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# Harnessing the Melanocortin System to Heal Inflammatory Diseases

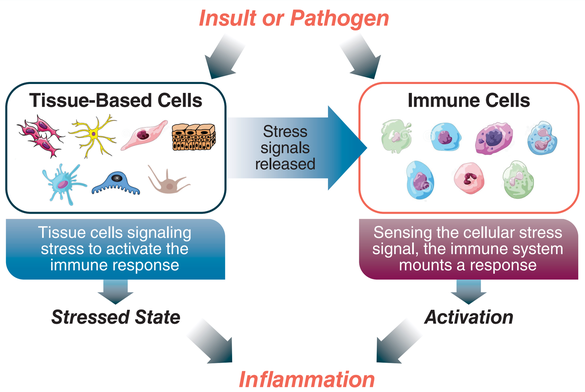
**Paul S. Kayne, PhD; Priyanka Dhingra, PhD; Alison Obr, PhD; John H. Dodd, PhD; Carl Spana, PhD**

Palatin Technologies, Inc., Cranbury, NJ

## INTRODUCTION

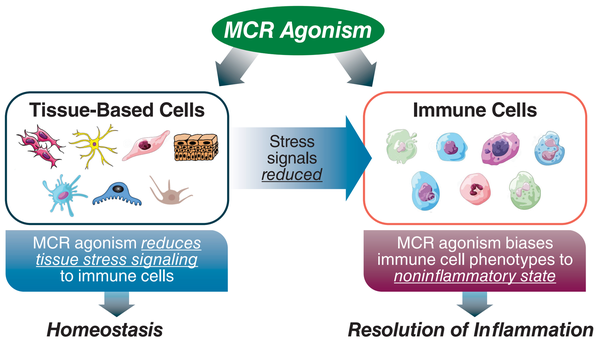
- Melanocortins are a family of hormone agonists that include several melanocyte-stimulating hormones (α, β, and γ-MSH) and the adrenocorticotropin hormone[1-3]
  - These hormones bind to melanocortin receptors (MCRs) to exert their effect
- The melanocortin system plays an essential role in resolving inflammation by returning tissue-based cells and the immune system to homeostasis from the inflamed state (**Figure 1**)[4,5]

### Figure 1. The Inflammatory Process in Health and Disease[4]




- In disease, the immune response persists to the detriment of the patient
- Anti-inflammatory medicines can be effective, but have potential issues[6-8]
  - They may block aspects of the immune response
  - They may impede the immune response in uninvolved tissues
  - Inhibiting the inflammatory system can lead to adverse events
  - Long-term use increases risk
  - Efficacy must be balanced against safety
- The melanocortin system is the endogenous pathway for resolving inflammation
- Melanocortins have a wide range of anti-inflammatory properties such as inhibiting leukocyte activation by suppressing proinflammatory cytokine production[9,10] and protecting tissues from the inflammatory response[10-12] (**Figure 2**)

### Figure 2. The MCR System and Stress[5,10,13-15]




MCR, melanocortin receptor.

**Palatin's compounds harness the melanocortin system in patients with disease to return them to a healthier state**

- To create therapeutic candidates to exploit this, 3 peptides were designed to agonize melanocortin receptor 1 (MC1R), 1 of the 5 MCRs (also including MC2R, MC3R, MC4R, and MC5R)
- Two of these agonists are in clinical trials: PL9643 for dry eye disease (DED) and PL8177 for ulcerative colitis (UC). The third, PL9654, has been studied in multiple retinal disease models

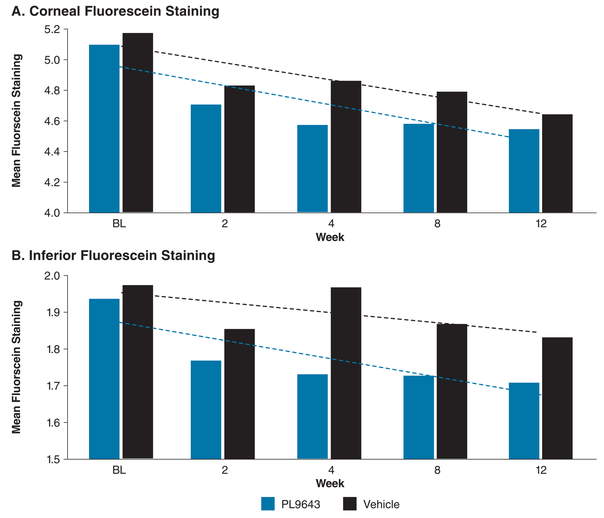
### *PL9643 FOR DED*

- Melanocortin agonists have the potential to treat ocular conditions and pathologies from dry eye to diabetic retinopathy (DR) with at least the same efficacy as glucocorticoids but with a better safety profile[16-18]
- PL9643 is a synthetic MCR pan-agonist (not active at MC2R) being investigated for anti-inflammatory ocular indications, including DED

### *Phase 3 MELODY-1 Study*

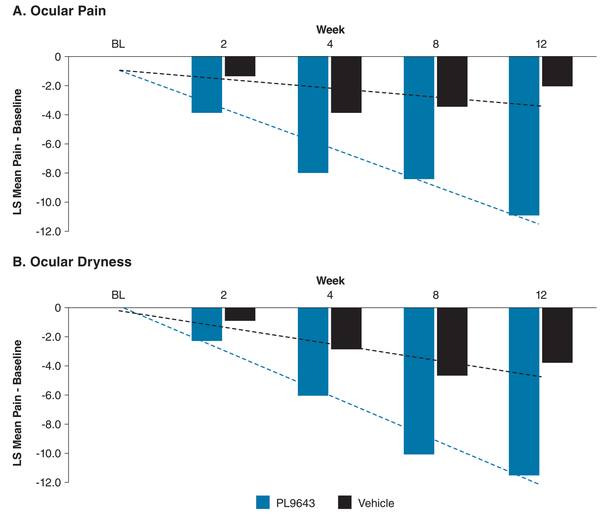
- MELODY-1 (NCT05201170)[19] was a phase 3, 12-week, multicenter, 1:1 randomized, double-masked, vehicle-controlled adaptive design study in patients to evaluate the efficacy and safety of PL9643 ophthalmic solution in patients with moderate or severe DED (safety population n=575; **Figure 3**)
- The Ora controlled adverse environment® challenge model controls the environment for relative humidity, airflow, and visual tasking and was used to standardize the evaluation of signs and symptoms of DED
- PL9643 demonstrated a rapid onset of efficacy and multiple symptom endpoints, including the coprimary pain endpoint, which met statistical significance ($P<0.05$) at the 2-week timepoint and continued to improve over the 12-week treatment period. Also, at the 2-week timepoint, multiple sign endpoints, including all 4 fluorescein staining endpoints, met statistical significance ($P<0.05$; **Figures 4** and **5**)

### Figure 4. MELODY-1 Efficacy Signs: Corneal and Inferior Fluorescein Staining Over 12 Weeks of PL9643 Treatment




Corneal staining was measured by the Ora Calibra® Corneal and Conjunctival Staining Scale. Lower staining represents improvement. BL, baseline.

### Figure 5. MELODY-1 Efficacy Symptoms: Ocular Pain and Dryness Over 12 Weeks of PL9643 Treatment



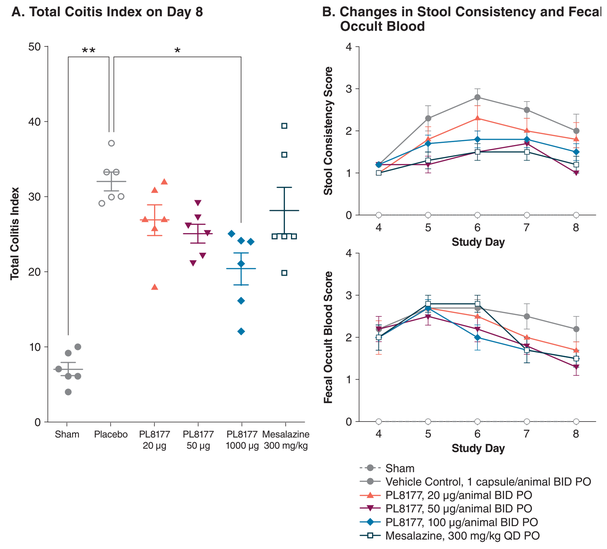

Ocular pain and dryness were scored by patients using visual analog scales. BL, baseline.

- Importantly, PL9643 treatment demonstrated an excellent safety and tolerability profile
- 2 additional phase 3 trials (MELODY-2 and MELODY-3) are set to commence 1Q 2025

### *PL8177 FOR UC*

- PL8177 is an MC1R–specific agonist that has demonstrated MC1R binding affinity and functional activity that mirrors that of α-melanocyte-stimulating hormone[10,20]
- MC1R is expressed on the colon luminal surface, and mouse models have demonstrated an important role for MC1R in a dextran sulfate sodium (DSS)–induced model of colitis[21]
- In a DSS induced rat model of colitis, treatment with oral PL8177 100 µg showed statistically significant improvement ($P<0.01$) in the total colitis index (**Figure 6A**) after 7 days of treatment compared with placebo (vehicle)

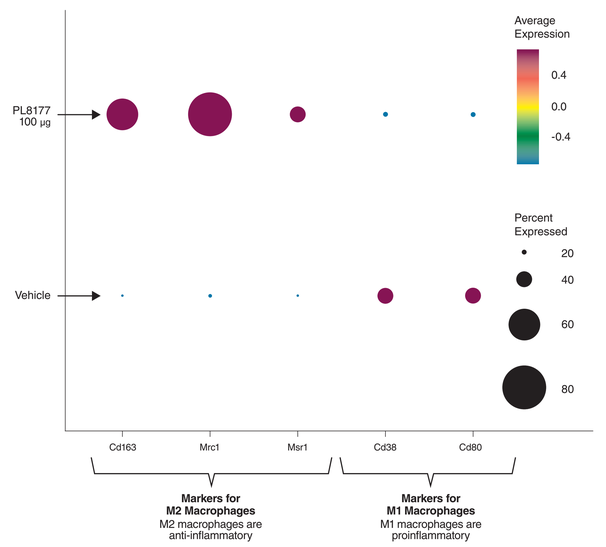
### Figure 6. PL8177 Improves the Total Colitis Index, Stool Consistency, and Occult Blood Score in DSS-Treated Rats




**$P<0.01$. Animals (n=24) were dosed with 20, 50, 100 µg PL8177 BID for 7 days vs control (placebo) and mesalamine (positive control). Total colitis index scoring (score range, 0–60) to assess inflammatory damage was based on independent observers examining and summing the scores from 3 sections from each colon per animal. All animals, except those in sham group, received 5% DSS in the drinking water (to induce colitis) for 3 days, from day 1 to day 3, and then changed to normal drinking water for the following 5 days. Tissue harvest occurred on day 8. Data are mean (SEM). BID, twice daily; DSS, dextran sulfate sodium; PO, by mouth; QD, once daily.

- Oral PL8177 at 50 µg/animal showed significant ($P<0.05$) improvement in stool consistency score from day 5 to day 8 and significant ($P<0.05$) improvement in fecal occult blood score on day 8 when compared with the vehicle group (**Figure 6B**)
- Histopathologic examination of the colon samples showed that PL8177 maintained colon structure and barrier and reduced immune cell infiltration compared with vehicle
- Single nuclei RNA sequencing (snRNA-seq) analysis demonstrated changes consistent with disease modification following treatment, including a shift in macrophage state from the proinflammatory M1 phenotype to an anti-inflammatory M2 state (**Figure 7**)

### Figure 7. PL8177 Treatment Biases Macrophages to the Anti-Inflammatory M2 State



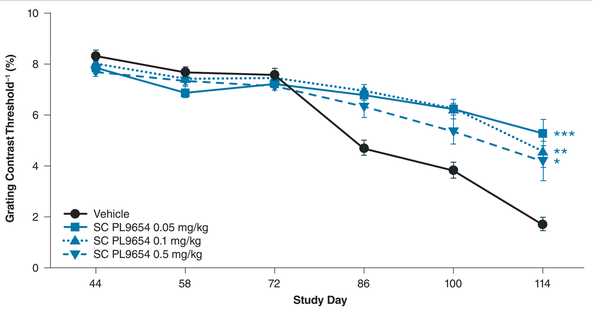

Colon samples were analyzed with snRNA-seq and data-independent acquisition tandem mass spectrometry-based proteomics. snRNA-seq, single nuclei RNA sequencing

- Oral PL8177 is currently in a double-blind, placebo-controlled phase 2a study evaluating its safety, tolerability, and efficacy for UC, with intermediate readout expected this year (NCT05466890)[22] (4Q2024; **Figure 8**)

### *PL9654 FOR DR*

- PL9654 is a synthetic MCR pan-agonist (not active at MC2R)
- Subcutaneously administered PL9654 was investigated in a streptozotocin (STZ) rat model (n=28) of DR and its effects on ocular inflammation, retinal cell population composition, and gene and protein expression were investigated
- PL9654 0.05–0.5 mg/kg twice daily (BID) was dosed on days 4–113 of the study and showed significant efficacy in reducing vision loss in STZ-treated rats compared with vehicle
- All treatment arms showed a progressive decline in contrast threshold values. However, the rate was much slower in the PL9654 treatment groups compared with the vehicle (placebo) group, and at day 113 all PL9654 treatments had statistically significant reduction in loss-of-contrast threshold (**Figure 9**)

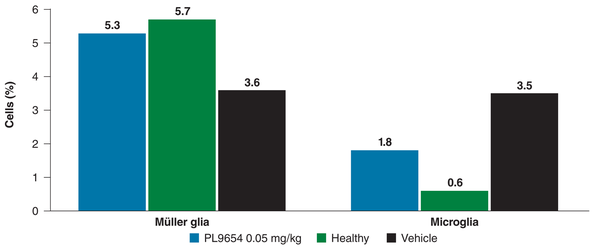
### Figure 9. Changes in Visual Contrast Threshold Over Time in STZ Rat Model of DR




Values are mean (SEM).
*$P<0.05$, **$P<0.01$, ***$P<0.001$ vs vehicle (Mann Whitney U test). DR, diabetic retinopathy; SC, subcutaneous; STZ, streptozotocin.

- Histopathology showed less photoreceptor degeneration, improved retinal thickness, and maintenance of the blood-retinal barrier
- snRNA-seq showed molecular-level changes consistent with disease modification, and gene set enrichment analysis showed negative enrichment of inflammatory pathways with an increased proportion of Müller glia and a decreased proportion of microglia compared with vehicle that was more similar to healthy retinas (**Figure 10**)

### Figure 10. PL9654 Treatment Decreases Relative Microglia Cell Population and Increases Müller Glia in STZ Rat Model of DR



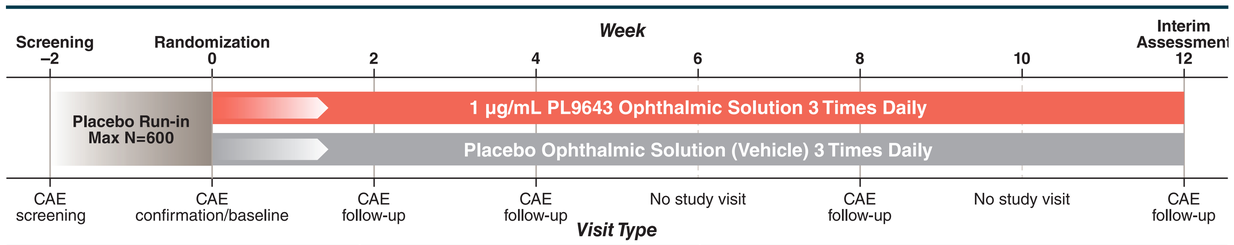

| Müller Glia[23,24] | Microglia[25,26] |
|---|---|
| • Are responsible for the homeostatic and metabolic support of retinal neurons<br>• Control the composition of the extracellular space fluid<br>• Provide trophic and antioxidative support of photoreceptors and neurons<br>• Regulate the tightness of the blood-retinal barrier | • Maintain normal homeostasis<br>• Provide immune surveillance<br>• Cause shift to amoeboid shape when activated<br>• Migrate to site of injury<br>• Can produce proresolution cytokines |

DR, diabetic retinopathy.

## SUMMARY AND CONCLUSIONS

- PL9643 ophthalmic solution demonstrated effectiveness across multiple clinical signs and reduced symptomatic ocular pain, indicating that PL9643 is having a positive affect across multiple regions of the eye in patients with moderate and severe DED, with a generally well-tolerated safety profile
- PL9643 offers a potentially differentiating efficacy profile from currently available treatments for DED
- In rat animal models of UC, oral PL8177 was found to be efficacious in reducing colonic damage and inflammation and improving stool consistency and fecal occult blood; results were supported by histopathological analysis and by snRNA-seq data
- A phase 2, double-blind safety and efficacy trial is in progress in adult participants with active UC
- Subcutaneous BID administration of PL9654 reduced vision loss and photoreceptor degeneration in the STZ rat model
- Genomic and proteomic analysis shows that PL9654 0.05 mg/kg causes a reduction in microglia and negative enrichment of genes associated with immune-related pathways, suggesting a reduction in inflammatory processes
- Together, these results support the continued development of PL9643, PL9654, and PL8177 as potentially new treatments for these inflammatory diseases

### Figure 3. MELODY-1 Study Design




**Study Subjects**
- DED duration ≥5 years
- Inferior corneal staining score >1
- Eye discomfort score ≥25 as measured by the VAS

**Co-Primary Sign Endpoint (Week 12)**
Inferior corneal fluorescein staining

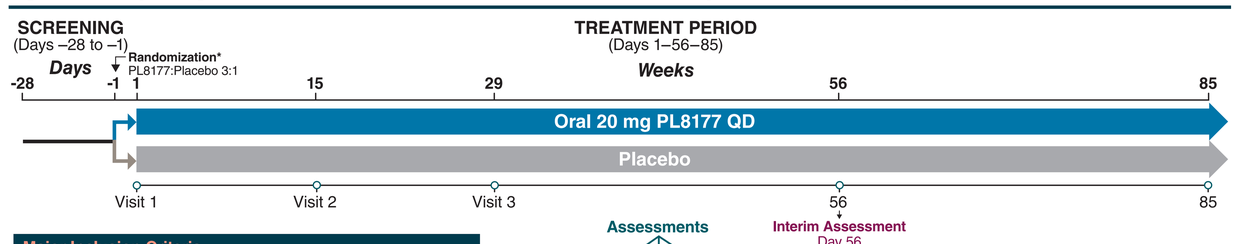
**Co-Primary Symptom Endpoint (Week 12)**
Ocular pain

**Key Secondary Endpoints (Week 12)**
- Conjunctival sum lissamine green staining
- Total sum lissamine green staining
- Tear film break-up time

**Other Secondary Endpoints Include**
Burning, foreign body sensation, eye dryness, eye discomfort, ocular discomfort

CAE, Ora controlled adverse environment®; DED, dry eye disease; VAS, visual analog scale.

### Figure 8. Study Design for Double-Blind, Placebo-Controlled Phase 2a Study of PL8177 in Participants With UC




**Major Inclusion Criteria**
- Age ≥18 to ≤75 years of age (adult males and nonpregnant, nonlactating females)
- UC diagnosis ≥6 months prior to screening and has active UC (MES ≥2 during screening sigmoidscopy
- Endoscopic disease extending to at least 5 cm proximal to the anal verge, and minimum involvement of at least 50% of the macroscopically most affected colonic treatment
- Demonstrated intolerance, lack of response or inadequate response to aminosalicylates, and not currently taking anti-TNF or other biologic and/or small molecule therapies

**Assessments**
*Safety:* AEs, IBDQ-32 questionnaire, vital signs, physical examination, ECGs, clinical laboratory assessments
*Efficacy:* MES, SFS, RBS, 3-component Mayo score (sum of RBS, SFS, and MES), PRO-2 (sum of SFS and RBS), IBDQ-32, Geboes score, Ulcerative Colitis Endoscopic Index of Severity, HEMI
*PK:* Blood and fecal samples for levels of PL8177 Biomarkers: CRP, calprotectin, lactoferrin, inflammatory cytokines
*Intestinal Biopsies:* To determine immune cell type population proportions and composition and B-cell and T-cell receptor clonality

[a]16 patients (12 PL8177, 4 placebo) will be enrolled for treatment until visit 4 (day 56) when data will be assessed in an interim assessment, after which an additional 12 patients could be enrolled or, depending on the conclusions of the interim assessment, additional patients beyond the target sample of 28 patients could be enrolled to a maximum of 84 patients. AE, adverse event; CRP, C-reactive protein; ECG, electrocardiogram; HEMI, histologic-endoscopic mucosal improvement; IBDQ-32, 32-item Inflammatory Bowel Disease Questionnaire; MES, Mayo Endoscopic Subscore; PK, pharmacokinetic; QD, once daily; RBS, Mayo Rectal Bleeding Subscore; SFS, Mayo Stool Frequency Subscore; TNF, tumor necrosis factor; UC, ulcerative colitis.

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