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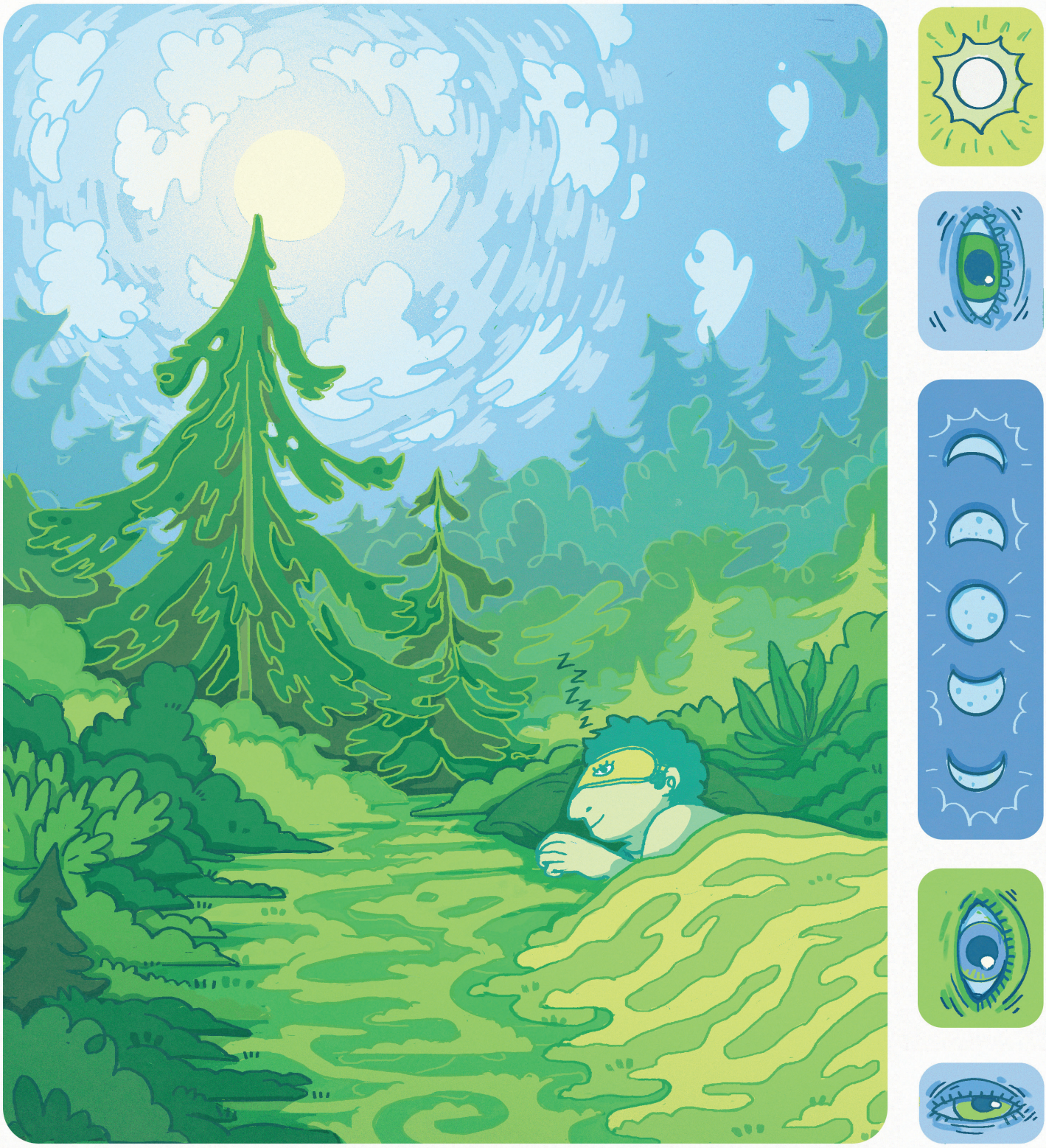
OFTALMOLOG



Keeping an eye on our circadian rhythm

Full article on page 25

EDITORIAL

Dear Colleagues,

Tor P. Utheim

We begin this issue of Oftalmolog with the Outstanding Nordic PhD Awards. These awards highlight the exciting work of emerging scientists in ophthalmology. As last year, we determined the winners based on the total CiteScore of the papers published in their theses, as further described on page 4. We congratulate Maria Xeroudaki from Sweden, who won the first prize with the highest score ever (90.2) in Oftalmolog. Niina Harju from Finland was in second place, and Ingvild Ramberg from Denmark received third prize. We welcome anyone who defended their thesis in 2023 to reach out to us by October 1, 2024, to be included in the upcoming 2024 issues and be considered for the next PhD awards. In this issue, we present the highlights of five recent theses, covering topics from the front to the back of the eye, including oculoplastics and the eye as a window to the brain.

We are pleased to continue our latest series, *Oftalmolog's* Portrait of Excellence, with Professor Jakob Grauslund as the second colleague in the spotlight. Learn more about his amazing academic journey, including becoming a professor at the age of 38 and supervising over 90 students, in the full interview on page 15. We welcome nominations of future candidates for the Portrait of Excellence so we can highlight their achievements and inspire young doctors and researchers with their stories. In the same vein of inspirational stories, in this issue, our Danish colleagues discuss how research can lead to legal changes, with the aims of helping patients and clinicians alike.

Two of our previous Oftalmolog Best Paper Awardees return in this issue with a most exciting update on the latest research on circadian rhythms and why ophthalmologists and others should care. Their peer-reviewed narrative review can be found on page 25.

We are also pleased to present an example of recent top-notch research in the Nordics. If you or your colleagues are interested in having your work featured in an upcoming issue of *Oftalmolog*, please send an email to info@oftalmolog.com. We also feature exciting ongoing research. On page 39, we present the newly established EU network, Restore Vision, involving several Nordic partners.

We hope to see many of you in the beautiful Kuopio, Finland, for the Nordic Congress of Ophthalmology in 2024. The deadline for early-bird registration is March 31, 2024, and the deadline for abstract submission is April 1, 2024. Furthermore, do not miss the ocular inflammation and infection course, which will feature world-class speakers, on April 18–19, 2024, at St. Erik Eye Hospital, Stockholm, Sweden.

The editorial board will consider all manuscripts submitted by February 15, 2024, for publication in our next issue. Please do not hesitate to reach out to us with any questions. All articles published in 2024 will be eligible for *Oftalmolog's* 2024 Best Paper Awards. The winners of the 2023 Best Paper Awards will be announced in the upcoming issue.

The Editorial Board wishes all our readers a Merry Christmas and a Happy New Year.

Tor Paaske Utheim
Editor-in-Chief

www.oftalmolog.com

MANUSCRIPTS:

Manuscripts can be sent to info@oftalmolog.com. For guidelines about manuscripts, deadlines, and distribution, visit www.oftalmolog.com.

NEXT ISSUE:

Summer 2024

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COVER:

The cover of this issue was inspired by the narrative review on page 25: What happens when circadian rhythms go wrong, and why we should care. The eyes play an important role in regulating our circadian rhythms and understanding the how and why things can go awry with this vital system in important for overall health and well-being.

Meet the 2022 nominees

In previous issues

Johanna V. Berggren
Lund University, Sweden
Perfusion Monitoring in Oculoplastic Reconstructive Surgery

Niina Harju
University of Eastern Finland
Regulation of oxidative stress and inflammatory responses in human retinal pigment epithelial cells

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Gunhild Falleth Sandvik
University of Oslo, Norway
An ophthalmological study of adults with Marfan syndrome: Ten-year of follow-up and an evaluation of photophobia, glare and pupillary response

Markus Olsen
University of Oslo, Norway
The Pro-resolving Mediators Maresin 1, Maresin 2 and Annexin A1 in Maintenance of Ocular Surface Health

Maria Xeroudaki
Linköping University, Sweden
Advanced Surgeries, Medicines and Materials for Corneal Regeneration

Stine Bolme
Norwegian University of Science and Technology (NTNU)
Task-shifting Intravitreal Injections to Nurses

Ingvild Ramberg
University of Copenhagen, Denmark
Human Papillomavirus-related Neoplasia of the Ocular Adnexa

Henrik Holvin Jacobsen
University of Oslo, Norway
Extravascular Molecular Transport in the Human Visual Pathway

Håvard Hynne
University of Oslo, Norway
Clinical Aspects and Potential Biomarkers in Dry Mouth and Dry Eye Disease

Ivan Potapenko
Copenhagen University, Denmark
Artificial intelligence in age-related macular degeneration

Outstanding Nordic PhD Awards 2022

In this issue

Johan Aspberg
Lund University, Sweden
Aspects of screening for open-angle glaucoma

We are very grateful to our generous sponsor, **Santen**, which provides the funding for the Outstanding Nordic PhD Awards. With their support, we are able to highlight some of the brightest minds and young leaders in their disciplines.

Santen
Imagine Your Happiness

More information on the award can be found on our website, www.oftalmolog.com.

The perspective of the Editorial Board

Criteria

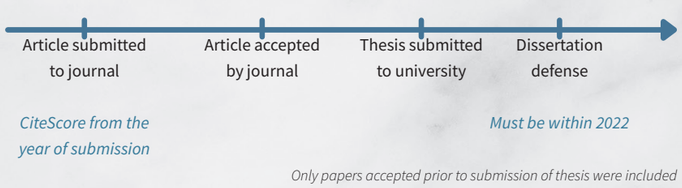
All dissertations defended in the Nordic region between January 1 and December 31, 2022, were eligible for nomination for the 2022 Outstanding PhD Awards. Nominations had to be submitted to *Oftalmolog* before October 1, 2022. Nominations were accepted from anyone.

We have decided to use the sum total of the CiteScores for each article included in the thesis. Review articles were excluded from the calculations. Although literature reviews are also valuable, not all universities accept these as thesis components. Additionally, journals solely focused on reviews generally have a higher CiteScore due to the nature of their content. Thus, by excluding reviews, we aimed to make comparisons fairer. Furthermore, correspondence letters were excluded.

All papers accepted for publication by a journal prior to the submission of the thesis to the university were included in the calculation. Manuscripts included in the thesis that were not accepted by a journal at the time of thesis submission were not included in the total CiteScore.

The CiteScore for each included article was determined based on the year the individual article was submitted to the given journal. For example, if a manuscript was submitted in 2018, the 2018 CiteScore was used, even if the paper was not published until 2019.

Timeline for articles eligible for consideration for the Outstanding PhD Award



Only papers accepted prior to submission of thesis were included

What is a CiteScore?

CiteScore is one of many metrics used to evaluate the impact of a journal. It was developed by Scopus, a subsidiary of Elsevier. Elsevier has created many metrics and databases, which can be useful for evaluating the quality of scientific publications.

The main benefits of using CiteScore include (1) it is stable and robust as it takes into account the citations over the past four years, which is important when comparing these with articles published in different years and (2) most publications are indexed in Scopus. More information and all CiteScores can be found at https://www.scopus.com/sources.

https://www.scopus.com/sources

Deadline for nominations for the 2023 award:

October 1, 2024

More information on the award can be found on our website, www.oftalmolog.com.

Dissertations
FROM THE NORDIC REGION

First place:
NOK 80,000

Total CiteScore:
90.2

Can Porcine Collagen Replace Human Donor Corneas?

Maria Xeroudaki
Linköping University, Sweden
Advanced Surgeries, Medicines and Materials for Corneal Regeneration

Second place:
NOK 30,000

Total CiteScore:
23.1

A Hot Topic: RPE cells as critical players in the retina

Niina Harju
University of Eastern Finland
Regulation of oxidative stress and inflammatory responses in human retinal pigment epithelial cells

Third place:
NOK 15,000

Total CiteScore:
20.9

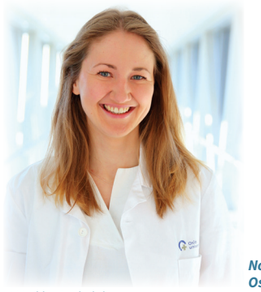
Human Papillomavirus– A Contributor to Ocular Cancer Development

Ingvild Ramberg
University of Copenhagen, Denmark
Human Papillomavirus-related Neoplasia of the Ocular Adnexa

Can a Fish a Day Keep the Doctor Away?

Omega-3 fatty acid–derived resolvins on the ocular surface

Dissertations FROM THE NORDIC REGION



Nora Botten
Oslo University Hospital

On May 4, 2023, Nora Botten defended her thesis "Specialized pro-resolving lipid mediators resolvin D1, resolvin D2, and resolvin E1 in the maintenance of ocular-surface homeostasis and in prevention of ocular-surface inflammatory disease" at the University of Oslo (UiO), Institute of Clinical Medicine. The research was carried out at the Department of Medical Biochemistry, Oslo University Hospital (OUH), and Schepens Eye Research Institute, Harvard Medical School. Her main supervisor was Tor Paaske Utheim, Department of Ophthalmology, OUH, with co-supervisors Darlene Ann Dartt, Schepens Eye Research Institute, Harvard Medical School, and Kim Alexander Tønseth, Department of Plastic and Reconstructive Surgery, UiO.

Key points:

- Goblet cells in the conjunctiva secrete mucins into the tear film to maintain ocular-surface health.
- Omega-3-derived resolvins contribute to the resolution of inflammation and the return to homeostasis.
- Resolvins activate multiple intracellular signaling pathways in goblet cells that, in turn, stimulate the secretion of mucins into the tear film.
- Resolvins regulate goblet cell function and could represent a novel approach for treating ocular-surface inflammation.

Introduction

One characteristic of ocular-surface inflammatory diseases, such as dry eye disease and allergic conjunctivitis, is the dysregulation of goblet cells in the conjunctiva, leading to the over- or under-secretion of glycoproteins into the tear film. Goblet cell secretion is tightly regulated, and either increased or decreased secretion can lead to inflammation. Specialized pro-resolution mediators, such as omega-3 fatty acid–derived resolvins, contribute to the resolution of inflammation. In preclinical studies, resolvins have shown promising actions in the treatment of inflammatory diseases, including ocular-surface inflammatory disease. Thus, this study aimed to determine whether and how resolvins regulate secretion from healthy conjunctival goblet cells.

Methods

Goblet cells from rat and human conjunctiva were cultured and used for experiments. Receptor expression was determined using PCR, siRNA, Western blotting, and immunofluorescence microscopy. Intracellular signaling pathways activated by resolvins were then investigated using two different methods. First, we measured the intracellular Ca^{2+} concentrations in goblet cells using Fura-2. Second, we measured the secretion of high-molecular-weight glycoproteins from goblet cells using an enzyme-linked lectin assay with the lectin horseradish peroxidase–conjugated UEA-1. In each experiment, half of the cell culture dishes were incubated with pharmacological inhibitors known to inhibit one specific intracellular signaling molecule. Goblet cells in the cell culture dishes were then stimulated with one resolvin.

Results

Resolvins in the D and E series activated different receptors on the goblet cell surface to trigger multiple intracellular signaling pathways. The activation of intracellular signaling increased Ca^{2+} or stimulated the secretion of mucins into the tear film. The resolvins that were investigated in this project activated many of the same intracellular signaling molecules, such as phospholipase C (PLC). PLC produces molecules such as inositol trisphosphate, which releases Ca^{2+} from intracellular stores in the endoplasmic reticulum within goblet cells. We also discovered differences in the intracellular signaling pathways activated by resolvins. Two examples are the cyclic AMP signaling pathway and activation of the epidermal growth factor receptor, which are activated by only some resolvins, but not others, to increase Ca^{2+} or stimulate secretion into the tear film.

Conclusion

Resolvins activate multiple intracellular signaling pathways to stimulate secretion in healthy goblet cells from the conjunctiva. Dysregulation of mucin secretion from goblet cells is a characteristic of ocular-surface inflammatory diseases. Regulation of goblet cell secretion is important to maintain ocular-surface homeostasis and prevent inflammation. Resolvins could represent a novel approach to treat inflammation on the ocular surface.

Remaining questions:

- If investigated in vivo, do resolvins regulate goblet cell function and stimulate the secretion of mucins into the tear film?
- Would treatment with resolvins be more effective at reducing inflammation on the ocular surface than today's treatments for dry eye disease and allergic conjunctivitis?

References

1. Botten N, et al. Resolvin D2 elevates cAMP to increase intracellular [Ca^{2+}] and stimulate secretion from conjunctival goblet cells. *FASEB J.* 2019 Jul;33(7):8468-8478.
2. Botten N, et al. Resolvin D2 uses multiple Ca^{2+} -dependent signaling pathways to stimulate mucin secretion in rat and human conjunctival goblet cells. *J Cell Physiol.* 2022 Oct;237(10):3816-3833.
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Screening for a brighter future:

Aspects of screening for open-angle glaucoma

On December 15, 2022, Johan Aspberg defended his thesis "Aspects of screening for open-angle glaucoma" at the Department of Clinical Sciences in Malmö, Lund University, Sweden. His main supervisor was Professor Boel Bengtsson, PhD, with co-supervisors Professor Anders Heijl, MD, PhD, and Dorothea Peters, MD, PhD.

Johan Aspberg
Department of Clinical Sciences in Malmö, Lund University, Sweden

Key points:

- A large population screening for glaucoma in Malmö, Sweden, has reduced the cumulative incidence of blindness by 50% over a 20+ year period.
- The average time from which open-angle glaucoma can be detected by screening to its clinical diagnosis was estimated at 10 years, long enough for repeated screening with at least 5-year intervals.
- Estimates of the prevalence of glaucoma blindness greatly varied when applying different criteria for impairment. Omitting visual field status seriously underestimated glaucoma blindness.
- Glaucoma cases detected today had less visual field loss than in the 1990s, but a considerable proportion still had severe vision loss in at least one eye, with a high risk of developing bilateral blindness.

Glaucoma is the leading cause of irreversible blindness worldwide. The most common form is open-angle glaucoma, with a prevalence of 2% in white populations over 40 years of age. Around half of the cases in developed countries are undiagnosed because symptoms are few in the early to moderate stages of the disease. A late diagnosis is the major risk factor for blindness, and many believe that earlier diagnosis through screening could reduce the prevalence of blindness from glaucoma.

In paper I, we investigated how estimates of vision impairment from glaucoma were influenced by applying different criteria for impairment. A large screening of almost 33,000 participants aged 57–77 years had been conducted for open-angle glaucoma in Malmö, Sweden, in the 1990s. In paper II & III, we evaluated its effect on bilateral blindness from glaucoma and estimated open-angle glaucoma's preclinical detectable phase (PCDP), i.e., the average time from which glaucoma can be detected by screening to its clinical diagnosis. In paper IV, we presented results from a 2020 glaucoma screening of people aged 77–89 in Malmö. Finally, paper V compared the amount of baseline visual field damage in the patients diagnosed at the large screening in the 1990s to patients diagnosed from 2013 to 2017.

Results

Paper I: If one excludes visual field status in the assessment of glaucoma blindness, the prevalence will be seriously flawed; 65% of the patients by the World Health Organization (WHO) and 54% by the United States criteria were blind by visual field constriction but not by visual acuity. By the US definition, 30% more patients were classified as blind than by the WHO definition. Paper II: Our results suggested that bilateral low vision and blindness from glaucoma may be reduced by around 50% with population screening. Paper III: The mean PCDP was estimated by two different methods to be over 10 years, with the lowest 95% CI of 8.7 years. The results suggested that repeated screening could be performed at an interval of at least 5 years. Paper IV: The prevalence of glaucoma was high in people aged 77–89 years. However, the cases detected at the screening had a low risk of developing severe glaucoma during the remainder of their lives, since most had early stages of glaucoma and normal intraocular pressure. Paper V: Visual field damage at presentation in clinically diagnosed patients in Malmö improved in the last 20 years. Still, almost 20% had severe visual field loss in at least one eye, with a high risk of developing glaucoma blindness.

Conclusions

Estimates of the prevalence of glaucoma blindness vary greatly depending on which vision impairment criteria are applied. Visual field status should not be omitted from the assessment because this seriously underestimated glaucoma blindness. Population screening for glaucoma halved the number of blind individuals in the screened part of the population. Our results on the PCDP length for glaucoma allow for repeated screening with at least 5-year intervals. Screening in the oldest age groups would probably not be cost-effective since the cases detected had a low risk of developing blindness from glaucoma. The glaucoma cases detected today had less visual field loss than in the 1990s, but 20% remain at risk of developing bilateral blindness due to severe vision loss in at least one eye.

Future directions:

- In future studies, we will try to estimate the amount of over-diagnosis in the 1990s screening, i.e., cases detected by screening that would never be detected during their remaining lifetime.
- We will also investigate at what age glaucoma screening would be most effective at preventing blindness.

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1. Heijl A, Aspberg J, et al. (2011) The effect of different criteria on the number of patients blind from open-angle glaucoma. *BMC Ophthalmol.*, 11:31.
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The power of science:

Research leads to change in generic-substitution law

When filling a prescription, a generic is most often dispensed due to the generic-substitution law. However, generics are allowed to contain different additives than the branded drug, including the preservative. Recently, the Danish Medicines Agency changed the legislation to state that generics must contain the same preservative as the branded drug. Researchers joined forces with Fight for Sight, Denmark, and this continuous dialogue led to the legislation change.

The generic-substitution law

According to the European Medicines Agency, a prescribed branded drug can be substituted with a generic drug because they are considered identical to the branded drug regarding safety and efficacy. The active pharmaceutical ingredient, dispensation form, and indication must be the same for branded and generic preparations.[1] The efficacy and safety studies performed on the branded drug are, therefore, considered applicable to the generic drug as well. However, inactive ingredients may vary. This includes preservatives. For example, until recently, the branded travoprost eye drop Travatan® contained the preservative Polyquad®, whereas the generic alternatives contained benzalkonium chloride (BAK). For a Travatan prescription, an eye drop with BAK may thus be dispensed. Because the pharmacy is required to dispense the cheapest product, the patient most often receives a generic BAK-preserved eye drop. Because the prices change frequently, patients may receive a different product with varying additives at every dispensation. Patients and clinicians alike are not necessarily aware of the potentially varying additives.

Anne Hedengran, MD, PhD Student
Department of Drug Design and Pharmacology, University of Copenhagen, Denmark
Department of Ophthalmology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

Miriam Kolko, Professor and Glaucoma Specialist
Department of Drug Design and Pharmacology, University of Copenhagen, Denmark
Department of Ophthalmology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

Consequences of substitutions

The generic-substitution law is a particular problem concerning eye drops. BAK is widely accepted as an ocular-surface irritant, causing more side effects than alternative preservatives, such as Polyquad. In a preclinical study on human conjunctival goblet cells, Polyquad did not induce cell death even after 2 hours of exposure, whereas BAK caused significant cell death.[2] With damaged goblet cells or decreased goblet cell density, the risk of ocular discomfort and other adverse effects increases. Thus, when substituting safer preservatives with BAK, the tolerability of the eye drop may decrease. When the tolerability decreases, the risk of poor adherence increases, along with the risk of poor quality of life and decreased disease control. This can be catastrophic for glaucoma patients because it may lead to irreversible visual field defects or even blindness. Other additives, such as phosphates, can also increase the risk of local adverse effects. Furthermore, varying additives may impact the efficacy of the active pharmaceutical ingredient because they may alter the drug uptake.

Law change

Research assessing the damaging effect of BAK has recently led to a change in the generic-substitution law. As of March 2023, the Danish Medicines Agency changed the legislation to state that a generic eye drop cannot contain a different preservative than the branded product. This is a major win for patients and clinicians alike because the safety profiles of branded and generic eye drops now must be more comparable. Patients will likely experience less variation in the tolerability of these eye drops and have increased adherence and confidence regarding their medication. Furthermore, the change underlines the importance of basic research.

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In the spotlight

Jakob Grauslund—balancing theory and practice in Odense

In the latest edition of Oftalmolog's *Portrait of Excellence, our Editor-in-Chief asked some investigative questions of another exceptional colleague from the Nordic Region—Jakob Grauslund. Professor Grauslund has not only excelled in the clinical field but also been a leader in academia, becoming Head of Research at age 35. In this article, he shares some insight into how he managed to balance it all and why he is hopeful for the future, having supervised more than 90 students over the years.*

What does a typical day look like for you?

As a Clinical Professor, my days are split between clinical and academic duties. In the clinic, I mainly work as a Chief Physician in medical retina—treating mostly diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion. Likewise, I am honored to manage the Diabetic Retinopathy Grading Centre at the Steno Diabetes Center Odense, which is a telemedicine-based facility serving more than 7,000 patients annually from eight different hospital units in our region. Although these are all high-volume facilities, I really enjoy this part of my work, as it is amazingly fruitful to be a part of an outstanding team, which helps so many patients maintain and improve their vision.

On academic days, I work on my key projects in the morning, as life has mercilessly turned my personality into an early-rising type A person. This leaves the afternoon (and on a lucky day, the evening) for meetings, teaching, and other activities.

Becoming the first Scandinavian member of the Macula Society.

Jakob Grauslund — by the numbers

Appointed Clinical Professor at age **38**
193 peer-reviewed publications, including **32** so far in 2023
Principal supervisor of **78** Master's and PhD students
Main author of Danish guidelines for screening and treatment of diabetic retinopathy
Scientific fingerprint for diabetic retinopathy: **#1** in Northern Europe, **#16** world-wide

Enjoying Amsterdam with the great Anne Katrin Sjølie

You were appointed Head of Research and Clinical Professor at a fairly young age. How has the journey been so far?

I had the amazing fortune to be supervised by Professor Anne Katrin Sjølie, who was one of the most outstanding and dedicated human beings I have ever met. She taught me so many important lessons in science and life. When she sadly passed away, I abruptly found myself as a 35-year-old resident, who was suddenly Head of Research and main supervisor of five PhD students. Having a family with two small kids as well, these were challenging years, and, to be honest, it really took me some years to find my own way. In the end, what tended to work the best for me was just having a small piece of paper in my drawer saying: "What would Anne Katrin do in this situation?" Having made peace with the fact that there is no miracle solution for most problems, and getting inspiration from the people that I admire, is really something that has helped me through the years.

How has the field of medical retina changed over the last 15 years, and what will the future bring?

The introduction of intravitreal therapy has really revolutionized ophthalmology, and it is amazing to witness how the number of blind people is decreasing rapidly. However, this has also turned ophthalmology into the busiest specialty of all, and with the increasing aging of the population, we might just have seen the tip of the iceberg.

How did you became interested in doing research?

I went into research pretty open-minded but also without major ambitions. However, it did not take Anne Katrin long to open my eyes to all of the opportunities to make new discoveries and change the field. It was really amazing to learn from her example of how the journey of research can change the lives of so many.

What would be your keys for successfully building a strong team?

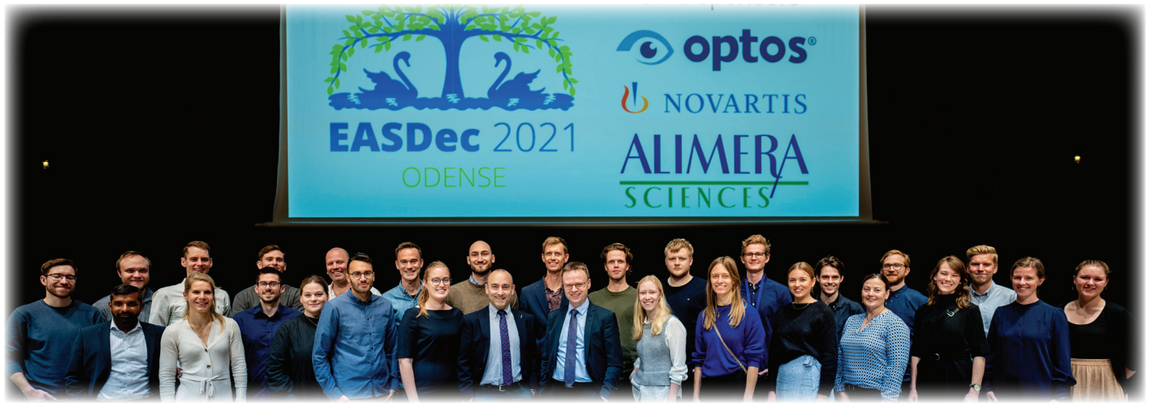
Over the last 10 years, I have had the amazing honor of acting as the principal supervisor of 78 PhD and master's students, who have all been unique in their own way. As a research leader, it is so important to build up a group of people interacting and helping each other. The former American president Franklin D. Roosevelt might have put this the best: "I am not the smartest fellow in the world, but I sure can pick smart colleagues." This is really the philosophy of our research group. We all work hard and are dedicated to attracting young talent before they graduate from medical school. Through the years, it has really been amazing to watch people growing from pregraduate researchers through PhD students to ophthalmic residents and, ultimately, highly esteemed senior doctors and high-class academic faculty members.

> "I am not the smartest fellow in the world, but I sure can pick smart colleagues."
>
> Franklin D. Roosevelt

Quality time with his research group— in both formal (top of next page) and more informal (above) meetings.

What is your vision for future research and innovation at the Eye Department at Odense University Hospital?

For my part, I do most of my research in the screening and treatment of diabetic retinopathy and medical retinal diseases, including setting up national initiatives in artificial intelligence, virtual learning, and epidemiological, register-based research, as I believe that these are some of the keys that will take us to the future in ophthalmology. Nevertheless, what excites me the most is that we now have a variety of research areas spearheaded by a number of excellent Associate Professors: Anne Stage Vergmann (virtual learning), Lasse Cehofski (translational science), Yousif Subhi (evidence-based ophthalmology), Anders Vestergaard (glaucoma and real-world validation studies), and Jimmi Wied (education and ophthalmic surgery). Having all of these remarkable people on the team really makes the future look bright.



In recent years, you have been heading major national initiatives on research and clinical guidelines. What has been your experience with this?

First of all, it is a great honor—and good fun too—to be heading national initiatives on academic and clinical issues. Bringing so many dedicated experts together from the entire country can really make a difference, and, actually, it connects very well to the last question. In the upcoming years, we really need to take a close look at how we should make the best of our resources. One of the most important discussions here would be to consider whether any patients could safely attend fewer ophthalmic visits than previously. Having this in mind, we are currently launching new clinical guidelines for diabetic retinopathy screening in Denmark, which would extend the screening intervals for most patients. This can reduce the annual number of screening visits in Denmark by approximately 50,000. For me, that is quite a lot, and I hope that this may open up similar initiatives for other ophthalmic diseases.

How would you advise future colleagues on the verge of embarking on a journey in ophthalmic research?

Step 1: Find an excellent and dedicated supervisor
Step 2: Ask some of his or her students whether they are happy to be a part of the group
Step 3: Go for it and give it all that you have! Work hard, stay open-minded, meet your deadlines, and put all of your enthusiasm and personality into the project and the group.
Step 4: Enjoy the journey, and do not forget to use the gifts that you learn from research for the rest of your career.

Family trip to Yosemite National Park

Football supporters: Jakob and Noah rooting for their favorite team — Sønderjyske.

With so much great work in the clinic and on cutting-edge research, do you have any spare time for family and friends?

I have tried (but not always succeeded) to work hard and remain dedicated while at work and then keep the computer shut while at home. I really enjoy spending time with my fantastic wife and our two amazing kids, Noah and Vilma, aged 10 and 13. We love traveling, playing football, reading about history, drinking port wine (ok—that is mostly me), and spending time with our family and friends. As a good colleague once told me: "Remember that in 25 years, the only ones that remember all of your working hours are your kids."

Evaluation Criteria for the 2024 **Best Paper Awards**

1) How interesting the subject is to our readers
2) Quality of language, pictures, illustrations, and figures

Points (1) and (2) have equal weight. Articles will be evaluated by an independent panel of judges, chosen by the Editor-in-Chief.

There will be three article prizes in 2024. The first prize (gold) is NOK 80,000, whereas silver and bronze will be awarded NOK 30,000 and NOK 15,000, respectively. All articles published in *Oftalmolog* in 2024 will be evaluated for the prize, regardless of subject. There are no guidelines attached to the prize money; thus, how it is spent is limited only by the imagination.

The editors hope that the article prizes will attract high-quality articles in *Oftalmolog* from authors of all ages in the field of ophthalmology. We call for collaboration, where younger clinicians and researchers can draw on the experience of more established eye doctors.

- the Editorial Board

We are very grateful to our generous sponsor, **Théa**, for their donation and support in making these awards possible.

#NeverStopLearning

Théa
let's open our eyes

The **2023 Best Paper Award** winners will be announced in the next issue!

Surgery of dislocated intraocular lenses

Laura Armonaite
St. Erik Eye Hospital (Karolinska Institute), Stockholm, Sweden

Intraocular lens (IOL) dislocation is a well-known complication of cataract surgery that usually requires surgical repositioning either through an IOL exchange or by repositioning of the existing IOL. Neither technique is superior to the other, according to the literature. In addition, the presence or absence of a capsular bag (i.e., in-the-bag or out-of-the-bag type of dislocation) is seldom considered when choosing the surgical technique. This thesis aimed to deepen the knowledge regarding surgery of different types of dislocated IOLs and the management of uveitis–glaucoma–hyphema (UGH) syndrome.

Study I was a retrospective case-control study that evaluated the efficacy and safety of out-of-the-bag dislocated IOL suturing to the iris by comparing this method with an IOL exchange with a new IOL sutured to the sclera (**Figure 1**). The study showed that both surgical methods were similar, except that surgically induced corneal astigmatism and the number of postoperative visits were significantly lower in the iris group.

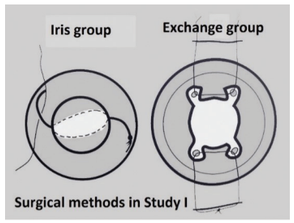


Figure 1. Surgical methods in Study I

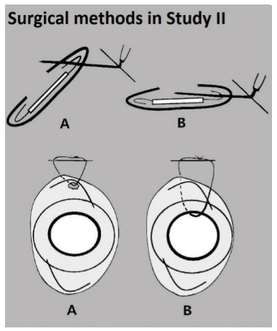


Figure 2. Surgical methods in Study II

Study II was a randomized study that focused on in-the-bag dislocations and compared the traditional surgical method ab externo scleral suture loop fixation (method A in **Figure 2**) and a new surgical technique developed by Dr. Armonaite: Embracing the continuous curvilinear capsulorhexis (CCC; method B in **Figure 2**). The difference between the methods is that in the traditional method, the suture perforates through the capsule and does not include the CCC, whereas in the CCC method the suture embraces the CCC. Both methods resulted in a good 3D IOL position, although the CCC method might be more advantageous in the presence of a thin and fragile (i.e., not fibrotic) capsule because the round CCC provides a tear-resistant opening; therefore, tearing of the bag by the suture is unlikely. In patients without fibrosis, the IOL tilt was 7° when the modified method was used, compared to 15.5° of IOL tilt with the traditional method. However, the result was not statistically significant because the subgroup of patients without capsule fibrosis was very small. Additionally, swept-source anterior segment optical coherence tomography (SS-AS-OCT) was found to be useful for IOL 3D position measuring after IOL repositioning, as well as for measuring the capsular bag thickness. IOL-induced astigmatism is low: 0.075 D for 1° of IOL tilt.

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On May 12, 2023, Laura Armonaite defended her thesis "Malpositioned and dislocated intraocular lenses: management, complications and surgical repositioning" at Karolinska Institute, Department of Clinical Neuroscience, Division of Eye and Vision, Stockholm, Sweden. Her main supervisor was Professor Anders Behndig, Umeå University, Department of Ophthalmology, with co-supervisor Professor Anders Kvanta, St. Erik Eye Hospital/ Karolinska Institute, Department of Eye and Vision.

Key points:

- Out-of-the-bag dislocated IOL suturing to the iris is a safe and effective method with less surgically induced corneal astigmatism and fewer postoperative appointments than IOL exchange.
- The modified method Embracing the CCC is another alternative for IOL fixation that might be advantageous when the capsular bag is not fibrotic.
- Surgical treatment does not necessarily stop UGH syndrome, and half of patients will need IOP-lowering therapy despite UGH resolution. Therefore, the follow-up time for these patients should be long. IOL-donesis may cause UGH syndrome, and iris defects are not specific to UGH syndrome unless they are shaped like a haptic or optic edge.

Study III, which investigated UGH syndrome, showed that surgical treatment was effective in 77% of patients and significantly improved visual acuity compared to the conservative treatment. Various types of IOL malposition can cause UGH syndrome, and the absence of visible iris–IOL contact on examination does not rule out this condition. Clinical examination on slit-lamp was more useful for detecting iris–IOL contact than AS-OCT or ultrasound biomicroscopy. IOL-donesis is a risk factor for developing UGH syndrome. Approximately half of patients with UGH syndrome may need IOP-lowering therapy in the long run after UGH resolution; all patients with UGH require a long follow-up time after UGH resolution.

Future directions:

- To investigate different surgical techniques for IOL repositioning.
- To find the most effective treatment for UGH syndrome.

One size does not fit all:

Tailoring treatment for eye diseases

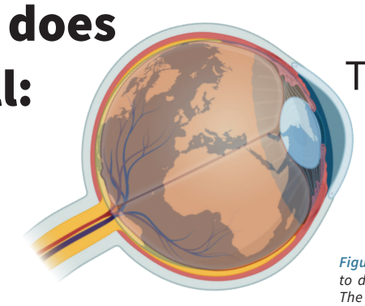

Figure 1. The global need for eye care is estimated to dramatically increase in the coming decades. The figure was created with BioRender.com

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Heidrun Elisabeth Lode
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On February 1, 2023, Heidrun Elisabeth Lode defended her thesis, "Strategies to improve treatment of retinal eye diseases" at the Faculty of Medicine at the University of Oslo (UiO) and Oslo University Hospital (OUH) in Norway. The PhD was conducted at the Department of Ophthalmology, Department of Pharmacology, and Department of Immunology at OUH Ullevål and Rikshospitalet in Oslo. The supervisors of the project were Professor Morten Carstens Moe, MD, PhD, Department of Ophthalmology, OUH Ullevål, and Professor Jan Terje Andersen, PhD, Institute of Clinical Medicine and Department of Pharmacology, UiO, Department of Immunology, OUH Rikshospitalet.

Key points:

- The new compounding procedure resulted in increased patient focus and cost savings.
- Collaboration with a medical device company led to the design of a tailored syringe.
- More albumin than antibodies exist in the eye.
- Albumin may be a good alternative carrier of VEGF inhibitors.

Introduction

One of the leading causes of vision loss in the industrialized world is age-related macular degeneration (AMD). In its most aggressive form, neovascular AMD (nAMD) leads to a rapid and permanent loss of central vision, resulting in difficulties recognizing faces, reading, and watching television, if left untreated. The development of nAMD is driven by an overproduction of growth factors, particularly vascular endothelial growth factor (VEGF), which promotes the growth of disease-causing blood vessels. Importantly, antibody-based biologics targeting and neutralizing VEGF have revolutionized the treatment of nAMD and other retinal diseases.

A burden for the patient and healthcare system

Retinal diseases, including nAMD, are often chronic and require long-term monitoring and treatment, burdening both patients and healthcare systems. Additionally, current clinical practice at many eye clinics can lead to loss of costly biologics, and withdrawal occurs under sub-optimal conditions, increasing the risk of complications. Moreover, most syringes used for IVIs are coated with silicone oil (SiO), which can lead to the deposition of SiO in the eye, causing symptomatic floaters and potential inflammatory reactions.

Figure 2. Multiple syringes are withdrawn from the same vial under aseptic conditions at the hospital pharmacy to improve patient care and achieve considerable cost savings. Figure created with BioRender.com

Focusing on the patient

By establishing and ensuring the quality of a method for compounding VEGF inhibitors in a syringe without SiO, we have improved the workflow by allowing health care personnel to focus on the patient rather than the preparation of the syringe. The syringes are now prepared under sterile conditions in the hospital pharmacy, potentially reducing the risk of infections following the injection while significant cost savings are achieved. This method has now been implemented in many eye departments across the Nordic countries.

During this work, an unmet need became evident for a syringe tailored for IVIs with high accuracy, with no dead volume, and without SiO. This challenge was addressed by initiating a collaboration with the Dutch medical device company, SSJ Solutions, through the technology transfer company, Inven2, resulting in a syringe specifically designed for ocular injections. As part of this PhD project, these syringes underwent extensive testing to ensure the same efficacy of the medications after withdrawal and storage. The syringes have recently been approved for the European market.

Improved efficacy and fewer injections

Most of the biologics used to treat nAMD are antibody-based, but little is still known about how these drugs are handled by the eye. We know from the literature and our studies that naturally very low levels of antibodies exist in the eye, and they are rapidly transported out after injection, causing the need for repeated treatment. Several studies have shown the presence of a receptor in the eye called the neonatal Fc receptor (FcRn), which acts as a regulator of antibodies. Additionally, FcRn is important for regulating a transport molecule in the body called albumin, which is naturally present in high levels in the eye. Therefore, we have investigated albumin as an alternative fusion partner for VEGF inhibitors. This may provide new information on how the bioavailability of biologics can be enhanced, and this work should motivate further research and development of antibody-albumin fusion formats for the improved treatment of retinal eye diseases.

Future directions:

- Further knowledge on how albumin and antibodies are transported will pave the way for more intelligent design of new treatments.
- Antibody-albumin fusion formats should be explored and developed for the improved treatment of retinal diseases.

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What happens when circadian rhythms go wrong, and why we should care

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Introduction

The circadian clock is a complex, evolutionarily conserved system that exists across multiple levels in almost every organism on Earth. The normal function of this circadian system relies on perfect synchrony across cells and tissues. When this is threatened, the clock contributes to the pathophysiology of a vast range of diseases, including diabetes, neurological disorders, and cancer. Modern lifestyles have created many obstacles to normal circadian function, ranging from pervasive changes, such as decreased daytime light exposure and increased nighttime artificial light exposure, to more extreme changes, such as chronic jet lag due to shift work. A constant minor desynchrony even arises from the difference between an individual's internal circadian clock and the external day, as the internal circadian period likely deviates from the 24-hour external period depending on factors such as age and genetics. Although it is difficult to study human circadian rhythms and the consequences of disrupting them, epidemiological and animal models suggest that the disruption of the circadian system has profound health consequences. In addition to being vulnerable to these effects, the eyes also play a crucial role in the circadian system, so any threats to the eye may have effects that extend well beyond the eye itself.

What are circadian rhythms?

The circadian system

Imagine the crescendo of an orchestra, with each musician contributing a unique melody that blends into one cohesive symphony. The orchestra is the analogy most often used to describe the circadian system—the natural timekeeper shared by almost every organism on Earth in some form. The conductor in this analogy is a small group of cells in the hypothalamus called the suprachiasmatic nucleus, or, more commonly, the master clock. Instead of gestures of the baton, the signals of this conductor are hormonal and neuronal, sent around the body to anticipate the timing of our environment. Almost every tissue in the body possesses its own circadian clock capable of a distinct rhythm but harmonized by the master clock, at least in healthy individuals. Distinct circadian clocks are also found in various components of the eye, including the retina. However, the neural retina is special among these peripheral clocks since it is not under the control of the master clock. Referring again to the orchestra analogy, it merits a special role, perhaps as the score that the conductor consults to lead the rest. This is because the most important timing signal of the circadian system is light, which is detected and interpreted by the retina before it is transmitted to the master clock via a specialized tract that directly links the retina

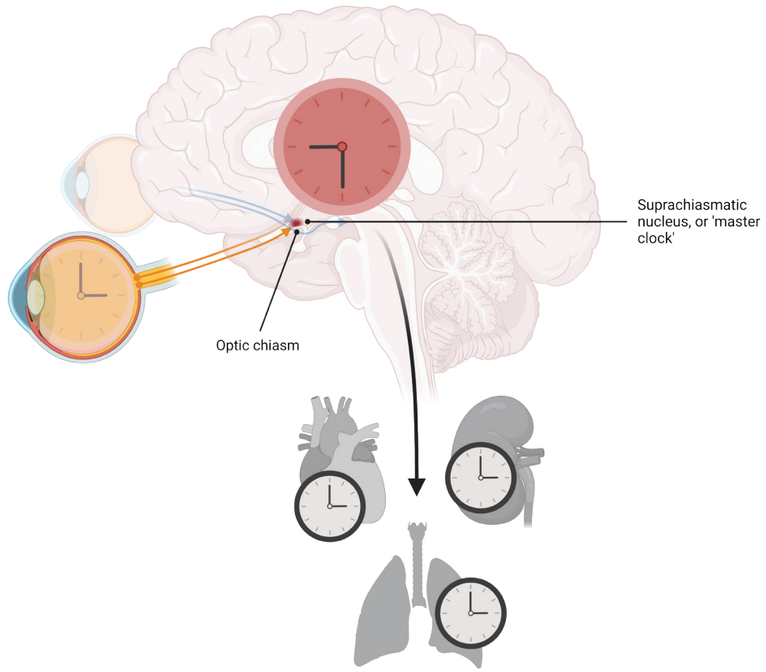

Figure 1. The circadian system is led by a master clock in the brain called the suprachiasmatic nucleus. This master clock, a bilateral structure in the anterior hypothalamus, uses both neuronal and hormonal signals to keep peripheral tissue clocks around the body in time with the external day. While the retina also has a tissue clock, it holds a special place in this system. Instead of taking timing cues from the master clock, it provides the master clock with the light information through the retinohypothalamic tract that it uses to tell time. This means that any threats to the eye have the potential to impact the timing of the entire body. Created with BioRender.com.

to the master clock (**Figure 1**).

The centrality of the retina to the circadian system is exemplified by the position of the suprachiasmatic nucleus, which is nestled directly above the optic chiasm. It is here that a specialized tract from the retina diverges from the visual processing neurons to feed direct light information to the master clock. This tract, the retinohypothalamic tract, is comprised of specialized retinal cells that facilitate body timing. These are a third class of relatively recently discovered photosensitive cells in the eye, the intrinsically photosensitive retinal ganglion cells, so called because of their possession of the photopigment melanopsin. These cells make up less than 1.5% of ganglion cells and have roles ranging from circadian timing to the pupillary light reflex and sleep timing.[1]

The molecular circadian clock

The smallest level of the circadian system is the molecular clock, an intricate network of proteins that regulate each other to create a feedback loop. In this loop, clock genes produce proteins that inhibit their own activity in a daily pattern, creating a rhythmic oscillation that cycles once every 24 hours. The relevance of this clock stems from not only how the clock genes interact with each other but also how they directly control the expression of thousands of other genes to drive rhythmic gene expression, metabolic activities, and other processes in the cell. Somewhere between 10 and 15% of all gene transcription is rhythmic, and as many as 50% of mammalian genes are predicted to be rhythmically expressed in at least one tissue.[2] The eye is no exception to this; as many as 9% of genes are expressed rhythmically in the retina.[3] Circadian rhythms exert a profound impact on visual function and eye health, influencing genes associated with angiogenesis,[4] inflammation,[5] and responses to hypoxia,[6] among others.

The importance of circadian rhythms for overall health

Due to its multiple levels of organization and because all circadian clocks take cues from the environment, including not only light but also feeding and activity, the circadian system is susceptible to disruption at many levels. This disruption can occur in the relationship between the master and peripheral clocks, the relationship between the cells within a clock, or even between the clock and the external environment. Circadian disruption refers to a disturbance or interruption of the body's natural circadian rhythm, with serious consequences. A well-aligned circadian rhythm promotes restorative sleep, improves cognitive function, enhances mood, and supports optimal metabolism. It also optimizes the timing of digestion, nutrient absorption, and detoxification processes. As such, circadian disruptions, including those caused by shift work, jet lag, or excessive exposure to artificial light at night, can lead to misalignment, which has been associated with an increased risk of various health issues, including sleep disorders, obesity, diabetes, cardiovascular disease, and even certain types of cancer. Notably, the World Health Organization classified circadian disruption as a probable carcinogen in 2007.

Are circadian rhythms important for healthy eyes?

The rhythmic nature of the eye, especially the retina, may not come as a surprise, considering that the eye's purpose is to accommodate vision across light changes that span many folds of magnitude every day, from starlight to midday sun. These same light changes preoccupy the circadian system in its quest to correctly orientate us with the timing of our environment. Some rhythms in the eye come from the light itself, but of the 2,670 genes in the retina that have a rhythmic pattern of expression, around 2,400 are under the control of the genes that make up the circadian clock.[7] Circadian rhythms in the eye are responsible for many aspects of vision, including visual acuity, contrast sensitivity, color vision, and adaptation to darkness. To make this happen, many fundamental processes in the eye are under the control of the circadian clock, like photoreceptor disc shedding,[8] melatonin and dopamine action,[9] and electrical responses to light.[10]

The circadian clock in the retina is more complicated than some clocks in other organs of the body. It might be more accurately described as a collection of clocks since the various layers and cells of the retina possess their own rhythms in clock gene expression.[11,12] Because of this complexity, when the clock gene expression of the whole retina was initially measured together, distinct rhythms blended to give the impression of an unrhythmic tissue. We now appreciate that the retina is instead complexly rhythmic, with synaptic connections and electrical communication between the layers of the retinal clock giving rise to daily morphological and biochemical changes that researchers are still characterizing. Each layer contains cells

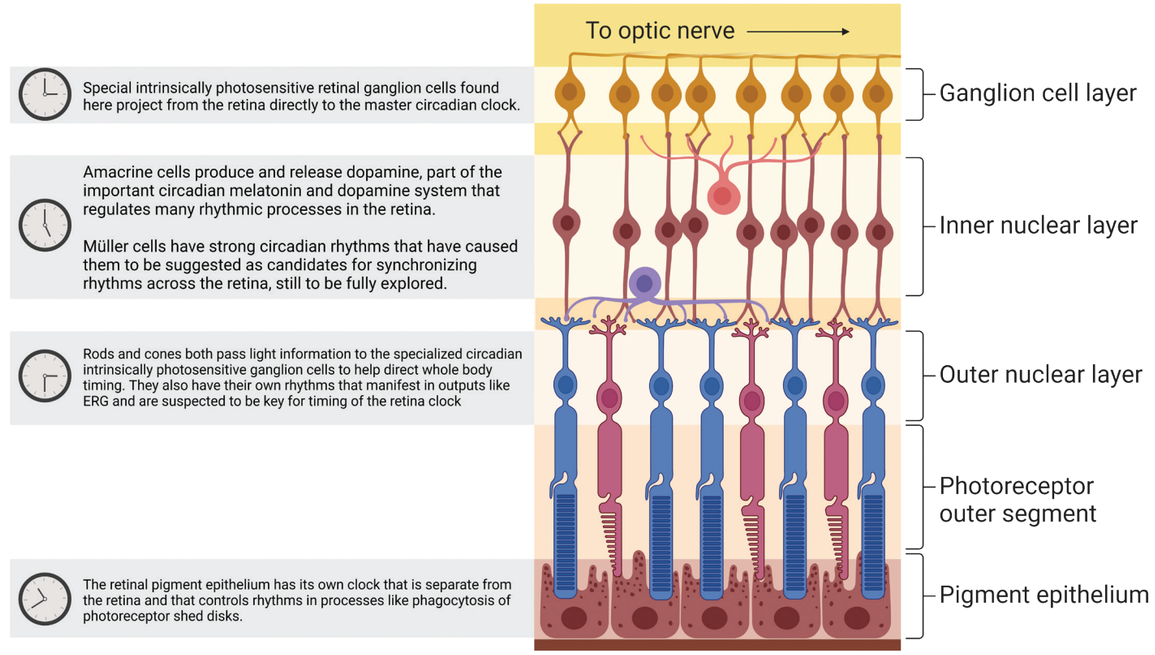

Figure 2. Each layer of the retina plays a role in generating circadian rhythms either for the retina itself or for the circadian system as a whole. Within each of these layers, different cell groups express clock genes and proteins that serve to optimize cellular physiology and contribute to either timing in the retina or timing of the wider circadian system. More is known about how the retina directs the timing of the master clock than how it regulates itself, but some of the key players in the retinal circadian clock are the photoreceptors, Müller glial cells, and amacrine cells. Created with BioRender.com.

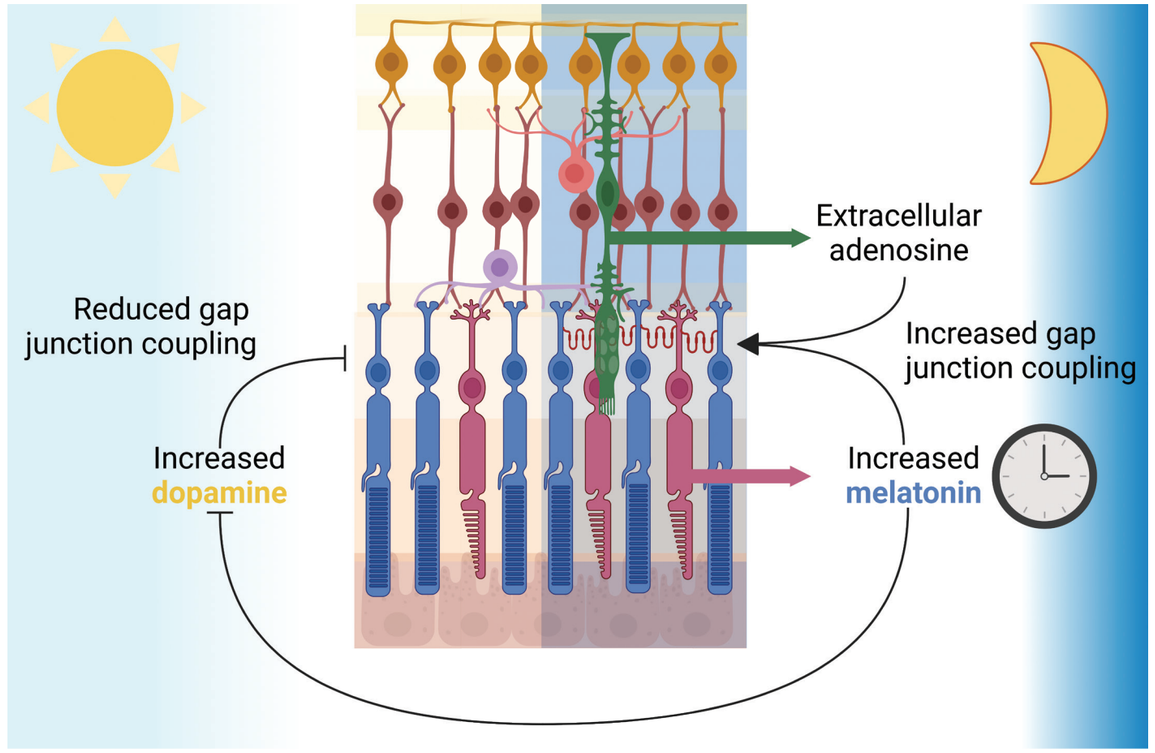

Figure 3. Driven by the circadian clock, melatonin levels increase in the dark and decrease in the light; dopamine levels follow the opposite pattern, whereas extracellular adenosine increases at night. In these two clock systems, the inverse relationship between melatonin and dopamine and the changes in adenosine levels are important for maintaining the normal function of the eye. Each plays many roles in the retina, but one circadian function is the changing level of connectivity between rod and cone photoreceptors. More gap junction coupling at night enables better vision in dim lighting conditions, whereas during the day, cone-mediated vision with high spatial accuracy is prioritized. Created with BioRender.com.

that are important for either the circadian rhythms of the entire circadian system or the rhythms in the retina itself (**Figure 2**). The full control of the retinal clock is yet to be fully elucidated, but several cell groups, including the photoreceptors, have been implicated, and most cells, including glial cells,[13] contain a circadian clock.

The earliest purpose of circadian rhythms in the eye is to shape normal development, although less is known about the role of the circadian clock in development in general. We know that the circadian clock guides the timing of cell division as the retina develops and that suboptimal timing can impact cell fate, leading to too many or too few different cell groups.[14] If the circadian clock is lost in these developing cells, changes occur when the cells exit the cell cycle, and this leads to changes in the final numbers of neuronal cells, such as retinal ganglion and amacrine cells,[14,15] and in the spectral identity of cone photoreceptor cells.[16]

Taking rhythms into account in practice

In the developed eye, the role of the clock changes to protection and homeostasis. Intense light damage to photoreceptors, for example, is twice as bad at night as it is during the day.[17] Circadian rhythms also continue to control diverse functions. This can be seen in some techniques that we use to monitor the eye, such as the electroretinogram (ERG). The electrical response of the retina to light is under circadian control, and this can be seen in the ERG response depending on the time of day that it is recorded.[10,18] For example, the cone ERG response in mice peaks at dawn and dusk, which makes sense from an evolutionary perspective in nocturnal animals that seek food at these times.[10] This rhythm was originally thought to be driven by cone photoreceptor cells. More recently, research has shown that changes in the ERG response from day to night arise from regulation by rod cells, specifically the control of electrical coupling between rods and cones.[19] This rhythm facilitates a boosted response in dimmer lighting, with the circadian clock anticipating light changes to optimize vision from day to night. Daily changes in gap junction coupling between rods and cones have been attributed to both extracellular adenosine levels and the melatonin and dopamine cycle, all of which are under circadian control[20,21] (**Figure 3**).

The daily pattern and interactions of melatonin and dopamine have been implicated in many rhythmic processes in the eye and in many disease processes. Melatonin, which is strongly associated with sleep, is a hormone primarily produced by the pineal gland in the brain, but it is also produced in the retina. Its release is under circadian control in the retina, and the nature of this release was first used to prove that the retina has its own endogenous circadian clock, namely that it followed a circadian pattern that continued even in darkness but was entrained by light.[22] Dopamine is a neurotransmitter found in both the brain and the retina. Melatonin and dopamine interact to represent a duality of function. Melatonin in particular has been implicated in various eye diseases because of its role in regulating circadian rhythms and protecting against oxidative stress.

Like the ERG response, intraocular pressure (IOP) also fluctuates throughout the day under circadian regulation through the management of the balance of aqueous humor production and drainage.[23] Several studies have revealed rhythmic fluctuations in IOP, with peak levels often observed during the early hours of the day.[24,25] This circadian regulation occurs through direct neural control via sympathetic innervation and hormonal control,[23] specifically by melatonin.[26] Glaucoma, a leading cause of irreversible blindness worldwide, is characterized by progressive damage to the optic nerve, which is often associated with increased IOP. Acknowledging IOP rhythms

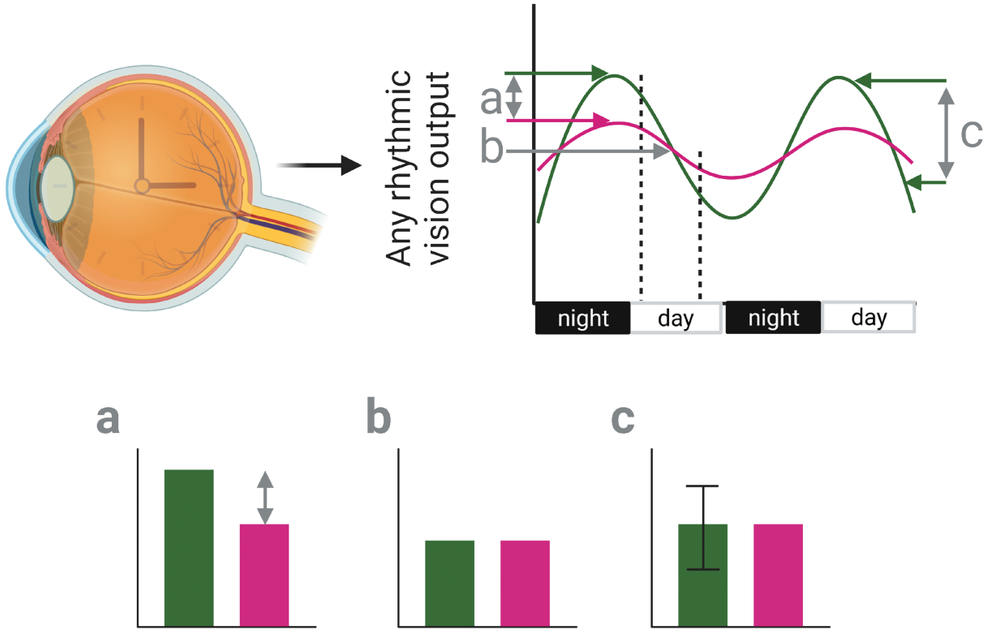

Figure 4. Circadian control in the eye means that many outputs can change from day to night. *Examples of rhythmic outputs include the electroretinogram-measured retinal response to light and intraocular pressure. When any biological process is under circadian regulation, or, in the case of the eye, regulated by light, the timing of the measurement influences the output. Moreover, in research, a disease might not significantly change an output at a specific time but may instead change the rhythm, leading to a pathology that is undetected because of the time of sampling. Choosing the right time of day to record a rhythmic output carefully might (a) reveal differences, whereas choosing the wrong time (b) could disguise them. It is also important to consider that (c) comparing measurements taken at different times will result in undesirable variance in experimental groups. Created with BioRender.com.*

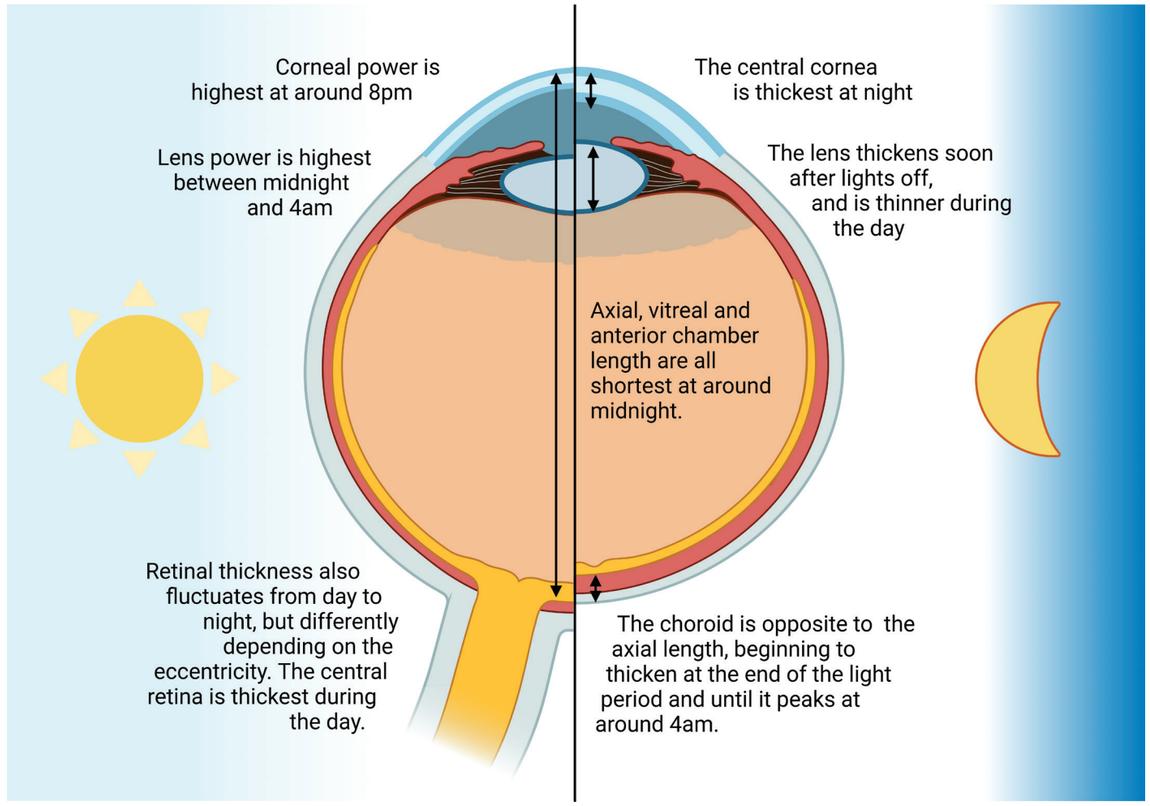

Figure 5. Many dimensions of the eye change from day to night and are driven by several different mechanisms, including an influx of water into the cornea while the eyelid is closed during sleep. *Some changes in the rhythms of different measurements have been reported in individuals with myopia, including a higher amplitude rhythm in axial length across the day and less change in choroid thickness. Understanding these rhythms in the growing eye might provide insight into the development of myopia. Created with BioRender.com.*

is valuable in the development of glaucoma therapies; for example, these rhythms are important when considering the timing of medication administration to target the peak IOP and optimize treatment efficacy. This is part of why some treatments, such as prostaglandin analogs, are recommended for use in the evening, whereas β-blockers, which do not have a 24-hour effect, are taken in the morning when they might coincide with the expected peak in IOP. Considering rhythms when advising patients is complicated by the individual variations in all rhythms, including in IOP, and by the further effects of multiple treatments on rhythms.[27] For example, multiple eye drops have been shown to flatten IOP variation. In practice, patient adherence must also be considered, and better adherence to morning administration of once-daily treatments is well-evidenced.[28] Glaucoma and IOP changes are also associated with retinal vein occlusion; although circadian rhythms have not yet been directly associated with this pathology, it is interesting to note that the incidence of macular ischemia is elevated in patients who lack normal circadian rhythms in systemic blood pressure, specifically those who lack a dipping pattern in nocturnal blood pressure.[29] Together, these observations point to a crucial role of the circadian system in fine-tuning the timing of pressure changes in the eye and a wider system that merits further study. These examples of circadian-regulated measurement outputs of the eye also raise another point for consideration in healthcare and research. Rhythms and timing should both be considered when evaluating measurements to provide a clearer picture of what is happening with an individual patient or with a whole patient cohort (**Figure 4**).

Disrupted eye rhythms and disease

Many aspects of modern life threaten circadian rhythms, most of which relate to light and thus affect the retinal clock as well. Prolonged nighttime exposure to artificial light, particularly the blue light emitted by digital devices and indoor lighting, interferes with the circadian system and leads to irregular sleep patterns and reduced sleep duration. This not only has an immediate and direct effect on the eye by harming the eye's regenerative and repair processes during rest, but these modern circadian disruptions also have long-term impacts on many aspects of eye health. Preclinical studies have linked circadian disruption to a range of pathologies of the eye, including age-related macular degeneration (AMD),[30] glaucoma,[31] and diabetic retinopathy.[32] Circadian disruption has even been linked to myopia, with the rising prevalence of the circadian challenges listed above providing a convenient explanation for the rapidly growing but geographically uneven occurrence of the condition. Many ocular dimensions vary daily,[33] (**Figure 5**) and removing the circadian clock from the eye in experimental animal models induces myopia similar to that seen in humans.[34]

How does circadian disruption affect eye health?

When circadian challenges, including shift work and early or late behavior tendencies, are replicated in otherwise healthy animal models, worrying changes such as decreased metabolic efficiency and disrupted cardiac

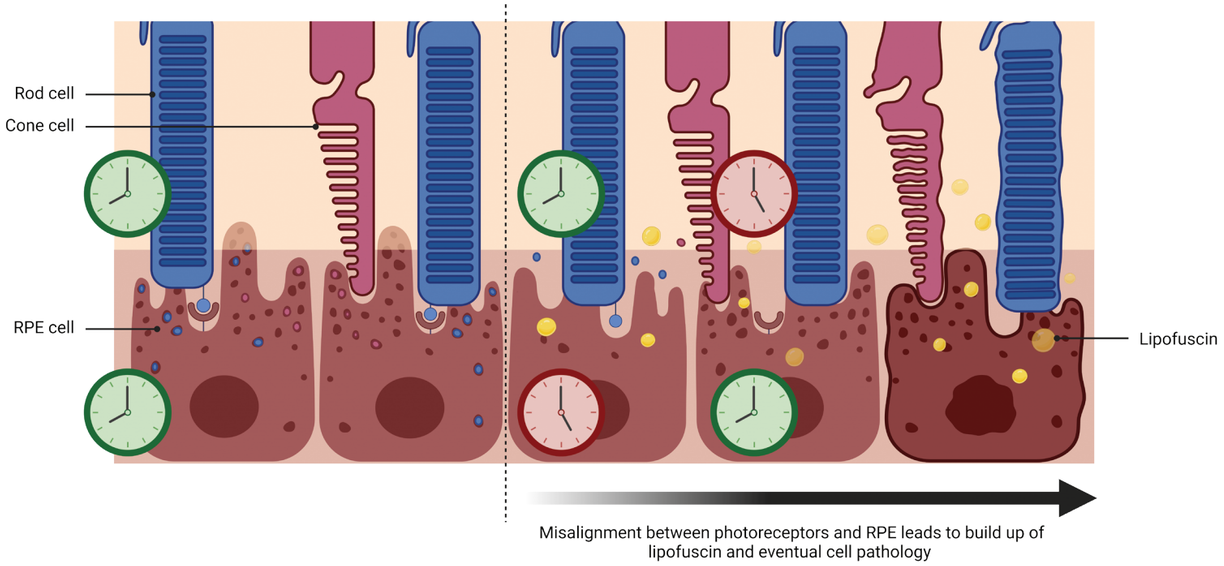

Figure 6. Misalignment between the retinal pigment epithelium (RPE)-driven phagocytosis peak and photoreceptor disc shedding is one hypothesis as to why photoreceptors seem to be particularly affected in animal models of circadian misalignment. Studies have shown that even a three-hour shift in the timing of the RPE phagocytosis peak can drive a buildup of lipofuscin in the RPE and eventually a loss of RPE and photoreceptor cells.[43] Created with BioRender.com.

function result.[35] Considering the extent of circadian rhythmicity in the eye, it stands to reason that the eye also suffers when daily rhythms are disturbed. Indeed, visual acuity, retinal thinning, and photoreceptor decreases are observed in mice when their circadian rhythms are disrupted.[36] The mechanisms at play in these models are still under investigation, but one hypothesis to explain harm to photoreceptors in particular is a potential timing conflict between the neuroretinal clock and the retinal pigment epithelium (RPE), the photoreceptor's closest neighbors in the eye. This hypothesis is based on the fact that the neuroretinal clock sets its time independently from the central body time. The RPE also has a clock that dictates the rhythms of many of its functions, including some that are crucial to the health of the photoreceptors. One such function is the clearing away of debris shed by the photoreceptors every day as part of their normal cycle. However, the RPE clock is controlled separately from the clock in the rest of the retina. In situations in which an individual's body timing does not correspond to their external light cycle, misalignment between these two clocks might occur.

The clock in the retina is entrained by light, with either the light itself or the resulting circadian rhythms dictating the daily timing of a wide range of processes. This is not true for the RPE,[37,38] which takes its timing cues from elsewhere, including melatonin levels. This raises the possibility that these two tissues could stop working harmoniously. One of many crucial jobs of the RPE is to phagocytose the photoreceptor's outer segments, which are shed normally every day, thus preventing photoreceptor degeneration due to a buildup of harmful materials.[8] This phagocytosis is circadian-controlled, with most happening around two hours after light onset to coincide with when the rods shed the most.[39,40] We know that this phagocytosis is important for general health, but the presence of a rhythmic pattern with a peak at the right time is key for the health of both the RPE and the photoreceptors.[41,42] Even a small shift in the timing of the phagocytosis peak can lead to photoreceptor pathology[43] (**Figure 6**). It is not yet clear how this rhythm, or the synchronization between the RPE and retina, is achieved, but like the retina, the RPE possesses its own circadian clock. In normal disc shedding, early morning rod shedding precedes a burst of RPE phagocytosis to rapidly clear the shed debris. Rod cells even exhibit a conserved phosphatidylserine domain, which signals for phagocytosis upon light onset.[44] These two pieces of evidence might suggest photoreceptor control; however, the peak in this 'eat me' signal is lost in mice without RPE rhythms.[42] Moreover, the genetic silencing of the clock in the RPE but not in the retina abolishes daily rhythms of phagocytosis.[45]

An example in disease: diabetic retinopathy

Diabetic retinopathy is one of the most common threats to vision, and its prevalence is increasing worldwide; therefore, it continues to be a subject of great focus in research and treatment development. The occurrence of circadian disruption in diabetes is now widely acknowledged, as is the appreciation that circadian disruption might play a role in the rapid rise of the disease, particularly for type 2 diabetes. The role of disruption in diabetic retinopathy is of growing interest. Many normal eye rhythms have already been observed to be disrupted in diabetic retinopathy, including retinal thickness,[46] pupillary diameter,[47,48] melatonin level,[47,49] and metabolic function.[3,50]

Interestingly, several of the treatments currently used or under investigation for diabetes target circadian rhythms. Melatonin, already mentioned several times, is one. Another treatment of note is metformin, which activates positive modulators of the molecular circadian clock[51] and changes the expression of the clock genes. These observations led to testing of the effects of metformin in the eye in animal models of type 2 diabetes, in which the drug upregulated an enzyme involved in melatonin production and melanopsin, the circadian photopigment produced by the intrinsically photosensitive retinal ganglion cells.[52] Conversely, panretinal photocoagulation, the first-line therapy for proliferative diabetic retinopathy, may exacerbate circadian disruption. This has been suggested because abnormal fluctuations of cortisol (in this case used as a marker of circadian disruption) have been reported in laser-treated patients,[53] possibly as a result of damage to the retinal ganglion cells; this topic requires further studies.

Angiogenesis, the formation of new blood vessels and a key process in many disease courses, is intricately linked to circadian rhythms in both development and disease. Studies have shown that the expression of genes involved in angiogenesis, such as vascular endothelial growth factor (VEGF), exhibits a circadian rhythm in the retina and RPE.[4,26] Moreover, circadian disruption has been shown to impair angiogenesis in the retina, and rhythmic environmental light is needed for normal vessel density.[54] The disruption of circadian rhythms may contribute to retinal diseases that involve angiogenesis, such as diabetic retinopathy and AMD.

The growing evidence that AMD is linked to circadian disruption is supported by many observations in experimental models. Without circadian rhythms in the eye, mice show a greater decline in photoreceptors as they age and faster deterioration of cone cell viability and function, like that observed in aging.[55] Together, these observations have even precipitated calls for the development of a 'chronoprotective system' at a recent meeting of experts,[56] possibly centered around the use of melatonin. Circadian rhythms are known to weaken and become dysregulated with age, and these changes are likely to contribute to and have been associated with age-related eye disease.[57]

Conclusion

In conclusion, the profound influence of circadian rhythms on eye health cannot be overstated. The maintenance of healthy sleep–wake cycles is paramount to the well-being of the eyes, and disruptions to these rhythms can contribute to a range of ocular conditions and threaten normal visual function. Recognizing the critical connection between internal clocks and eye health and public awareness of the importance of circadian rhythms are crucial, along with the support of ongoing studies and advancements in circadian rhythm research. Appreciating circadian rhythms creates opportunities to optimize treatment delivery, enhance precision medicine applications, and improve the reproducibility of the measurements we take, both in the clinic and the lab. Examining the circadian clock might also unveil new disease mechanisms that affect the rhythm if it is not balanced at any single time of day, possibly providing novel therapeutic targets. By understanding the intricate connection between circadian rhythms and the eye, we can develop strategies to mitigate the adverse impact of circadian disruption on eye health and promote ocular well-being in our modern, light-saturated world.

Conflict of interest
Nothing to disclose

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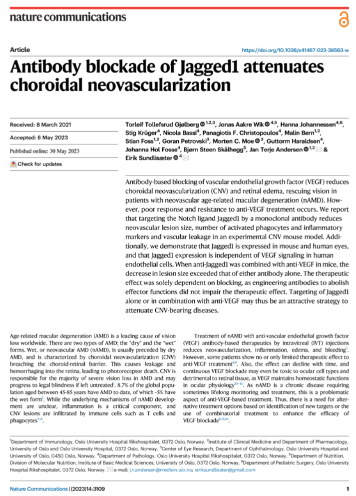
Taking it up a notch:
Scientific advances from the Nordic Region

Top-notch scientists at work. *Authors Torleif Tollefsrud Gjølberg (left) and Eirik Sundlisæter (right) doing animal experiments at the Department of Comparative Medicine, Rikshospitalet*

"These encouraging research findings illuminate the role and importance of other disease drivers than VEGF in the pathology of nAMD. The strength of this research lies partly in the cross-disciplinary research team, where expertise in immunology, pathology, and ophthalmology has come together to reveal novel treatment possibilities. We strongly believe that this realization may pave the way for new treatment options and are motivated by the huge impact this may have for patients in need."

–Torleif Tollefsrud Gjølberg

Our Nordic colleagues' work was featured in a recent Nature Communication publication. Their findings offer hope for novel treatment pathways for a leading global cause of vision loss: neovascular age-related macular degeneration (nAMD).


nature communications

Article

Antibody blockade of Jagged1 attenuates choroidal neovascularization

A team of researchers from the University of Oslo and Oslo University Hospital in Norway recently published their findings using a cutting-edge animal model to determine the elusive role of a known ligand involved in the development of vascularization seen in wet AMD.

Their findings could have major implications and novel treatment potential for many patients worldwide.

You can read a summary of their work in this issue of *Oftalmolog* on page 36.

In the press

Do you have a colleague working on cutting-edge research? Have they recently published on a topic that would be of interest to our readers? Let us know and we will reach out to feature the work in an upcoming issue of *Oftalmolog*. Email us at info@oftalmolog.com.

Top-notch research:

Antibody blockade of Notch ligand Jagged1 attenuates choroidal neovascularization

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Department of Pathology, Oslo University Hospital Rikshospitalet

Age-related macular degeneration (AMD) is a leading cause of vision loss worldwide. The two types of AMD are "dry" and "wet." Wet or neovascular AMD (nAMD) is usually preceded by dry AMD. It is characterized by choroidal neovascularization (CNV), which breaches the choroid–retinal barrier. This causes leakage and hemorrhaging into the retina, leading to photoreceptor death. CNV is responsible for most of the severe vision loss in AMD and may progress to blindness if left untreated.

Treating nAMD with anti-vascular endothelial growth factor (anti-VEGF) antibody-based therapeutics by intravitreal (IVT) injection can reduce neovascularization, inflammation, edema, and bleeding. However, some patients show little or no therapeutic effect of anti-VEGF treatment. The effect can also decline over time, and continuous VEGF blockade may even be toxic to ocular cell types and detrimental to retinal tissue because VEGF maintains homeostatic functions in ocular physiology. New treatment options are thus needed.

To date, the role of Notch signaling in CNV development has been elusive. We found that a monoclonal antibody targeting Notch ligand Jagged1 reduced CNV development in an experimental mouse model. Hence, Jagged1 is an attractive target in CNV pathogenesis, which can be targeted alone or in combination with anti-VEGF to attenuate CNV-bearing retinal disorders.

Evidence supports the involvement of immune cells in wet AMD. T cells, macrophages, and monocytes have been identified in eyes from wet AMD patients. The Notch signaling pathway (**Figure 1**) enables inflammation through interaction with other inflammatory pathways and undoubtedly plays an important role in pathological angiogenesis. We have previously reviewed the role of Notch signaling in various inflammation-driven diseases, including AMD.

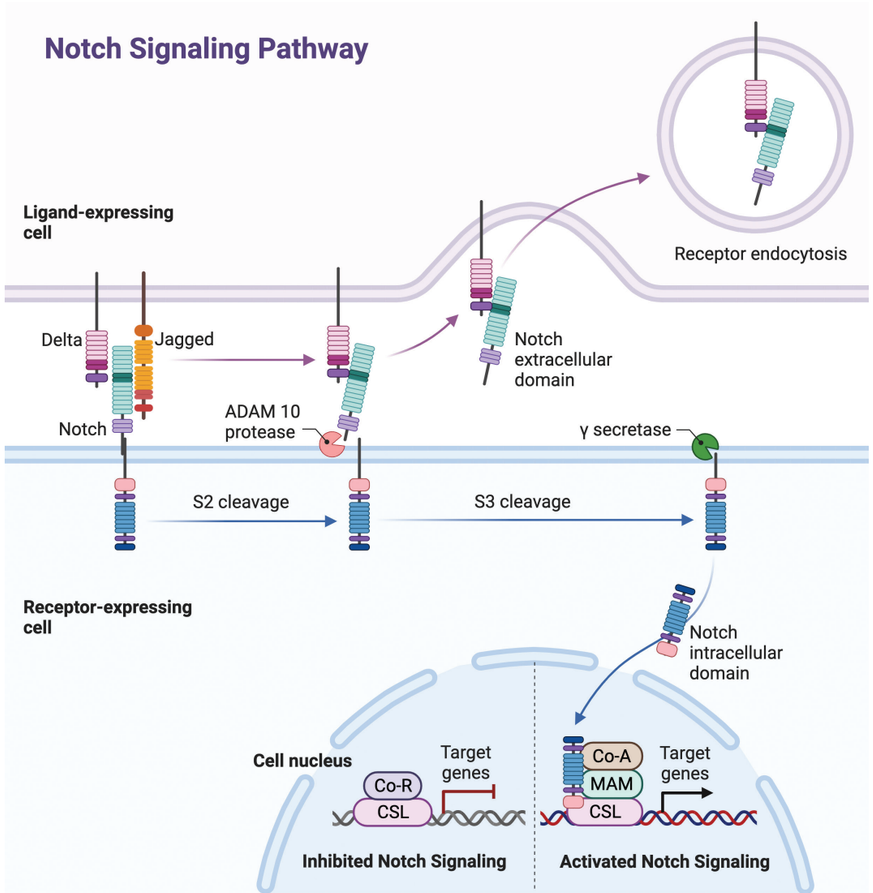

Figure 1: The Notch signaling pathway. Ligand-expressing cells express Notch ligands of the Jagged and Delta families. Their extracellular domains interact with those of Notch receptors on ligand-expressing cells, creating a mechanical pull on the resulting complex that exposes a cleavage site in the Notch receptors. This allows for so-called S2 cleavage by ADAM 10 protease, which releases the Notch extracellular domain to be endocytosed by the ligand-expressing cell and enables S3 cleavage of the remaining part of the Notch receptors by γ-secretase. This releases the Notch intracellular domain, which translocates to the cell nucleus and activates Notch signaling.

We hypothesized that Jagged1 is a relevant target in AMD. Through immunohistochemistry on postmortem human eyes with anatomical signs of dry AMD, specifically subretinal drusen deposits and retinal pigment epithelium changes, we noticed that Jagged1 was occasionally expressed by the inner endothelial cell layer of choroidal blood vessels (**Figure 2**). Although human donor eye samples with wet AMD were not available, we further identified Jagged1 in a laser-induced CNV mouse model (**Figure 3a**). Targeting the Notch ligand Jagged1 with a monoclonal antibody reduced vascular leakage (**Figure 3b**) and neovascular lesion size (**Figure 3c**). Importantly, targeting Jagged1 reduced CNV formation in vivo, and the therapeutic effect was enhanced by simultaneous administration of anti-VEGF (**Figure 3d**). As such, anti-Jagged1 may be given as monotherapy or combinatory therapy with anti-VEGF. We also found that anti-Jagged1 reduced the number of activated phagocytes (**Figure 3e**) and inflammatory markers (**Figure 3f**) in the experimental CNV model.

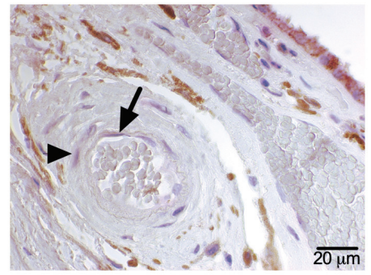

Figure 2. Ocular tissue with dry age-related maculopathy, immunostained to show pigment changes. The immunoreactivity is seen in endothelial cells of choroidal arteries (arrow) and smooth muscle cells lining the vessel (arrowhead). Figure reproduced with permission from Gjølberg et al., Nature Communications, 2023 (CC BY 4.0).

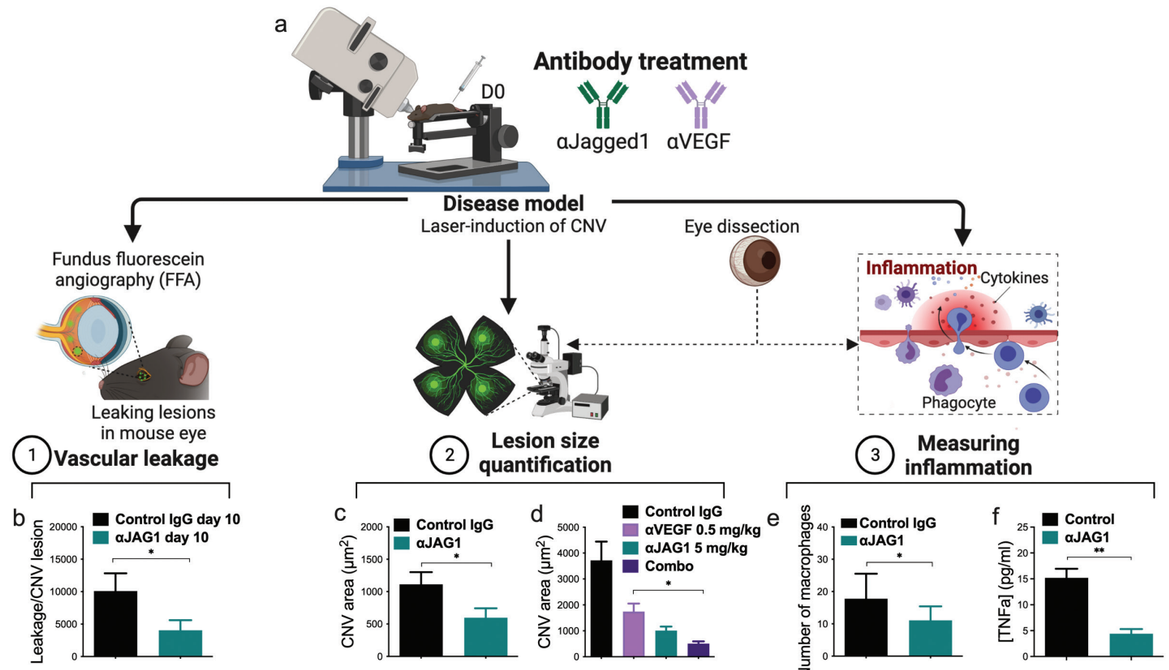

Figure 3: Jagged1 blockade reduces disease burden in a state-of-the-art mouse model of nAMD. (a) A high-intensity laser ruptures the blood–retina barrier, resulting in pathological choroidal neovascular (CNV) lesions characterized by vascular leakage and inflammation. The therapeutic effect of the injected antibodies was addressed by measuring 1) vascular leakage, 2) the extent of neovascularization, i.e., lesion size, and 3) inflammatory markers. Jagged1 blockade reduced (b) vascular leakage and (c) the size of CNV lesions. In addition, (d) anti-Jagged1 and anti-VEGF together further reduced lesion size. (e–f) Anti-Jagged1 also reduced inflammatory markers. Adapted with permission from Gjølberg et al., Nature Communications, 2023 (CC BY 4.0).

To translate our encouraging findings on Jagged1 targeting into clinical practice, the concept must be tested in established larger-animal models for laser-induced CNV and intravitreal injections, preferably in non-human primates, which are extensively used for preclinical evaluation.

The complete report of our findings is available online (open access) at https://www.nature.com/ncomms/

Acknowledgments

We would like to particularly thank the Research Council of Norway, The Norwegian Association of the Blind and Partially Sighted, and Dr. Jon S. Larsen Stiftelse for research grants, as well as the Medical Faculty, University of Oslo, for the small retinal imaging platform.

RESTOR(E)ing VISION across Europe:

a consortium collaborating to conquer seven rare anterior eye diseases

Rare Eye Diseases (REDs) collectively represent a major cause of visual impairment and blindness for children and young adults in Europe.[1] Importantly, REDs also affect adults and the aging population. The onset and progression of many REDs are characterized by common pathophysiologic mechanisms. Defective wound healing of the cornea and ocular surface, excessive inflammation, nerve degeneration, stem cell dysfunction, and abnormal vessel ingrowth are common denominators in many REDs, representing a critical medical problem and an area of unmet medical need.

The RESTORE VISION Consortium (**Table 1**) proposes, for the first time, a ground-breaking approach to disrupt these atypical mechanisms with the aim of making therapy more effective. Our novel approach, to foster translation into clinical practice, is based on the repurposing of existing drugs and the development of new drugs, totaling 9, all with preliminary data showing remarkable effects in restoring the cell physiology, immune response, avascular conditions, neural function and signaling environment in the cornea in the context of rare diseases from animal models into clinical trials. In Europe, approximately 30 million people suffer from blindness and visual impairment.[2] The prevalence and number of EU cases of the seven REDs addressed in this project are displayed in **Figure 1**. We estimate that there are around 500,000 European patients suffering from the seven REDs that the Restore Vision project addresses. This represents approximately 1.7% of the total European population living with visual impairment and blindness.

The overall conceptual plan for the project comprises three main streams of activity, running in parallel. **Stream 1**: preclinical verification and development; **Stream 2a**: clinical studies for which data exists; **Stream 2b**: clinical studies for which additional data will be collected; and **Stream 3**: ethics, regulatory, exploitation, and management.

Stream 1 involves preclinical studies to test the efficacy of the drugs in the RED models, verify their mechanisms of action (MoA), confirm drug targets in human samples, and, in a subsequent round, test the newly formulated eye drops in the RED models showing the greatest efficacy.

Stream 2 involves clinical studies, with ethical, regulatory, and safety/toxicity data on the eye drop formulations made available in the preparatory phase. For those cases in which drugs are already used in the eye or where first-in-human data exists, these activities will proceed directly to clinical investigations (**Stream 2a**). RESTORE VISION drugs already at an advanced stage of development but still in need of additional preclinical data or improved formulation for RED will be grouped in **Stream 2b**. Following the Scientific Advisory Board and consortium reviews, the most therapeutically active compounds with highest probability of being effective in more than one RED will be brought forward for human ethical approval and clinical trial preparation. The RESTORE VISION project will test the presence of the targets in human samples of the disease, mitigating the risk of targeting a process irrelevant in humans. Some data from **Stream 1** will support the second stream (such as eye drop formulation, MoA) but components of **Stream 2** will run parallel,

Thomas Ritter, PhD (middle left), author of this article and head of the consortium, University of Galway, with the RESTORE VISION investigators at the kickoff meeting

Table 1. Public, private, and patient partners of the RESTORE VISION consortium. Nordic partners in bold.

Participant organization name	Country	Type
National University of Ireland Galway (NUIG)* *Coordinator	Ireland	Academic
Linköpings Universitet (LiU)	**Sweden**	**Academic**
Ospedale San Raffaele SRL (OSR)	Italy	Academic
Universidad Miguel Hernández de Elche (UMH)	Spain	Academic
INSERM UMRS 1138 (INS)	France	Academic
Klinikum der Universitaet zu Koeln (UKK)	Germany	Academic
Aniridia Europe (AE)	**Norway**	**Patient**
Cell2Cure (C2C)	**Denmark**	**SME**
KÔL Laboratories (KÔL)	France	SME
Catalyze Group (CAT)	Netherlands	SME

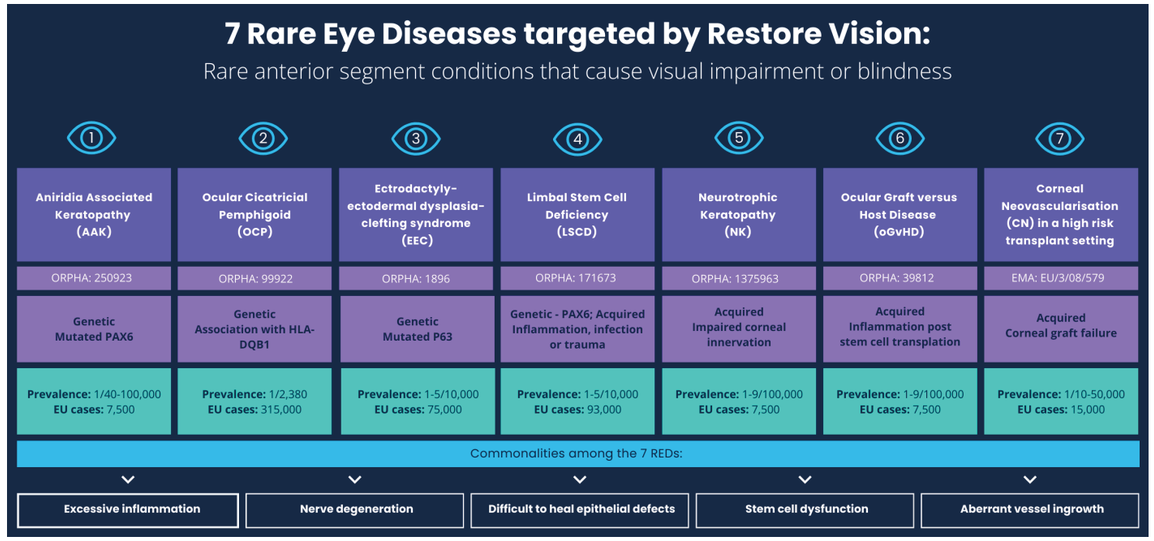

Figure 1. The family of REDs targeted in this project, their respective Orpha codes, and their pathogenic commonalities.

with both streams commencing in the first year of the project.

Stream 3 provides for the non-scientific components including ethics, regulatory, management, dissemination, and exploitation. In addition, trial design for future trials based on results obtained herein is established to speed up the translation. This third stream will feed into the key activities within the first two streams, as shown in **Figure 2**.

We adopt the approach shown in **Figure 2** as a streamlined way to evaluate promising new and repurposed drug candidates for translation into the first clinical studies. Many rare diseases of the cornea and ocular surface do not have effective treatment options today, with patients and doctors struggling to find appropriate treatment. At the same time, academic research is not generally equipped to bring new drug candidates into clinical use, lacking the resources and knowledge present in pharmaceutical companies and regulatory bodies. In RESTORE VISION, a unique team of project partners will work towards moving several drug candidates further along the pipeline to clinical use. Importantly, although rare diseases are, by definition, not often seen in ophthalmology clinics, the common denominator of these diseases in terms of corneal inflammation, neurotrophic deficit, dry eye, wound healing problems, vascularization and stem cell dysfunction affect many more patients with different ocular conditions. The knowledge generated within the project is thus expected to have wide implications for the treatment of corneal disease.

More information at www.restorevision-project.eu.

www.linkedin.com/company/restorevision/

@restorevis_eu

References

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2. European Blind Union, *About Blindness and Partial Sight: Facts and Figures.*

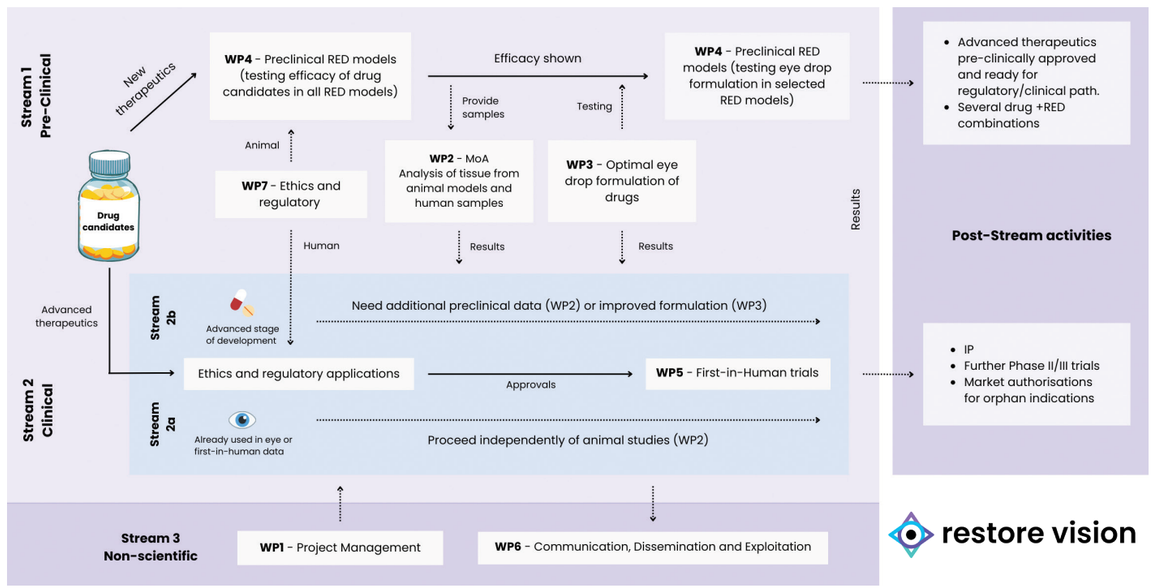

Figure 2. The overall RESTORE VISION conceptual plan.

Welcome to Kuopio

NOK 2024
5–8 August 2024

Dear colleagues,

The next Nordic Congress of Ophthalmology (NOK) will be on August 5–8, 2024, in Kuopio, Finland (www.nok2024.fi). The congress will be held at the Kuopio Music Centre, which is one of Finland's most significant concert and congress centers and the heart of musical life in the province. Kuopio, the capital of Lakeland, is in the eastern part of Finland. It is the eighth-largest city in the country and the largest city in the North Savonia region. Kuopio is surrounded by the beautiful Lake Kallavesi. Kuopio is one of the most lake-rich areas in the world; altogether, we have nearly 200,000 lakes in Finland.

Photo by Wille Markkanen

Photo by Wille Markkanen

It is difficult to go anywhere without seeing beautiful lakes. Currently, Kuopio is one of the hottest migration cities in Finland. It has a diverse economy and an internationally recognized university. It offers one of the country's biggest year-round travel destinations within the same municipality. Lakeland provides authentic Finnish culture, cuisine, sauna experiences, abundant "green gold" forests, and breathtaking lake sightseeing. One of the most famous scenic points is Puijo Tower, which rises 75 meters above the ground and 306 meters above sea level. At the top, you'll find a unique restaurant that rotates around the clock for a full 360-degree view of the spectacular landscapes below. It overlooks the largest national urban park.

Coming to Kuopio is easy from anywhere in Europe (see the map below). You can get to Kuopio from Helsinki in around an hour by airplane. Alternatively, you can travel by train directly from Helsinki airport. This approximately 4-hour journey allows you to see even more of our beautiful nature.

Important dates:

- **15 December 2023 –** Registration opens and call for abstracts
- **31 March 2024 –** Deadline for early-bird registration
- **1 April 2024 –** Deadline for submission of abstracts
- **15 June 2024 –** Notification of acceptance of abstracts
- **5–8 August 2024 – Congress** Welcome to Kuopio!

Photo by Wille Markkanen

Photo by Tapio Haaja

You are warmly welcome to Kuopio NOK 2024.

Kai Kaarniranta
Mika Harju
Juha Hagman
Saara Ahtola
Liisa Marttila
Niko Kivinen
Oona Martikainen

Photo by Wille Markkanen

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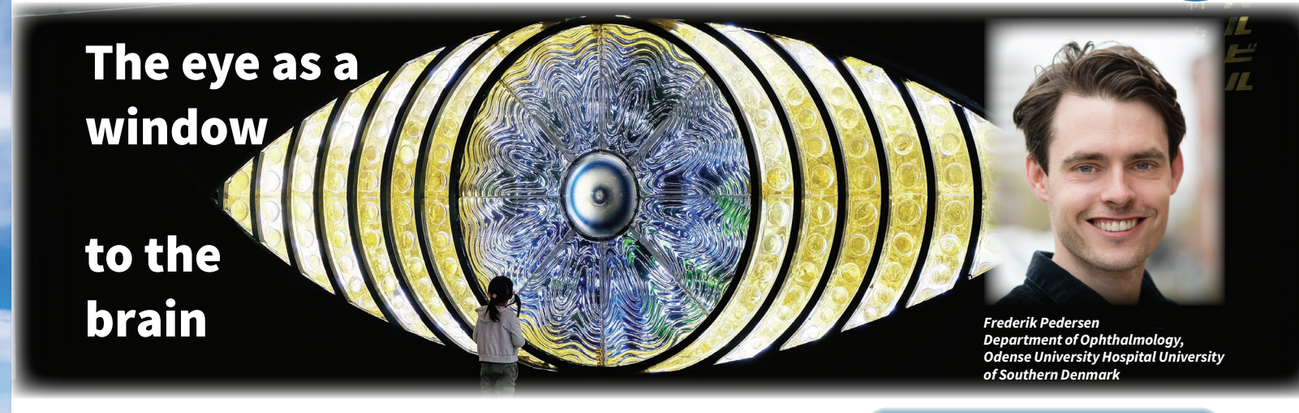
The eye as a window to the brain



Frederik Pedersen
Department of Ophthalmology, Odense University Hospital University of Southern Denmark

On June 22, 2023, Frederik Pedersen defended his thesis, "Diabetic retinopathy as a marker of cognitive dysfunction and depression: A clinical and epidemiological approach," at the Dept. of Ophthalmology, Odense University Hospital, University of Southern Denmark. The main supervisor was Professor Jakob Grauslund, M.D., Ph.D., D.M.Sc., Dept. of Ophthalmology, Odense University Hospital, Dept. of Clinical Research, University of Southern Denmark, Steno Diabetes Centre Odense, Denmark. The co-supervisors were Associate Professor Lonny Stokholm, scient.san.publ, Ph.D., Dept. of Clinical Research, University of Southern Denmark; Professor Tunde Peto, M.D., Ph.D., Centre for Public Health, Queen's University Belfast, Northern Ireland, UK; and Professor Frans Pouwer, Ph.D., Dept. of Medical Psychology, Amsterdam UMC, The Netherlands.

Key points:

- DR was associated with a significantly increased risk of Alzheimer's disease.
- We found no indication of a bidirectional association between DR and depression in patients with type 2 diabetes.
- Old age with type 2 diabetes and mild cognitive impairment was associated with retinal structural alterations compared to cognitively healthy controls.

In recent years, retinal neurodegeneration has been recognized as an early event in diabetic retinopathy (DR). Given that the eye and brain share similar embryologic origins, anatomical features, and physiological properties, observations suggest that the retina provides a unique "window" to the brain. Systemic neurodegenerative diseases, such as Alzheimer's disease and depression, have been linked to diabetes, but less is known regarding their association with DR. With a register-based and clinical approach, this dissertation thus aimed to investigate DR as a marker of Alzheimer's disease and depression, using real-world data. It also aimed to explore in a clinical setting whether non-invasive retinal parameters were associated with mild cognitive impairment, a pre-state of dementia, in individuals with type 2 diabetes.

We first evaluated the risk of Alzheimer's disease in patients with DR. Patients with DR had a 34% increased risk of Alzheimer's disease compared to patients with diabetes without DR. We then examined the bidirectional association between depression and DR in patients with type 2 diabetes. In this epidemiological study of more than 240,000 patients with type 2 diabetes, we did not find DR to be independently associated with depression. Finally, we examined the association between retinal non-invasive parameters and mild cognitive impairment. In this observational cross-sectional study, we included elderly patients with type 2 diabetes without known retinal diseases except for non-proliferative DR. All participants had a broad neuropsychological evaluation performed to determine their cognitive status. Based on this evaluation, participants were divided into two groups: those with mild cognitive impairment and those without cognitive impairment. We then performed retinal examinations including retinal oximetry, color fundus photography, optical coherence tomography (OCT), and OCT-angiography. Patients with mild cognitive impairment had a thinner macular ganglion cell layer and macular retinal nerve fiber layer compared to patients without cognitive impairment. In contrast, we found no differences in retinal microvascular or oximetry parameters between the groups.

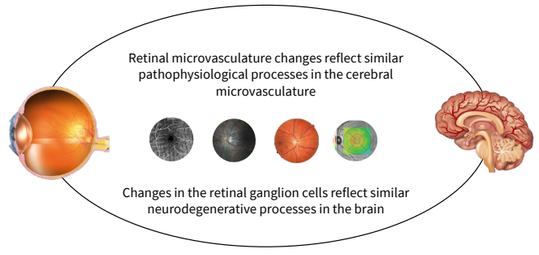


Figure 1. The retina may be a window to study neurodegenerative disorders due to the common anatomical and physioloigcal properties. This might involve non-invasive retinal parameters. For the clinical study, we utilized (from left to right) optical coherence tomography (OCT) angiography, retinal oximetry measurements, color fundus photos and OCT to assess various retinal parameters and their association to mild cognitive impairment

Future directions:

- Future studies should use longitudinal designs to investigate how retinal parameters can be used to detect and monitor cognitive impairment.

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