Protective Effects of 2 Melanocortin Agonists Delivered by Intravitreal Injection in Mouse Models of Retinopathy

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Background
- Melanocortins have a wide range of activities, including inhibition of leukocyte activation, inhibition of inflammation, and protection of tissues.13
- The melanocortin system plays a key role in promoting resolution of the inflammatory process.4
- Melanocortin agonists have demonstrated anti-inflammatory effects in various experimental models of inflammatory disease.5
- Targeting this pathway may protect against ocular disease.

Objective
- To investigate the effects of two melanocortin receptor pan-agonists, PL8331 and PL9654, administered via intravitreal injection in mouse models of ocular disease.

Methods
Study 1
- In study 1, the effect of monthly administered PL8331 was investigated in a mouse model of diabetic retinopathy using C57BL/6 mice (N=16; Figure 1).

Results
Study 1
- Figure 3. Retinal Sections from Healthy, PL8331-Treated Diabetic Mice, and Untreated Diabetic Mice
- figure 2. Study 2 Design
- In study 2, the effects of monthly administered PL8331 or PL9654 were investigated in a mouse model of age-related macular degeneration using C57BL/6 mice (N=48; Figure 2).

Study 2
- There was a significant increase in VEGF expression in the neuroretina of diabetic mice compared with nondiabetic mice, but not in the retinas of diabetic mice treated with PL8331 (Figure 4).
- Laser retina burns resulted in increased angiogenesis in vehicle-injected mice (Figure 6).
- Mice treated with anti-VEGF antibody, PL8331, or PL9654 showed statistically significant reduction in angiogenesis.

Summary and Conclusions
- PL8331 treatment preserved retinal thickness and mitigated optic nerve cupping in a mouse model of diabetic retinopathy.
- PL8331 therapy promoted preservation of retinal structure observed by RGC survival and histology of the retina.
- PL8331 suppressed VEGF production in the diabetic retina, suggesting that PL8331 treatment may block vascular leakage and neovascularization.
- In a mouse model of age-related macular degeneration, PL8331 and PL9654 reduced retinal leakage, angiogenesis, and fibrosis compared with control to an extent equivalent to anti-VEGF treatment.
- In conclusion, intravitreal delivery of the melanocortin agonists PL8331 and PL9654 significantly reduced several markers of retinal damage in mouse models of eye injury, supporting the continued development of PL8331 and PL9654 for the treatment of ocular disease.

Support
- Palatin Technologies Inc.

Acknowledgments
- Writing and editorial assistance was provided by Miranda Tradewell for The Curity Rockefeller Group, LLC, Tarrytown, NY, USA, which was funded by Palatin Technologies Inc.

Disclosures
- John Dodd, Marie Makhлина, Wei H. Yang, and Carl Spana are employees of Palatin Technologies Inc. Andrew W. Taylor received consulting fees from Palatin Technologies Inc. Tat Fong Ng received consulting fees from Palatin Technologies Inc.

References

Figure 1. Study 1 Design

Figure 2. Study 2 Design

Figure 3. Retinal Sections from Healthy, PL8331-Treated Diabetic Mice, and Untreated Diabetic Mice

Figure 4. VEGF Expression in Healthy and Diabetic-Treated and -Untreated Mice

Figure 5. Retinal Ganglion Cell Density in Healthy Control, Diabetic-Treated and -Untreated Mice

Figure 6. Areas of Leakage Measured Using Fundus Fluorescein Angiography

Figure 7. Mean Angiogenesis in Retinas of Mice Who Received Ocular Laser Burns

Figure 8. Mean Area of Fibrosis in Retinas of Mice Who Received Ocular Laser Burns