



## WHAT'S HAPPENING AT THE CLINICAL AND TRANSLATIONAL SCIENCE CENTER?

### CTSC Investigator: *Dr. Ellen Ginzler* – *Rheumatoid Arthritis Research*

Dr. Ginzler is Professor of Medicine and Chief of the Division of Rheumatology at SUNY Downstate. One of her major research interests concerns rheumatoid arthritis (RA). RA has long been associated with increased cardiovascular risk, but despite substantial improvements in disease management, mortality remains high. Atherosclerosis associated with vascular inflammation is more prevalent in RA than in the general population. The systemic pro-inflammatory state present in patients with RA accelerates the progression of atherosclerosis through chronic endothelial activation. In this multicenter –supported study, Dr. Ginzler and her co-workers are working within the CTSC to investigate the effects on vascular inflammation of TNF antagonists plus methotrexate (MTX) versus triple therapy (MTX plus hydroxyl- chloroquine plus sulfasalazine) in patients with RA. They hypothesize that TNF antagonists will reduce inflammation in the carotid arteries and aorta to a greater extent than triple therapy. While triple therapy has been shown to produce similar outcomes to TNF antagonists plus MTX with respect to pain, function, and disease activity, it is unclear whether the more rapid control of inflammation and disease activity produced by TNF antagonists will translate into greater reduction of vascular inflammation. Another aim of this study is to compare the effects on vascular inflammation of achieving disease remission versus not reaching remission. The investigation also seeks to compare the effects on joint inflammation of TNF antagonists versus triple therapy. Several recent trials have demonstrated similar improvements in clinical measures of disease activity for these two treatment strategies, but it is unclear whether objectively measured joint inflammation at 6 months will be similar. Finally, her study is examining the correlation of candidate cardiovascular (CV) disease and RA disease biomarkers (e.g., IL-6, C-reactive protein, serum amyloid protein, ICAM-1) with treatment-associated reduction in vascular inflammation. There is considerable overlap between markers of CV risk and RA disease activity.

### CTSC Investigators: *Drs. Deborah Gustafson and Howard Minkoff* - *WIHS*

Dr. Gustafson, Professor of Neurology, and Dr. Minkoff, Professor of Obstetrics and Gynecology, are members of the Women's Interagency HIV Study (WIHS) at Downstate. WIHS is a large, comprehensive prospective cohort study designed to investigate the progression of HIV disease in women. The WIHS began in 1993 in response to growing concern about the impact of HIV on women. This NIH-funded multi-center project has 10 clinical sites across the U.S. The core study visit, conducted twice a year, includes a detailed and structured interview, physical and gynecologic examinations, laboratory testing and periodic neurocognitive assessments. After more than 20 years, the WIHS continues to investigate questions at the forefront of HIV research, spanning topics such as women's reproductive health, clinical outcomes (for example, cardiovascular disease, diabetes, and others), the effectiveness of antiretroviral therapy and most recently, the impact of aging. Investigators at the Brooklyn WIHS site are particularly interested in the cognitive, metabolic, cardiovascular and behavioral factors related to HIV as women age.

## DID YOU KNOW...?

### Disease: *Rheumatoid arthritis (RA)*

**Epidemiology:** RA is a systemic chronic inflammatory disease that mainly affects the synovial joints. The disease has a worldwide prevalence of 1% and affects women and men disproportionately (~2:1, respectively). RA commonly affects people between the ages of 40 and 70 years, with incidence of the disease increasing with age. The signs, symptoms and clinical course of RA can be extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive disease that is associated with significant physical and psychosocial morbidity and premature mortality. Joint destruction from synovitis can occur rapidly and early in the course of the disease.

**Translational Science Aimed at RA:** Rheumatoid arthritis is an autoimmune disorder in which the body's immune system mistakenly attacks joints. Discoveries of

the immune effector cells and cytokines involved in the pathophysiology of RA has allowed scientists to translate this knowledge into therapeutic treatments for RA using a range of biological agents -- antibodies and antagonists that target immune mediators of this disease. Clinical trials, such as those being conducted by Dr. Ginzler, aim to optimize therapeutic regimens using specific biological agents. But this approach is not a panacea. Studies are underway to understand why currently available options don't work for everybody.

Research aimed at identifying other therapeutic targets has shown that synoviocytes also contribute to RA by invading joint cartilage and secreting damaging enzymes and inflammatory molecules. It's not clear why or how these cells leave the joint lining and invade the surrounding cartilage. It's also not clear how the immune system instructs these cells to participate in the disease process. But clues are now emerging. Pre-clinical studies have identified an enzyme (a phosphatase named RPTP $\sigma$ ,) which is increasingly produced in synoviocytes as arthritis progresses, suggesting that the enzyme might play a role in RA. RPTP $\sigma$  modulates inflammation and joint damage suggesting that targeting this enzyme could represent a novel way to treat RA.

<https://www.ncbi.nlm.nih.gov/pubmed/25995222>

### FUNDING OPPORTUNITIES: RA RESEARCH

The [Rheumatology Research Foundation](#) offers several funding opportunities to support investigations related to rheumatoid arthritis. For information, visit their website.

### UPCOMING TRANSLATIONAL RESEARCH SEMINAR

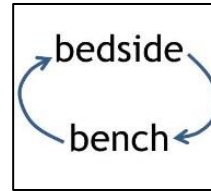
“Evolving Understanding of HPV Infection in  
HIV+ Women and Its Clinical Implications”

Howard D Strickler, MD, MPH  
Albert Einstein College of Medicine

May 9, 2017, 12:00 PM, Alumni Auditorium, HSB

## TRANSLATIONAL RESEARCH AT DOWNSTATE

**Investigator:** *Dr. Stacy Blain – Cancer Research*



Dr. Stacy Blain, Assistant Professor of Pediatrics and Cell Biology, is an NIH-funded investigator leading a translational study on the role of cyclin D-cdk4 (D-K4) and p27 in breast cancer. D-K4, which regulates the cell division cycle, has been a highly sought after therapeutic target because it drives cancer proliferation in a majority of human tumors, including ER/PR+, Her2- breast cancer. Cdk4/6 specific inhibitors, such as Palbociclib, have shown clinical efficacy, but resistance or lack of response has emerged as a problem. Her group is studying mechanisms that allow breast cancer cells to become resistant and ways to identify non-responders. They demonstrated that another kinase, cdk2, compensates for loss of cdk4 activity to rescue Palbociclib-arrested breast cancer cells, suggesting that inhibition of both kinases is required to achieve durable response. Dr. Blain and co-workers developed a novel strategy to inhibit a required activator of cdk4 as a modality to arrest proliferation. D-K4 activation is dependent on its association with another protein, p27, which in turn must be Y phosphorylated to allow the ternary p27-D-K4 complex to open up and bind to ATP. If p27 is not Y phosphorylated, the complex is inactive. If p27 is Y phosphorylated, the complex is turned on. Their approach to block p27 pY arrested proliferation and caused tumor regression in animal models of breast cancer. They also showed that the intensity of pY staining could predict whether a cell line would respond to Palbociclib. In collaboration with Drs. Lisa Dresner, Susan Gottesman and Jonathan Somma, they are testing this in a small clinical trial. They were able to further stratify a cohort of otherwise pathologically identical ER/PR+, Her2- breast cancer patients. With this information, they were able to make predictions about Palbociclib response, with the ultimate goal of getting the right drug to the right patient at the onset of treatment.

### CTSC MEMBERS

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### HOW TO BECOME A CTSC MEMBER

The CTSC is a Center within the Institute for Genomic Health (IGH), Dr. Michele Pato, Director ([michele.pato@downstate.edu](mailto:michele.pato@downstate.edu)). Downstate faculty conducting IRB-approved studies are welcome to apply for CTSC membership. There are no fees associated with membership.

For more information, visit <http://www.downstate.edu/ctsc>

CTSC Newsletter comments and suggestions? Email Dr. Richard Coico, CTSC Director: [richard.coico@downstate.edu](mailto:richard.coico@downstate.edu)