Date: Friday May 23rd 2025 AM

Dear Esteemed Advisors and Colleagues,

Greetings.

Today I am pleased to share with you of OTI's PCT #2 publication early this month. This patent discloses the breakthrough discovery of glaucoma disease root cause: *"chicken and egg, which comes first?* The problem of glaucoma is the outflow engine broken. At a cellular level, it is the pressure sensing cell loss and sensor functional irregularities, underpinning the IOP diurnal irregularities (random spike), which kills the neurons at the retina in patients with glaucoma. Matrix metalloproteinase (MMP) based platform therapy is the "*holy grail*" and has the potential to **Reverse and Stop** the disease progression. Currently MMP treatment can be delivered *temporarily* by Durysta and iDose at One time due to drug related side effects, or SLT laser limited to early stage glaucoma. OTI-2024/Trabodenoson is the best in this new therapeutic domain, its eye drop will be used as a *drug holiday stabilizer* to keep patients TM clean with elastic youth. Also it can be made in sustained release (SR) intracameral implant (AC rod) as loading dose or *drug holiday inducer*. Based on clinical evidence, estimated about 80%-90% glaucoma patients may only need One bottle to keep their sight healthy with intermediate loading dose for every 3-4 years or longer. This is the future for glaucoma specialty care.

Why is MMP therapy so powerful?

As a trained retinal surgeon and stem cell biologist, I had the privilege to work on the first human embryonic derived hRPE transplant for GA/AMD and Stargardts macular degeneration (https://pubmed.ncbi.nlm.nih.gov/31482011/), and Lineage's OpRegen hRPE transplant. I first noticed that the RPE graft survival depends on a healthy Bruch's membrane, otherwise, they will die. Prof John Marshall's early research demonstrated that MMP-9 treatment can turn 60-year-old human Bruch's membrane with 40-year-old hydraulic conductance, which was the scientific basis of retinal rejuvenation laser in DME (first London trial). Connecting dots, I discovered Trabodenoson derived MMP on TM rejuvenation (https://pubmed.ncbi.nlm.nih.gov/33405971/). The relation of the RPE and Bruch's membrane is similar to the relation of pressure sensing cell and its underlying basement membrane (ECM) at the TM, both serve as "water pump". MMP is an enzyme and removes the ECM debris and providing a healthy *cushion* for the pressure sensing cell metabolic functionality, just like Bruch's to the RPE survival.

Why glaucoma patients become poor or non-responders and inevitably need invasive drainage surgery at advanced stage? It is just like GA patients that need hRPE transplant

when massive lineage neuronal cells die off. RPE, pressure sensing cell and cornea endothelium are neural lineage and monolayer endothelium or epithelium, lack of self-renewal in adult mammalian eyes. To protect the pressure sensing cell health is to vision health in glaucoma. This is the power of MMP therapy for glaucoma.

Special thanks to our talented IP attorney, Dr Chris Cowles, PhD/JD and his team for their dedicated support of OTI's patent projects. I am grateful for Duane Morris LLP and their Patent Pro Bono Team (Sima Kulkarni, JD, Sam Apicelli,JD and Jon Lourie, JD) to help with the first PCT filing, which was recently completed the national phase filings to Europe, Canada, Japan, China, Australia and India, in addition to the US filing in 2023.

Thank you **ALL** for your being a part of OTI's journey, a journey to cure for glaucoma blindness, we are 5 years away to complete the Phase 3 pivotal trials to transform glaucoma specialty care in decades to come!