

# Rheumatology

## Biologics: Past, Present, and Future

There has been great progress in the past 15 years in new therapies for rheumatoid arthritis. There are now 4 TNF $\alpha$  inhibitors, as well as a T cell costimulation inhibitor, a B cell cytokine inhibitor, and a B cell depletion antibody approved by the FDA for therapy of RA. These new drugs are biologicals, that is, they are proteins or glycoproteins that are produced by live cells in vitro and purified from culture medium. They are expensive to produce and can cost patients or health care providers over \$15,000 per year of therapy. Thus these therapies are not available to many patients without adequate health care insurance. What does the future look like for RA therapy? Therapy with biologicals is likely to remain expensive, as drugs with new mechanisms of action will require extensive clinical testing before FDA approval, and older molecules have not been replaced by lower priced biogenerics. My goal as a scientist is to find new therapies that have more durable effects and require infrequent treatment.



During much of my career I have studied biological therapies. I was fortunate to help discover one of the RA therapies together with my colleagues at Bristol-Myers Squibb in 1990. We discovered that soluble CTLA4-Ig binds to antigen presenting cells (APC) and blocks costimulation of T cells. We published the results in JEM in 1991 (J. Exp. Med., 173:721-730, 1991). The recombinant human CTLA4-Ig that we made was later named Abatacept and was studied in multiple clinical trials by Bristol-Myers Squibb. Abatacept (brand name Orencia) was approved for therapy of RA in 2008.

In contrast to the rapid progress with new biological therapies for RA, progress has been slower for SLE. Only one biological, belimumab (Benlysta), that blocks a B cell survival signal, is FDA approved, while costimulation inhibitors Orencia and B cell depletion therapy (Rituxan) did not meet their end-points for approval in SLE. Other biologicals in clinical testing in SLE such as inhibitors of IFN $\alpha$  provide hope for future therapy.

One research program I am working on with Dr. Keith Elkon here in UW Rheumatology studies the potential of recombinant nuclease fusion proteins for therapy of SLE. These nuclease fusion proteins digest and destroy pathogenic immune complexes that stimulate production of IFN $\alpha$ , and show promising results in murine SLE models. Another research program studies the potential for CD40 inhibitors to promote tolerance in autoimmune models. I hope in the future to be able to help discover new drugs and approaches that will allow rheumatologists to think more about tolerance therapy, where short-term treatment is able to achieve long-term disease remission.

To read more about Dr. Ledbetter, please see Lara Foote's biography online: <http://depts.washington.edu/rheum/newsletter/ledbetter.html>

### Inside:

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## DR. SANDOVAL JOINS DIVISION

**Dr. David Sandoval** joined the Division of Rheumatology in October as Assistant Professor of Medicine. He moved from Spokane, WA.

**Dr. Sandoval** received his MD from San Marcos School of Medicine in Lima, Peru. After doing residency at St. John's Hospital in NY, he completed his Rheumatology fellowship at the University of Alabama-Birmingham.



**Dr. Sandoval** has been in private practice for the last 20 years. He brings significant experience into the Division. One of his passions is teaching and he is looking forward to contributing to the training of fellows, residents and students. Dr. Sandoval has participated in multiple clinical trials and plans to engage in research activities as well. Please join us in welcoming Dr. Sandoval to the Division.

## 2011 ACR ANNUAL MEETING

This year, the **2011 ACR** (American College of Rheumatology) **Annual Meeting** was held in **Chicago, IL** from November 5<sup>th</sup>-9<sup>th</sup>. Many of our faculty and fellows presented the following this year:



**Dr. Keith Elkon** gave an ACR Immunology update for clinicians on Apoptosis, Phagocytic Clearance and Autoimmune and Inflammatory Diseases.

**Dr. Greg Gardner** moderated the ACR review course, presented two workshops on Arthrocentesis, and moderated a session on Gout.

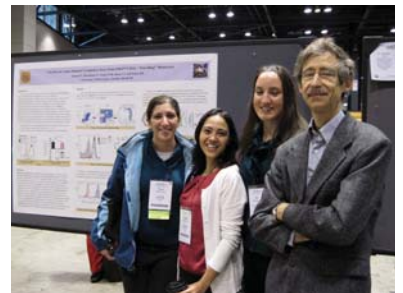
**Dr. Mary Bach** presented the following poster with **Dr. Gardner**: "Recalcitrant Orbital Inflammatory Disease Responsive to Treatment with Infliximab."

**Dr. Michael Cho**, recent graduate of the UW Rheumatology Fellowship Program, was lead author of a poster entitled "Sex-dependent modulation by progesterone of interferon-alpha induced gene expression in human leukocytes." **John Zheng**, senior

medical student at the UW was a contributing author. Through work in the lab of **Dr. Grant Hughes**, Dr. Cho and John Zheng showed how progesterone, a female sex steroid, can enhance the stimulatory effects of a key pathogenic cytokine in human SLE.

**Dr. Pradipta Ghosh**, Acting Instructor in the Division of Rheumatology, presented a poster at this year's meeting. She is a lead co-author on the poster entitled: "C1q Diverts Lupus Immune Complexes Away from CD14dimCD16+ "Patrolling" Monocytes." The authors of this poster highlight a novel way in which C1q may be modulating inflammation in lupus.

**Dr. Natalia Giltiy**, Acting Instructor in the Department of Immunology, is focused on the role of innate receptor TLR7 on the development of autoreactive B cells in murine lupus. This is a collaborative study between **Drs. Elkon and Clark labs**. Her presentation was part of the Dubois Lectureship to showcase lupus research.



*Authors: Natalia Giltiy, Nikita Kolhatkar, Xizhang Sun, Jinoh Kim, Matt Buechler, Jessica Hamerman, Edward Clark and Keith Elkon*

*Title: "TLR7 overexpression drives autoantigen-mediated expansion of transitional and follicular B cells independently of type I IFN signals"*



**Dr. Peter Simkin** is a co-author (with J Kushi, C Gohr, B Jubeck, and A Rosenthal) for the following presentation: "A novel method of basic calcium phosphate crystal quantification in synovial fluid using a tetracycline binding assay." They identified and quantified the apatite crystal content of synovial effusions using a new method based on the calcium binding properties and the inherent fluorescence of tetracycline. They then compared these findings to those with their established but cumbersome technique based on radiolabeled etidronate and found that the tetracycline idea worked out very well. Thus, the tetracycline based method promises to provide more practical recognition of what is probably the most common microcrystal in patients with swollen osteoarthritic joints.

**Dr. Vivian Stone** (co-author **Dr. Ghosh**) is the lead author on the poster entitled: "A Paradoxical Increase in Th17 cells in Patients with High IFN Activity in Systemic Lupus Erythematosus." In this poster, the authors show that lupus nephritis disease activity correlates more strongly with increased levels of Th17 cells than with IFN score, suggesting that anti-cytokine therapy will likely require targeting of multiple molecules in different disease subsets.

**Alan Wong**, chief research scientist in the lab of **Dr. Grant Hughes**, was lead author of a poster entitled "A progesterone receptor regulates T cell dependent immune responses in vivo." In collaboration with the lab of Dr. Edward Clark. (Dept. Immunology, Dept. Microbiology, Washington National Primate Research Center, UW), Alan Wong presented the first known genetic evidence showing that the intracellular progesterone receptor, long known for its functions in reproductive tissues, is a regulator of immune functions in mice.

## GRAND ROUNDS NOW AVAILABLE ONLINE



Starting this year, **Rheumatology Grand Rounds** will be recorded and **available online**.

Using the Camtasia Studio program, we will be able to document our Grand Rounds. It will be audio recorded with the PowerPoint slides. The lectures will be available on Screencast, which is linked to our website.

To view past archived videos, please go to Rheumatology website and click on the conferences link to view the latest Grand Rounds video:

<http://depts.washington.edu/rheum>

To go directly to our Screencast website, please go to:

<http://www.screencast.com/users/UWRheum>

## CLINICAL PROFESSOR EMERITUS



**Drs. John Dickson, Maurice Skeith, and Kenneth Wilske** have recently been appointed as **Clinical Professor Emeritus**. They are recognized for their long and valued service to the University in clinical care and teaching in Rheumatology.

**Be green!**

If you would like to receive the newsletter electronically, please email [rheum@uw.edu](mailto:rheum@uw.edu).

## RHEUMATOLOGY RESEARCH TO MOVE TO SLU IN 2013

On July 6<sup>th</sup>, the groundbreaking ceremony for the construction of **Phase 3** took place at UW Medicine **South Lake Union (SLU)**. This building will house researcher investigators in **Rheumatology**, Vision Sciences, Immunology, Kidney research, Infectious Diseases, and CERID (Center for Emerging and Re-emerging Infectious Diseases). The first building of Phase 3 will be an 183,000 sq. ft. laboratory building and will be ready for occupation in **Spring, 2013**.



An architect's rendering of the future UW Medicine South Lake Union Phase 3.1, now under construction. To view the current construction, please go to: <http://oxblue.com/pro/open/sellen/uwmedlakeunion>

In addition to **Elkon** (Rheumatology), **Van Voorhis** (Allergy and Infectious Diseases), **Van Gelder** (Vision Sciences) and **Goverman** (Immunology), the Chair of the Department of Medicine, **Dr. William Bremner**, the CEO and Dean of the School of Medicine, **Dr. Paul Ramsey**, the new UW President, **Dr. Michael Young** and the Seattle Mayor, **Mike McGinn** were in attendance.

*"This third phase of UW Medicine's expansion at South Lake Union will allow us to bring together additional researchers from critically important areas and build upon the collaborative work of these scientific leaders in state-of-the-art facilities,"* said **Dr. Paul Ramsey**. *"The new space will present tremendous opportunities for scientists across multiple research disciplines."*

## RECENT GRANTS & AWARDS

**Dr. Mary Bach** - Nominated and accepted as ACR Fellows Subcommittee Member for a two-year term starting November 2011.

**Dr. Keith Elkon** - Alliance for Lupus Research (ALR) Research Grant, 08/01/11 – 07/31/13. Research Focus: Investigation of the cellular pathways linking tartrate resistant acid phosphatase (TRAP), type I interferon, and human lupus

**Dr. Grant Hughes** - Research Grant from the Society of Family Planning, 10/1/2011 – 09/30/2012. Research Focus: Interferon Pathway Targeting by Depo-Provera in Women

## MAKE A NOTE - SAVE THE DATE

**March 29, 2012**  
**Save the Date!**

**Betty Diamond, MD**  
12<sup>th</sup> Lane Lecture Speaker  
Professor, Dept. of Microbiology & Immunology and Medicine  
North Shore-Long Island  
Jewish Health System



**Lane Reception will follow later that evening**

Division of Rheumatology  
1959 NE Pacific St  
Campus Box 356428  
Seattle, WA 98195



## RECENT PUBLICATIONS & ARTICLES

**Bakewell CJ, Gardner GC.** A Survey of Arthrocentesis and Soft-Tissue Injection Procedures Performed in Primary Care Practice: Effect of Resident Training and Using Data to Shape Curriculum. *J Rheumatol* 2011;38:1986-1989.

**Elkon KB, Stone VV.** Type I Interferon and Systemic Lupus Erythematosus. *J Interferon Cytokine Res.* 2011 Aug 22. [Epub ahead of print]

Chaplin JW, Kasahara S, Clark EA, **Ledbetter JA.** Anti-CD180 (RP105) Activates B Cells To Rapidly Produce Polyclonal Ig via a T Cell and MyD88-Independent Pathway. *J Immunol.* 2011 Oct 15;187(8):4199-209. Epub 2011 Sep 14.

Gadi VK, **Nelson JL,** et al. Soluble donor DNA and islet injury after transplantation. *Transplantation.* 2011 Sep 15;92(5):607-11.

Chan WF, **Nelson JL,** et al. Microchimerism in the rheumatoid nodules of rheumatoid arthritis patients. *Arthritis Rheum.* 2011 Sep 27. doi: 10.1002/art.33358. [Epub ahead of print]

Gammill HS, **Nelson JL,** et al. Pregnancy, microchimerism, and the maternal grandmother. *PLoS One.* 2011;6(8):e24101. Epub 2011 Aug 30.

**Peng Y, Elkon KB.** Autoimmunity in MFG-E8-deficient mice is associated with altered trafficking and enhanced cross-presentation of apoptotic cell antigens. *J Clin Invest.* 2011 Jun 1;121(6):2221-41. doi: 10.1172/JCI43254. Epub 2011 May 2.

## OPPORTUNITIES FOR GIVING

**T**here are several ways that you can support programs and initiatives in the Division of Rheumatology. We have established three Professorships and one endowment through generous donations. In addition, several gift funds that target specific programs are the Rheumatology Graduate Medical Education Fund and the Rheumatology Discretionary Fund.

Send Checks to:

Division of Rheumatology  
1959 NE Pacific St  
Campus Box 356428  
Seattle, WA 98195

To learn more about these opportunities for giving, please visit:

<http://depts.washington.edu/rheum>  
or contact our office at 206-543-3414.

## THE FINE PRINT

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