

# BRASS

BRIGHAM AND WOMEN'S HOSPITAL RHEUMATOID ARTHRITIS SEQUENTIAL STUDY

Volume 1, Issue 2

Funded with the Generous Support of Millennium

July 2005

## AND 900 IT IS: A BIG 'THANK YOU' FROM THE DIRECTORS

We hit our goal and enrolled our 900th patient in March. Without your generous donation of time it would not have been possible. Thank you.

We will continue to recruit new patients. Reaching 900 enables us to carry out meaningful studies on our data and assess trends from analysis of your blood. The study will continue for at least

another three years, and we look forward to seeing you each year at your follow-ups. We have started presenting preliminary findings from the study at rheumatology conferences around the world. You can read more about where and what we presented on page two. We thank you for dedicating your time to

research that will hopefully begin to answer some of the remaining questions about RA. We are embarking on an exploration of the world of personalized medicine that will one day enable doctors to customize treatment with one peek at a person's genetic make-up.

- Dr. Nancy Shadick
- Dr. Michael Weinblatt

### Our Statistics:

Patients enrolled: 908

Patients at one-year follow-up: 540

Patients at two-year follow-up: 115

### Some useful RA resources:

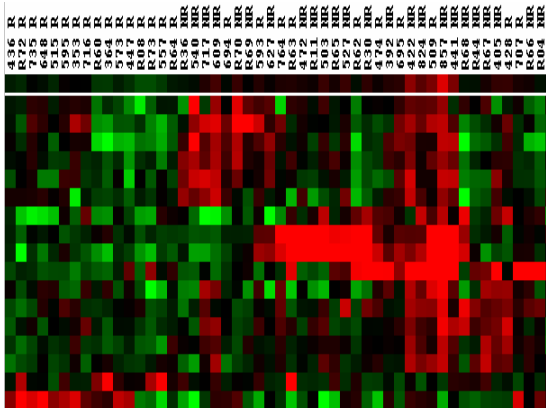
The Arthritis Foundation website, [www.arthritis.org](http://www.arthritis.org), has general information about rheumatic disease, as well as specific RA-related news. You can search the website for the Massachusetts chapter to get local information.

The Brigham Arthritis Center has a website with information about doctors and treatments at [www.brighamandwomens.org/arthritis](http://www.brighamandwomens.org/arthritis).

## RA GENES: ARE YOUR CHILDREN AT RISK?

Rheumatoid Arthritis, like many autoimmune diseases, has a genetic component. But so do most things these days. What does this really mean for your family?

Your children are more likely to develop RA than the general population. Your family probably has a general susceptibility to autoimmune disorders (when the body mediates an immune attack against its own cells either systemically, as in lupus, or against a particular group of cells, as in the beta cells of the pancreas in Type I diabetes). You may have an aunt with autoimmune thyroid disease, a mother with inflammatory bowel disease and a son with diabetes. Studies have



Gene Chip: Predicting response from your genetic picture

indicated that there is a differentiate between what is common genetic pathway part of it and what comes from a foreign attacker. The HLA has thousands of different alleles (sequences of genes that together produce a certain trait) at different locations. Several of these alleles are significantly associated with development of RA, while others have been found to be associated with other autoimmune or inflammatory diseases. Our study—in addition to examining clinical trends across the various symptoms you have described to us—is looking at this genetic component, trying to determine which parts of the genes might be associated with reactions to particular arthritis drugs. A certain location, for example, on the Human Leukocyte Antigen (HLA) that helps your body to

(Continued on page 4)

### *What you recommend for pain and flares:*

66% of you had a flare in the last six months. 35% used a new medication to treat the flare, and 40% increased current medications.

In addition to medication, many of you use heat, cold packs or steam to treat your pain. Hot tubs and pools are particularly popular. Several of you tried chiropractors, acupuncture or Chinese healing arts. For some of you, exercise helps relieve the discomfort of a flare, while others say rest and sleep are important.



## THE TRAIL OF BLOOD: HOW WE PUT YOUR TUBES TO USE

**Laboratory procedure:** Immediately after we draw your blood, some of it goes to labs in the hospital and some travels with our courier, Adam, over to Cambridge for analysis at the labs of our partner Millennium Pharmaceuticals. We test for a variety of components, including indicators of inflammation, genetic material like RNA and DNA and certain proteins that serve as markers on the surface of cells.

**Analysis:** We receive and log in the results. They are entered anonymously and compiled. We can then perform statistical analysis to determine trends.

**Presentations and research:** Your data has made its way around the globe this year. In April, Dr. Shadick traveled to

Nice, France to describe the registry and some preliminary findings to a distinguished group of RA researchers from around the world. Last fall, our doctors presented initial genetic and clinical findings from the registry to fellow rheumatologists at the American College of Rheumatology (ACR) conference in San Antonio, Texas. Academic researchers and pharmaceutical companies around the country have expressed interest in collaborating with the registry. We're working on articles for several rheumatology publications, as well as presentations for next fall's ACR conference in San Diego.

We'll let you know when results are published. Feel free to call us or ask one of the research assistants in the clinic for more information.

## WHAT YOU WANTED TO KNOW ABOUT YOUR HEALTH

Many of you have been asking whether herbal remedies, acupuncture and exercise can relieve your arthritis. There are no definitive answers unfortunately, but here is the latest word from the medical community.

### **Herbal supplements:**

Multivitamins and calcium supplements are certainly important for good health, especially in RA patients who may be at risk for osteoporosis due to the medications they take. Data on herbal supplements is less definitive. Recent reviews of studies conducted in the United Kingdom and the United States testing the effectiveness of herbal supplements found that devil's claw, glucosamine and chondroitin were effective in relieving pain of osteoarthritis; for RA, they pointed to the anti-inflammatory gamma-linolenic acid, and evening primrose oil as potentially

For more information :

—*Selected CAM therapies for arthritis-related pain.* Clin J Pain. 2004;20(1):13-8.

—*Supplementation of fish oil and olive oil in patients with RA.* Nutrition. 2005;21(2):131-6.

—June 2, 2005 issue of Arthritis & Rheumatism.

effective in controlling some symptoms. Gamma-linolenic acid is an essential fatty acid found mainly in plant oils that cannot be produced by the body. While many hypothesize that glucosamine and chondroitin may be beneficial for RA patients, there is no conclusive evidence. Studies have shown that pain and fatigue improved modestly in RA patients who took several grams a day of fish oil omega-3 fatty acid, which acts as an anti-inflammatory and thus can reduce the need for NSAID medications like ibuprofen or naproxen; it seems that particular acids in fish oil—eicosapentaenoic acid and docosahexaenoic acid—are responsible for the beneficial effects.

**Acupuncture and Massage:** A UK review found that acupuncture might have some promise in relieving back pain and certain osteoarthritis pain, especially of the knee. But there is no research pointing to specific benefits for RA patients. Similarly, massage may show some promise for relief of certain kinds of backaches and RA-related pain.

**Exercise:** Exercise therapy can be effective for a variety of chronic disorders, both as a psychological outlet and to control physical pain. A recent study of 25 patients followed for 15 weeks found that people who exercise more had less fatigue and greater hand grip. Weight-bearing exercise may slow the progression of osteoporosis. Recent studies, however, have also shown that high intensity, weight-bearing exercise in patients who have joint damage can accelerate damage progression. You should discuss your exercise program with your doctor and find the right combination of rest and exercise for you.

## BRASS RESEARCH MAKES HEADLINES OVER THE YEAR

The BRASS group presented these abstracts at the American College of Rheumatology conference last fall. They were published in the *Arthritis & Rheumatism* supplement. If this all sounds like Greek to you (it should unless you're in the health field!), please ask for explanations if you're interested.

1. Discovery and validation of multidimensional biomarker sets in a large single-site Rheumatoid Arthritis patient registry
2. Determinants of DMARD medication change in Rheumatoid Arthritis: The effect of physician-patient agreement and measures of disease activity
3. Dietary caffeine intake and methotrexate efficacy in Rheumatoid Arthritis
4. Retrospective genetic analysis of efficacy and adverse events in a Rheumatoid Arthritis population treated with methotrexate and anti-TNF- $\alpha$
5. Serological biomarkers that correlate with ACR response criteria in RA
6. Genetic polymorphisms contribute to clinical markers as predictors of DAS remission in patients with Rheumatoid Arthritis
7. Rheumatoid Arthritis as a polygenic trait: Multiple gene x gene and gene x gender interactions influence disease risk and age at onset
8. Analysis of RA symptom severity using transcriptional profiling and genetics
9. Clinical and genetic variables associated with disease severity and risk correlate with radiographic changes in a cohort of subjects with RA

## THE PLAYERS: PROFILES OF KEY MEMBERS OF THE TEAM

### Drs. Nancy Shadick and Michael Weinblatt, BRASS Co-directors

Dr. Nancy Shadick, one of the lead investigators on the study, has been at Brigham's Arthritis Center for 12 years. She divides her time between research, seeing patients and teaching aspiring doctors. She is an epidemiologist and health services researcher and sees patients with lupus and other bone and joint diseases. Before BRASS, she worked on several large Lyme disease research studies with thousands of subjects on Martha's Vineyard and Nantucket, and has published on lupus, RA and Lyme disease.



Dr. Shadick attended New York University for medical school and did her residency at Columbia—also her undergraduate alma mater. She is originally from New York.

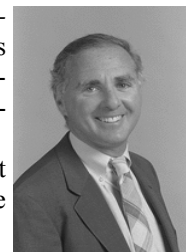
She lives with her husband, an infectious disease doctor at the University of Massachusetts, her two young children and her cat, Mittens.

Dr. Michael E. Weinblatt, the Co-Director of Clinical Rheumatology, has been at the Brigham for 26 years. His major research interest is therapeutic interventions in RA, and he has published over 130 articles and reviews, primarily focusing on RA.

In 1997, he received the Arthritis Foundation Virginia P. Engalitcheff Award for Impact on Quality of Life for work on methotrexate. In 2005, he received the

Carol Nachman Prize for his work on the development of methotrexate therapy for RA. He served as an Associate Editor of *Arthritis and Rheumatism*. In 2001, he was president of the American College of Rheumatology.

He is an avid cyclist and is cycling across the U.S. for the second time.



### The Project Manager

Nancy Maher, the team's project manager, has worked with Dr. Shadick for almost four years. She came to us from Boston University where she was researching the genetics of Parkinson's disease—and where she received her Masters of Public Health.

She has a particular interest in RA genes and the genetic overlap with other autoimmune diseases.

Ms. Maher is a native of Peabody and the mother of three grown boys. The youngest is headed to college, the oldest works for the Secret Service and her middle son wrestles in Japan.

### The Team Statistician

Lori Chibnik, the team statistician, is analyzing the trends in our research. She is currently studying for her Ph.D in biostatistics at Boston University, where she received a Masters of Public Health in biostatistics and international health.

Before coming to Boston, Ms. Chibnik was a volunteer with the Peace Corps in Moldova (in the former Soviet Union), where she taught health education and started a camp for girls. She speaks Romanian and Hebrew and is working on learning Finnish.

Ms. Chibnik lives with her two cats—one from Chicago and the other from Moldova.

## DISCOVERING NEW ARTHRITIS DRUGS

Although science has made great strides in finding new treatments for RA, we still have no cure and only imperfect control for most patients. The process of drug discovery is a long, complicated, and expensive one, with an average cost of nearly \$1 billion for each new drug approved by the Food and Drug Administration and an average time of 12 years from discovering the molecule behind its success to getting FDA approval.

Even more daunting, the failure rate is about 92%, so fewer than 1 in 10 drugs that start the trip make it to the end! That's where you come in—by participating in the BRASS study, you are helping to cut the costs and time needed to get

new drugs to patients. Our best hope for shortening this process is to find better tests—biomarkers—that tell investigators whether a drug is working or not.

We don't actually mind a negative answer, if we can get it quickly—in one to two years—and for “only” a few million dollars instead of 12 years and a billion dollars!

That's why Millennium Pharmaceuticals, a leading biopharmaceutical company based in Cambridge, has invested time, scientific expertise and millions of dollars to help make the BRASS registry the world's premier source of biomarker information for RA.

—Millennium Pharmaceuticals

## WORKING THROUGH THE FATIGUE

Recent studies have identified fatigue as one of the most challenging manifestations of RA and perhaps the best indicator of how active your disease is. Between 50% and 80% of RA patients suffer from significant fatigue. Most describe it as a heavy, draining loss of energy that can make even getting up to dress in the morning an ordeal. Greater levels of fatigue often result from increased pain and may lead to periods of depression.

Fatigue may indicate a flare in disease activity. Inflammation, caused in part by increased levels of chemicals called cytokines, is thought to be one of the major arthritis-related causes of fatigue. But there are also many other disease-related factors that may make you feel unusually tired.

Other physical factors inducing fatigue could be anemia (low levels of iron-containing, oxygen-carrying molecules in your blood), hypothyroidism (low levels of the hormone produced by the endocrine

gland at the base of your neck) or other hormone irregularities. RA patients are more susceptible to these problems and may also be more at risk of developing fibromyalgia, a nerve-related autoimmune disorder that causes significant fatigue. In addition, poor sleep or nutrition and significant pain can contribute to fatigue.

Studies have reported that the fatigue of RA seems to be readily treatable with exercise and a little bit of planning. Some tips for reducing fatigue?

1. Check with your doctor for blood tests to eliminate causes such as anemia or hypothyroidism.
2. Try to get consistent and uninterrupted sleep (same number of hours). Long-term use of prescription sleep medications results in lower quality sleep so try to use natural means to promote good sleep habits.
3. Keep the pain under control—pain can be draining.
4. Try to set aside time to do some activities that you find less stressful.
5. Accept changes to your lifestyle. Realize that your day may be more productive if you allow yourself that extra hour of sleep.

For more information see:

—*Impact of fatigue on health-related quality of life in Rheumatoid Arthritis*. Arthritis Care and Research.;51(4):578-85.

—*Well-being in Rheumatoid Arthritis: The effects of disease duration and psychosocial factors*. J. Health Psychol. 2005;10(3): 457-74.

## GENETICS

(Continued from page 1)

HLA might be associated with a positive response to methotrexate and another with arava-induced lung problems.

We have found some general associations between certain genes and negative responses to methotrexate and anti-TNF drugs. We hope that, through the identification of these and other genes, someday RA patients will be able to walk into the

## PRIVACY

**HIPAA, the Health Insurance Portability and Accountability Act, was established under federal law on April 14, 2003 to protect the privacy of individual health care information. Before enrolling in BRASS, each of you read and signed the HIPAA regulations for our study that explained the precautions and protocol in place to protect your privacy. Some participants have expressed concern about who has access to information from questionnaires, blood tests and x-ray reports. Patients receive anonymous study identification numbers when they enroll in BRASS. Your names and personal information, therefore,**

### The BRASS Staff

Principal Investigators: Nancy

A. Shadick, MD, MPH; Michael E. Weinblatt, MD; and Michael B. Brenner, MD

Project Manager: Nancy E.

Maher, MPH

Statistician: Lori B. Chibnik, MPH

Research Assistants: Jessica A.

Bilics, BA; AnneMarie Boyd,

BS; Jenny E. Heller, MPhil;

Betsy Murphy, BA

Issue Editor: Jenny E. Heller