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APPLICATION NOTES

TECHNICAL NOTE: DEVELOPMENT OF THE SODIUM IODATE INDUCED MODEL OF RETINAL DEGENERATION AND AMD

Introduction:
Retinal degeneration is a group of diseases that cause vision impairment and may lead to blindness and are generally caused by damage to the retina or gradual deterioration as is the case with retinitis pigmentosa or age-related macular degeneration (AMD)[1]. While retinitis pigmentosa is reported to be the most common retinal degeneration disease with a prevalence of 1 in 4000 people, AMD also has a significant prevalence and it is estimated that close to 20 million Americans live with a form of AMD[2]. Recently, 2 new therapies were approved for dry AMD, Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) that both target the complement cascade in the immune system and have been shown to slow disease progression[3]. However, at this time, there is no cure for dry AMD which is likely to grow in prevalence due to aging populations and lifestyle choices. Due to the unmet clinical need for a dry AMD cure, the drug discovery community is actively working on the identification of new therapies using established preclinical animal models. A well-established model of dry AMD is the sodium iodate induced mouse model. In this model, sodium iodate, an oxidizing agent, is systemically injected into a rodent model to induce retinal degeneration that mimics dry AMD.

In this technical note, Biomere and JOINN Laboratories report the characterization of a rat model of retinal degeneration using sodium iodate.

Experimental Design:
The study used male Brown Norway Rats that were divided into 3 Groups of 4 animals. On Day 0, the animals were dosed systemically through a single tail IV injection.

- Group 1 received Hank's Balanced Salt Solution as a control.
- Group 2 received Sodium Iodate at a concentration of 40mg/kg.
- Group 3 received Sodium Iodate at a concentration of 60mg/kg.

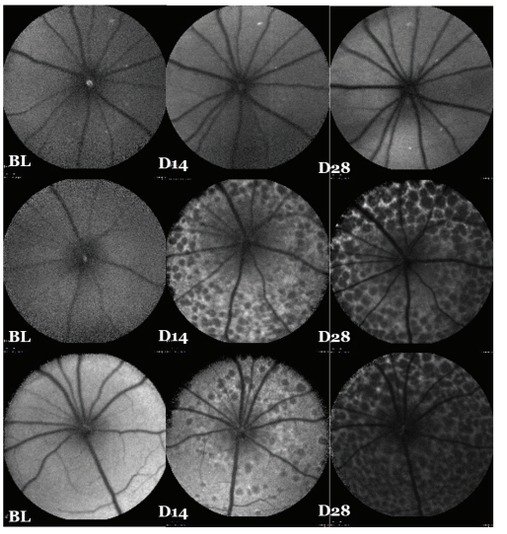
The study animals received OCT scans, Fundus autofluorescence imaging, and full field ERG analysis at baseline, Day 14, and Day 28. The OCT and FA images were captured on a Heidelberg Spectralis following pharmacologic mydriasis induction with tropicamide and phenylephrine. The ERG data was acquired using the Diagnosys Celeris ERG platform following isoflurane sedation, using 0.01, 0.1, 1, 3, and 10 cc/m2 light intensities following dark adaptation. On Day 28, the study animals were euthanized and whole eyes were collected for H & E histological staining.

Results:
Imaging: The Group 1 cohort did not demonstrate any lesions post injection while the retinal thinning identified by OCT was less pronounced in Group 2 compared to Group 3. These changes are consistent with retinal degeneration.

ERG analysis: Both A wave and B wave amplitudes were reduced following injection in Groups 2 and 3 from Day 14 onwards at all light intensities but the A and B wave implicit times remained constant independent of the groups.

Histology (H&E) staining: The histology slides for Groups 2 and 3 showed marked cell atrophy in the retinal pigment epithelium layer.

Figure 1: Autofluorescence analysis of the fundus shows lesions involving 90% of the fundus area by day 28 post sodium iodate injection at 40 mg/kg (Group 2) and 60 mg/kg (Group 3).



(Group 1)
Vehicle

(Group 2)
Sodium Iodate
40 mg/kg

(Group 3)
Sodium Iodate
60 mg/kg

Figure 2: OCT analysis shows dose-dependent retinal thinning in Groups 2 and 3 in response to sodium iodate. The control (vehicle) showed minimal retinal thinning.

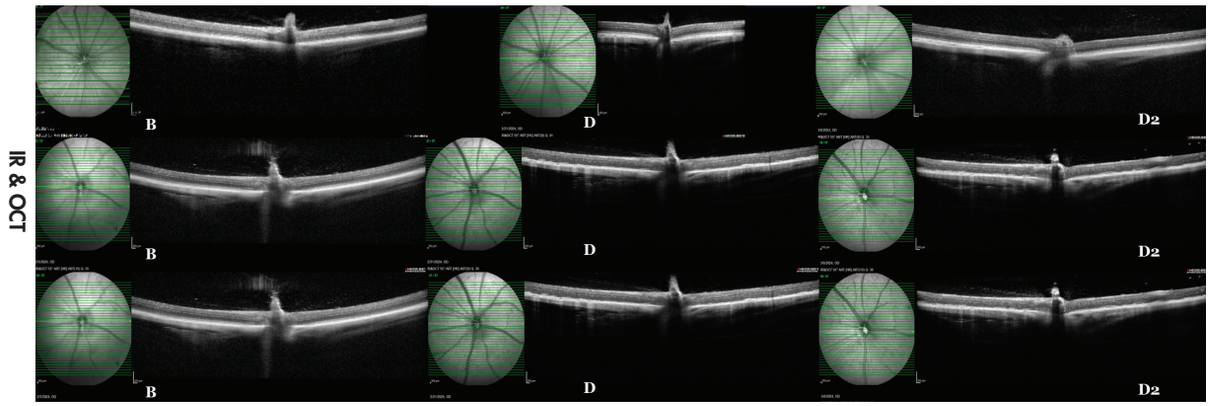


Figure 3: Full field ERG analysis showed both A wave (top panel) and B wave (bottom panel) amplitudes were reduced following injection in Groups 2 and 3 from Day 14 onwards at all light intensities.

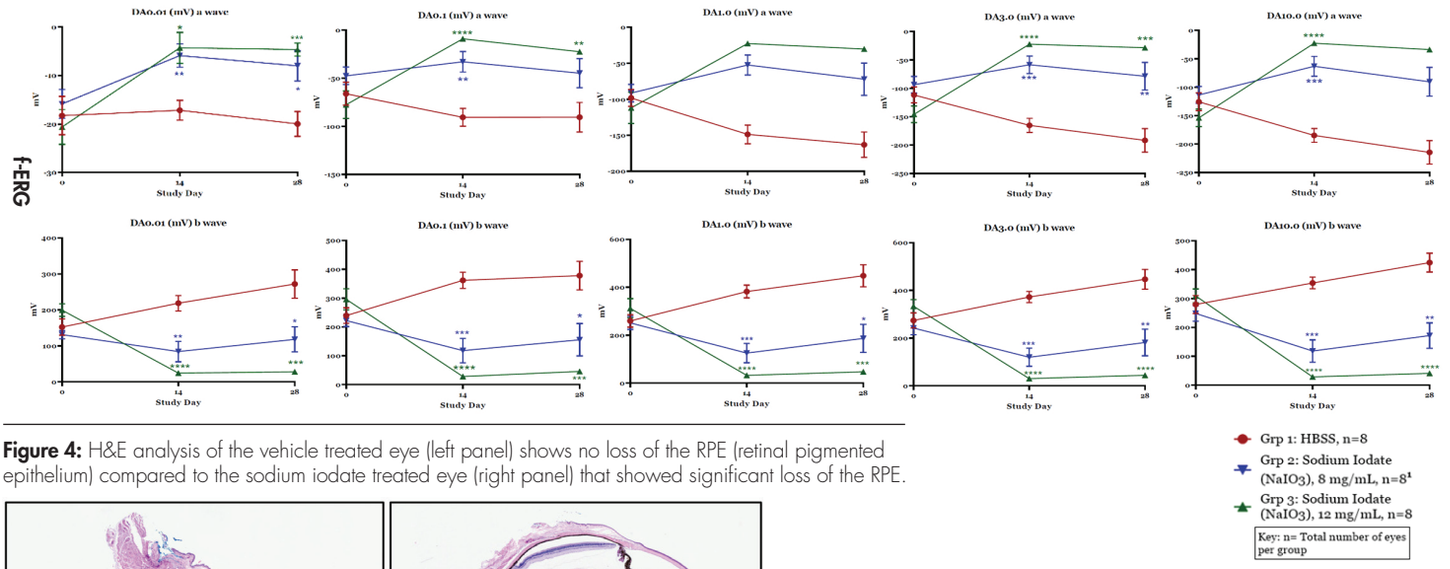
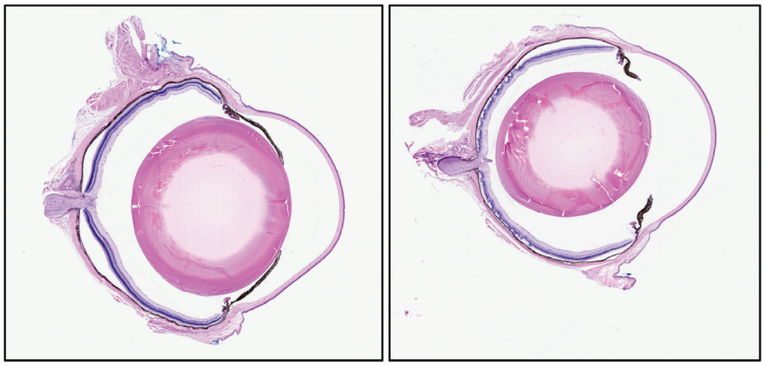


Figure 4: H&E analysis of the vehicle treated eye (left panel) shows no loss of the RPE (retinal pigmented epithelium) compared to the sodium iodate treated eye (right panel) that showed significant loss of the RPE.



Summary:

The study showed that Group 3 that received the highest dose of sodium iodate had lesions that showed profound retinal degeneration by Day 28. The progression from Day 14 to Day 28 was consistent between animals, with obvious lesions involving 90% of the fundus by Day 28. The results indicate that the sodium iodate rat model is well suited to evaluate new therapies for dry AMD that are administered systemically (IVT) or locally via subretinal injection.

References:

1. https://www.mayoclinic.org/diseases-conditions/retinal-diseases/symptoms-causes/syc-20355825
2. https://preventblindness.org/amd-prevalence-vehss/#
3. https://www.nei.nih.gov/about/news-and-events/news/story-discovery-nei-funded-research-paves-way-new-dry-amd-drugs

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