Sjogren’s Syndrome: an overview

Arthur A.M. Bookman MD FRCPC
Coordinator, Multidisciplinary Sjogren’s Clinic,
University Health Network
Disclosures

• Member Medical Advisory Boards:
  – Eli Lilly Canada Ltd
  – Janssen Pharmaceuticals

• Principle Investigator Clinical Trials:
  – GlaxoSmithKline
  – Novartis

• Chair, Medical Advisory Board, Sjogren’s Society of Canada
What is Sjogren’s Syndrome?

A. The main cause of dry eye and dry mouth?
B. An autoimmune disease causing dry eyes and dry mouth?
C. The presence of parotid and lacrimal enlargement with dry eyes and mouth
D. An autoimmune disease that can cause systemic illness, dry eyes and dry mouth
E. An autoimmune disease that cannot be diagnosed without the finding of dry eyes and mouth
How do you make a diagnosis of Sjogren’s Syndrome?

A. Demonstrate dry eyes with any test that shows poor tear formation
B. Do a blood test to demonstrate autoantibodies
C. Do a minor salivary gland biopsy
D. Demonstrate the existence of predefined criteria
E. Demonstrate dry mouth by collecting saliva
Sjogren’s Syndrome can present with-

A. Shortness of breath
B. Skin rash
C. Joint pain and swelling
D. All of the above
E. B. and C. above
Learning Objectives

1. Be able to recognize true Sjogren’s Syndrome through the 2016 Classification Criteria
2. Be able to describe the mechanisms of water transport through Aquaporin
3. Discuss the focus of therapeutic options for Sjogren’s associated dry eye
4. Be able to list the extraglandular features of Sjogren’s Syndrome
WHAT IS SJOGREN’S SYNDROME?

Defined by a blood test? NO
Defined by a biopsy? NO
Defined by dry eyes and/or mouth? NO
Sjogren’s Syndrome

• Is an autoimmune disease
• That most prominently causes inflammation and malfunction of the salivary and lacrimal glands
• But also induces a highly overactive immune system
• And causes extra-glandular complications in up to 30% of patients
There have been 3 sets of internationally accepted criteria since 2002. They have cost millions of dollars to develop and test. The latest are the 2016 ACR-EULAR CLASSIFICATION CRITERIA.

SJOGREN’S SYNDROME IS DEFINED BY CRITERIA.
### 2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

<table>
<thead>
<tr>
<th>Item</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer's Test &lt; 5mm/5min</td>
<td>1</td>
</tr>
<tr>
<td>Van Bijsterveld Score ≥ 4/9 (Rose Bengal or Lissamine Green) or Ocular Staining Score ≥ 5</td>
<td>1</td>
</tr>
<tr>
<td>Unstimulated Salivary Flow ≤ 0.1ml/minute</td>
<td>1</td>
</tr>
<tr>
<td>Positive anti-Ro (SS-A) antibody test</td>
<td>3</td>
</tr>
<tr>
<td>Minor Salivary Gland Bx Focus Score ≥ 1</td>
<td>3</td>
</tr>
</tbody>
</table>

A score of ≥ 4 enables a classification as Primary Sjogren’s Syndrome

Shiboski et al. ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 35–45
Schirmer’s test ≤5mm/5min
### 2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

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<td>1</td>
</tr>
<tr>
<td>Ocular Staining Score &gt; 5</td>
<td></td>
</tr>
<tr>
<td>Unstimulated Salivary Flow ≤ 0.1ml/minute</td>
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</tr>
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A score of > 4 enables a classification as Primary Sjogren’s Syndrome

Shiboski et al. ARTHRITIS & RHEUMATOLOGY Vol. 69, No. 1, January 2017, pp 35–45
Van Bijsterveld score ≥4/9

(Rose Bengal or Lissamine Green dye)
Ocular Staining Score: 5/12  Fluorescein for CORNEA (cobalt blue light):

1. 1-5 PEE
2. 6-30 PEE
3. >30 PEE
4. over pupil = 1 point
5. confluent = 1 point
6. filaments = 1 point

MAX = 6
OCULAR STAINING SCORE: Lissamine green staining for conjunctiva

Top left = score 0 < 10 discrete individual green dots  
Top right = score 1 >10 and <33 green dots  
Bottom left = score 2 with 33 to 100 green dots  
Bottom right = score 3 > 100 individual green dots
SICCA Ocular Staining Score

**Staining pattern score:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dots</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-9</td>
</tr>
<tr>
<td>1</td>
<td>10-32</td>
</tr>
<tr>
<td>2</td>
<td>33-100</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Lissamine Green (conjunctiva only)  | Fluorescein (cornea only)

**Right Eye**

**Left Eye**

Extra points—fluorescein only:  
- □ +1 - patches of confluent staining
- □ +1 - staining in pupillary area
- □ +1 - one or more filaments

**Total Ocular Staining score:**

Total ocular staining scores of 0 to 12 per eye assess the range of severity for keratoconjunctivitis sicca.
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Shiboski et al. ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 35–45
ACR-EULAR Classification criteria

Unstimulated Salivary Flow <1.5ml/15 minutes
2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

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<tr>
<td>Schirmer’s Test $&lt; 5$mm/5min</td>
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</tr>
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<td>3</td>
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</tbody>
</table>

A score of $> 4$ enables a classification as Primary Sjogren’s Syndrome

Shiboski et al. ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 35–45
Ro

M. Ohlsson et al. Scandinavian journal of Immunology 56:456-469, 2002
Initiation: Autoantigens

Ro/SSA, La/SSB:

• Assoc with longer disease duration
• Assoc with extraglandular manifestations
• Assoc with higher focus score in MSGs
# 2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

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Shiboski et al. ARTHRITIS & RHEUMATOLOGY Vol. 69, No. 1, January 2017, pp 35–45
2016 ACR-EULAR Classification criteria

Minor salivary gland biopsy

Focus* score ≥1

* FOCUS = Clump of ≥ 50 lymphocytes

Criteria for an adequate biopsy:

- *focal lymphocytic sialadenitis*,
- *specimen size ≥ 4mm²*
Ultrasound: expanding role in diagnosis
THE GLAND IS NOT DESTROYED IN SJOGREN’S SYNDROME
WHY DOES IT STOP WORKING?
AQUAPORIN (AQP) WATER TRANSPORT MOLECULES
AQUAPORIN5 (AQP5) WATER TRANSPORT CHANNELS

Salivary Duct-drains to mouth

Transporting epithelial cell

Apical

Basal

Extracellular fluid
Subcellular distribution of aquaporin 5 in salivary glands in primary Sjögren’s syndrome

Dimitra Beroukas, Jenny Hiscock, Roland Jonsson, Sally A Waterman, Tom P Gordon

Figure 2: Confocal microscopy of aquaporin 5 staining in labial salivary glands
Control (A) and patient with PSS (B). Apical and intercellular canalicular localisation is seen. Scale bar=15 μm.
SJOGREN’S SYNDROME: DISTORTED LOCALIZATION OF AQUAPORIN5

Why does this happen?
- Antibodies to Aquaporin (SjS 28%, Devic’s Disease 100%)
- Disruption from Inflammation
- Radiation

Can we restore Aquaporin?
- In mice...yes
- In humans ....maybe
RESTORING AQUAPORIN MAY ALLOW SALIVA AND TEARS

CURRENT THERAPEUTIC STRATEGIES BEING INVESTIGATED:

gene therapies
- p-hAQP1 coupled to ultrasound
  - AdhAQP1, AVV2hAQP1, AdShh, AdHSP25

cell-based therapies
- salivary gland-derived epithelial stem cells
- nonepithelial cell types
- salivary gland organoids
- bioactive compounds

ultrasound therapies
- alone coupled to p-hAQP1 gene therapy
# 2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

## Item Points

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</table>

**TO WHOM DO THESE CRITERIA APPLY?**

Shiboski et al. *Arthritis & Rheumatology* Vol. 69, No. 1, January 2017, pp 35–45
ACR-EULAR Classification Criteria

To whom do these criteria apply?

1. Anyone who answers yes to validated questions for dry eye or mouth

2. Anyone who presents with Systemic Disease that might be explained by Sjogren’s (see ESSDAI)

ESSDAI: EULAR Sjogren’s syndrome disease activity index
Sjogren’s Syndrome Diagnosis

I. Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
Sjogren’s Syndrome
Diagnosis

II. Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
2016 ACR-EULAR Classification Criteria

New Concepts:
1. Anti-La in isolation is not a criterion
2. These are not criteria for secondary Sjogren’s Syndrome
3. These criteria can be applied to patients presenting with unexplained systemic disease
4. These criteria define patients for study or clinical trial
5. These are not diagnostic criteria
6. Absence of anti-Ro & -ve Bx = NO SJOGRENS
Sjogren’s Syndrome

EXTRA-GLANDULAR DISEASE
Sjogren’s Syndrome

• Primary Sjogren’s can overlap with:

- Sjogren’s Syndrome
- Primary Biliary Cirrhosis
- CREST Syndrome (Limited Scleroderma)

46 (17.9%) had AMA; 15 had PBC (5.7%)
6 had ACA (2.35%)
### Sjogren’s Syndrome: consequences of extra-glandular disease

<table>
<thead>
<tr>
<th>System</th>
<th>Multidisciplinary</th>
<th>Sjogren’s Clinic (262 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Pain</td>
<td></td>
<td><strong>137 (52.3%)</strong></td>
</tr>
<tr>
<td>Raynaud’s</td>
<td></td>
<td><strong>83 (31.8%)</strong></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td><strong>9 (3%)</strong></td>
</tr>
<tr>
<td>Intrstitl Neph.</td>
<td></td>
<td><strong>18 (6.8%)</strong></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td><strong>8 (3%)</strong></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td><strong>16 (6%)</strong></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td><strong>18 (6.8%)</strong></td>
</tr>
<tr>
<td>Hypothyr</td>
<td></td>
<td><strong>45 (17.9%)</strong></td>
</tr>
</tbody>
</table>
Rash and Anti-Ro antibody

.....seen in Subacute Cutaneous Lupus
Neonatal Lupus Rash and Anti-Ro antibody.....
Congenital Heart Block and Anti-Ro antibody.....

8 weeks; 2.95 kg

5 years; 17.2 kg
Sjogren’s Syndrome and Pneumonitis (3%)
Sjogren’s Syndrome and Raynaud’s Phenomenon (32%)
Sjogren’s Syndrome and Vasculitis (6%)
Sjogren’s with Non-Hodgkins B-Cell Lymphoma (7%)
SJOGREN’S SYNDROME MANAGEMENT

LOCAL MEASURES FOR DRY EYE AND SJOGREN’S SYNDROME
Blepharitis

**Rx:**
- Hot compresses
- Lid Scrubs
- Liposomal Spray

www.Eyedolatryblog.com
Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease

Figure 1. Change from baseline in corneal staining. Mean value ± standard error. Graded on a scale from 0 to 5.
Table 3. Most Common* Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>CsA 0.05% (n = 293)</th>
<th>CsA 0.1% (n = 292)</th>
<th>Vehicle (n = 292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning eye</td>
<td>43 (14.7%)</td>
<td>47 (16.1%)</td>
<td>19 (6.5%)</td>
</tr>
<tr>
<td>Stinging eye</td>
<td>10 (3.4%)</td>
<td>13 (4.5%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Discharge eye</td>
<td>9 (3.1%)</td>
<td>2 (0.7%)</td>
<td>7 (2.4%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>9 (3.1%)</td>
<td>3 (1.0%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>6 (2.0%)</td>
<td>9 (3.1%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>5 (1.7%)</td>
<td>9 (3.1%)</td>
<td>12 (4.1%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>3 (1.0%)</td>
<td>10 (3.4%)</td>
<td>4 (1.4%)</td>
</tr>
</tbody>
</table>

CsA = cyclosporin A.

* Those reported by ≥3% of patients in either cyclosporine group.
LIFITEGRAST (Xiidra®)

Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that inhibits T-cell-mediated inflammation (an underlying factor in Dry Eye Disease)

It is an ICAM-like adhesion molecule that attaches to LFA-1 on T-cells Preventing them from attaching to ocular epithelium

Figure from Journal of Pediatric Ophthalmology and Strabismus. 2015;52(2):75
Fluorescein Staining of Cornea

Staining is scored 0-4 in each area

Significant Primary Outcome at 84 days

Placebo

5.0% LIF

Total

Inferior

Superior

Central

P=0.0007

P=0.0392

P=0.0148
Xerophthalmia

Steroid Drops
• Best used as initial treatment for distressful dry eye
  – No more than 5-30 days
  – Beware glaucoma

Autologous Serum Drops
20% diluted serum

www.reviewofoptometry.com
Management of Xerophthalmia

Moisture Guard Spectacles:

www.dryeyepain.com
Xerophthalmia

Punctal Plugs
- Lower lids;
- add Upper lids

Beware:
- Proper Sizing
  - Infection/Loss
- Overflow tearing
  - Schirmers < 6-7mm/5 min

Cauterization
- Can recannulate
Scleral Contact Lens

Image from www.Sarahartman.com
SLK
Superior-Limbic Keratoconjunctivitis

- Upper bulbar Conjunctiva: foldings, hyperemia, redundancy, and filament formation
- Resulting in: Foreign body sensation, photophobia, excessive blinking and ocular burning and pain
- Can be resected

Seen with
- Hypothyroidism
- Graves Disease
- Sjogren’s Syndrome
Xerophthalmia
Complications

Filamentary Keratitis
Diagnosis: Slit Lamp Examination

Treatment:
• Autologous serum
• Steroid
• Scleral Contacts
• Surgery
SYSTEMIC TREATMENT FOR SYSTEMIC COMPLICATIONS
Systemic management

- **Prednisone**
  - Minimal effect on parotomegaly, no effect on xerostomia, exhaustion, xerophthalmia

- **Hydroxychloroquine**
  - 3 double blind control trials: Ineffective for xerostomia, xerophthalmia, fatigue or most systemic features
  - Helpful for cutaneous vasculitis, arthralgia
Immunosuppression

- No controlled trials for:
  - Cyclophosphamide
  - Methotrexate
  - Mycophenolate
  - Cyclosporin

BIOLOGICS: ‘rituximab’

Diagram showing the mechanism of action of rituximab. It targets CD20 on B cells, leading to apoptosis. It also activates complement (CDC) and immune effector cells via ADCC.

Legend:
- Yellow = Variable regions: mouse
- Red = Constant regions: human
<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Dass, et al 2008</td>
<td>Reduction of fatigue VAS in Sjogren syndrome with rituximab</td>
<td>17 patients: Benefit (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Effectiveness of Rituximab in SjS</td>
<td>30 patients: USSF &amp; SSF improved x 6 mos</td>
</tr>
<tr>
<td>J.M. Meijer et al. 2010</td>
<td></td>
<td>120 pts. Failed at 24 wks (2 of 4 <strong>VAS scores</strong>- Global, Pain, Fatigue, Dryness)</td>
</tr>
<tr>
<td>V. Devauchelle-Pensec et al 2014</td>
<td><strong>TEARS</strong> (22.4% vs. 9.1%; P &lt; 0.036). Salivary Flow and Parotid U/S improved</td>
<td>133 pts. Failed at 48 wks to dec. <strong>VAS</strong> fatigue &amp; oral dryness by 30%</td>
</tr>
<tr>
<td>S. Brown et al 2014</td>
<td><strong>TRACTISS</strong> Salivary Flow improved</td>
<td></td>
</tr>
</tbody>
</table>
MAYBE WE ARE DOING IT WRONG

• Failure of medication may indicate:
  – **Wrong outcome measures**
    • Intractible end-organ damage
    • Composite VAS scores
  – **Wrong patients**
    • Established disease
    • Few extra-glandular variables
  – **Wrong targets**
    • Reactive BAFF
    • Antigen processing
    • Germinal Centre formation
SO…..WE INVENTED ESSDAI:
The **EULAR Sjögren’s Syndrome Disease Activity Index**

<table>
<thead>
<tr>
<th>12 Domains (weight)</th>
<th>Activity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional (3)</td>
<td>0, 1, 2</td>
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<tr>
<td>Lymphadenopathy (4)</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>Glandular (2)</td>
<td>0, 1, 2</td>
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<tr>
<td>Articular (2)</td>
<td>0, 1, 2, 3</td>
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<tr>
<td>Cutaneous (3)</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>Pulmonary (5)</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>Renal (5)</td>
<td>0, 1, 2, 3</td>
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### Ongoing Trials in PSS Listed at ‘Clinical Trials.Gov’:

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Sponsor</th>
<th>No. subjects</th>
<th>Inclusion criteria</th>
<th>Primary end point</th>
<th>Estimated completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02291029</td>
<td>CFZ 533, anti-CD40 monoclonal Ab</td>
<td>Novartis</td>
<td>30</td>
<td>ESSDAI ≥6</td>
<td>ESSDAI change W12</td>
<td>July 2016</td>
</tr>
<tr>
<td>NCT02334306</td>
<td>AMG 557/MEDI587, anti-ICOS-L monoclonal Ab</td>
<td>MedImmune/Amgen</td>
<td>42</td>
<td>ESSDAI ≥6 Anti-SSA/SSB and IgG &gt;16 g/L or RF +</td>
<td>ESSDAI change D99</td>
<td>November 2016</td>
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<tr>
<td>NCT01782235</td>
<td>Tocilizumab Phase 3</td>
<td>Strasbourg University</td>
<td>110</td>
<td>ESSDAI ≥5 Anti-SSA/SSB</td>
<td>Improvement ESSDAI ≥3</td>
<td>March 2017</td>
</tr>
<tr>
<td>NCT02149420</td>
<td>VAY 736, anti-BAFF-R monoclonal Ab</td>
<td>Novartis</td>
<td>30</td>
<td>ESSDAI ≥6 ANA (≥1:160) Anti-SSA/SSB Sal. flow &gt;0</td>
<td>ESSDAI change W12</td>
<td>June 2017</td>
</tr>
<tr>
<td>NCT02067910</td>
<td>Abatacept Phase 3</td>
<td>Gröningen University and BMS</td>
<td>88</td>
<td>ESSDAI ≥5 Disease duration ≤7 Positive parotid biopsy</td>
<td>ESSDAI W24</td>
<td>July 2018</td>
</tr>
<tr>
<td>NCT02610543</td>
<td>UCB5857 Pi3kinase inhibitor</td>
<td>UCB</td>
<td>58</td>
<td>ESSDAI ≥5 Anti-SSA/SSB Sal. flow&gt;0</td>
<td>ESSDAI change W12</td>
<td>March 2017</td>
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<tr>
<td>NCT02631538</td>
<td>Belimumab/Rituximab co-administration</td>
<td>GlaxoSmithKline</td>
<td>70</td>
<td>ESSDAI ≥5 Anti-SSA/SSB Sal. flow&gt;0</td>
<td>Number of participants with SAEs W104</td>
<td>October 2018</td>
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What is Sjogren’s Syndrome?

A. The main cause of dry eye and dry mouth?
B. An autoimmune disease causing dry eyes and dry mouth?
C. The presence of parotid and lacrimal enlargement with dry eyes and mouth
D. An autoimmune disease that can cause systemic illness, dry eyes and dry mouth
E. An autoimmune disease that cannot be diagnosed without the finding of dry eyes and mouth

Answer: D
How do you make a diagnosis of Sjogren’s Syndrome?

A. Demonstrate dry eyes with any test that shows poor tear formation
B. Do a blood test to demonstrate autoantibodies
C. Do a minor salivary gland biopsy
D. Demonstrate the existence of predefined criteria
E. Demonstrate dry mouth by collecting saliva

Answer: D
Sjogren’s Syndrome can present with-

A. Shortness of breath  
B. Skin rash  
C. Joint pain and swelling  
D. All of the above  
E. B. and C. above

Answer: D
CONCLUSIONS

• Sjogren’s Syndrome has been better defined
• Diagnosis is made by criteria
• Criteria now recognize the many patients that present with systemic illness
• Dryness is disproportionate to the pathology in the glands
• Aquaporin distortion may be the explanation that offers hope for more effective therapy for dry eyes & mouth
• New drugs are in trial for systemic disease
THANK YOU