Novel Diagnostics in Sjögren’s

To enhance clinical care and move research forward in Sjögren’s, the Sjögren’s Syndrome Foundation (SSF) has set the development of Novel Diagnostics as a top priority for its 2013 research program. (To learn more about the SSF Research Program, how to apply, and 2013 priorities for awards, visit www.sjogrens.org/research.) The SSF kicked off the announcement of this priority with a program focused on Novel Diagnostics at the SSF annual luncheon meeting during the American College of Rheumatology conference in November. “Better and more precise ways are desperately needed to diagnose and monitor Sjögren’s patients,” says SSF CEO Steven Taylor. “Advocating for improved diagnostics is an important part of our Foundation’s strategy for meeting the SSF Five-Year Breakthrough Goal – To shorten the time to diagnose Sjögren’s by 50% in five years!”

Held in Washington, D.C., the SSF meeting at ACR brought about 80 clinicians and researchers who packed the room to hear about new concepts in the pipeline. SSF Medical and Scientific Advisory Board Chair Denise Faustman, MD, PhD encouraged attendees to think about new targets that could be explored for diagnosis: “It’s time this disease moved away from an invasive procedure – the lip biopsy, and that we came up with a non-invasive ‘gold standard’ for identifying Sjögren’s patients. A simpler, more decisive diagnostic test will help everyone – patients, clinicians, researchers and insurers, and it will lead to earlier diagnosis.

Emerging Evidence May Lead to Hope for Early Detection and Intervention for Sjögren’s

by Stephen Hsu, PhD1,2, Douglas Dickinson, PhD3, and Scott DeRossi, DMD2

Sjögren’s syndrome (SS) affects 1-3% of the population in the United States.1 Complications resulting from SS significantly decrease quality of life. If the onset of autoimmune disorders such as SS could be diagnosed at a stage prior to the appearance of symptoms, then more therapeutic options could be developed to prevent and delay the onset of disease. Unfortunately, the pathogenesis of this disease is poorly understood. This has made early detection, prevention and intervention prior to the onset of overt...
symptoms impossible to-date. Thus, from a medical perspective, the current focus on SS is largely diagnosis (which itself may take many years) and treatment of symptoms, not the underlying disease. Current standard of care is unable to address disease progression.

For the treatment of symptoms, the first generation of agents developed consists of over-the-counter products aiming to moisturize the oral lining or to deliver agents that can be helpful in reducing the oral health effects of dry mouth. These include xylitol, a naturally occurring sugar-alcohol, and certain antimicrobial salivary enzymes. Although generally well-tolerated, these agents require continuous application. The next generation comprised prescription medications that provide pharmaceutical stimulation to the salivary gland. These were approved by the FDA more than a decade ago and are associated with many adverse side effects such as sweating, diarrhea and cardiac complications and poor patient compliance. Thus, currently used approaches are all aimed at temporary relief of certain symptoms without addressing the root of the problem – the gradual loss of function in the salivary gland cells – due to the lack of knowledge of when and what triggers the change in the salivary glands.

Clinicians and researchers understand that the initiation of disease, the incubation period, could last for years (and perhaps decades). Most existing theories for the origin of SS hold that abnormalities in the innate immune system play the key role in disease pathogenesis. The immune system's action on the glands leads to salivary dysfunction (and other abnormalities) caused by the loss of function of glandular cells and eventually cell loss through immune system-induced cell death. In these theories, the salivary glands themselves are initially normal and their cells are simply bystanders. Based on these ideas, immunosuppressant and other therapies targeting the immune system as a whole were developed to manage the disease. Unfortunately, these relatively indiscriminate therapies are associated with increased risk for infection, cancer and other long-term consequences.

Recently, researchers found that the salivary gland epithelial cells themselves play a key role in both the onset and continuation of this autoimmune disorder. One proposed mechanism points to the glandular epithelial cells as the source of initial events. The involvement of salivary gland cells in the pathogenesis of SS is an exciting phenomenon, because it suggests that the immune system might simply perform its “normal” function: to clear molecules it recognizes as “foreign” by attacking the targets with cytokines, antibodies and “killer” cells. However, although altered expression of various genes and proteins has been found previously in SS patients, these alterations occur long after the appearance of overt symptoms.

Therefore, we initiated an effort to search for changes in the salivary gland cells prior to disease onset, first in animal models, then in human samples obtained from SS patients. Our group has also focused on plant-derived natural antioxidants for the protection of secretory glands. One group of these natural and non-toxic compounds is obtained from a popular beverage in East Asia: green tea.

Epidemiologic studies indicate that genuine differences in the prevalence of SS among various regions and communities exist. In China, one study suggested the prevalence of primary SS was 0.03%, whereas serological screening showed 0.33% prevalence of primary SS (Fox criteria). In Japan, the estimated crude prevalence rates for SS were only 1.9 and 25.6 per 100,000 in males and females, respectively. A survey conducted by the Japanese Ministry of Health and Welfare indicated the SS prevalence was just 0.06% among females. Although there is a lack of direct statistical comparison between the U.S. population and either the Japanese or Chinese population, it is apparent that SS and xerostomia are significantly more prevalent in the U.S. population. Notably, China and Japan have the largest populations of green tea consumption.

Our group previously found that autoimmune-associated symptoms (SS, psoriasis, type-1 diabetes) in animal models can be managed by certain molecules present in green tea leaves. The most recent findings from our group, published in the journal of Autoimmunity, described a longitudinal study using the NOD.B10. H2-B mouse model for human primary SS. The study design investigated changes in the salivary gland and pancreas at several time points when the animals are characterized as “healthy” – that is, before the appearance of lymphocytic infiltration in the salivary glands (a characteristic sign for SS).

Remarkably, as early as 6 weeks old, these animals showed significant oxidative DNA damage and DNA repair activities in the salivary gland in comparison to control mice, BALB/c, that do not develop SS-like disease. These oxidative stress-induced abnormalities continued to increase through an 8-week period, during which a significant decrease in a key antioxidant defense enzyme, peroxiredoxin 6, became apparent. On the other hand, animals fed with EGCG, a major component of green tea antioxidants, showed significantly less oxidative DNA damage. In addition, in EGCG-fed animals, levels of a DNA repair marker PCNA (proliferating cell nuclear antigen) and the antioxidant enzyme peroxiredoxin 6 were similar to the normal control counterparts. These results suggest that during a long period in which animals are otherwise categorized as “healthy,” oxidative stress was increasing to damaging levels in the salivary gland and gradually causing increased oxidative damage to vital molecules such as DNA. If the oxidative stress...
continues to elevate, the antioxidant defense enzyme system could be compromised, leading to extensive oxidative damage or structural modification to vital molecules, including DNA, RNA, lipids and proteins. In turn, this may result in apoptosis (programmed death) of cells that accumulated damage beyond repair. Importantly, when these molecules are in their abnormal oxidative form and exposed to the immune system during degradation of a cell, the immune system may misrecognize these molecules as “foreign” and mobilize a powerful but normal immune reaction against them, causing injury to the salivary gland (or the pancreas), including additional oxidative damage. Consequently, a vicious feedback loop forms that sustains an immune attack on the tissues, leading to more lymphocytic infiltration, inflammation, and loss of function.

A potential argument is that events observed in mice may not happen in the human body. However, similar results were found in salivary tissues obtained from SS and xerostomia patients. In humans, the immune system and the antioxidant system are two vital defense systems in our body. The antioxidant defense system is constantly engaging oxidative stress from free radicals either produced by our own mitochondria, or from medication, radiation, chemicals, or even food components. This system consists of many inducible or constitutively expressed enzymes such as glucose-6-phosphate dehydrogenase (that produces NADPH, a reducing agent), glutathione peroxidase, catalase, peroxiredoxin (that convert hydrogen peroxide to water), and superoxide dismutase (which converts toxic superoxide to less toxic hydrogen peroxide), etc., in order to protect cells and tissues from oxidative damage. Our group reported that in SS patients and xerostomia patients, peroxiredoxin 6 and glutathione peroxidase 1 are significantly lower and PCNA levels are significantly higher than healthy individuals. These results indicate that similar to the mouse model, the down regulation of the antioxidant defense enzymes may be the result of an undetected “incubation” period that lasts for years. However, an encouraging finding is that when cultured human salivary gland cells are exposed to EGCG, the protein level of peroxiredoxin 6 is increased many times, which matches the animal data.

Our current effort is to identify biomarkers for the early detection of abnormalities that could lead to autoimmune disorders such as SS and type-1 diabetes, ideally years ahead of any detectable symptom, and to investigate prevention and intervention using plant-derived, non-toxic natural compounds. A double-blind, placebo-controlled, randomized clinical trial will soon be completed in our university’s College of Dental Medicine using a natural formula containing plant extracts (including green tea extract) and an appropriate amount of xylitol to evaluate it as a new generation of potential therapeutic medications.

In conclusion, with newly emerged discoveries, it is time to revisit the decades-old theories, approaches, medications, and symptom-relief products for the pathogenesis of autoimmune disorders such as SS and the approaches for diagnosis and treatment/management. In the near future, we may be able to detect signs for autoimmune disorders when individuals are apparently completely “healthy,” and we could design approaches to prevent or delay the onset of autoimmune diseases for years or even decades. Future research directions also should include the identification of the
Attention for Sjögren’s at ACR Increases Dramatically

Sjögren’s was highlighted more than ever before at the American College of Rheumatology (ACR) annual meeting held in November in Washington, D.C. “We are pleased that our relationship with the ACR continues to grow, increasing opportunities to educate rheumatologists and encourage researchers in Sjögren’s,” says Steven Taylor, SSF CEO. Sessions on Sjögren’s at ACR included:

- The Foundation-led presentation on the SSF Clinical Practice Guidelines initiative with Moderator Frederick Vivino, MD and presenters Steven Carsons, MD and Ann Parke, MD. Speakers discussed the rigorous process underway as the Foundation has been tackling key clinical questions in the management and treatment of Sjögren’s. A full article covering this topic will appear in a future issue of the *Sjögren’s Quarterly*.

- A presentation on the 2012 ACR Classification Criteria for Sjögren’s moderated by Lindsey Criswell, MD, MPH, Dsc with Stephen Shiboski, PhD presenting.

- An SSF-hosted discussion meeting entitled “Criteria in Sjögren’s – Steps Forward” and chaired by Caroline Shiboski, DDS, PhD and Xavier Mariette, MD. While the American European Consensus Group criteria has been in wide use by investigators worldwide since 2002, ACR recently provided tentative endorsement of new criteria developed by the Sjögren’s International Collaborative Clinical Alliance (SICCA) Registry and published in 2012. The international community came together to discuss ways to ensure international collaboration as criteria is validated and refined. A meeting summary along with steps forward that were delineated will be published in the 2013 spring issue of the *Sjögren’s Quarterly*.

- The SSF luncheon meeting on Novel Diagnostics that packed more attendees than at any previous meeting. See cover story in this issue of the *Sjögren’s Quarterly*.

- The Sjögren’s Syndrome Study Group led by Jacques-Eric Gottenberg, MD. The study group covered “From Pathogenesis to New Therapeutic Perspectives of Primary Sjögren’s Syndrome.”

- Two “Meet the Professor” sessions on “Controversies in Sjögren’s” led by Alan Baer, MD.

- A Curbside Consult on “Sjögren’s Syndrome: Challenges in Clinical Practice” led by Frederick Vivino, MD.

- Two oral poster sessions and a poster tour on Sjögren’s. The number of abstracts on Sjögren’s submitted to ACR tripled and the number accepted nearly doubled to 76 this year. Oral presentation sessions on selected abstracts doubled to two with one on clinical aspects of Sjögren’s moderated by E. William St.Clair, MD and Athanasios G. Tzioufas, MD and a second session on Pathogenesis and Sjögren’s moderated by Xavier Mariette, MD, PhD and Lindsey A. Criswell, MD, MPH, Dsc. In addition, a Poster Tour in Sjögren’s was scheduled and led by Jacques-Eric Gottenberg, MD.

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Achievement Award and, while noting the nation’s difficult financial condition also recognized the importance of a national commitment to research.

**Sequestration Would Devastate Research**

All of NIH faces major economic uncertainty as sequestration (across-the-board cuts for the federal government) is set to take place on March 1 if Congress does not reduce the deficit. In addition, the current continuing resolution that is keeping the federal government going will end March 27 unless continued or a FY2013 budget is passed. If sequestration takes place, the NIH would be cut by 8.2% or $2.518 billion dollars with as many as 2,300 fewer grants funded. This could have devastating ripple effects for years to come on medical and scientific research carried out in the U.S.

**NIEHS Job Announcement**

The National Institute of Environmental Health Sciences (NIEHS) at the National Institutes of Health (NIH) has announced that it is looking for a Director of Clinical Research to lead clinical-translational research at the senior investigator (tenure-eligible) level. The position can include an independent laboratory. NIEHS supports research on potential environmental triggers into autoimmune disease and includes the Environmental Autoimmunity Group. The SSF is a member of the Friends of NIEHS. Applications are due February 28, 2013. More information is available at http://niehs.nih.gov/careers/jobs/director_clinical_research_program_dir_1301.cfm.

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...to detect virus particles, blood biomarker proteins and nucleic acids. The assays tested by the Maverick incorporate the most commonly tested autoimmune antigens including those identified with Sjögren’s – SSA and SSB. Numerous references providing background information and validation for the use of silicon photonics and multiplexing can be found on the Genalyte, Inc. website at www.genalyte.com. Dr. Gleeson presented on this topic during the 8th International Congress on Autoimmunity in May 2012 in Granada, Spain in his talk entitled, “Novel Multiplexing Platform for the Detection of Auto–Immune Antibodies in Serum Samples with Rapid Time to Result.”

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If you would like to receive information on how you can Leave a Legacy to support the Sjögren’s Syndrome Foundation’s critical research initiatives or to support one of our many other programs, please contact Steven Taylor at 800-475-6473.

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**References**