD80 and CD86), giving the cells an immunosuppressive function. Using a mouse model of RA, treatment with modified DCs decreased the T cell response and led to an overall reduction in the development of the disease.

States Dr. Inman, "The results of our study support the use of gene manipulation in DCs to generate tailor-made immunosuppressive vaccines to treat autoimmunity."

The Journal of Immunology. 2010, 184(11), 6457-6464

In a concurrent study, Dr. Inman examined the therapeutic effect of treating their mouse model of RA with a drug that reduced levels of the protein CD40. As depletion of CD40 in DCs created an immunosuppressive state, they treated mice with their drug and were able to prevent development of RA.

"We have demonstrated a simple and easy method to selectively inhibit disease progression. The possibility of using such methods of immune modulation may be a more natural and easily tolerated means of treating autoimmune disease," explains Dr. Inman.

Arthritis Research & Therapy. 2010, 12(1), R13

Arthritis and Autoimmunity Research Centre

2010 Activity Report

Clinical Trials: Safer Dosage for Drug Treatment of Ankylosing Spondylitis



Dr. Robert Inman has investigated a new drug treatment for ankylosing spondylitis (AS) through a clinical trial examining a lower and safer dosage in AS patients. The drug, infliximab (IFX), is a synthetic antibody that targets tumour necrosis factor- α , which is known to be elevated at sites of inflammation in AS patients.

Dr. Inman explains, "IFX-treated patients showed significant improvement in measures of disease activity, pain, inflammation, and quality of life over the course of the study. The low dose IFX was effective in reducing the signs and symptoms of active AS, and was generally safe and well tolerated."

Journal of Rheumatology. 2010, 37(6), 1203-1210

New Set of Linked Genes Associated with Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a long-term disease that causes inflammation of the joints between the spinal bones and between the spine and pelvis, eventually causing the affected spinal bones to join together. However, exactly how AS develops is not completely understood. Recently ERAP1, a gene encoding a protein involved in blood pressure regulation, was shown to be associated with the disease. Surprisingly, ERAP2, which is functionally and structurally similar to ERAP1, is by itself not associated with AS. However, in a study involving 199 Caucasian families with AS, Drs. Florence Tsui, Robert Inman and colleagues found that mutations in ERAP1 and ERAP2 together are linked with the development of AS.

"Our work identifies an AS-associated ERAP1 ERAP2 grouping, which provides a framework for future studies of genes linked to susceptibility for familial AS," suggests Dr. Florence Tsui.

Annals of the Rheumatic Diseases. 2010, 69, 733-6

Arthritis and Autoimmunity Research Centre

2010 Activity Report

Common Risk Factors in Autoimmune Disease

While the genetic basis of autoimmune diseases is commonly accepted, the identity of the genes involved in these diseases remains a mystery. Ankylosing spondylitis (AS) is a common inflammatory arthritis that affects the pelvis and spine. Other autoimmune diseases like Crohn's disease frequently occur within families and individuals affected by AS. The labs of Drs. Dafna Gladman and Robert Inman were involved in a multi-national study examining genetic factors common to these diseases.

Examination of genetics profiles in a set of 2,773 patients revealed variations in two different genetic regions that overlapped in AS and Crohn's disease. The first region contained a gene, *KIF21B*, a member of a family of genes previously identified as being associated with rheumatoid arthritis, type 1 diabetes and multiple sclerosis. The second variation was found in another gene, *STAT3*, known to mediate immune function.



"These findings suggest common pathways for AS and Crohn's disease and further highlight the involvement of common risk variants among multiple autoimmune diseases."—Dr. Gladman

PLoS Genetics. 6 (12).2011

Research Activity



2010 Publication Activity Snapshot

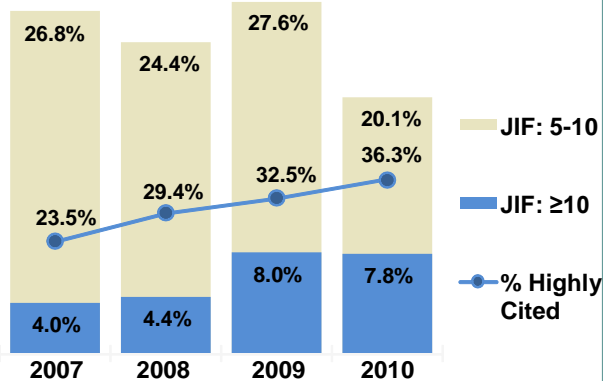
Publication and citation data for AARC investigators reflect articles and reviews indexed in Thomson Scientific electronic resources (Web of Science, Journal Citation Reports, and the Essential Science Indicators).

2007-2010 publication activity

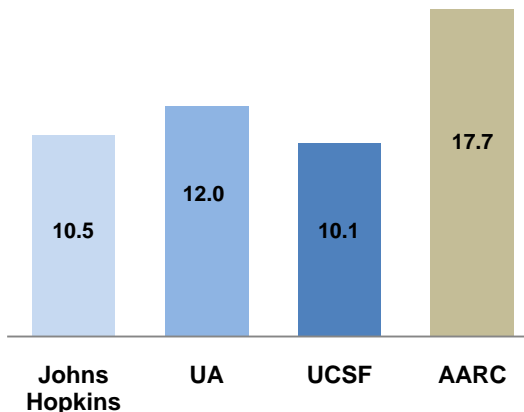
- 617 publications (almost 18 per investigator)
- 41 in top journals, an additional 165 in higher-impact journals.
- 31% of papers are amongst the top 10% most highly-cited.

AARC Investigators published more papers and were more cited than high-impact peer groups and have increasing proportions of high-impact papers.

AARC Top Papers



Papers per Investigators



Citation: The number of times a work is referenced or used by others indicates its impact on a body of knowledge. Citations accumulate over time and rates vary considerably by subject area.

Journal Impact Factor scores indicate the relative citation impact of the journal and is extremely variable by field.

High-impact journals, represent <2% of all journals, score 10 or more, indicating papers receive an average of 10 cites within their first 2 years of publication. **Higher-impact journals**, represent <4% of all journals, score between 5 and 10.

Highly-cited paper: Papers with a citation count placing it amongst the top 10% of papers published in the year and subject-area. High-impact groups commonly have 20%-25% of papers achieving this standing.

Arthritis and Autoimmunity Research Centre

2010 Activity Report

Top Papers Spotlight

Though hundreds of thousands of papers are published each year, few emerge to influence the direction of peers' research. The number of times a publication is used or cited by another indicates its impact. A small proportion can achieve the standing of "high-impact" papers. The following highlights AARC investigators' high-impact works from 2010.

Top 0.10%

Dr. Katherine Siminovitch authored "Variants at *IRF5-TNPO3*, 17q12-21 and *MMEL1* are associated with primary biliary cirrhosis" which appeared in *Nature Genetics*.

Abstract:

We genotyped individuals with primary biliary cirrhosis and unaffected controls for suggestive risk loci (genome-wide association $P < 1 \times 10^{-4}$) identified in a previous genome-wide association study. Combined analysis of the genome-wide association and replication datasets identified *IRF5-TNPO3* (combined $P = 8.66 \times 10^{-13}$), 17q12-21 (combined $P = 3.50 \times 10^{-13}$) and *MMEL1* (combined $P = 3.15 \times 10^{-8}$) as new primary biliary cirrhosis susceptibility loci. Fine-mapping studies showed that a single variant accounts for the *IRF5-TNPO3* association. As these loci are implicated in other autoimmune conditions, these findings confirm genetic overlap among such diseases.

Dr. Siminovitch also co-authored "Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci." which appeared in *Nature Genetics*.

Top 1% papers

The following papers are in the 99th percentile based on citations to date.

Drs. P Fortin, D. Gladman and M Urowitz were co-authors of "The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus" published in *Arthritis & Rheumatism*.

Dr. R Inman was lead author on "A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis", published in the *Journal of Rheumatology*. He was also co-author for "RNAi-mediated CD40-CD154 interruption promotes tolerance in autoimmune arthritis", published in *Arthritis Research & Therapy* and "Treatment of autoimmune arthritis using RNA interference-modulated dendritic cells", in the *Journal of Immunology*.

Dr. F Tsui was a co-author on "Serum cytokine receptors in ankylosing spondylitis: relationship to inflammatory markers and endoplasmic reticulum aminopeptidase polymorphisms", published in the *Journal of Rheumatology*.

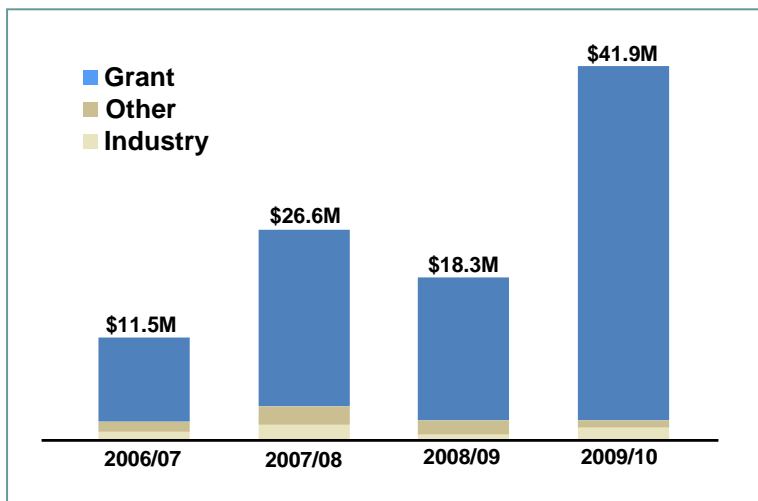
Dr. M Gignac was co-author on "Productivity loss due to presenteeism among patients with arthritis: estimates from 4 instruments", published in the *Journal of Rheumatology*.

Drs. C Bombardier, M Gignac and E Badley were co-authors of "Reliability, validity, and responsiveness of five at-work productivity measures in patients with rheumatoid arthritis or osteoarthritis", published in *Arthritis Care & Research*.

Arthritis and Autoimmunity Research Centre

2010 Activity Report

Active Research and Awards



Each year AARC investigators pursue funding for research involved in laboratory settings or directly with patients through financial grants or awards. Sources for research funding include governmental granting agencies, foundations, industry partners.

The work of the 38 AARC investigators in 2009/2010 has led to a 230% increase in funding from the previous year. In particular, 30% of funding received from the 2009/2010 period came from a substantial Canadian Foundation for Innovation infrastructure grant.

