1. No.
   2023G012

2. Title
   Circadian Clock-Based Mechanistic Elucidation of the Effects of Cigarette Smoke Components on Tear Film Oil Layer Regeneration Stem Cells and Development of Novel Dry Eye Disease Treatment

3. Period
   2023-2025

4. Summary
   This study focused on meibomian gland dysfunction (MGD), a major cause of dry eye disease, to investigate the impact of cigarette smoke on intracrine steroidogenesis and its underlying mechanisms. In the first year, we demonstrated that cigarette smoke extract (CSE) significantly reduces intracrine activity in mouse meibomian glands and established gland cell–specific transgenic mouse models. Subsequently, we identified androstenedione, androsterone, and epiandrosterone as metabolic markers reflecting intracrine activity in human meibum and established their detection methods (Nguyen Pham et al., iScience 2025). In the final year, we revealed a pathological vicious cycle in which reduced intracrine activity and inflammation mutually exacerbate each other, and identified CD38-mediated NAD degradation as a key molecular mechanism (Hamada et al., eLife 2026). Importantly, CD38 inhibition restored NAD levels and intracrine activity, suggesting a novel therapeutic strategy. These findings provide molecular insights into smoking-related ocular surface dysfunction and may contribute to the development of preventive and therapeutic approaches. Future studies will validate these mechanisms in humans through multi-cohort analyses using CD38 and NAD as molecular indicators.