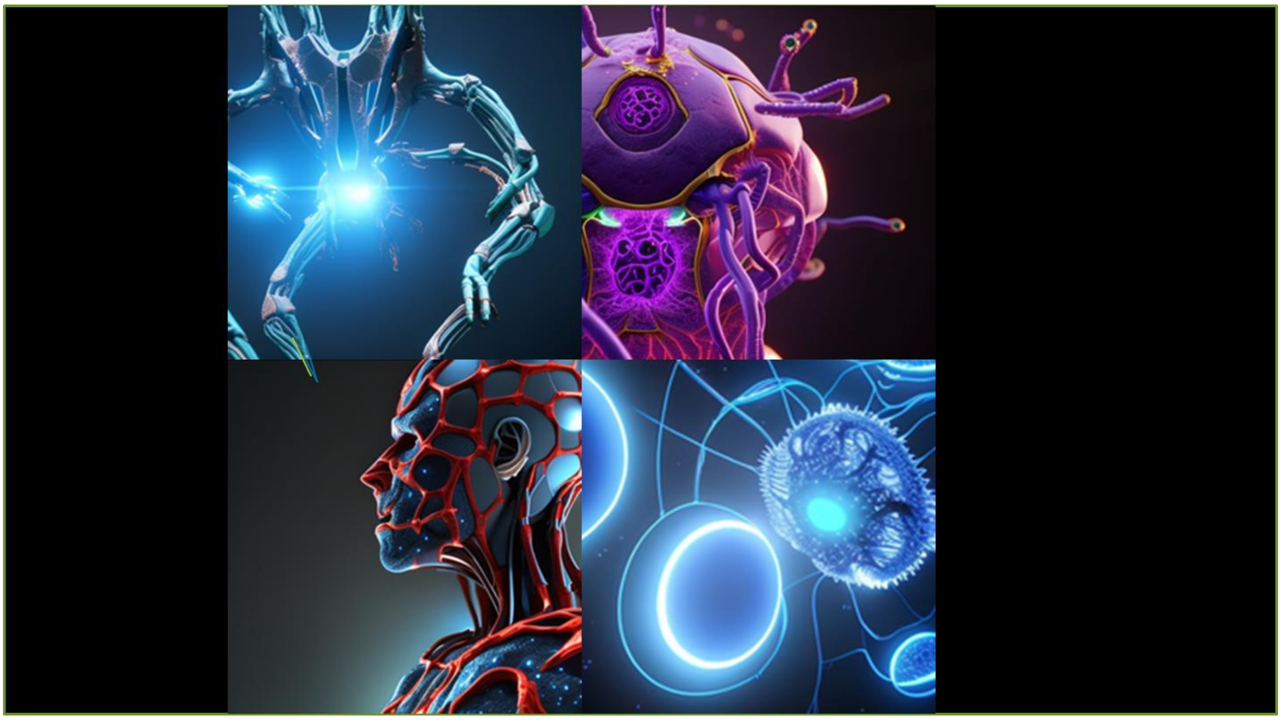
Guts, Nerves, and Nanobiobots: The Evolution of Ocular Therapeutics



Gut Microbiome, Trigeminal Nerve, Nanotechnology - made with Hotpot AI Art Generator

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The gut is increasingly recognised as a crucial contributor to psychological and neurological health. Recent clinical trials, summarised in a review by Russell *et al.* (2023), are attempting to mitigate ocular pathology by modifying the microbial mix associated with particular disease states.

Relationships include *Anaerotruncus* with neovascular age-related macular degeneration (nAMD), and irritable bowel disease (IBD) with higher odds of developing glaucoma. Faecal microbiota transplants (FMT), currently being evaluated as a treatment for Major Depressive Disorder (MDD), may also be relevant to patients with Sjogren syndrome plus dry eye symptoms. Notably, dry eye disease is more prevalent in women and the elderly (Epitropoulos *et al.*, 2022), groups vulnerable to unique interrelated endocrinological, disgestive, pain, psychological, and disease risks.

Some types of dry eye, corneal function, as well as the array of symptoms linked to heavy digital device use may be alternatively addressed via Cranial Nerve V. The trigeminal nerve is described by White in Young (2023) as a 'two-way highway to hell' from a pain standpoint, with implications for quality of life, anxiety, and depression. Eyecare clinicians in this space are using neuromodulation, neurostimulation, and contoured prism lenses as therapeutic techniques. These leverage on internal mechanisms to generate organic results including relief from trigeminal dysphoria and restoring production of chemically complete, natural tears.

Pathway discovery, manufacture, delivery and efficacy isn't enough, unfortunately. Challenges such as high unit costs can lead to low take-up and product failure, which is what happened to TrueTear®. Oyster Point's OC-01 (varenicline) nasal spray is the market inheritor in this case, a cholinergic agonist with the same trigeminal nerve target and endogenous tear outcome. As it is a chemical route instead of a device, you don't need to recharge or design mechanical and electrical components. An alternative dosage is being investigated for the potential to treat neurotrophic keratopathy as well (Oyster Point product pipeline).

The above gut and brain techniques utilise our knowledge of molecular and physiological pathways to restore homeostasis, arresting the downward spirals of inflammation implicated in a multitude of diseases. The scope is wide and corrections are occuring at the level of systems, with greater room for integrated, multi-pronged contributions to inherent functional states and mental health. The hope is that restoring an equilibrium disrupted by one disease state/spiral because of environmental stressors could be protective for proximal *and* distal tissue or cells.

This approach requires not just identification of interrelated elements and symptoms, but collaborations across various medical specialties. For example, the creators of Neurolenses made the connection between binocular vision issues, headaches, ocular and nerve health of their patients given environmental conditions (digital device use) and for this purpose, orchestrated collaboration between optometrists, opthalmologists, and neurologists (Thompson and Krall, 2022). Similar interdisciplinary initiatives would be expected for endocrinologically-based ocular health management, which again, extends to affect multiple systems. This route and list of specialists encompasses dry eye, pain perception, and even gut and brain pathophysiology in women linked to lifetime oestrogen hormone fluctuations.

Some clarity and analytical consensus on terms like 'trigeminal dysphoria', whether it counts as 'computer vision syndrome' or 'ocular surface disease', then facilitating patient ability to report and describe the constellation of symptoms has been a fundamental first step to systems level interventions and evaluation. The more distal, complex, and number of intermediary signals and steps, the harder this will be to get to and past clinical trials.

Mechanisms, pathways, and directionality of association underlying the gut-ocular pathology data are presently unknown. However: Inflammatory conditions, immune function, and murine models can serve as a basis for further ophthalmic clinical investigation and intervention. So that's one vector with a variety of novel microbiological techniques on the horizon, with greater uncertainty in terms of administration routes especially if the eventual target tissue is ocular. Let's not even get into how outpatient behaviour over the long-term could be affecting results.

Another recent review by Ahmed *et al.* (2023) covered the impediments to therapeutic efficacy and bioavailability of existing ocular drugs. The section *Future Technologies* includes smart nano-micro platforms, exosomes, and tissue engineering. These are more technologically complex and have a different pool of required expertise, with a longer time horizon for successful human trials and narrower scope for effects, implying higher precision and specificity in experiments. A potential downside is that they focus on biological (cellular level) pathways, leaving the target amidst an adverse physiological and environmental milieu that continues to contribute risk – but this is debatable. At both the cellular and systems level, there is the possibility that results of initial studies may not be generalisable to a broad range of contexts and genetic or physiological profiles. Lastly, high tech interventions do not confer the same degree of personal agency for patients, with a greater need for visits to specialised healthcare facilities with specific equipment.

The Ahmed *et al.* review also mentions patient compliance and adherence, or 'patient self-discontinuation' (Ayers, 2023). This factor underscores the need in therapeutics to consider not just traditional efficacy and cost but monitoring and patient awareness of timeline and value of results (See Baryakova *et al.* 2023), as well as ability of practitioners and patients to manage the condition at hand, including early identification. A probiotic seems a lot easier to swallow than nanosystems in your eyes or electrodes clipped into the nose. These are an even harder sell for the elderly and non-urban population who often exhibit a degree of resistance to medical products and procedures.

Sometimes this can be a stigma and perception issue. Patients may experience shame or fear about a diagnosis and become increasingly demoralised by the amount and variety of prescribed drugs. In such instances, compliance in terms of appointments, dosage, regularity, and effort is low, and psychological state and medical condition may deteriorate further.

All things considered, in early stage or non-severe cases, perhaps all the better if identifying and treating one distal malady more naturally happens to reduce pharmaceutical requirements elsewhere. It's certainly worth exploring, with investment in contact points that allow medical knowledge transfer and patient care collaboration.

Following that, being able to communicate in an impactful way that affects perception, experienced life quality, and informed, self-sustained behaviour might make all the difference in compliance and prevention of ocular pathology. More (often free) technologies are coming online that afford motivated and independent practitioners the opportunity to do things a little differently.

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