I & Vision Research Centre

AMD, Mercury, and Cone Fate Update

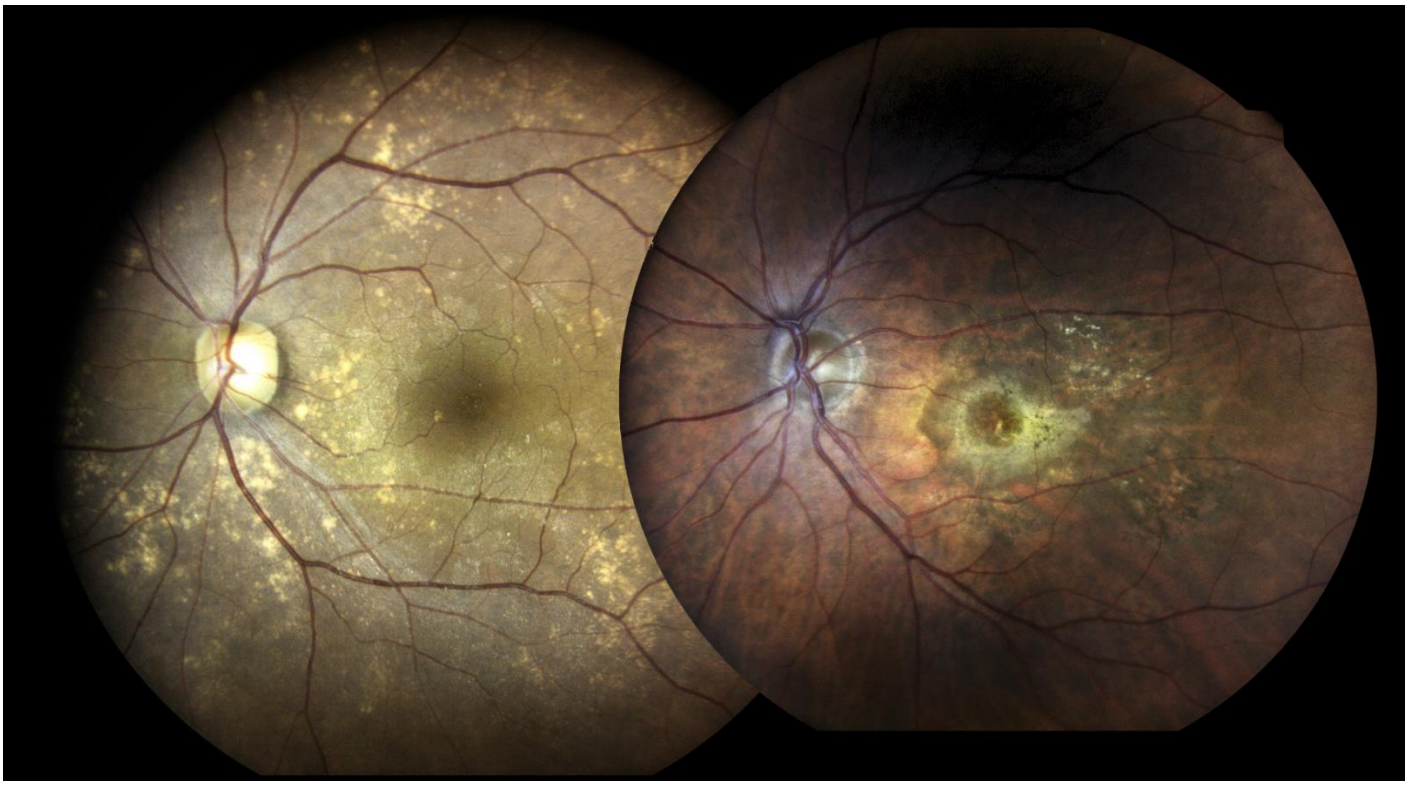

Image by IVRC: Age-related Macular Degeneration (Dry)

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Did you know that AMD is also an acronym for acid mine drainage? We didn't.

In any case, February was age-related macular degeneration (AMD) awareness month. One should be sufficiently wary of toxic mine leakages too, as they may affect vision, behaviour, and strategic security. Here we take a peek at the AMD news, what's up on Mercury, acid mine repurposing, mercury poisoning, and a couple of colour and vision mechanisms.

Part I: Age-related Macular Degeneration (AMD)

Overview

Macular degeneration refers to the deterioration of the central retina over time. There are two forms of AMD: Dry AMD is characterised by accumulation of deposits called drusen, slow atrophy, and potential breakdown of the retinal pigment epithelium (RPE) and cells of the macula. In late and severe stages dry AMD is characterised by geographic atrophy, with regions of dead cells that resemble continental maps in fundus imaging. The wet form involves abnormal blood vessel formations in the retina, mostly from the choroid, described as exudative or neovascular AMD. Subretinal haemorrhages are visible as dark spots in fundus imaging and fluid-filled swellings in optical coherence tomography (OCT).

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Dry AMD is divided into early, intermediate, and late stages, but can switch to wet at any of these and be accordingly categorised as late and severe AMD, which remains the leading cause of irreversible vision loss in elderly populations. Blindness from this condition is not total. Peripheral vision is often preserved, but loss of sharp, detailed central vision can lead to major impacts on functional independence, confidence, and lifestyle for those affected.

Interventions are necessary as the wet form of AMD can lead to rapid vision loss, while lesions and pathology in dry AMD can spread, though this does not occur for every patient (timeline and some percentages in Christiansen, 2024). Comprehensive eye examinations to detect and manage dry AMD before it progresses to geographic atrophy or the wet form are important for those aged 40 and above. Older cohorts and those at risk due to genetics (e.g. complement protein polymorphisms) and/or other chronic habits and conditions are advised to go for check-ups at least twice a year, though this general advisory differs by practitioner, country, and professional societies.

In terms of recent industry events, there could be a weensy bit of a problem building. Best-corrected visual acuity (BCVA) certainly matters for the patient and frontline healthcare workers, but the measure is less useful for more fashionable and grant-fundable analytical techniques and predictive models based on objective data from pricey machines like the OCT.

Rather than relying on coloured fundus imaging and autofluorescence, in 2023 the Classification of Atrophy Meetings group proposed new terminologies, biomarkers, and horizontal OCT scans for future clinical trials on geographic atrophy. Not every accessible clinic and practitioner has access to the equipment and algorithms, and there is some mismatch of perspectives in terms of acceptable risk and which endpoints should really matter in pharmaceutical evaluations. Beyond that, not every OCT device or deep learning segmentation method is created equal (See review by Ndipenoch et al., 2024). There are also new OCT modalities to consider that offer higher detail of choroidal layers, such as spatio-temporal (STOC-T) angiography, but how or if this could be used for AMD diagnoses is moot. Lizewski et al. (2024) point out limited use for the method where 'fluid spaces or low-scattering structures around the vasculature' occur. That being said, when applied to high patient volume healthcare spaces the automated option of deep learning for 'volumetric' OCT data instead of labour-intensive identification of AMD features in retinal and OCT scans could reduce clinician workloads and potentially improve diagnostics, data models, and disease understanding.

The challenge with wet AMD treatments and the gap for dry AMD therapeutics has been substantial for many years, and the growing elderly population means the number of those at risk for vision loss from AMD and other age-related ocular disorders is rising. There seem to be no handy calculations of current global prevalence, but a rampantly cited 2014 study placed the estimated figure for 2020 at 196 million. By 2050, Wang et al. (2022) project that new annual cases would hit 39 and 6.4 million for early and late AMD respectively, and wet AMD is said to affect 14 million people now.

This seemingly translates to alluring profit potential, with a recent purchase of Iveric, its dry AMD drug Izervay, and 'ophthalmology-focused capabilities' by a Japanese drugmaker for US$5.9 billion in May 2023. The current global market value for wet AMD treatments alone is around SG$13.2 billion annually. Competition is fierce and the array of molecules and genes targets under scrutiny and locked on for their biomedical market potential is larger than ever.

Mechanisms in Ageing & AMD

Risks are mostly age-related, hence the label age-related macular degeneration (AMD), with population incidence plotted on steep rising curves from the ages of 45 to 85 (proportion with early AMD: 0.5 to 5%; Late AMD: near 0 to

around 0.8%) in a meta-analysis by Wang et al., 2022. Quite noticeably there were regional differences in their age versus incidence data for females, and women in Asia had a flatter curve and lower age-related late AMD risks overall (Ibid., Figure 6). Smoking, high cholesterol, and other sources of vascular pathology are other known risk factors.

Several of the cellular pathways and degenerative processes responsible for cognitive decline and dementia diseases like Alzheimer's are found in AMD as well, particularly β-amyloid accumulation in retinal layers (Wang & Mao, 2021), oxidative and nitrosative stress (Toma et al., 2021), mitochondrial dysfunction, immune dysfunction, and vessel and cell losses in the ageing choriocapillaris (Lipecz et al., 2019). Controlling inflammation and the dysfunction of these pathways due to senescence is the general idea for arresting disease progression. Signals sent by RPE cell dysfunction are thought to be responsible for the large inflammatory component of AMD. Paired with the unique feature of choroid vessel dilation, there is likely a positive feedback loop between RPE damage and inflammation that eventually leads to the destruction of photoreceptors and neovascularisation in late stages (Zhao et al., 2015).

In terms of specific cellular and molecular mechanisms, differential protein expression including for immune system functions like AIM2 inflammasome (Cui et al., 2023) and the complement cascade (more below, see Patel et al., 2022) and the accumulation of drusen are recognised as crucial parts of AMD progression and severity. In a 2021 study (Cao et al.), 172 proteins were implicated in wet AMD treatment outcomes. Of the 172 they tested one, apolipoprotein B100, and found high levels to be protective against wet AMD, meaning patients could stop vitreous injection sessions after a year without risk of progression. There's also some interest in melanin (Berg & Berg, 2023; Kwon et al., 2022) and melatonin (for dry in Ku et al., 2023; wet in Lin, et al. 2023) levels at the RPE, impacting mitochondrial activity, immune pathways, rod photoreceptor outersegment phagocytosis, and build-up of oxidative stress and deposits.

Underlying much of the mechanistic basis for current therapeutics, consistent attention is being paid to the genetic polymorphisms underlying differences in protein expression for candidates that go on to develop RPE atrophy and wet AMD, not covered extensively here. It will continue to be a hot topic for the future if gene therapies and transcriptomics are forecast to offer the highest profit potential versus alternatives.

Dry AMD: Curve Bending & Loss Prevention

Prior to 2023, the only ways to slow progression of dry AMD and preserve retinal cells and sight long-term were through environmental risk factor reduction, increased physical activity and fitness, hydration, dietary intake of Omega-3s, and the supplemental formula for AREDS, changed to AREDS2 which is still undergoing patient-focused tweaks. Improvements to haemodynamics and antioxidant capability are some effects of this non-invasive intervention angle which has pretty decent power in terms of slowing disease progression. That is, if patients can be adequately educated, disciplined, and consistent with their choices and behaviours.

As of 2023, pegcetacoplan (Syfovre) and avacincaptad pegol (Iveric) are FDA-approved for late stage dry AMD. International markets are also in their sights. The injectable drugs target different aspects of disease progression, with dosing schedules of approximately once a month. Eventually, these in combination with improved predictive methods might be approved and applied to earlier stages of AMD, but there is some concern about the chosen endpoints, safety profile, and improper oversight and data-sharing for Syforve. Quite a bit worse: Both are fairly expensive (US$2,100 and US$2,190 per shot), still require frequent intravitreal injections, and both may increase risk of neovascularisation.

In December of 2023, an article (Wehrwein, 2023) pointed to requests from ophthalmologists for an independent assessment of Syfovre due to incidence of retinal vasculitis in recipients and high dropout rates during the phase 3

trials. The company Apellis Pharmaceuticals blamed a specific type of needle for the retinal vasculitis cases, but other side effects included symptomatic floaters in one-third of patients treated (Ibid.). The marketing application for Syfovre has been rejected by the European Medicines Agency despite modification of the kit to a smaller needle and an estimated 2.5 million people in the region living with geographic atrophy. In trial design, the endpoint was also a disappointment for healthcare providers as there was no difference between treated cohorts and sham for visual function, although lesion growth as an anatomical diagnosis was slowed up to 22% over two years. In earlier clinical trials that included earlier stages with nascent geographic atrophy, progression to geographic atrophy was reduced by 29%.

Drug Target: Complement System & Cascade

Syfovre targets and inhibits the protein called complement component 3 (C3), an integral part of a 'complement cascade' that is believed to be an underlying cause in several types of disease states, from AMD to periodontal issues. Perhaps the most flattering analogy is C3 being the 'Swiss army knife of innate immunity', according to Ricklin et al. (2016). The complement system as a whole gets the title of an Immune Sentinel (Mastellos et al., 2024), which is also pretty impressive. Complement serves multiple roles at different life stages and this further differs functionally based on tissue locations. Specifically in the context of AMD and to rephrase Shughoury et al. (2023), actors and features of the complement system have the following missions:

- **Overall: Tag, board, and kill intruders and unwanted elements**
- **Vascular dilation & membrane permeability – think Haussmann's boulevards**
- **Inflammatory actor recruitment & frenzy**
- **Detect and exploit weak points in the walls of disagreeable company**
- **Assemble forces for slicing and lysing**

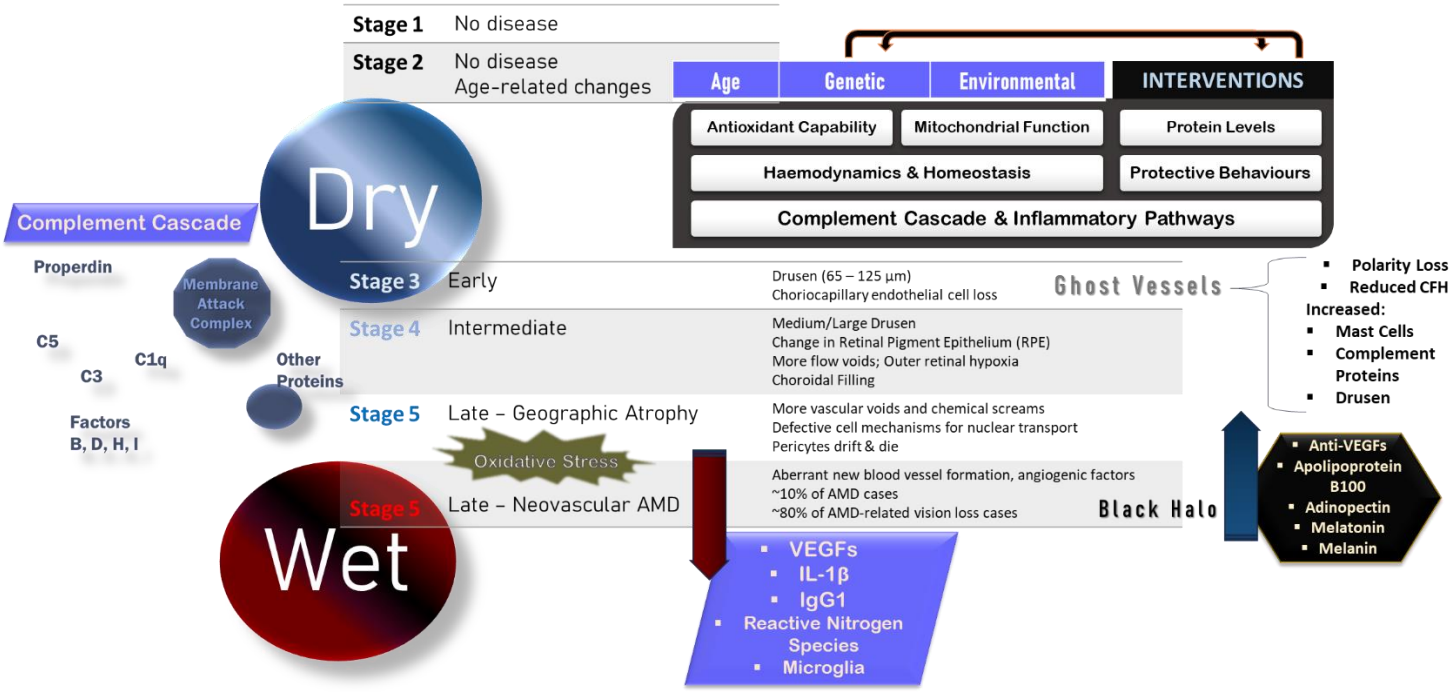
As dry AMD and geographic atrophy progresses, those 'unwanted elements' can become proximal RPE cells and photoreceptors. In a healthy state as directed by C3, the complement system is a crucial part of host defence systems that acts to tidy up foreign materials and dead cells. Complement proteins will bind and tag an identified pathogen for destruction by phagocytes – literally cell devourers – or when in conditions of high damage and immune dysfunction, start a destructive cycle for the entire area including healthy host cells.

Vessel dilation is a distinguishing pathological finding in wet AMD (Zhao et al., 2015), and testament to involvement of C3 and its multifaceted evolutionary potential. Example: Certain cobras have evolved repurposed C3 sequences to become CVF which facilitates rapid venom distribution in bitten prey through…? I hope you guessed it: Blood vessel dilation. C3 is also involved in retinal tissue regeneration and seems to be fundamental for early development in mammals and other vertebrates (Ricklin et al., 2016). A study published this February even showed that complement proteins in mouse-mother milk determined their infant's gut microbial health and therefore post-infection survival.

With a slightly better safety profile, Izervay inhibits complement component 5 (C5), a step in geographic atrophy's overactive immune response and the complement cascade that according to maker Iveric Bio, gives the command to attack retinal cells. The complement cascade involves a whole host of around 50 actors including numbered complement proteins, factors B, D, H, and I, a megazord formation called the membrane attack complex, and properdin. There are also three well-known routes called the classical, lectin, and alternative pathways, with the extrinsic pathway a newer but increasingly recognised conceptual addition. The list of non-canonical pathways and routes is steadily growing, but many may be specific to disease and tissue types (Mastellos et al., 2024).

Of the three basic pathways within the complement system, genes affecting the alternative pathway seem to be risk variants for AMD (Armento et al., 2021). Some of the first genome-wide association studies showed strong influence of complement factor H (See FH polymorphism in Figure 7 of Mastellos et al. 2024), and genetic data eventually directed the industry to C3 as a prime target for drug-based interventions (National Eye Institute, 2023). For later drugmakers with ambitions for AMD gene therapies instead, the complement system can act as a barrier to higher doses as the viral vectors (by nature) activate innate immunity and spark inflammation (In Ryan, 2024; Also see Shinjyo et al., 2021 for neurodegenerative consequences of complement activation via pathogens).

A review of complement system components and their targeted drugs for dry AMD is available in Patel et al. (2022).



By IVRC: Basic overview of AMD stages, types, signs, and some risk factors. Purple parallelograms to indicate progression risks and factors for dry and wet AMD types. Oxidative stress blob is a key pathogenic stimulus for both types of Stage 5 AMD. Black shield for some protective factors against wet AMD. Black arrows to indicate an example of interacting factors, in the case of gene therapy or differential response to drugs due to polymorphisms. Compiled from Lipecz et al. (2019), Patel et al. (2022), Cao et al. (2021), Cui et al. (2023), Toma et al. (2021), Wang & Mao (2021).

Wet AMD Options

Intravitreal anti-VEGF Injections

For several types of cancer and retinopathies including wet AMD, vascular endothelial growth factor (VEGF), its receptors, and different steps along its downstream signalling pathways are a major therapeutic target. This subset of anti-angiogenics is reviewed in Wang et al. (2024), and aflibercept (Regeneron's Eylea, VEGF-A, VEGF-B, and placental growth factor suppression) currently has the longest list of approvals for ocular use. Numerous other companies are gunning for their position of primacy in macular degeneration markets, with stock prices for all highly responsive to

news about product safety, efficacy, and competition. Could get interesting if the US$50 per shot ophthalmic formulation of bevacizumab (Lytenava) gets approved, as competitors are upwards of US$1214 or even double that per dose (Kirkner, 2024).

VEGF inhibitors (anti-VEGF) delivered via injection into the vitreous chamber of the eye are well-established for management of exudative/neovascular AMD. According to the National Eye Instute, earlier applications of anti-VEGFs reversed vision loss in most cases, which is possible as a result of cooling inflammation but not necessarily cell repair or restoration. There are some issues, hence the search for alternatives. First, drug resistance may develop, requiring a switch to a different pharmaeutical or dose increase, and cytotoxicity is a greater risk if the drug targets are VEGF receptors instead of VEGFs, which is why only the latter are typically cleared for use in retinopathies (Wang, 2024). The needling itself poses risks for ocular tissue, treatment is considered burdensome in terms of travel, times, and expense, and primary patient profile can contribute to a high dropout rate. The number of intravitreal injections, clinic visits, and expense required differs case by case, but in general and in many contexts, it can be challenging for seniors to make it to monthly/bimonthly appointments without consistent social and physical support, e.g. a ride there and back (Hazanchuk, 2023).

Frequency is actually variable due to individual, drug target/mechanism, and other factors. Some candidates may need an injection every month indefinitely, others may be able to stop after a year. Other anti-VEGF drugs like faricimab are becoming available with quarterly dosing schedules and quite positively, Treat-and-Extend (T&E) protocols have become standard practice. T&E is a personalised approach which limits the frequency of intravitreal injections based on the patient's particular drug response, keeping inconvenience and repeated eye-poke risks like retinal detachments and haemorrhages to a minimum.

Aside from the persistent issue of dropouts, a significant portion of compliant patients (15-40%) do not or only partially respond to existing anti-VEGF therapies. One of the ways to improve anti-angiogenic efficacy and control choroidal neovascularisation (CNV) was found to be vigorous exercise, which caused release of adinopectin protein and thus reduction of the inflammatory response in myeloid cells (Cui et al., 2023). This meant that for CNV model mice forced to run on treadmills, vascular leakage and neovessel formation was significantly reduced at days 3 and 7.

Unfortunately, incorporating an exercise regimen into wet AMD eyecare for elderly cohorts may be even more challenging than attending a clinic for intravitreal shots. If fitness trainers and supports were instead available, it would certainly be beneficial for not just vision and pharmacological efficacy but the sociopsychological and physical wellbeing of ageing patients. It would be hard to match the Cui et al. (2023) mice for intensity, though. Six times per week, for 60 min, at 15 meters per minute (around 150 mouse body lengths). That's worthy of a 1980s video montage.

With regard to rising global risk of AMD and downsides of anti-VEGF methods, several biotech companies are in the process of crafting therapeutic alternatives while the research on environmental and molecular causes continues. Gene therapies as well as implanted drug delivery devices are some techniques designed to reduce the number of injections for wet AMD patients.

Gene Therapies by Adverum, 4DMT, Regenxbio

Several gene therapies are approaching Phase 3 trials. They are focused on reducing the frequency of intravitreal injections, improving efficacy of anti-VEGFs, and lowering neovascularisation and sight loss associated with action of molecules like VEGFs and angiopoietin-2 (Ang-2). Perhaps in future, they will incorporate segments for deft manipulation of complement proteins (See Ryan, 2024) and Interleukin-1β (IL-1β).

Adverum Biotechnologies' adeno-associated-virus (AAV) based Ixo-vec is part of the pack, and delivery includes a corticosteroid protocol (13 days for oral or 6 weeks for drops) to reduce the inflammatory response expected of AAV-based delivery (Masson, 2024). Ixo-vec increases expression of aflibercept, the same molecule injected as an anti-VEGF in Regeneron's Eylea, and has been repurposed from failed trials for diabetic macular oedema on the basis of safety. No adverse events were reported in Phase 2 data and 85% of patients in their high dose group could go 26 months injection free, with a possibility of 4.5 years. Secondary objectives include maintenance of BCVA, but the lower dose seems to be the better performer for reducing injection rates.

4D Molecular Therapeutics' therapy (4D-150) targets the gene for expression of an RNA strand VEGF-C inhibitor *and* aflibercept. Descriptions state a reduction of treatment burden by 90%, with a lengthy course (20 weeks) of corticosteroids and several 4D-150 shots.

ABBV-RGX-314 by Regenxbio is also aiming to be a one-time suprachoroidal as opposed to subretinal shot for control of wet AMD, diabetic retinopathy, and some other chronic retinal conditions. At the 6-month mark, 50% of patients were injection free.

Trends: Implants, Small Molecules, Transcription, Nomenclature

Implant-based delivery of anti-VEGFs is technically simpler and hopefully has less immune and inflammation related complications than an AAV-based gene therapy. Genentech's refillable port delivery system Susvimo (ranizibumab, inhibits VEGF-A) is one way to bypass injections, with thrice-yearly treatment schedule. It's since been voluntary recalled with new implants paused due to a manufacturing issue, with dislodgement occuring in 33 out of 1,419 cases. The implant has also been media-sidelined by their more recent project, another monoclonal antibody faricimab-svoa named Vabysmo which inhibits VEGF-A and Ang2 through standard intravitreal injection, on a 1 – 4 month dosing schedule after the first four monthly shots. Regardless, the Susvimo implant should be back on the table this year (Kirkner, 2024). Despite no issues for most early users the trial data show more side effects for the eye's anterior like endophthalmitis and possible allergic reactions to the foreign body.

Another implantable which releases daily doses of a small molecule multi-target tyrosine kinase inhibitor (axitinib) is Axpaxli by Ocular Therapeutix. This has reached Phase 3, and the company has received special permission to include treatment naïve patients in trials. Besides speeding up enrollment, this means data could apply for earlier wet AMD interventions with better preservation of BCVA.

In around 3 years, instead of intravitreal delivery with steroid drops, there could be smooth eye drop delivery of small molecules like BT2 for AMD. The product by Filamon Limited could be self-administered and targets no less than twelve different genes involved in neovascularisation. The company says it achieves this through suppression of transcription factor AP-1, a key regulator of pro-inflammatory and angiogenic gene expression. As a small instead of large molecule drug, development and manufacturing costs are lower, with market prices down the line to match. This represents a big regulatory and attitude change from just a few years ago (2022) where major safety concerns about small molecules kept them off the table for wet AMD and other retinopathies (Wang, 2024). Pharmacovigilance is still imperative for many of these molecules, with other applications in cancer and a record of adverse events.

INTERVENTIONS	Inject Intravitreally	Implant	Eye Drop	Other Actions
Dry	Syfovre – C3 Inhibitor Izervay – C5 Inhibitor			Nutrition Exercise AREDS2 Hydration
Wet	Anti-VEGFs e.g. aflibercept [VEGF-A, B, PIGF] faricimab [VEGF; Ang-2] Melanin Nanoparticles Gene Therapies e.g. Ixo-vec [aflibercept] 4D-150 [aflibercept + anti-VEGF-C] ABBV-RGX-314 [anti-VEGF] *Suprachoroidal	Susvimo – VEGF-A inhibitor (ranibizumab) Axpaxli – Tyrosine Kinase inhibitor	BT2 – Suppresses transcription factor AP-1	Treatment Compliance Treat & Extend Approach for Injections Exercise → Adinopectin Melatonin Supplementation

Table by IVRC: Selective summary of dry and wet AMD interventions

Beyond complement system targeting, expanding genetic toolkits, and small molecules, the industry is showing a definite predilection for sprinklings of the letter 'x' and 'v' in biotech organisation and drug names. The trend is expected to continue, as that's simply how these things are done. It's at least going better than some early public and professional attempts to name newly discovered exoplanets. They've improved with practice, but alas, personal favourite 'Starry Bunnies' hasn't made it to the celestial list… maybe for some rejuvenative eye drops?

Why not. It could be time for a novel nomenclature system in pharmaceuticals and healthcare. First, to stay on trend with last year's proposed revisions to dry AMD terminologies and biomarkers, second, because the monoclonal antibody boom already forced the World Health Organisation to scramble for international nonproprietary names (INNs) in 2021. Despite their declarations of having future-proofed the formulas for drug dubbing, are we really prepared? There is a possible tsunami of drug, molecule, and sneaky biosimilar discoveries on the horizon as artificial intelligence and other computing technologies start doing more analytical and modelling work for us (Narain, 2024). As it is, the sheer volume of un- and badly-named therapeutics and techniques is a challenge for the biomedical industry. Some issues could be seen as minor, for example difficulties with pronunciation and memorisation, but in reality this poses risks to safety of patients (Philpott, 2023) and of course, branding. For the latter it sometimes pays to do the unexpected, but it is unknown whether Draugr, Phobetor, and Lich would be particularly marketable as names for anti-angiogenics or laser therapies.

Predicting Progression and Vision Restoration

Aside from traditional diagnostics and gene therapy, the biomedical field is attempting several revolutions in healthcare through use of artificial intelligence (AI) and protein-based research for personalised medicine. Syfovre as an example is tied to Duke Eye Center's work on an OCT-based AI algorithm for prediction of geographic atrophy, while Johns Hopkins is looking at protein biomarkers in eye fluid to rewrite challenging anti-VEGF schedules.

There are still difficulties with experimentation and early drug testing due to the lack of an appropriate animal model. Human retinal organoids or 3D in vitro retinal models are one option, and are being tested to evaluate their viability for investigation of cis-regulatory elements (non-coding genome) in ocular disease. Although organoids are definitely an improvement, they still have major constraints as far as disease progression involving multiple interacting cells and pathways.

Understandably, the preventive side is complicated. However, there is another angle, which is the restoration of traditionally irreversible vision loss through retinal prosthetics. In future, this and other sensory-related losses could be recovered via devices based on unconstrained or convoluted neural networks (CNN) for artificial sensory encoding.

Viability for human retinas or AMD specifically at this stage is unknown, but a machine learning approach called an actor-model framework (Leong et al., 2024) has been able to mimic several aspects of natural mouse retinal ganglion cell processing to better downsample and transmit clearer static visual information. The framework which incorporates 'natural biological transformations' (Ibid.) was able to achieve efficient encoding and improved transmitted image quality compared to mathematical procedures. Study authors are hopeful that this will apply to visual prostheses, perhaps replacing lost macular function.

The above highlights a tendency for computer programmes to mimic not just intelligence but our biological characteristics, which has particular value for studying our most complicated organ – the brain – and saving a very precious resource: Money. As a recent example, an artificial intelligence system given physical constraints (essentially rules akin to the biochemical ones that govern our bodies) mimicked several human neural behaviours in order to solve complex tasks. As the field improves, studying such purpose-built artificial 'brains' through a screen or even paired to an augmented reality device might be a more effective and efficient option for several aspects of research and education. The retina is also brain tissue. If the data is good and system sufficiently clever, artificial retinal instead of animal or *in vitro* models could eventually be available for study and exploratory fiddling with AMD interventions.

Part II: Acid Mines & Mercurial Eyes

Before anyone gets too enthused about silvery-eyed Mercurian space princesses, perhaps a species 'more airy and ingenious than we', though definitely more salty. And sulfuric. Likely temperamental too, owing to the 'daily' highs in the 400s to lows of minus 180 degrees Celcius. Here, 'mercurial eyes' is meant in the sense of the pollutant accumulating in your neuro-ocular tissue. Also super exciting, but it in a *much* more negative sense.

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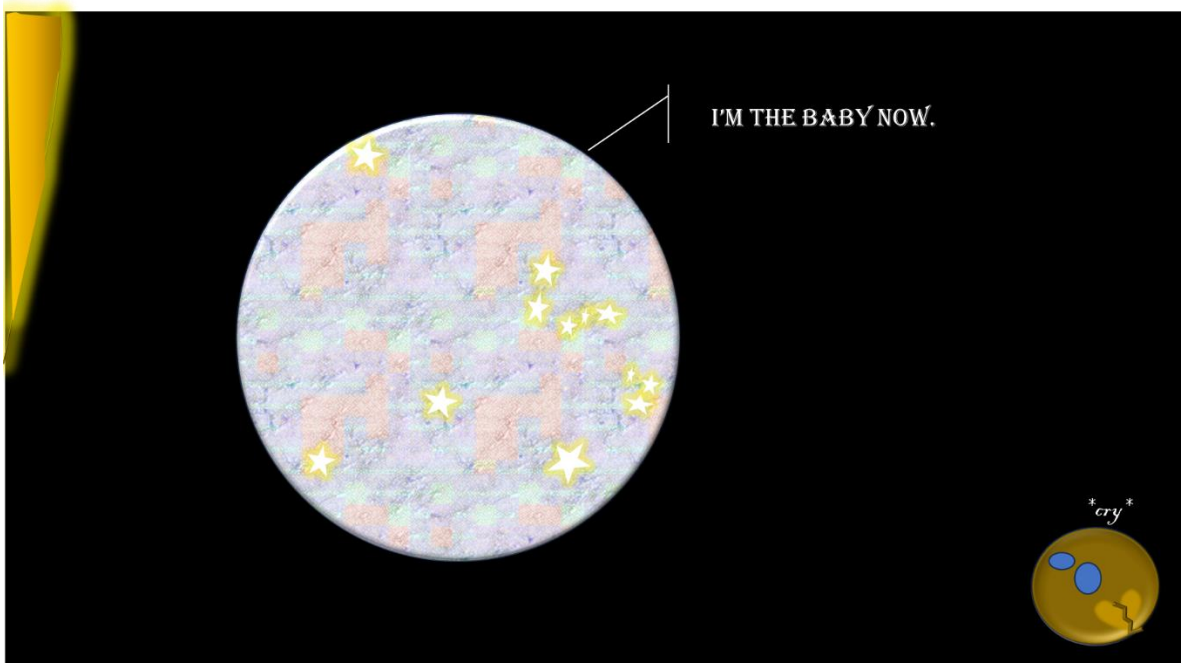

Image by IVRC

Our best shots of Mercury were by the MESSENGER spacecraft (2011 – 2015) which was given it's own special types of photoreceptors. Hundreds of thousands of images were later false-coloured by spectrometers to depict the planet's chemical, mineral, and physical composition for scientific study.

The highlights collection is here.

As part of the BepiColombo project, the Mercury Planet Orbiter (MPO) and Mio spacecraft are on their way over to replace MESSENGER. Mio will reach Mercury's orbit in late 2025, currently circling via gravity assists and data-basking in electromagnetic waves.

Prelude: Detour to planet Mercury

At first glance, this super-heated territory is seen as lifeless and inhospitable. However, that perspective is changing. A recent study by Rodriguez et al. (2023) suggests that volatile-rich layers around 2km thick lie beneath the dramatic cratered surface. The team proposed this on the basis of geomorphological mapping of glaciers in a particularly complex region of the planet's north pole, which has the *fantastic* name of 'The Borealis Chaos'.

Within, watery saline nodules shielded from adverse circumstances above by impact-blasted halite (also salt) could be nestled cosily. Similar to biochemical niches on Earth, the mix of volatile compounds, water, and conducive temperatures might serve 'depth-dependent Goldilocks zones' over on Mercury, suitable for the evolution of life and habitation (In Lea, 2023). Something to note if we are lacking in Lebensraum or catching the extra-terrestrial wanderlust. So far no fly-bys (which are really hard to do, by the way) have indicated that potential inhabitants huddled in sublimation hollows have air defence capabilities or armour. Maybe chemical weapons or rarer-on-earth elements. Irregardless, Mercury-affiliated irregular forces started firing first, itty bitty pieces hitting Germany on the 21st of January.

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The other AMD

On Earth, beautiful subterranean formations support numerous fragile ecosystems populated by mostly unpigmented, blind, meek, and tiny creatures, with the earth also housing a variety of elements we mine for assorted purposes. The subterranean systems created by humans when digging for gold, coal, and other metals can lead to a phenomenon known as acid mine drainage, the other AMD.

Acid mine drainage refers to the leak and chemical and environmental interactions of metal by-products during and after mining. It can amount to millions of tonnes a day discharged into water bodies, often in vivid reds, orange, yellow, and even deep dark brown or purple, with the hellish smell of sulfur to match. Abandoned low-tech mines like the open-pit style in Indonesia and historic coal mines of Appalachia seep reactive compounds into surrounding waters, either killing wildlife outright or initiating transformative processes that make their way down down food chains, life paths, and water supplies.

The situation is bad, but not entirely. Environmental regulation as well as private individuals and organised groups are striving to protect organisms and areas afflicted. There has been a lot of recent innovation in terms of passive treatment remediation, anti-bacterial products (CuS nanoparticles), and even producing commercially viable oil paint from assorted metal pigments.

A documentary about the latter project by Ohio University called 'Toxic Art' was made in 2023, with the first successful colour being a very unexpected violet – after several years of alchemical shenanigans conducted by the engineering and art departments. Round paintings with vivid flowing colours by John Sabraw showcase the array of colours sourced through their Ohio river cleanups.

Other than pretty paints, for the United States an even more strategically and economically enticing project is converting coal ash ponds and other mining byproducts to a domestic supply of rare earth elements (Fatunde, 2024). Rare earth element desposits are not uncommon but typically not economically viable to mine, hence the 'rare'. Currently they act as critical components of advanced healthcare and defence technologies as well as the envisioned energy industry transformation to renewables. For brain research and other types of non-invasive biomedical imaging, rare earth lanthanides offer the possibility of views at the *nano*scale (Casar, 2021), with existing use of elements like Ytterbium and Erbium in swept source OCT (Klein & Huber, 2017). This matters to the eyecare industry to some extent if rare earth supply is constrained while the demand for OCT-based diagnostics – and implicitly the number of the machines themselves – rises.

Given a recent export ban by the world's main supplier, innovation in terms of rare earth element extraction from mine tailings and pesky pollutants would serve as supplements for medical use and American national and economic security. Thirst is to the extent that space scientists have explored the possibility of using microorganisms to chew up asteroids, other planets, and our very own Moon to then spit out the desired lanthanides, scandium, and yttrium (Cockell et al., 2020).

Mercurial Cave Behaviours: More Circles and Angry Fish

In addition to tailings like iron oxides and heavy rare earths, gold mining and the traditional energy industry are major anthropogenic sources of mercury. Volcanoes are the dominant natural source, but we are apparently 7 times worse. The problem is that mercury is a largely invisible pollutant with severe neutoxic effects, hence the efforts to remove it from industrial, medical, and cosmetic use. Despite the Minamata Convention on Mercury, unethical

manufacturers still put mercury in skin creams because it suppresses melanin production, yielding that good 'ole silvery glow of irreversible tyrosinase inhibition and apoptosis (Chen et al., 2020).

We're also trying to limit environmental levels, and data on the consequences of exposure are a big part of gaining support and funding for those efforts. An article published in *Ecotoxicology and Environmental Safety* used zebrafish to investigate the effects of low level embryonic mercury ($HgCl_2$) exposures, finding ocular anatomical, social, and behavioural side effects. Researchers found a 'remarkable increase' in circling behaviours at larvae stages, a characteristic they likened to impaired social interaction skills in human autism spectrum disorders. The fish also showed 'impaired colour preference', attributed to a decrease in amino acid metabolites and unsaturated fatty acids (Bakar et al., 2023).

Results from the animal model demonstrate how low mercury levels might be affecting eyes and developing human brains. Of note but probably coincidental, there are peculiar overlaps with Pachón cavefish behaviour. Mentioned earlier in this article and probable basis to not fear subterranean Mercurians, besides also being depigmented, cave-dwelling species are typically less active and aggressive than their outer-roaming counterparts, with some other evolved characteristics including smaller sizes and loss of visual function. This is a general trend and there are exceptions, such as cave catfish and salamanders, where aggression even extends to cannibalism and the arisal of terrible bloodlust in response to the chemical screams of wounded conspecifics. Dragon's larvae indeed.

By contrast, Pachón cavefish are pretty chill. They and several other limestone cave dwelling communities are a subspecies of Mexican tetra fish, with their river-based kin classified as predatory and highly aggressive. Compared to surface type and other cavefish, Pachón cavefish show a dramatic trimming of their aggressive behavioural repertoire with one exception: Increased circling. Rodriguez-Morales et al. (2022) are unsure whether this is a sociobehavioural adaptation, actions related to foraging and exploration, or just a preference for circling in aggressive encounters. In support of the latter, the fish seem pretty happy about striking their enemies in the dark, where circling events are seen to reduce (Ibid., Figure 2) and a possible corroboration is that river fish lentectomised (blinded) in early ages are hyper-aggressive. According to a study mentioned in the discussion section, circling is an alternative to social interaction, similar to the 'autistic' patterns seen in mercury-exposed zebrafish.

More about Mercury (Hg) – Adult Exposures

Mercury exists in three forms, elemental, organic, and inorganic. In addition to type, exposure routes, duration, time of exposure, and genetic factors determine the effects on a person or organism (Olson, 2018). The organic form, particularly methylmercury, makes a beeline for the brain and eyes after exposure and easily crosses the blood-brain-barrier. Following Japan's Minamata disaster (1956), several studies have been conducted on the effects of chronic and acute human methylmercury exposure, with further research on populations affected in countries like Brazil, Spain, and Canada. If you recall safety risks mentioned due to confusing or unfamiliar drug names in Part 1, local incomprehension of the now international poison hazard symbol, the skull and crossbones, in Kirkuk, Iraq (1971) led to a mass poisoning where hundreds died and thousands were hospitalised from ingestion of mercury-coated grain. Victims included children born with severe brain damage as a result.

Animal models, post-disaster and contamination studies, and occupational hazard data are the main sources for studying the effects of adult mercury poisoning. In a voxel-based morphometry (VBM) review of Minamata disease patients, Hirai et al. (2023) found that damage was concentrated in the calcarine sulcus, thalamus, cerebellum, and somatosensory cortex, leading to the well-known symptoms of sensory disturbances, ataxia, and visual field deficits. Long-term exposure (Hg2+) through ingestion of contaminated fish or inhalation can also lead to colour vision

deficiencies mainly in the blue-yellow but also the red-green axis. Several decades ago it was found that for the calcarine fissure, only the anterior seems to atrophy which explains the loss of peripheral but not central vision (cited in Jackson, 2018).

How or why this happened was a bit contentious. Optical coherence tomography (OCT) and electrophysiological tests were employed by Pastor-Idoate et al., 2021 to investigate retinal involvement for the visual side effects. Multifocal and full-field electroretinograms (mERG, ffERG) showed alterations to rod cells as well as loss of peripheral, central, and paracentral function. The OCT results showed that these changes in response amplitude were not due to any structural changes in the retina or optic nerve, implying changes to photoreceptor function or eventual cytotoxicity. Generally, the molecular effects of mercury exposure include membrane depolarisation, glutamate excitotoxicity, and oxidative stress covered in Olson (2018) and Jackson (2018), who highlight that neurotoxicity effects can be delayed for several months or years.

Intriguingly, environmental genetics show that mercury toxicity can be mediated by an individual's genetic profile, where short nucleotide polymorphisms (SNPs) in coding regions affect protein shape and function. A review by Andreoli and Sprovieri (2017) points to genes in the glutathione detoxification system, for selenoproteins, and ATP-binding cassette transporters (ABCs) that influence antioxidative capacity, mercury clearing, and cell membrane permeability. Certain nitric oxide synthases influence cardiovascular susceptibility to mercury as well as risk of AMD (Ibid.; Toma et al., 2021). The authors also point to apolipoprotein APOE e4 in mercury susceptibility, which is classed as the major determinant of late-onset Alzheimer's. Absent mercury, the variant acts to drive up amyloid pathologies and vascular-related cognitive impairment in the brain (Yamazaki et al., 2019).

The link between mercury exposure and rising rates of dementia has been proposed but due to the number of symptoms (>200) and complexity of factors, precise mechanisms are still unclear. Paduraru et al. (2022) nevertheless point to oxidative stress, the gut microbiota, and β-amyloid protein production, where mercury exposures may exacerbate environmental and pathological processes in Alzheimer's and dementia. These deposits are also linked to ocular disease, and as such retinal imaging can be used to aid in early diagnosis of Alzheimer's (Wang & Mao, 2021). Against mercury at least, curcumin and N-acetylcysteine are highlighted as possible protectives in Paduraru et al. (2022). Curcumin may have some value for control of neovascular AMD and macular oedema as well due to its action as a tyrosine kinase inhibitor (See Chandra et al. 2023 and Dev et al., 2021).

Now, speaking of acids and colour vision…

Part III: Red/Green Cones and Iris Blue

Retinoic Acid (RA) means go Green

Recent experiments by Hadyniak et al. (2024) may have revealed the biological mechanism of long/medium wavelength cone fate determination. Using human retinal organoids, the team from Johns Hopkins University had earlier demonstrated how thyroid hormone suppression precipitates the first-step generation of short wavelength S/blue cones. These comprise around 8-12% of the total in humans, distributed quite evenly across the retina except for the very centre (Hussey et al., 2022).

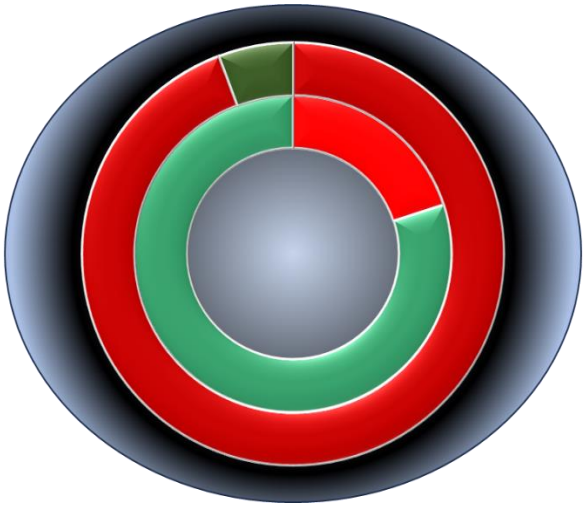
Using retinal organoids again along with a novel approach to visualise L/red and M/green opsin expression, Hadyniak et al. (2024) were able to demonstrate how high retinoic acid levels earlier in fetal development suppress L-cone formation. This then tapers off by day 130 post-conception. As the retina develops radially from the centre to the

periphery, gradually reduced RA signalling allows L-cones to dominate the peripheral retina. Experimenting with a few timeframes for immature cones (day 0 – 70), maturation (day 70 – 130), and terminal differentiation (day 130), varying RA levels altered eventual L/M populations in the artificial retinas. Only applying RA from day 130 – 200 yielded an L-cone proportion of 93%, while RA at days 43 – 130 resulted in 98% for the M-cone proportion.

Based on genetic data (n=738, all males with normal colour vision) and experimental results, they then linked this to a single-nucleotide polymorphism (SNP rs372754794) close to the gene for a receptor that mediates RA signalling. The study also validated the use of organoids instead of model organisms for ocular research. While insights from zebrafish, mice, and chickens pointed the team to genes of interest, they found significant interspecies differences following investigation with the human tissue (Ibid.).

Compiled in (Hussey et al., 2022), the human population shows high variability in the ratio of red to green cones, ranging from 1:4 (image below, inner circle) to 16.5:1 (outer circle), associated with a non-coding polymorphism in the gene NR2F2. (Hadyniak et al., 2024).

The peripheral retina is typically populated by L-cones, a subtype which arose later in the evolutionary history of select primates and humans. Of note, an extreme in the L/M cone ratio does not necessarily result in colour deficiency (Hussey et al., 2022).



Blue Eyes for Dark Vision

What can depigmented eyes do for you, whether by mercurial beauty cream application (don't do that) or the selection pressures of subterranean and Northern European habitation? Apparently over the short-term, give you better vision in low luminance conditions.

According to a preprint by Cain & Yamaguchi (2024), blue-eyed European descendants are able to read a distant wall-mounted code in dimmer conditions versus brown-eyed individuals (0.7 versus 0.82 lux) after a short adaptation period (30 seconds). The research was prompted by Yamaguchi's own experiences living in Europe, wondering why people kept their spaces so dark. So far this is only a theory and demonstrated association in a very small study, so the effect could be due to phenotypes other than the straylight effect in blue peepers. Countries with the highest

proportion of blue eyes in their populations – mostly Nordic – also have high prevalence of colourblindness, and Caucasians tend to have higher L/M cone ratios than Asians (Hadyniak et al., 2024; Gan et al., 2022). Rapid dark adaptation superiority could even have something to do with cone versus rod action and distribution patterns in the peripheral retina. Besides that, our contemporary collection of iris phenotypes are a product of not just the OCA2 regulatory mutant for blue but over a dozen genes which can have different effects on iris pigmentation for different ethnicities.

We don't actually know why there is only a European origin for blue eyes, or what specifically they're for given the mutation's origin in the tundra belt several thousand years ago. Perhaps a quick striking advantage as their enemies circle in the dark? For the existing stock of blue and range of other iris colours, there seems to be an association with domestication of ourselves and certain animals that we bring into the urban fold. More recently this neat relationship has been challenged by the multiple eye colours found in some species of definitely undomesticated big cats.

Our canine companions were covered several years ago by a GWAS study by Deane-Coe et al. illuminating the cause of Siberian husky heterochromia and blue. Clearly a popular topic, with over 26,800 article views since 2018. In contrast to the human blue, genetic data pointed to a mutation in a coding region instead which duplicated the mammalian eye development and pigment gene called ALX4. The same tandem repeat was linked years earlier to canine skeletal morphology, better enabling humans to practice selective breeding for a high diversity of dog breeds, acting as a type of 'evolutionary agility' (Fondon & Garner, 2004).

For macular degeneration, there are many claims but no conclusive data for the link between blue eyes and AMD across populations, but we know of one possible mechanism. Melanin in the RPE functions to protect cells from photochemical (e.g. ultraviolet or artificial blue light) damage, act as an antioxidant, clear drusen-like depositions, and facilitate photoreceptor turnover. Melanin variability in individuals and over time as they age means this could be a risk factor for some retinal diseases. Therapeutics proposed have included intravitreally injected bio-inspired melanin nanoparticles and sublingual melanin precursors. The nanoparticles in mouse models actually outperformed aflibercept in terms of anti-angiogenic activity (Kwon et al., 2022).

Ocular melanin is therefore another angle for AMD treatment, but this is much less popular in recent news and research. In light of blue eyes, it's an angle that underscores the pairing of eyes and brain. Example: The neuromelanin content associated with pigmented brown eyes also increases the speed of synaptic transmission and individual reaction times (In Cain & Yamaguchi, 2024). As such, melanin-targeted biomedical innovations could be applicable to both retinal and neuroprotection.

Conclusion

Even the MESSENGER spacecraft had colour vision cones in the form of filters. Tweaking the data from the 430, 700, and 1000 nm band filters produced this colour mosaic, an artificial enhancement for us to enjoy despite our human eyes. So very context-suited, but still so very limited, despite all our opsin mutations and red/green cone variabilities.

Other colour-*coded* readings enabled scientists to peer at the planet's geochemical composition to figure out its past and sub-surface life, finding high regional variability in ratios of magnesium and aluminium to silicon. This was distinct to the images for actual colour and morphology, and therefore a rich new analytical dimension for researchers. Also great news for Mercury, because the lack of exceptional goodies in scans means we're probably going to start biomining on Mars instead.

The data from MESSENGER's spectrometers has lower resolution than the monochrome files, but these provide more precise morphological data, much like the OCT does for anatomical biomarkers instead of coloured fundus imaging in AMD. Starting several years ago, researchers are still uncovering the underlying gene and regulatory sequences for this ocular disease.

With all these other AMD analytical angles covered, that begs the question: When and how do we get to a routine, non-invasive biochemical imaging dimension for clinical management of macular degeneration?

…and who gets to name the nanoparticles?

Disclaimer: *The material presented is for informational and entertainment purposes only, in summary of recent news and events. It neither reflects the views nor constitutes professional advice of the organisation. The major sources used are referenced below.*

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