Fighting Blindness with Drug Repurposing

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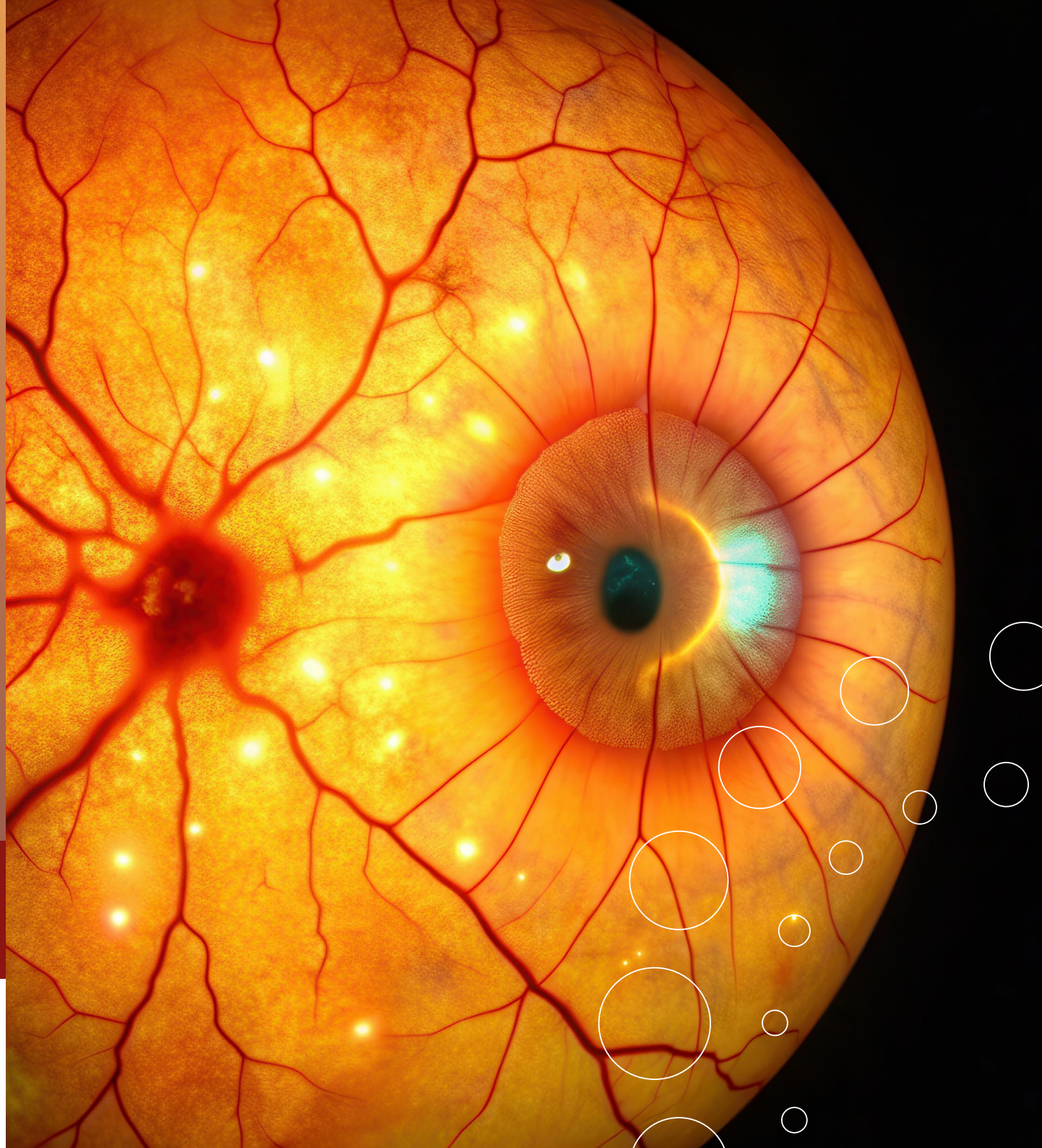

Fighting Blindness with Drug Repurposing

For many types of inherited eye disease, there are currently very limited treatment options. These conditions, which are linked to distinctive genetic mutations, can eventually lead to blindness. Dr Henri Leinonen from the University of Eastern Finland leads a research team at the Leinonen Retina Laboratory investigating degenerative eye diseases and exploring drug therapies to treat these devastating conditions. This work is bringing fresh hope to millions around the globe.

An Unmet Need

The retina is the layer of light-sensitive cells covering the back portion of the inside area of the eyeball. Light enters the eye and it is then focused onto the retina by the lens. The cells of the retina, the rods and cones, react and create nerve impulses, which are then sent to the brain to interpret what is being seen. Inherited retinal degenerations (IRDs) comprise a large group of conditions, all of which are caused by mutations in the genes which are vital to the healthy function of the retina. These mutations eventually result in retina cell death and, in turn, a progressive loss of vision.

Dr Henri Leinonen, based in the School of Pharmacy at the University of Eastern Finland, explains that most IRDs are lacking in treatment options. IRDs affect around 1 in 2000 people around the world, often leading to blindness developing during childhood. There is a significant unmet medical need for a large number of people with serious life-changing eye disease. His ground-breaking research at the Leinonen Retina Laboratory aims to investigate the molecular mechanisms underlying disease in retina cells, and to develop new drug treatments for retinal degeneration.

Treating Inherited Retinal Degenerations

Dr Leinonen notes that IRDs (such as retinitis pigmentosa) are linked with hundreds of distinct genetic mutations. As such, targeted gene therapy is not only impractical but prohibitively expensive, both now and in the foreseeable future. He adds that there is only one gene therapy currently approved for IRDs, and it's still unclear whether it can prevent the progressive nature of cell degeneration. Other options include untargeted disease-modifying treatment that aims to interrupt the mechanisms which drive the retinal cells to degrade across different IRD subtypes, regardless of the underlying genetic causes. Excitingly, certain methods of developing untargeted, and thus, more generally applicable disease modifying treatment, may offer a more attainable option for larger numbers of patients in a smaller timescale.

In describing his laboratory's research, Dr Leinonen explains they have two main research programmes. The primary project is dedicated to identifying new retinal degeneration treatments utilising drug repurposing and untargeted disease modifying treatment strategies, as outlined above. The second project aims to better understand the retina's homeostatic plasticity (its ability to adapt and function in certain disease situations). Dr Leinonen believes that once molecular pathways which enable the retina to adapt to sensory defects are identified, this will help guide the invention of new therapeutic targets that could be affected by repurposed drugs.

Drug Repurposing

Dr Leinonen highlights that the search for disease modifying treatments often uses drug repurposing, which can significantly reduce the development timeline and also minimise the risks and costs linked with new drug development. Drug repurposing involves using currently available drugs for treating different conditions to what they are usually used for – a kind of recycling of medicines. Novel drugs can take decades to be researched, developed and tested, costing hundreds of millions in the process with no guarantee of ever making it to market. Older drugs have a significant advantage in that they have already been through detailed tests required by drug regulatory agencies, such as ADME studies (absorption, distribution, metabolism and excretion in the body), and their safety profile is well understood. He stresses that it is a positive step that drug repurposing is becoming more

common, adding that it will likely play a significant role in the development of future treatments in general.

Dr Leinonen describes that his recent work has primarily focused on drugs that act on G protein-coupled receptors (GPCRs). GPCRs are like tiny sensors on the surface of our cells and they help to detect signals in the environment – things like light, smells, hormones, and neurotransmitters. With their selected GPCR drug cocktail, Dr Leinonen and coworkers intend to correct pathological cell communication that occurs during retinal degeneration, such as excessive intracellular calcium release. Their GPCR drug cocktail has demonstrated promising results against retinal degeneration, bringing new treatment hopes by repurposing older drugs.

The Triple Cocktail

Their cocktail contains a trio of drugs which are already prescribed but for other conditions: tamsulosin, metoprolol, and bromocriptine. Tamsulosin is used to treat benign prostate hyperplasia, a condition in males where the prostate gland becomes enlarged. Metoprolol, a beta-blocker, is used for blood pressure control and cardiac conditions. Bromocriptine is an old Parkinson's disease drug, but today used more for other indications such as hyperprolactinemia. These drugs all impact GPCR modulation, and when given together, they found a synergistic suppression of retinal degeneration severity.

In his postdoctoral research project at the University of California, Irvine (UCI), Dr Leinonen used a variety of animal models of IRD. The drugs were given systemically and then circulated through to the eye where they showed action against receptors that are found both in mouse and human retinas. The team reported that their cocktail (tamsulosin, metoprolol, bromocriptine) improved cone function and slowed degeneration in the various animal models they investigated. They also found improvement in night vision as well as metabolic functions in the retina. Additionally, the team highlighted that their previous research into this drug combination and its effectiveness was done solely on acute administration. Unfortunately, any treatments that show benefits with acute administration can, in fact, prove harmful with prolonged use. The new study was the first to provide data on chronic, long-term administration of this drug combination in multiple types of IRD models, with positive effects.

Looking to the Future

Dr Leinonen explains that the triple combination of drugs has been shown to have benefits in the acute treatment of a variety of IRD mouse models, and also in progressive diabetic retinopathy models. Some of the therapeutic effects can be seen if the same drugs are given as a single-drug treatment but only at much larger doses, and the effect is not well sustained, which is a prerequisite for successful retinal degeneration therapy. When administered at lower doses, the tamsulosin-metoprolol-bromocriptine combination shows very promising long-term effects, indicating that the drugs are working together.

This vital work is renewing hope for the millions impacted by degenerative retinal diseases, shedding new light on promising effective, long-term treatments. The recently published ground-breaking work has demonstrated the successful repurposing of three well-known drugs, potentially significantly reducing the timeline of treatment development. Dr Leinonen highlights that his laboratory's next crucial task is to understand further the therapeutic mechanisms involved to help facilitate treatment optimisation and preparation of clinical trials.

Article written by Luisa Postlethwaite, MPharm

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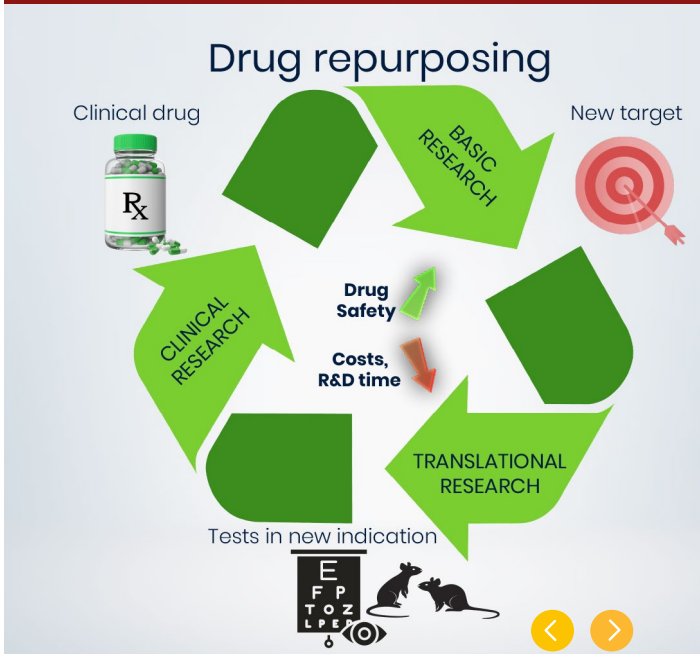

MEET THE RESEARCHER

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Dr Henri Leinonen obtained his MPharm and PhD/PharmD from the University of Eastern Finland. In 2016, he took up a postdoctoral position in the Department of Pharmacology at Case Western Reserve University, Cleveland, Ohio, USA, researching drug repurposing for retinal degeneration. He continued his postdoctoral work in this field at the Gavin Herbert Eye Institute and Department of Ophthalmology at the University of California, Irvine, between 2018 and 2021. In 2022, he became Adjunct Professor in Neuropharmacology, and he is currently also an Academy of Finland Fellow and Research Director in the School of Pharmacy at the University of Eastern Finland. He is a member of the scientific advisory boards for the Biobank of Eastern Finland, and Administrator for the Finnish Retina Register, as well an International Scientific Committee Member for the International Centre for Translational Eye Research in Warsaw, Poland. Over his career, he has won numerous early-career honours, including the Knights Templar Eye Foundation´s Career Starting Grant 2020, the Academy of Finland Fellowship 2021, and the FEBS Excellence Award 2024.

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FURTHER READING

H Leinonen, J Zhang, LM Occelli, *et al.*, A combination treatment based on drug repurposing demonstrates mutation agnostic efficacy in pre-clinical retinopathy models, *Nature Communications*, 2024, 15, 5943, DOI: https://doi.org/10.1038/s41467-024-50033-5

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