Identification and development of a 1st in class naturally-derived protein that drives mucosal healing and is orally delivered by an engineered cellular therapy targeting the gastro-intestinal tract.

Joseph Dal Porto, Ph.D., Chief Scientific Officer
On behalf of SECOND GENOME
Speaker Conflict of Interest Disclosure

Dr. Dal Porto is an employee of Second Genome.
455: potential for novel, 1st-in-class therapy to improve mucosal healing through Inhibition of PAI-1/2

**Discovery and Development**

- **Healthy**
- **Disease (IBD)**
- Microbiome comparison healthy vs. diseased
- Define and ‘mine’ microbial secretome
- Identify molecules for mucosal healing
- Identify target, characterize MOA, explore Rx opportunity
- Optimized potency, stability and developed for GI-restricted delivery

**Therapeutic Approach**

- SG-5-00455
  - orally delivered GMO
  - gut-restricted activity
  - good predicted safety
- Damaged mucosa
- Block PAI activity

Improved mucosal healing
455: Improve barrier function and promote repair through direct binding & modulation of PAI-1/2

Mucosal Barrier Damage
Chronic inflammation causes dysregulated healing responses which can lead to pathogenic matrix deposition, pro-inflammatory signaling and fibrosis.

Excessive PAI-1/2 impacts wound healing, immune cell modulation and tissue remodeling.

Disease phenotype
- Fibroblast-myofibroblasts differentiation
- Epithelial mesenchymal transition
- Exacerbated inflammatory response (e.g., neutrophilia)
- ECM accumulation → Fibrosis

Healthy phenotype
- Reduction in fibrosis
- Extracellular matrix regulation
- Increase matrix-metalloproteases activity
- Reduced inflammatory signaling

©ECCO’22 Virtual Congress - Speaker: Joe Dal Porto (CSO)
776 binds and modulates plasminogen activator inhibitors Type 1 & 2 (PAI-1/2)

**PAI-1 binding**

- **Octet assay**
  - $K_D \approx 2.5\,\mu M$
  - SOURCE: TGFβ-stimulated colonic fibroblasts (CCD18)

**Endogenous PAI-1 pull down**

**In vitro functional inhibition of PAI-1/2**

- **PAI-1**
  - TFPI-2 0776
  - TPX
  - SOURCE: TGFβ-stimulated colonic fibroblasts (CCD18)

- **PAI-2**
  - TFPI-2 0776
  - TPX

**Improvement in epithelial barrier function**

- Trans-epithelial electrical resistance (TEER)
  - 'Injury' to epithelial monolayer is induced by exposure to heat killed E. Coli (HK E. coli)
  - TPX: Tiplaxtinin, a Wyeth PAI-1 inhibitor no longer in development
  - MLCK - Myosin light chain kinase inhibitor peptide 18
455(776) inhibition of PAI-1/2 promotes mucosal healing in models of IBD

In vivo efficacy and improved epithelial matrices in DSS (6-day) colitis

Clinical Disease Score & Colon Wt/L

Reduced Collagen Deposition in Colon

Sirius red staining for collagen

In vivo efficacy & pharmacodynamic activity in DNBS (14-day) colitis

Clinical Disease Score

Active tPA in Distal Colon Tissue

Reduced Plasminogen in Distal Colon

Reduction of wound healing factors in DNBS (14-day) colitis

Reduced Fibrinogen in Distal Colon
455 – broad therapeutic potential in pathologies where intestinal mucosal healing is disrupted

**Phase 1 and Phase 2**

- **SAD/MAD**
  - Dose escalation
  - **Dose 1** → Dose 2
  - Ph1b: High dose
  - 4 week study
  - Ph2: Low dose
  - Monotherapy
  - Add-on to 5-ASA/αTNF

**Late stage development**

- Moderately to severely active Ulcerative Colitis.
- Moderately to severely active Crohn’s Disease.
- Pouchitis.

IND filing in 2022, Ph1b POM data expected in 2023

©ECCO’22 Virtual Congress - Speaker: Joe Dal Porto (CSO)
Second Genome’s novel mucosal healing therapeutic program

**Indication:**
Inflammatory bowel diseases (IBD)

**Administration:**
Oral capsule, via engineered L. lactis

**Goal:**
promote mucosal healing

**Discovered:**
Healthy human microbiome

- **Peptide:** SG-2-0776
- **Target:** PAI-1 / PAI-2
  - **Stage:** IND Enabling
  - **IP filed**

**Summary**

- 455 is a novel class of therapeutic targeting PAI-1/2 to drive mucosal repair mechanisms directly in the GI tract
- Offers the ability to modulate a previously untargeted mechanism that is preclinically well validated and active in patients with inadequate response to IBD medicines
- Strong precision medicine strategy potential to identify target patient population
- Expected favorable safety and product profile supports potential use as adjunct therapy in IBD