Inflammation Pathways

Siam Oottamasathien, MD FAAP FACS
Associate Professor of Surgery and Pediatric Urology
Research Associate Professor of Medicinal Chemistry
Director of Pediatric Urology Basic Science Research
Disclosures

A. I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
   – Glycomira Therapeutics, LLC
Background and significance

- **Mechanisms** driving inflammation, specifically those involved in pelvic pathways are crucial to elucidate.

- Enhanced understanding which unravels “real” *bench to bedside* approaches.

- Innovative **biologic** and **biopolymer** therapeutics targeting pelvic inflammatory pathways.
Innovative therapeutics

- Semi-Synthetic GlycosAminoGlycan Ethers (SAGEs) – targeting Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)
- Amnion/Chorion (AmnioFix™) Powder – targeting IC/PBS
- Silk-ElastinLike Protein Polymers (SELPs) – biopolymer carrier targeting Radiation-Induced Proctitis (RIP)
SAGE compounds

• Novel therapeutic polysaccharides developed from modified hyaluronic acid (HA)

• Unique sulfation and alkylation patterns to mimic Heparin without anti-coagulant profile, preserving potent anti-inflammatory effects

• US Patent Methods for Treating or Preventing Urological Inflammation #8,343,942
SAGE as an anti-inflammatory (preclinical)

- Hypothesis: SAGE compounds can attenuate anti-microbial peptide (LL-37) induced cystitis

- SAGE pre-treatment “bladder armor”: minimal inflammation, MPO 22X diminished activity

- SAGE post-treatment: moderate inflammation, PMNs in deeper layers, MPO 2.5X diminished activity

Oottamasathien, Prestwich et al. J Urol. 2011
SAGE versus other anti-inflammatories (preclinical)

- SAGE vs Heparin vs Chondroitin Sulfate vs Sodium Pentosan Polysulfate
- SAGE outperformed in almost all measures (bladder weight, necropsy score, histology score, IL-6, PTX-3, MPO, SAP)

SAGE attenuates pain (preclinical)

- Time course experiment (12h, 24h, 48h, 72h)
- SAGE attenuated pain to near saline control levels at almost all time points and all von Frey filament forces

Figure 15. SAGE attenuation of LL-37 induced cystitis pain. (A) Saline instillation only (control); (B) LL-37 instillation only; (C) SAGE pretreatment followed by LL-37 challenge. (B) illustrates LL-37 induced cystitis elicits significant bladder pain. (C) illustrates SAGE's ability to attenuate pain to near saline control levels at almost all time points and all von Frey filament forces.
SAGE preserves voiding patterns (preclinical)

- Saline vs LL-37 vs SAGE pre-treatment followed by LL-37, voided spot assay (VSA) at 24 hrs (4 hr evaluation)

- SAGE pre-treatment preserved voiding patterns to near saline (control) levels

Saline  LL-37  SAGE pre-treatment
SAGEs are potent mast cell inhibitors (preclinical)

[LL-37] μM

Oottamasathien, Prestwich et al. J Urol. 2013
SAGEs are potent IL-33 inhibitors (preclinical)
Amnion/Chorion powder (preclinical)

- Evidence for efficacy mostly from Wound Healing studies, unknown as an intravesical agent or in surgical applications
Amnion/Chorion anti-inflammatory (preclinical)

- A/C pre-treatment yields significant reduction in MPO activity (1.33 ng/mL)
- A/C post-treatment yields moderate reduction in MPO activity (5.88 and 8.79 ng/mL)
Amnion/chorion attenuates pain (preclinical)

- Moderate reduction in pain for both A/C pre-treatment and post-treatment approaches.
Amnion/chorion preserves voiding patterns (preclinical)

- LL-37 vs A/C pre-treatment followed by LL-37 vs LL-37 followed by A/C post-treatment, voided spot assay (VSA) at 24 hrs (4 hr evaluation)

- A/C pre-treatment preserved voiding patterns to near saline (control) levels

 LL-37
 Amnion/chorion pre-treat
 Amnion/chorion post-treat
SELP compounds

- Silk-Elastinlike Protein polymers are innovative hydrogels
- Aqueous at Room T then Solid at Body T
- Enables sustained delivery of therapeutics over an extended period of time
- Advantage: control over gelation kinetics and viscosity, bioactive agent release, biodegradation and elimination
SELP with SAGE

• Urologic application: radiation therapy for pelvic cancer (e.g. prostate)

• Controlled release of SAGE from SELP: reduce frequency of administration, improve drug pharmacokinetic profile, reduce systemic side-effects, increase drug concentration at site of action

• Goal: SELP-SAGE to ameliorate radiation-induced proctitis (RIP)
SELPI with SAGE

- Thermoresponsive enema transitions in < 5 min from liquid to solid gel
- Gels then release 50% of their payload within 30 min
- Rheology at 37°C SAGE (100 mg/mL) with SELP: enhances rate of gelation, reduction of final rigidity = rapid gel and soft
SELP with SAGE (preclinical)

- SELP hydrogel enhances SAGE delivery

- In-vivo results: labeled SAGE demonstrated diffuse and deep rectal tissue penetration (30 min dwell, 3 hr evaluation)
SELP with SAGE (preclinical)

- 35 Gy of radiation exposure

- SAGE in SELP demonstrated a protective effect within 7 days of radiation (preserved tissue architecture and minimal evidence of inflammation)
SELP with SAGE (preclinical)

- 35 Gy radiation exposure, pain evaluation after 1 week
- Response rates: 75% SELP alone vs 56.7% SELP with SAGE (1 gm filament)
- Successful attenuation of pain with SELP-SAGE compounds
Summary

• **Significance**
  – Understanding Inflammation Pathways crucial towards identification of future therapeutic targets

• **Innovation**
  – Collaborative efforts with Medicinal Chemistry, Pharmaceutical Chemistry, Nanomedicine yields true “bench to bedside” therapeutics and novel approaches

• **Impact**
  – SAGE and Amnion/Chorion technology may be viable treatment options for IC/PBS
  – SELP biopolymer carriers combined with drug therapeutics could treat a diverse array of disease conditions
Funding

- NIH NIDDK **R01 – 1R01DK100868-01**
  Treatment of Bladder Pain by Novel Glycosaminoglycan Derivatives

- Huntsman Cancer Institute – University of Utah Pilot Grant
  Enhanced Delivery of Glycosaminoglycan Ethers for Prevention of Radiation Induced Bladder Cystitis and Rectal Proctitis

- MiMedx – Basic Science Pilot Grant
  Benign Urologic Disease Investigation of Amniotic Membranes
THANK YOU