**Introduction**

An important and timely topic in the field of autoimmunity is the discovery and identification of genes associated with various autoimmune diseases, including Sjögren’s syndrome (SS). The impressive, burgeoning molecular genetics technology that has been developed over the past two decades has provided the platform/substrate for defining the complex molecular genetics of autoimmune disorders.

Complex disorders, in contrast to single-gene disorders, are multi-factorial conditions caused by the interaction of multiple genes and environmental factors. Each gene has a relatively small effect/contribution to disease; and few, if any, are absolutely required for disease to manifest. Complex autoimmune disorders for which substantial genomic data (Genome-wide associations (GWA)) have been obtained include: rheumatoid arthritis

Continued on page 2 ▼

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**The Role of Human Genetics in Identifying Clinically Relevant Therapeutic Targets in Sjögren’s**

by Elaine Alexander, MD, PhD
Chairman, Sjögren’s Syndrome Foundation
Medical and Scientific Advisory Board

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**Swollen Salivary Glands**

by Ava J. Wu, DDS
Clinical Professor, Department of Orofacial Sciences, and Co-Director, Salivary Gland Dysfunction Clinic
University of California, San Francisco, School of Dentistry

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**Swollen Salivary Glands**

Sometimes the major salivary glands can become swollen and/or painful in Sjögren’s syndrome (SS). About one-quarter of SS patients will experience salivary enlargement at some time. Any sudden, extreme or prolonged salivary gland swelling should be investigated. Clinicians need to identify the cause before determining management of the problem.

The three major salivary glands pairs are located in the cheek area in front of the ear and extend straight down to the bottom of the jawline (parotid), under the jaw (submandibular) and under the tongue (sublingual). Ducts carry salivary products from these glands into the oral cavity. In addition to the major salivary glands, hundreds to thousands of minor salivary glands are located throughout the inner lips, cheeks, palate and throat.

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Various types (and numbers) of organs can be involved including: exocrine and endocrine glands, solid organs, hematopoietic system, and neuromuscular/skeletal systems. The potential pathophysiologic process(es) involved in producing physiologic dysfunction in different organs are, in most cases, not well established and are unlikely to be identical in all involved organs.

Much less is known about the very common autoimmune disorder SS.

SS is a complex, multi-system disorder, which has variable clinical expression and severity in different individuals. Various types (and numbers) of organs can be involved including: exocrine and endocrine glands, solid organs, hematopoietic system, and neuromuscular/skeletal systems. The potential pathophysiologic process(es) involved in producing physiologic dysfunction in different organs are, in most cases, not well established and are unlikely to be identical in all involved organs.

Human genome-wide association studies (GWAs), in which hundreds of thousands of single-nucleotide polymorphisms (SNPs) are tested for association with a disease in hundreds or thousands of persons, have revolutionized the search for genetic influences on complex traits. In the past 5 years, GWA studies have identified SNPs implicating hundreds of robustly replicated loci (i.e., specific genomic locations) for common traits. The identified variants have low associated risks and account for little disease heritability. Potential explanations for low disease heritability include: rare variants, which are not captured by current GWA studies, structural variants, which are poorly captured by current studies, other forms of genomic variation, or interactions between genes or between genes and environmental factors.

Despite their value in locating the vicinity of potential disease-causing genomic variants, few of the SNPs identified in GWA studies have clear functional implications that are relevant to disease mechanisms. Narrowing an implicated locus to a single variant that directly causes disease susceptibility by disrupting the expression or function of a protein has proven elusive to date. This will be a key step in SS in improving our understanding of the mechanisms of disease and in designing effective strategies for risk assessment, management, and treatment.

The Role of the Sjögren’s Syndrome Foundation in Synergizing SS Research

The support and funding of critical basic science and clinical research in the field of SS has become an increasingly important goal for the SSF. Since 2000, the SSF has funded over $1.5 million in competitive research grants to prestigious academic investors for the study of SS. In 2010, two of the SSF grants were competitively awarded to established academic investigators studying genome-wide associations in SS.

One of the important venues in which the SSF fosters synergy and collaboration between scientists, clinicians, and industry is the recently organized annual luncheon meeting at the annual meeting of the American College of Rheumatology (ACR). The SSF/ACR annual meeting scientific program has become an important forum for discussion of timely, cutting-edge scientific topics and emerging medical and clinical development issues. As Chairman of the SSF Medical and Scientific Advisory Board, I selected the topic of SS genomics for the scientific topic for this meeting and asked our two 2010 grant awardees as well as an additional stellar investigator from France to speak and a leading renowned clinical geneticist to moderate the program. The SSF meeting was held on Monday November 8, 2010 at the ACR/ACHRP annual scientific meeting in Atlanta, Georgia.

A list of program participants and a summary of the speakers’ presentations follow. The speaker summaries include background, an overview of their laboratory expertise and accomplishments, and an outline of their research plans for SS genomic research over the next several years. It is our plan to have these investigators update the SSF and scientific/clinical friends/colleagues on their progress at a future annual SSF/ACR meeting.

Moderator

Peter K. Gregersen, MD
Center for Genomics and Human Genetics, Feinstein Institute for Medical Research

Speakers

Kathy Moser, PhD
Oklahoma Medical Research Foundation (OMRF), Oklahoma City, Oklahoma

The Genetic Basis of Human Sjögren’s Syndrome

The goal of the OMRF is to identify and characterize the molecular basis of the pathogenesis of human SS using powerful, comprehensive genetic approaches. Genetic associations have now been described for over 2,200 human disorders. The human genome contains...
When moderate to severe Dry Eye patients drop ≥4 times a day, give them

More Freedom to Go DROPLESS

LACRISERT®: All-day relief in a single daily dose*

- Significant improvement in subjective symptoms, objective signs, and activities of daily living requiring high visual acuity.
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- Simple and easy placement.
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*LACRISERT® is indicated in patients with moderate to severe Dry Eye syndromes, including keratoconjunctivitis sicca. LACRISERT® is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions. LACRISERT® is also indicated for patients with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.

LACRISERT® is contraindicated in patients who are hypersensitive to hydroxypropyl cellulose. The following adverse reactions have been reported in patients treated with LACRISERT® but were, in most instances, mild and temporary: blurring of vision, eye discomfort or irritation, matting or stickiness of eyelashes and red eyes. If improperly placed, LACRISERT® may result in corneal abrasion.

Please see brief summary of Prescribing Information on adjacent page.
The function of the salivary glands is to produce saliva. Saliva has a role in initiating digestion; protecting, preserving and repairing oral soft tissue; facilitating taste; buffering acids; and modulating viral, fungal and bacterial populations. For example, antibodies are found within saliva that have the ability to cause bacteria to clump so that they are not able to bind to the oral tissue and cause an infection. Proteins floating within saliva also can have a direct killing effect on bacteria. When one is not able to produce sufficient amounts of saliva whether because of disease or dehydration, then it is believed that the protective effects of saliva are also diminished, and one becomes prone to oral infections.

Uncontrolled diabetes, bulimia, alcoholism, and vitamin deficiencies have been associated with diffuse salivary gland swelling, usually the parotid glands. There also have been isolated reports of salivary gland swelling associated with certain drugs: phenylbutazone, iodine, phenothiazines, valproic acid and captopril. This paper will focus on the common causes of swelling of the major salivary glands, as it is rare to have swelling of the minor salivary glands. The major causes of salivary gland swelling include obstruction, infection, tumor and inflammation of the salivary glands.

**Major causes of salivary glands swelling**

1. **Obstruction of the Salivary Gland**
   - Obstruction of the salivary glands occurs because of the presence of a stone, mucous plug or anatomical stricture within the salivary duct system preventing saliva from flowing unimpeded from the salivary glands into the oral cavity.
   - Individuals with chronic obstructive processes can experience recurrent acute bacterial infection of the gland. This is thought to be the result of an inability of the salivary gland to maintain a continual outflow of saliva into the mouth, diminishing the cleansing effect and allowing bacteria to migrate from the oral cavity into the ductal system and initiate an infection.
   - The classic symptom of salivary gland obstruction is a sharp, stabbing pain in the body of the affected salivary gland. Associated rapid swelling of the salivary gland may occur but resolve when the backed-up saliva is able to bypass the obstruction.
   - Obstruction will typically affect only a single gland at a time.

2. **Infection of the Salivary Glands**
   - The classic viral infection affecting the salivary glands is mumps. Constitutional symptoms of fever, chills, joint pain, muscle aches and fatigue may be present along with a very painful swelling of the parotid glands on both sides of the face. The submandibular glands are affected less often. Saliva exiting the gland will typically be clear.
   - A bacterial infection can also occur secondary to salivary gland obstruction or in an individual with slow to no salivary flow. An associated fever may occur and purulent material observed exiting the salivary gland. The patient will have difficulty opening the mouth because of swelling. The skin over the salivary gland may be red, warm and painful to touch.
   - Other infectious agents that can cause infection of the salivary gland or the lymph nodes within the salivary gland or are associated with salivary gland swelling include: histoplasmosis, tuberculosis, brucellosis, cytomegalovirus, coxsackie A, hepatitis C, human immunodeficiency virus and some strains of influenza virus.

3. **Tumors of the Salivary Gland**
   - Benign and malignant tumors usually occur as a painless, discrete enlargement in one of the major salivary glands. Less often, a tumor will appear as a diffuse swelling.
   - If a tumor grows rapidly, it may impinge on a nerve and cause pain, loss of movement or sensation on the affected side of the face. A tumor may also impinge on a duct causing swelling and pain associated with eating.
   - Because of an increased risk of lymphoma developing in the salivary glands of patients with Sjögren’s, checking for its potential development is especially important.
Changing the Future of Women's Health

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A Restorative Moisturizer to Alleviate Atrophic Vaginitis & Maintain Natural Protection.

Only LUVENA® PreBiotic Moisturizer/Lubricant™ utilizes a unique LPG Enzyme System to inhibit "harmful" bacteria growth - Combined with a proven GLYCOGEN PreBiotic System to help restore the natural flora balance of the vagina.

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<th>Replens Vaginal Moisturizer</th>
<th>K.Y.* Long Lasting Vaginal Moisturizer</th>
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“Role of Human Genetics” Continued from page 2 ▼

approximately 3 billion base pairs of DNA and includes ~25,000 genes. Known variation in the human genome now includes >30 million single nucleotide polymorphisms (SNPs). Additional variants that are “structural” in nature include >11,700 copy number variants (CNVs). CNVs can result from insertions, deletions, duplications, triplications and translocations. Thus, the scope of potential variants contributing to complex diseases is vast. To date, far fewer than 1% of the ~25,000 genes in the human genome have been evaluated for a role in SS. Without discovering the genetic basis of SS, a complete understanding of this complex disease is not possible.

Unbiased screens of the entire human genome using recently developed genome-wide association (GWA) approaches have been successfully applied to numerous complex human diseases. Over 400 GWA studies have been published since 2007 and have typically screened 300,000-500,000 SNPs in cases and controls at a density that essentially tests some (but not all) variation in every gene. This approach has been spectacularly successful and provides an important and encouraging precedent for genetic studies in SS. Over 30 GWA studies have now been published for various autoimmune diseases and have identified hundreds of genetic variants that confer risk to autoimmunity. Furthermore, genes that are indisputably associated with multiple autoimmune diseases are common. Importantly, key biological pathways continue to be revealed and characterized as these studies progress.

SS shares many clinical and immunological similarities with autoimmune diseases such as SLE and, less so, RA. Like these diseases, we hypothesize that the underlying genetic basis of SS is similarly complex and involves multiple genes, a considerable proportion of which are also associated with diseases that exhibit overlapping clinical features such as SLE or, to a lesser extent, RA. Our human genomic program involves two stages. First, we are using GWA approaches to identify novel candidate genetic variants associated with SS. This involves testing over 1 million SNPs for association. Next, these results will be used to select SNPs for further study and test for replication of results in additional cases and controls, thus establishing true associations. For every genomic association that is established, we and others will work to characterize the effects on phenotype. Such studies will include fine mapping and resequencing to pinpoint causal alleles, functional studies to determine how associated variants influence biological pathways and cellular processes, evaluation of the relationship to clinical manifestations, and development of mouse models that are relevant to known genetic variation influencing human SS.

This effort is clearly only the beginning of what we expect will be a long term global endeavor to identify the biological mechanisms operative in SS and rapidly accelerate progress towards much needed improvements in diagnostic and therapeutic approaches for SS.

References

7. Miceli-Richard C, Gesteermann N, Ittah M, et al. The CGGGG insertion/deletion polymorphism of the IRF5 promoter is a strong

Corinne Richard-Miceli, MD, PhD
Hôpital Bicêtre, Paris-Sud University, France

Genetic and Epigenetic Contribution to pSS Susceptibility

Until 2007, the most important genetic associations with pSS were alleles of the major histocompatibility complex (MHC) and more specifically the ancestral haplotype HLA-A1-B8-DR3-DQ2. An association between HLA-DRB1 alleles restricted to pSS patients with autoantibodies was further reported by our group. More recent data regarding the pathogenic mechanisms involved in pSS have supported the role of the interferon (IFN) pathway through an IFN signature, both in peripheral blood mononuclear cells (PBMCs) and in salivary glands. Following these observations, research has focused on genes involved in innate immunity and the IFN pathways. Such approaches have successfully demonstrated the role of two crucial genes in both diseases (i.e. SS and SLE: interferon regulatory factor 5 (IRF5)), a gene implicated in type 1 IFN regulatory factor 5 (IRF5), a gene implicated in type 1 IFN secretion after stimulation of innate immunity and in type 1 IFN signal transduction and STAT4, a gene involved in type 1 IFN expression.

Our group has been widely involved in characterization of the genetic factors involved in pSS susceptibility. We first reported a significant association of IRF5 rs2004640 and confirmed a significant association of a CGGGG insertion located in the promoter region of IRF5 with pSS. The most important contribution of our group, apart from the demonstration or replication of IRF5 polymorphisms with pSS, has been to elucidate the functional consequences of the IRF5 CGGG insertion on IRF5 mRNA expression among patients in PBMCs and in resident salivary gland epithelial cells (SGECs) which are the target of autoimmunity in this disease. Of interest, in SGECs, increased expression of IRF5 mRNA was observed among patients carrying the 4X CGGGG IRF5 risk allele only after reovirus infection, emphasizing the importance of both innate immunity and viral infection in pSS susceptibility. Then, we confirmed a replicated association of STAT4 rs7582694 polymorphism and pSS with a recessive effect and found a strong correlation between mRNA levels of STAT4 and type 1 IFN-induced genes. Thus, STAT4 might be involved in not only type 2 IFN production but also type 1 IFN-mediated effects.

Continued on page 10 ▼
HOW ARE YOUR SJÖGREN’S PATIENTS BALANCING THEIR DRY-MOUTH SYMPTOMS?

EVOXAC® CAN HELP.

Dry-mouth symptoms of Sjögren’s aren’t always recognized as a medical problem until they start disrupting daily lives.1,2 Yet adequate salivary flow is essential for good oral health, initiating enzymatic food digestion, facilitating taste bud sensation, and more.3,4 If your patients are having trouble with their dry-mouth symptoms due to Sjögren’s syndrome, learn how EVOXAC (cevimeline HCl) can help.5-7

Learn how EVOXAC can help increase salivary flow in patients with dry-mouth symptoms associated with Sjögren’s syndrome at EVOXAC.com.

IMPORTANT SAFETY INFORMATION

EVOXAC (cevimeline HCl) is indicated to treat the symptoms of dry mouth in patients with Sjögren’s syndrome.

- Cevimeline HCl is contraindicated in patients with uncontrolled asthma, known hypersensitivity to the drug, and when miosis is undesirable, e.g., in acute iritis and narrow-angle (angle-closure) glaucoma
- Cevimeline HCl can potentially alter cardiac conduction and heart rate and produce transient changes in hemodynamics. Cevimeline HCl should be administered with caution and under close medical supervision to patients with a history of cardiac disease, controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease
- Cevimeline HCl should be administered with caution to patients taking beta-adrenergic antagonists because of the possibility of conduction disturbances and to patients with a history of nephrolithiasis or cholelithiasis
- If a patient sweats excessively while taking cevimeline HCl, dehydration may develop
- Caution should be advised while driving at night or performing hazardous activities in reduced lighting
- Safety and effectiveness in pediatric patients have not been established
- Cevimeline HCl is metabolized by the P-450 isozymes CYP2D6 and CYP3A4, thus there may be potential for interaction between cevimeline HCl and other compounds
- Special care should be exercised when cevimeline HCl is taken by geriatric patients, considering the greater frequency of decreased hepatic, renal, or cardiac function
- The most frequently reported adverse events associated with the pharmacologic action of a muscarinic agonist (>10% incidence) in clinical trials of cevimeline HCl were: excessive sweating, nausea, rhinitis, and diarrhea. Consult the full Prescribing Information for other adverse events

References:

Please see next page for brief summary of full Prescribing Information for EVOXAC.
EVOXAC® Capsules (cevimeline hydrobromide)

INDICATIONS AND USAGE
Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren’s Syndrome.

CONTRAINDICATIONS
Cevimeline is contraindicated in patients with congested arteries, known hypersensitivity to cevimeline, and when myasthenia is uncontrolled, e.g., in acute illness and in patients with high serum glucose levels.

WARNINGS
Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be at increased risk for treatment-related changes in heart rate or rhythm induced by EVOXAC®. Cevimeline should be used under the supervision of a physician with a history of cardiovascular disease, or with aortic stenosis, or chronic obstructive pulmonary disease.

PULMONARY OBSTRUCTION
Cevimeline can potentially increase airway resistance, bronched smooth muscle tone, and bronchodilatation. Cevimeline should be administered with caution and under close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

OVERDOSE
Optimal formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with cerebrovascular changes, and to cause impairment of depth perception. Cevimeline should be administered while driving at night or performing hazardous activities in meals increased by lighting.

PRECAUTIONS
General
Cevimeline is characterized by an exaggeration of all parasympathetic effects. These include: mydriasis, dryness, tachycardia, bradycardia, emotional lability, flushes, palpitations, mild rash, arthralgia/myalgia, and rhinitis.

Cevimeline should be administered with caution to patients with a history of gastrointestinal disorders. Of the patients treated in controlled clinical studies, 10% of patients had lower gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting, abdominal pain). Abdominal cramping, diarrhea, and nausea are common adverse effects that can be seen following initiation of therapy.

Patients should be advised that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient swallows an intact capsule while taking cevimeline, debridement may develop. The patient should drink extra water and contact a healthcare provider.

Drug Interactions
Cevimeline should be administered with caution to patients taking beta-adrenergic antagonists, because of the possibility of cardiovascular disturbances. Drugs with parasympathomimetic effects administered concurrently with cevimeline can be expected to have additive effects. Cevimeline may interfere with other anticholinergic effects of drugs taken concurrently.

Drugs which inhibit PGP450 and CYP2D6 also inhibit the metabolism of cevimeline. Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experiences, as they may be at a higher risk of adverse events. In a 12-week study, cytholate PGp450 baiiies, IAD, 200, 2010, 2013, 2014, and 2015 were not inhibited by exposure to cevimeline.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Life-time carcinogenicity studies were conducted in C57-B mice in 1998-2000, and a statistically significant increase in the incidence of adenocarcinomas of the bladder was observed in female rats that received cevimeline at a dose of 100 mg/kg/day (approximately 10 times the maximum human exposure based on an oral assumption). No other significant differences in tumor incidence were observed in either male or female rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an in vitro chromosomal aberration test in mammalian cells, a mouse lymphoma test at 500 mg/kg, and an intracutaneous assay conducted in vivo in mice.

Cevimeline did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 43 days prior to mating and throughout the period of mating and gestation at 100 mg/kg/day (approximately 10 times the maximum recommended dose for a 60 kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at doses up to 45 mg/kg/day from 14 days prior to mating through day 20 of gestation exhibited a statistically significantly greater number of implantations than did control animals.

Preparatory
Cevimeline is associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats for 14 days following mating through day 20 of gestation at a dose of 45 mg/kg/day (approximately 10 times the maximum recommended dose for a 60 kg human). No fetuses were observed to be born with external or internal malformations. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding
It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, especially at the breastfeeding period, the potential for adverse reactions to the drug in the breastfed child should be considered before administering this drug to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Although clinical trials of cevimeline included subjects over the age of 65, the number was not sufficient to determine whether they respond differently from younger subjects. Special care should be exercised when cevimeline is administered to an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

ADVERSE REACTIONS
Cevimeline was administered to 1777 patients during clinical trials worldwide, including 824 patients and patients with other conditions. In a placebo-controlled study in 279 patients with Sjögren’s syndrome, patients received 15 mg of cevimeline twice daily for 6 months, from 60 mg to 60 mg, of whom 93% were women and 7% were men. Demographic distribution was 98% Caucasian. No patient had more than 2% of adverse events, and those in 1346 patients discontinued treatment due to adverse events with cevimeline.

In addition, the following adverse events were reported in Sjögren’s patients during clinical trials:

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In the total number of patients exposed to the doses at any time during the study.

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Olga Baker, DDS, PhD is Principal Investigator on an NIH grant for her research entitled, “Effect of SS-associated cytokines on salivary gland dysfunction.” This is her second NIH grant since receiving an SSF Research Grant in 2006 for her project, “Effects of proinflammatory cytokines on polarized salivary epithelium.” Dr. Baker has also published two new journal articles this year. They are:


Dr. Baker is an Assistant Professor in Oral Biology, School of Dental Medicine, University at Buffalo, State University of New York (SUNY).

Umesh Deshmukh, PhD, an Assistant Professor at the University of Virginia, is building upon the work from his SSF grant by partnering on a project in Sjögren’s with the University of California at Davis and another project with the University of Florida at Gainesville. He also is the Principal Investigator for a 2010-2012 NIH grant for his project, “Innate Immunity Activation in Pathogenesis of Sjögren's Syndrome,” and was invited to speak during the Sjögren’s Study Group during ACR this past fall. Dr. Deshmukh received a 2009 SSF Innovative Concept Grant for his project entitled, “Adenosine receptor agonist: Novel therapeutic agents for Sjögren’s syndrome.” His SSF grant was supported by the Leach Family.

Natalia Giltiay, PhD has been appointed Senior Fellow at the Immunology Department of the University of Washington in Seattle. Dr. Giltiay continues her work in the field of autoimmunity and plans to resume her focus on Sjögren’s in the near future. She was awarded an SSF Research Grant in 2008 for her project, “Role of Act1 in development of Sjögren’s Syndrome.”

Patricia Mongini, PhD recently published a journal article that continues to build on the work from her 2007 SSF Innovative Concept Grant for her project entitled, “B cell-expressed COX-2 and Sjögren’s syndrome development.” The article is:


Dr. Mongini is an Associate Investigator at the Feinstein Institute for Medical Research, New York.

Cuong Nguyen, PhD is a current 2010 SSF Research Grant recipient for his project entitled, “Suppression of TH17 cells using IL-27 gene therapy: A potential therapeutic approach for the treatment of Sjögren’s syndrome patients,” at the University of Florida, Gainesville. Dr. Nguyen already has published three journal articles since the start of his SSF grant:


Lindsey Criswell, MD, MPH
University of California at San Francisco, San Francisco, CA

Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren’s Syndrome

Recent genome-wide association studies have been remarkably successful in identifying genes that contribute to the development of RA, SLE and other complex human diseases. However, recently identified genetic variants explain only a portion of the heritability of these diseases. For example, the ~30 RA risk gene variants identified to date explain only ~35% of the heritability of the disease, and the ~25 SLE risk gene variants identified to date explain less than 10% of the heritability of SLE. This raises the important question of what explains the “missing heritability?” One possibility is that many more genetic variants, each of which contributes only slightly to disease risk, will be identified through performance of even larger genetic studies. Since most of the recent genetic studies have focused on SNPs (single nucleotide polymorphisms), it is also possible that different types of genetic variation, such as variation in the numbers of genes inherited, explains at least some of the missing heritability. It is also possible that interactions between genes, or between genes and environmental factors, explain some of the missing heritability. Recent evidence also suggests that “epigenetic” factors may play an important role in the development of autoimmune diseases. Further, such epigenetic factors may represent a link between genetic and environmental factors in terms of disease susceptibility.

Thanks to a recently awarded grant from the Sjögren’s Syndrome Foundation, we will have the opportunity to examine the contribution of epigenetic factors to the development of Sjögren’s (SS). Epigenetics refers to inherited changes in gene expression that are caused by mechanisms other than DNA base sequence changes. Our study will focus on one important type of epigenetic mechanism, DNA methylation, in which the addition of a methyl group to a gene decreases the expression of that gene. A dramatic example of the potential impact of changes in DNA methylation is provided by the Agouti mouse model. These mice are normally yellow, obese and diabetic. However, after exposure to a diet high in methyl content the offspring (and their subsequent offspring) are brown, thin and not diabetic. Further, after exposure to a demethylating agent the subsequent offspring once again become yellow, obese and diabetic. Several examples illustrating the importance of DNA methylation in humans also exist, including a recent study of identical twins discordant for SLE (i.e., one twin has SLE and the other does not). Javierre and colleagues studied 5 twins discordant for SLE and analyzed the degree of DNA methylation at ~800 sites in the genome. They found that the SLE twin had lower levels of DNA methylation overall and especially at ~50 genes known to play important roles in the immune system. Other work also implicates DNA methylation in the risk of autoimmune disease in humans, but little is known about DNA methylation and risk of SS.

We have thus proposed a pilot study in which we will characterize the DNA methylation profiles of 30 individuals with well-characterized SS meeting established diagnostic criteria and compare their profiles to that of 30 normal healthy controls. Our laboratory will utilize a recently developed method for DNA methylation profiling that will allow us to examine ~450,000 methylation sites genomewide, and we will correlate genetic results with the pathobiologic evaluation of three fluids or tissues: peripheral blood, saliva, and minor (labial) salivary gland biopsy tissue. The valuable biospecimens to be used in this project will be provided by the Sjögren’s International Collaborative Clinical Alliance (SICCA, http://sicca.ucsf.edu). We are grateful for the opportunity to study epigenetic factors in SS and look forward to sharing the results of this pilot project once they become available.

Summary

In 2011, the genetics of SS remain largely unexplored. It is anticipated that genetics will provide insight into key biologic pathways and pathogenic mechanisms in SS. It is projected that multiple genes, probably more than 100, will be involved. Genes will include those involved in the immune system as well as multiple potential target organs. Genes are predicted to vary with clinical disease subphenotypes, stressing the importance of accurate and meticulous clinical observations and description. Genes are likely to vary with population background.

The urgent and ultimate goal in SS is discovering, if not a cure, at least more effective, safe therapies. Identification of disease mechanisms, pathways, and targets is essential to the therapeutic clinical development process for complex diseases, including SS. Recently, the SSF has launched a campaign to expand its research grant program to support research that will lead to identification of therapeutic targets for SS. The emerging clinical research developments should provide an important impetus for industry to partner with the SSF and academics to accelerate the process of clinical trial development and registration of novel drugs for SS.
Helping patients understand that their dry mouth needs to be managed 3 ways is key to counseling. Why? Because if left untreated, dry mouth can lead to some fairly serious dental problems. While sipping water may help, it doesn’t lubricate and protect the mouth the way saliva does. The Biotène system, with its protein-enzyme formulations, offers products in each of the 3 management areas.

1. **Soothe & Moisturize:** Only Biotène offers the choice of a portable spray for on-the-go comfort, a soothing liquid and an effective gel that offers relief, especially at night.

2. **Daily Cleaning:** Only Biotène has 2 mouthwashes to reduce bad breath, and 3 cavity-preventing fluoride toothpastes that are specifically designed for dry mouth sufferers. Plus, our products are alcohol and SLS-free.

3. **Saliva Stimulation:** To help stimulate salivary flow throughout the day, Biotène provides 2 breath-freshening gums.

*Recommend the Biotène system of products to all your patients with dry mouth symptoms.*
4. Inflammation of the Salivary Gland

- Inflammation of the salivary gland can cause swelling. Inflammation can occur as a result of repeated infections, chronic obstruction or tumor of the salivary gland system.

- Chronic inflammation in Sjögren’s can result in salivary gland swelling. For most, this is an episodic occurrence. The swelling can occur in multiple glands at the same time and may be associated with little to no discomfort. For others, the salivary gland swelling is chronic.

- When salivary gland swelling is persistent, close follow-up is necessary because of an increased risk of transition to lymphoma.

**Tests for causes of salivary gland swelling**

- Magnetic resonance imaging (MRI) and computerized axial tomography (CAT Scan) are used to look for structural abnormalities, stones, tumors and details of tumor invasion.

- Fine needle aspiration for cytology may be used if the swelling is discrete and not diffuse.

- Sialography is used to examine duct architecture. This procedure is contraindicated in an individual with a bacterial infection of the gland.

- Sialoendoscopy is used to directly examine duct architecture. The procedure may be used to remove a stone, dilate the ducts or place a sialostent.

- Salivary gland biopsy

- Salivary gland scintigraphy

- Culture and sensitivity of saliva may be done to determine the appropriate antibiotic.

**Management of salivary gland swelling**

1. What to do about obstruction of the salivary gland

- Initial management includes gentle massage of the salivary gland or a “milking” action to try to push saliva past the obstruction allowing the pressure/swelling to partially or completely resolve. (See the Patient Education Sheet in the Fall 2010 issue of the Sjögren’s Quarterly on “How to Massage Salivary Glands.”)

- A mucolytic agent may be used for 5-10 days in an attempt to thin saliva, allowing the saliva to easily pass through the salivary ductal system.

- Drinking plenty of water should be recommended to maintain a well-hydrated state which increases the amount of saliva, helps thin the saliva and keeps it moving through the ductal system.

- Sugar-free hard candies or gum may be used to gently encourage salivary flow. Medication to stimulate salivary flow should not be used during this period as it is difficult to control saliva flow once the medication is taken. Warm compresses may be placed on the cheek or jaw area to increase comfort.

- Acetomenophen or ibuprofen may be taken to reduce associated pain and inflammation.

- Antibiotics may be prescribed if there are signs and symptoms of an infection.

- A medical professional will want to rule out the presence of a stone or stricture with imaging. Any purulent material coming out of the gland orifice may be cultured to determine the appropriate antibiotic. If a stone is not passed, it may be removed by sialoendoscopy or by surgical means, depending on its location.

2. What to do about infection of the salivary gland

- Ensure that your patients are practicing excellent oral hygiene, as this may aid healing and prevent re-infection.

- Warm salt water rinses may be soothing.

- A 0.12% chlorhexidine oral rinse may be considered on a limited basis to decrease levels of bacteria within the mouth.

- Strategies to gently increase salivary flow may be helpful (sugar-free sour drops or gum).

- Tell patients to drink plenty of water to stay hydrated.

- Prescribe an antibiotic as needed. Antibiotics should only be used in case of symptomatic infection and not for gland swelling alone.

- Lab tests may be ordered to rule out a viral infection, other systemic diseases or to get a baseline view of a patient’s metabolic status.

- Complete resolution of the swelling and pain can take several weeks. Failure to improve would suggest abscess formation, stone, or a tumor causing obstruction. Specialized imaging would then be necessary to differentiate between these causes.

3. What to do about tumors of the salivary gland

- Salivary gland tumors are typically managed by an otolaryngologist.

4. What to do about inflammation of the salivary gland

- A patient with SS and chronic salivary gland swelling should be under the care of a Rheumatologist or physician familiar with SS, as there is an increased frequency of lymphoma in this setting.

When salivary gland swelling occurs in a patient, it is important for the medical professional to recognize that symptoms associated with various causes of salivary gland swelling can overlap and that it is important to differentiate between them. A complete history and physical, blood tests, specialized imaging and a biopsy may be performed. Vital signs should be taken to determine if sepsis is an issue. In rare cases, a salivary gland infection can progress to an abscess resulting in airway compromise. When the cause of the salivary gland swelling is identified, proper therapeutic measures and follow-up may be initiated.

**References**


Ask your physician to prescribe Numoisyn today!

Works fast... and lasts.

For Xerostomia

Numoisyn Liquid
Prescribing Information

Ingredients: Water, sorbitol, linseed (flaxseed) extract, Chondrus crispus, methylparaben, sodium benzoate, potassium sorbate, dipotassium phosphate, propylparaben.

How Supplied: 30 mL per bottle or 300 mL per bottle.

Therapeutic Group: Numoisyn Liquid is an oral solution formulated for the relief of chronic and temporary xerostomia (dry mouth), which may be a result of disease, medication, oncology therapy, stress, or aging.

Indications: Numoisyn Liquid is indicated for the treatment of symptoms of dry mouth. Numoisyn Liquid relieves the symptoms of dry mouth by enhancing swallowing, improving speech mechanics, and lubricating the oral cavity like natural saliva. Numoisyn Liquid may be used to replace natural saliva when salivary glands are damaged or not functioning. The viscosity is similar to that of natural saliva.

Contraindications: Numoisyn Liquid are contraindicated in patients with a known history of hypersensitivity to any of the ingredients.

Special Precautions for Use: As Numoisyn Liquid contains linseed (flaxseed) extract, patients with irritable bowel syndrome or diverticular disease or those on a high linseed diet may experience abdominal discomfort.

Warning: Federal law restricts Numoisyn Liquid to sale by, or on the order of, a physician or properly licensed practitioner.

Interactions: There are no known interactions between Numoisyn Liquid and any medicinal or other products.

Directions for Use: Shake bottle well. Take 2 mL (about 1/2 teaspoon) of Numoisyn Liquid and rinse around in the mouth before swallowing. Use as needed.

Side Effects: Patients may experience difficulty in swallowing, altered speech, and changes in taste. If side effects persist or become severe, patients should contact a physician.

Storage: Store at room temperature. Do not refrigerate. Use within 3 months of first opening.

Please Note: Numoisyn Liquid is translucent and may contain some natural particles that do not affect the quality of the product.

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Numoisyn Lozenges
Prescribing Information

Ingredients: Sorbitol (0.3 g per lozenge), polyethylene glycol, malic acid, sodium citrate, calcium phosphate dibasic, hydrogenated cottonseed oil, citric acid, magnesium stearate, and silicon dioxide.

Pharmaceutical Form: Oral lozenge

Contents: 100 lozenges per bottle. Net weight of 40 g (0.4 g per lozenge).

Therapeutic Group: Numoisyn Lozenges are oral lozenges formulated to promote lubrication of oral mucosa that may be dry due to a variety of circumstances, including medication, chemotherapy or radiotherapy, Sjogren’s syndrome, or oral inflammation.

Indications: Numoisyn Lozenges are indicated for the treatment of xerostomia (dry mouth). Numoisyn Lozenges provide temporary relief of dry mouth due to damaged salivary function. Numoisyn Lozenges are formulated to support the natural protection of teeth provided by saliva so that no damage occurs to teeth with repeated use of the lozenges.

Contraindications: Numoisyn Lozenges are contraindicated in patients with fructose intolerance or a known history of hypersensitivity to any of the ingredients.

Warning: Federal law restricts Numoisyn Lozenges to sale by, or on the order of, a physician or properly licensed practitioner.

Interactions: There are no known interactions between Numoisyn Lozenges and any medicinal or other products.

Directions for Use: Let one Numoisyn Lozenge dissolve slowly in the mouth when needed. To obtain optimal effect, move the lozenge around in the mouth. Repeat as necessary. Do not exceed 16 lozenges in 24 hours.

Side Effects: Excessive consumption can cause minor digestive problems.

Storage: Store at room temperature. KEEP OUT OF REACH OF CHILDREN.

Overdose: No overdoses have been reported to date.

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**NIH-Funded Research: Effect of BAFF on threshold of B cell tolerance**

Principal Investigator: David A. Nemazee, PhD, Professor, Department of Immunology, The Scripps Research Institute, La Jolla, California

*Editor’s Note: The NIH awarded $3.5 million to nine investigators for research into Sjögren’s syndrome in 2006 in response to a Request for Applications (RFA). We announced the recipients in the 2007 Winter issue of the *Sjögren’s Quarterly*, and we continue to highlight individual projects periodically for Quarterly readers. Dr. Nemazee’s five-year study is funded by the National Institute of Dental and Craniofacial Research (NIDCR); it started in July, 2006, and is scheduled to end in April, 2011.*

Dr. Nemazee is investigating the role of BAFF (B cell activating factor) and regulation of immune tolerance on the development of Sjögren’s. BAFF is important to B cell proliferation and function. We know that Sjögren’s is associated with B cell hyperactivity, and, that according to studies in mice, autoreactive B cells are more dependent on BAFF than non-autoreactive cells. However, we do not know precisely how BAFF promotes the autoimmune disease process.

Dr. Nemazee and his colleagues discovered an inhibitory BAFF splice isoform, delta BAFF, which might play a key role in modulating the effects of BAFF activity that is too high or too low, and they targeted it for further investigation. They also asked the questions of whether BAFF might affect B cells indirectly through T cell dysregulation and whether BAFF might rescue only B cells that produce autoantibodies of low affinity. Their laboratory aims to determine, in a polyclonal immune system: 1) whether or not BAFF over-expression selectively rescues low-affinity self-reactive clones; 2) whether reduction in BAFF levels by delta BAFF over-expression leads to subnormal levels of basal autoantibody activity and more stringent self-tolerance; and 3) whether autoantibody formation and B cell tolerance are altered in T-cell deficient, BAFF over-expressing mice.

Dr. Nemazee is an immunologist whose lab, The Nemazee Laboratory at The Scripps Research Institute, focuses on how B lymphocytes learn and distinguish between self and non-self antigens. While self-reactive cells occur frequently, the way the immune system deals with these cells can go wrong. Dr. Nemazee’s goal is to determine how and why this happens so that autoimmune diseases such as Sjögren’s can be treated and even prevented.

"Research" Continued from page 9 ▼


With several additional journal articles in the works, Dr. Nguyen shows a true commitment to his focus on Sjögren’s. Dr. Nguyen’s SSF grant is supported by the Galewood Foundation.

**Amirala Pasha**, DO-candidate at the College of Osteopathic Medicine, University of New England was recently selected from a pool of 250 submissions to present a poster at the 2010 Internal Medicine of the American College of Physicians in Toronto, Canada, formerly the Annual Session of the American College of Physicians in Toronto, Ontario. Pasha was a 2009 SSF Student Fellowship Recipient for his project entitled, “The effects of corneal cooling on tear production, blink rate and sensation,” which was supported by the Bannon Humphrey Foundation.

**New Phase 3 Study Launched in the U.K.**

Simon Bowman, PhD, FCRP has received a £1 million award from a medical research charity to launch a Phase 3 clinical trial in the United Kingdom (U.K.) testing the efficacy of rituximab (Rituxan®) in Sjögren’s. Dr. Bowman is a rheumatologist with the University of Birmingham Medical School in the U.K. and an Associate Member of the SSF Medical and Scientific Advisory Board. Arthritis Research UK awarded the funding. Dr. Bowman is collaborating with Arthritis Research UK Professor of Rheumatology at Leeds University, Paul Emery and the Leeds Clinical Trials Unit; Professor Costantino Pitzalis of Queen Mary, University of London; and other colleagues.

The study will include up to 110 Sjögren’s patients, run five years and use fatigue and dryness as the principle symptoms measured. Dr. Bowman ran a smaller trial previously in Sjögren’s and rituximab which enjoyed promising results. Other numerous Phase 1 and 2 trials in rituximab and Sjögren’s include those in the U.S. supported by NIAID at Duke University and the University of Pennsylvania (2005), in the Netherlands at the University Medical Centre Groningen (2006-2008), in Denmark at the University of Copenhagen (2007-2010) and an ongoing trial in France spearheaded by University Hospital in Brest (2008-2013).

Rituximab is a chimeric anti-CD20 monoclonal antibody that was first developed for use in non-Hodgkin’s B cell lymphoma which occurs in Sjögren’s at a relative risk of about 7%. It has since received regulatory approval for use in rheumatoid arthritis (RA) in the U.S. and other countries.
Raynaud’s Syndrome (sometimes called Raynaud’s phenomenon) is defined as repeated episodes of color changes in the fingers and/or toes with exposure to cold temperatures or during episodes of emotional stress. The color changes are due to a spasm of the blood vessels that feed the fingers and toes. The digits typically turn very white, then can take on a bluish color with prolonged exposure to the cold, and finally can turn very red as blood flow resumes. Raynaud’s Syndrome occurs in approximately 15-30% of patients with Sjögren’s syndrome.

Some things that you can do to control your Raynaud’s Syndrome include:

- When you know that you will be exposed to cold temperatures, wear layered clothing. This will keep your core body temperature warm and keep the vessels feeding the fingers and toes from spasm.
- Always carry a jacket with you on outings, as you may find yourself in an unexpectedly cool area.
- Wear a hat and cover your face and ears with a scarf in cold temperatures.
- Always wear hand coverings in cold temperatures. Mittens are best, as they will use the body heat generated by your fingers. However, a good pair of insulated gloves is also helpful.
- Wear heavy socks or layers of socks to keep feet warm at all times.
- Keep your home and office space comfortably warm (greater than 70 degrees is best).
- Avoid reaching into the freezer both at home and in the grocery store.
- Use insulated containers when handling cold drinks or food.
- Rinse food with warm water instead of cold water.
- Wear protective gloves when washing dishes.
- Use disposable heat packs as needed for your hands and feet. These are available at many sporting goods stores.
- Always let the water warm up before getting into the shower, and keep the bathroom door closed while bathing or showering to hold in heat.
- When possible, have a loved one warm up your car before getting into it on a cold day.
- Moisturize your hands and feet every day to prevent your skin from cracking.
- When your hands or feet start to feel cold, wiggle your fingers and toes, move your arms and legs around to get blood flowing, or put your hands under your armpits to warm them up.
- If you have access to water when a flare starts, run warm water over your fingers and toes until skin color returns to normal.
- Do not smoke — this constricts the blood vessels that feed the hands and feet.
- Talk to your doctor about your symptoms. Several medications can be used to help the vessels stay dilated, including a class of blood pressure medications called calcium channel blockers. Some medicines, such as beta blockers used for high blood pressure, may make Raynaud’s worse.
SSF Presents Outstanding Abstract Awards at ACR

The Sjögren’s Syndrome Foundation (SSF) recognized three young investigators for their exceptional work in Sjögren’s during the American College of Rheumatology (ACR) Annual Meeting. Kaleb M. Pauley, PhD of the University of Florida, Gainesville won the SSF Outstanding Abstract Award for her poster presentation entitled, “Receptor-Mediated Small Interfering RNA Delivery in Sjögren’s Syndrome.”

Two Honorable Mention Awards also were presented. Jacques-Olivier Pers, DDS, PhD of Brest University, Brest, France was recognized for his abstract, “Delta4BAFF, an Alternate-Splice Isoform that Acts as a Transcription Factor to Enhance BAFF Production in Primary Sjögren’s Syndrome.” Nienke Roescher, MD, MSc of the Academic Medical Center-University of Amsterdam, The Netherlands, was recognized for her abstract, “Local TACI-Ig Gene Therapy of the Salivary Gland of NOD Mice Reduces Auto-Immune Inflammation by Affecting the B Cell Compartment.”

The SSF Outstanding Abstract Award is designed to recognize excellent research and encourage new investigators to continue their focus on Sjögren’s. The winner receives US$500.00 along with a framed certificate. Elaine Alexander, MD, PhD, SSF Medical and Scientific Advisory Board Chair, presented the awards during the Sjögren’s Syndrome Study Group co-led by Nikolay Nikolov, MD and Gabor Illei, MD, PhD, MHS.

Abstract Submission and Registration Available

for the 11th International Symposium on Sjögren’s Syndrome

www.sjogrensymposium-athens2011.org

Athens, Greece, September 28th to October 1st 2011