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DRUG DISCOVERY UPDATES #09

DDup

iPSC-BASED DRUG DISCOVERY: Target*RD*

A promising approach for fighting retinal degenerations

evotec — DDup

What's inside this issue?

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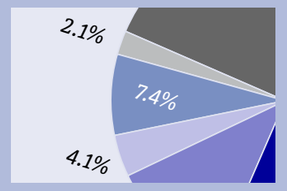

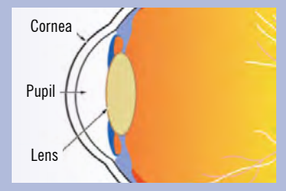

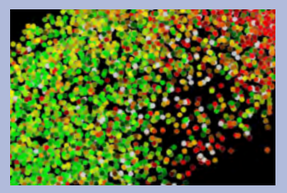

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DEAR FRIENDS
OF EVOTEC

A message from Evotec CEO
Dr Werner Lanthaler

Welcome to this ninth issue of DDup, an Evotec publication providing you with more insights into the company and its capabilities. This edition will provide an overview of our unique and innovative iPSC-based drug discovery programme Target*RD* (Retinal Disease) which we have developed in collaboration with our colleagues from the Centre for Regenerative Therapies TU Dresden. This issue is the second part of our DDup iPSC series, the first part was published in May 2019, dedicated to Evotec's leading iPSC platform. Our intention with the Target*RD* programme is to fight retinopathies like age-related macular degeneration (AMD), a leading cause of blindness globally, associated with very limited treatment options.

Evotec has started numerous iPSC-based drug discovery projects in the past few years and has steadily advanced the development of its iPSC platform, by establishing the largest high-quality iPSC bank and diverse human disease models for high-throughput screening. Our ambition is to advance selected programmes with partners dedicated to iPSC-based drug discovery.

With our Target*RD* programme, we are very optimistic to overcome the significant problems associated with traditional drug discovery efforts in the field of retinal degenerative diseases. We will show that our iPSC-based approach delivers more predictive models with a considerably better chance of successful clinical translation. Our first goal within Target*RD* is to develop efficient drugs for AMD, but we also see possibilities to target genetic retinopathies in the future.

This edition marks the beginning of a series of DDups focussing on Evotec's internal iPSC-based drug discovery efforts. Future editions will provide more insights on additional drug discovery programmes, as more and more possibilities arise from this platform.

Thank you for reading this issue of DDup, for your thoughts, input and hopefully also the cooperation in this field with us. I hope you find this latest edition of DDup of particular interest and as always please do not hesitate to contact us.

Yours sincerely,
for the management of Evotec
Werner Lanthaler,
CEO of Evotec SE

CHAPTER 01

FACTS & FIGURES

AGE-RELATED MACULAR DEGENERATION (AMD)

Leading cause of vision loss in people over the age of 50 with limited treatment options

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- Although incidence rates of wet AMD are much lower, the disease accounts for 90% of legal AMD-related blindness
- There is no early or intermediate stage of wet AMD and it is always preceded by the dry form of the disease
- Dry AMD may advance and cause loss of vision without turning into the wet form of the disease
- It is also possible for early-stage dry AMD to suddenly change into the wet form

The exact causes of AMD are not really known, but may be related to a combination of heredity and environmental factors, including smoking and diet.

Factors that increase your risk of macular degeneration include:

- Age
- Family history and genetics
- Race
- Smoking
- Obesity
- Cardiovascular disease

TWO TYPES OF AMD

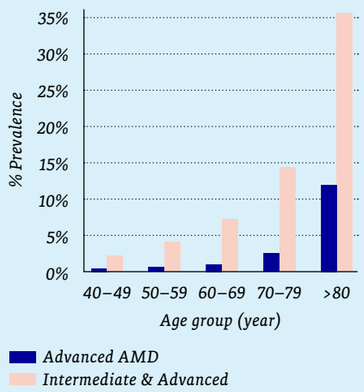
DRY FORM:
~85–90
of AMD patients

WET FORM:
~10–15%
of AMD patients

THE HIGHEST RISK OF DEVELOPING AMD IS RELATED TO AGING

- The risk of getting intermediate and advanced AMD increases from ~4% for those aged 50–59, to more than 35% for those over the age of 80
- About 4% of people with early AMD progress to late-stage AMD within a year. Over 2–3 years, 32% of people go from mild to moderate visual impairment and 46% of those with moderate sight loss progress to severe visual impairment

Prevalence of AMD among adults 40 years and older in the US



UNSATISFACTORY SITUATION REGARDING TREATMENT OPTIONS:

- **Wet AMD:** Anti-VEGF injections, laser coagulations or photodynamic therapy – treatments can only slowing down progression of the disease
- **Dry AMD:** There is NO treatment approved for advanced dry macular degeneration

WHAT IS THE CHALLENGE?

- ***NO PREDICTIVE IN VITRO MODELS***
- ***NO PREDICTIVE IN VIVO MODELS***
- ***STRONG GENETIC HETEROGENETY***

→ ***LACK OF SUITABLE MODELS TO STUDY DISEASE MECHANISMS***

Enormous public health issue related to aging

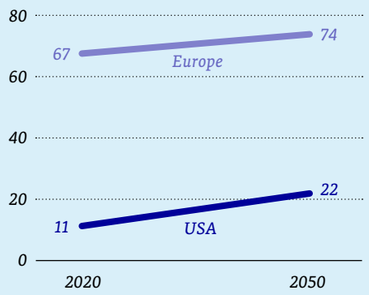
—

Globally, more than 190 million people are affected by AMD and this figure is expected to increase to more than 285 million in 2040.

Numbers are expected to increase steadily due to:

- Ageing population – according to the UN there were 901 m people over the age of 60, some 12% of the global population. By 2050 the number of people over the age of 60 is predicted to increase to 2.1 bn – 22% of the population
- Lack of sufficient treatment options – no cure for AMD possible yet; especially dry AMD is a field of high unmet medical need

Expected growth rates for AMD in million for Europe and USA



SIGNIFICANT FINANCIAL BURDEN FOR HEALTHCARE SYSTEMS WORLDWIDE

- Estimated global cost of visual impairment due to age-related macular degeneration is $ 343 bn, including $ 255 bn in direct health care costs
- Estimates of the direct health care costs of visual impairment due to AMD in the US, Canada, and Cuba is approximately $ 98 bn

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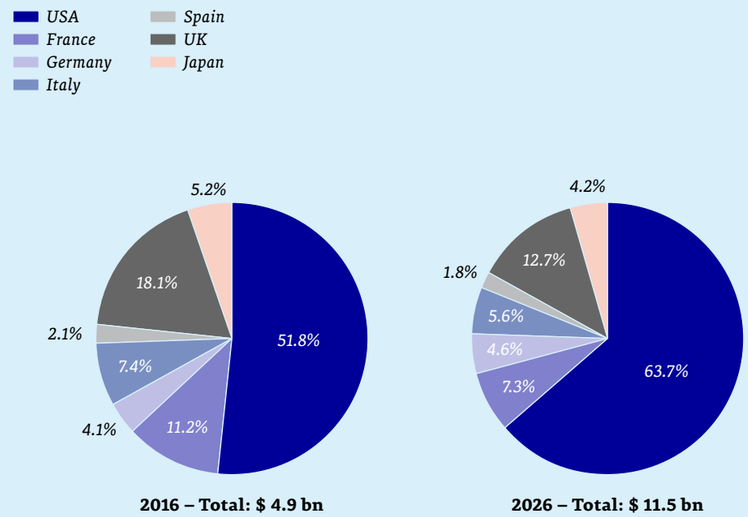
DESPITE LIMITED TREATMENT OPTIONS, THE MARKET FOR AMD IS HUGE

Sales within AMD markets were estimated to be $ 4.9 bn across the seven major markets in 2016. This is expected to reach $ 11.5 bn in 2026, at an impressive Compound Annual Growth Rate of 8.9%, according to GlobalData.



2016 – Total: $ 4.9 bn **2026 – Total: $ 11.5 bn**

Strong increase in sales will be driven by:

- **Increasing prevalence of wet AMD**
- **Rising number of drug approvals for wet AMD**
- **First launch of drugs to treat dry AMD**

RENOWNED EXPERTS

CHAPTER 02

IN RETINA DISEASE RESEARCH

Prof. Dr Mike O. Karl

Professor of Retinal stem cell research and neurogenesis at the CRTD

Mike received his doctorate from the University of Hamburg, and trained as a junior research fellow at the University of Pennsylvania, Philadelphia. He went on to postdoctoral studies at the University of Washington, Seattle, in the lab of Thomas Reh. He is currently Professor of Retinal stem cell research and neurogenesis at the Center for Regenerative Therapies Dresden (CRTD), an institute of the Center for Molecular and Cellular Bioengineering (CMCB), as well as at the Carl Gustav Carus Faculty of Medicine of the TU Dresden, and affiliated with the German Center for Neurodegenerative Diseases (DZNE) of the Helmholtz Association.

The overall objectives of Mike's research are to develop human stem cell derived organoid and cell systems, to apply these to understand mechanisms of neuronal degeneration and regeneration, and thereby to find new therapeutic strategies. His work focuses on the retina, and the intersection of stem cells, developmental biology and neurodegenerative diseases. One major current goal of his MOKALAB research team is to model complex interactions of neuronal and glial pathologies, which are a hallmark of age-related macular degeneration (AMD) and at least the late stages of most other retinal diseases.

He has published over 60 journal articles, reviews, book chapters and conference proceedings, nearly all in the field of retinal cell biology, development and diseases. He was honored by the Innovative Ophthalmology Research Award ARVO-AFER and twice by the EYEnovative Award. His research has been funded through grants by the DFG and BMBF, and many private foundations.

Prof. Dr Marius Ader

Professor Cell Replacement at the CRTD

Marius performed his PhD studies at the ETH Zürich and ZMNH Hamburg and received his degree from the University of Bielefeld. He completed his post-doctoral studies in Hamburg at the ZMNH and University Eye Clinic, before moving to Trinity College Dublin, Ireland. Since 2008, he works at the CRTD, first as a group leader and since 2014 as professor for Cell Replacement in the Mammalian Retina, CRTD/DFG-Center for Regenerative Therapies Dresden, Technische Universität Dresden, Germany.

INTERVIEW

EVOTEC'S CSO CORD DOHRMANN INTERVIEWS PROF. DR MARIUS ADER AND PROF. DR MIKE O. KARL ON RETINAL PIGMENT EPITHELIUM DRUG DISCOVERY

Cord Dohrmann, CSO of Evotec ("Cord"): Why is studying RPE cells so important?

Marius and Mike: The RPE (Retinal Pigment Epithelium) is essential for visual function and a key component for light detection by photoreceptor neurons. RPE is affected in several retinal degenerative diseases including AMD and retinitis pigmentosa (RP). Thus, maintenance of RPE function, either by drug- or gene-based therapy, or by RPE cell replacement therapy through cell transplantation upon RPE loss due to cell atrophy, are key therapeutic approaches for various retinal diseases. Besides functioning as part of the blood-retina-barrier and involvement in the transport of diverse biomolecules, ions, and fluids in and out of the retinal tissue, RPE secures recycling of the visual chromophore retinal by isomerisation the all-trans into the 11-cis form. 11-cis-retinal forms together with opsins the photopigments within the outer segments of photoreceptors that actually allow their activation by light. A crucial function that

»RPE cells handle an enormous metabolic load and thus represent the super-phagocytoser in the body«

we are particularly interested in is the phagocytosis of outer segments. A defect in RPE phagocytosis causes vision loss and photoreceptor degeneration. With engulfment of one tenth portion of each outer segment every day, RPE cells handle an enormous metabolic load and thus represent the super-phagocytoser in the body! Studying this process in RPE cells might allow to identify general principles that also apply for other phagocytosing cells in the body. Further, understanding and controlling RPE functions is also key for successful structural and functional restoration upon RPE cell transplantation therapy.

Cord: What is unique in this approach and how is it different to other initiatives?

Marius and Mike: In 2010, we built a research team and project called Cleansight at the TU Dresden, which was headed by Dr Seba Almedawar (CRTD) and originally started on the mutually complementary expertise on photoreceptor and RPE replacement therapy (Dr Marius Ader, CRTD), human RPE phagocytosis and retinal organoids (Dr Mike Karl, CRTD and DZNE) and a patented method for the efficient generation of a human RPE system derived from human pluripotent stem cells developed from basic stem cell and regeneration research (Dr Elly Tanaka, CRTD). We reasoned that our efficient human RPE system provides experimental access to human models for RPE physiology and pathology, mechanistic studies and larger scale experiments and therapy discovery that previously were limited. To test our hypothesis, we developed several projects funded among others by the State of Saxony, DFG, BMBF VIP+ and the patient organisation ProRetina (Germany e.V.). Our key selling points: To develop and validate a larger scale assay to provide a platform for therapy testing and discovery that in the future could

»The resulting RPE models and data provide a new research approach and potential targets to therapeutically control RPE phagocytic function and waste removal.«

be further upscaled for high-throughput screening – either through a start-up company or in collaboration with an industry partner. Further, we sought to apply this human RPE platform to identify mechanisms and compounds that control cellular waste removal by RPE phagocytosis which represent a highly promising route to develop novel therapeutics for a broad patient spectrum, as accumulation of cellular waste products, particularly outer segment particles, are commonly seen in a number of retinal degenerative diseases.

Cord: What are your expectations for this approach? What are the key aspects that can be achieved with iPSC-derived RPE cells?

Marius and Mike: We sought to gain effective access into basic cell biology, specific pathomechanisms, human models reproducing patient physiology and pathology, as well as robust and reproducible larger scale studies closer to the level of patient cohort studies than classic cell culture or animal model experimental designs. For example, the first paper published by the Cleansight team shows for the first time that RPE cell membrane ensheathment of outer segments is required for POS fragmentation before internalisation – reminiscent of a Pac-man-like biting function (Almedawar et al. 2020). Further, since our human system enables also the generation of RPE cells derived from pluripotent stem cells of patients, we could show that RPE mediated OS ensheathment, fragmentation, and internalisation were abolished in MERTK mutant RPE, and rescue of MERTK expression in retinitis pigmentosa (RP38) RPE counteracted these defects. These results suggest that loss of ensheathment due to MERTK dysfunction might contribute to vision impairment in RP38 patients. The resulting RPE models and data provide a new research approach and potential targets to therapeutically control RPE phagocytic function and waste removal. Accumulating waste is a hallmark of most retinal degenerative diseases and aging, which might cause or contribute to disease onset and progression. Further, in work not yet published we developed and optimised the human RPE platform for larger scale screening and applied it to identify classes of compounds that modify RPE phagocytosis function. In future work, lead candidates can be developed with our system and it needs to be assessed for which patients and when such a therapy might be applicable.

Cord: Apart from funding, where do you see Evotec's key contribution?

Marius and Mike: With its excellent track record in drug discovery and development and its great experience in the development of high-throughput screening platforms, Evotec is an integral part in the translational process from bench to bed side. Its industrial perspective is of fundamental importance to develop our experimental work and bring it to the next level towards identification and commercialisation of innovative compounds for the treatment of currently uncurable blinding diseases. Teamworking and communication at eye level facilitates a highly motivated and constructive academia-industry collaboration.

»Evotec is an integral part in the translational process from bench to bed side.«

Cord: When do you think clinical trials and ultimately the patients will benefit from the iPSC RPE programme?

Marius and Mike: This is obviously hard to predict given the known uncertainties in the development of new therapies. However, based on our positive experience with a small scale, academic screening trial, it is expected within the coming years to identify a number of potential lead compounds with a significant influence on RPE function. The latter will be verified by secondary assays and *in vivo* animal testing, which will be a great fundament for initiating first phase I clinical trials.

Cord: Thank you for your time.

Dr Cord Dohrmann (CD) is Chief Scientific Officer and Member of the Management Board at Evotec. Dr Dohrmann has spent over 20 years in biomedical research at leading academic institutions and in the biotech industry.

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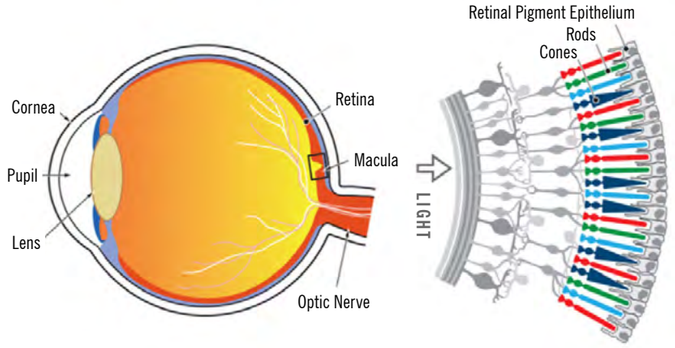
CHAPTER 03

TARGET*RD*

THE RATIONALE BEHIND



Vision is our most precious sense. Humans perceive up to 80% of all impressions by sight and surveys of people around the globe show that vision is the sense that people fear to lose most. According to the World Health Organisation (WHO), at least 2.2 billion people suffer from vision impairment or blindness globally. This number is set to rise dramatically in the coming years, due to global population growth and increased life expectancy. The most common eye diseases are age-related macular degeneration (AMD), diabetic retinopathy, glaucoma and cataract, affecting approximately 500 million people worldwide. Whilst some visual impairments, such as cataract, can be corrected through surgery, most eye diseases are currently not effectively treated.

The leading cause of incurable vision loss and blindness worldwide is caused by retinal degeneration. The retina is a diverse cell layer at the back of the eye where photoreceptors function in concert with Retinal Pigment Epithelial (RPE) cells to sense light and ultimately enable vision (see Figure 1 – picture of eye/retina). So far, mutations in over 250 genes have been identified that cause photoreceptor and/or RPE cell dysfunction or cell death, resulting in permanent vision loss. There are currently no treatment options available to stop or even reverse retinal degeneration. The reason for this is the vast genetic and phenotypic complexity of retinal diseases, coupled with a lack of predictive *in vitro* and *in vivo* models to understand disease mechanisms. Therefore, it is vital to identify and develop new models, which enable elucidation of retinal disease mechanisms and that reliably predict the efficacy of therapeutic compounds.

To address this unmet need and enable the development of life improving treatment options for patients, Evotec has teamed up with the Centre for Regenerative Therapies (CRTD) in Dresden. The CRTD has a longstanding interest in neurodegenerative diseases and the research groups of Prof. Dr Marius Ader and Prof. Dr Mike O. Karl have contributed significantly to advance our understanding of retinal diseases in recent years. The Target*RD* project is utilising the advances in induced pluripotent stem cell (iPSC) technology to generate iPSC-derived RPE cells from patients. Using this approach, we will be able to investigate disease pathology not only in a highly relevant retinal cell type, but also within the genetic context of the specific retinal disease.

The comprehensive approach of using novel, stem cell based, retinal disease modelling approaches, and Evotec's drug discovery expertise coupled with the academic excellence from the CRTD, will enable us to make significant progress towards developing therapies for patients.

CHAPTER 04

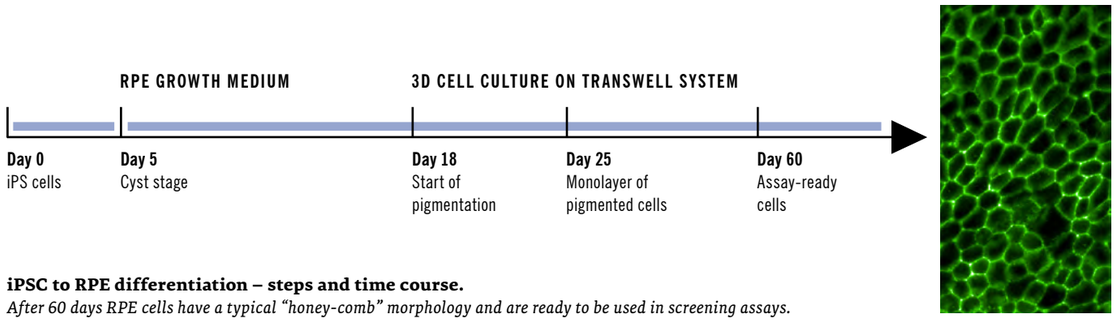
TARGET*RD* PROGRAMME

CHALLENGES AND SOLUTIONS FOR RETINAL DEGENERATIONS

Retinal degenerative diseases are the leading cause of blindness worldwide, but the development of suitable therapies is hampered by the complexity of disease phenotypes and lack of suitable disease models.

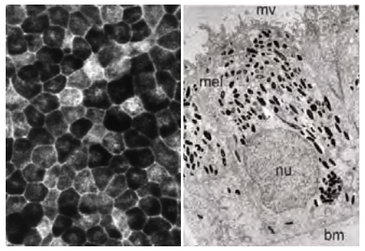
Most drug candidates are withdrawn in early discovery phases or during clinical trials due to lack of efficacy, since the current drug discovery paradigm relies heavily on animal disease models, which are often not predictive for human disease. Therefore, using human disease models would significantly increase the predictive power for drug outcomes, but for retinal degenerations, highly invasive biopsies are not a feasible option.

At the same time, suitable *in vitro* cell models are lacking for most retinal cell types. For example, we are currently only able to study photoreceptors, with a morphology close to *in vivo* cells, by differentiating iPSCs into 3D optic cups. Differentiation into these organoid structures is time consuming and they are not yet suitable for high-throughput screening. Similarly, rapidly dividing immortalised retinal cell lines do not display typical cell morphology or function of their *in vivo* counterparts. For example, immortalised RPE cells are not pigmented or polarised and lack expression of typical RPE proteins. Therefore, we urgently need more predictive models, which are closer to the human situation and that are, at the same time, able to capture the complexity of the disease. We believe this is the only vital approach, to enable successful drug discovery programmes for retinal degenerations with a better chance of successful clinical translation. Here Evotec, together with the CRTD, has developed a protocol to produce efficiently and robustly industry scale, high quality human iPSC-derived RPE cells. The main advantage of using patient iPSCs is that disease phenotypes and mechanisms can be studied within the context of the patient genome.



iPSC to RPE differentiation – steps and time course.
After 60 days RPE cells have a typical "honey-comb" morphology and are ready to be used in screening assays.

A



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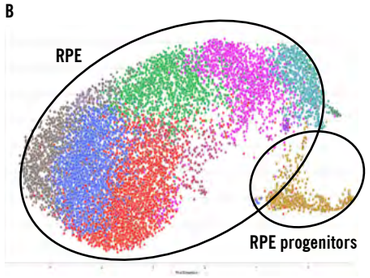
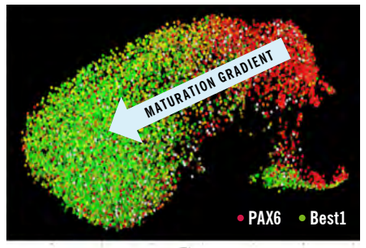




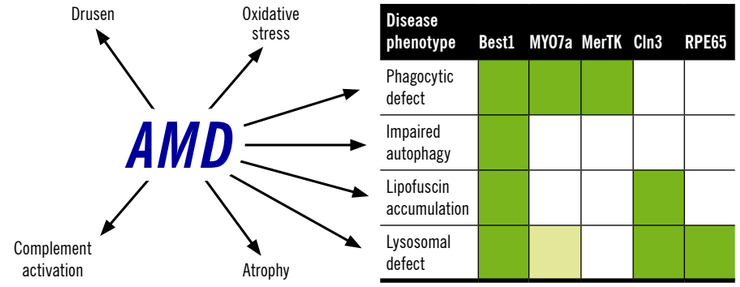
Characterisation of iPSC-derived RPE cells. (A) *iPSC-RPE cells are pigmented and highly polarised. They express apical microvilli, tight and adherens junctions.* **(B)** *Single cell RNA sequencing shows a homogenous RPE cell population following iPSC differentiation. RPE cells from a maturation gradient from early, Pax6 positive, RPE cells to mature, Best1 expressing, cells.*

Taken individually, most retinopathies are rare, nevertheless many retinal diseases share mutual pathological features, for example, phagocytic defects or the intracellular accumulation of fluorescent material, such as lipofuscin, in the RPE cell layer. This suggests that different disease manifestations converge on common cellular pathways. Targeting these pathways would allow us therefore to find new modalities for a wider range of retinopathies. Many morphological features in RPE cells of genetic retinopathies, such as Best and Batten disease, are also found in the retinas of AMD patients. AMD is a very common disease in the elderly, yet the underlying disease mechanism is still unknown. AMD presents as the common dry (~90% of cases) or rarer wet form. Here, wet AMD is defined by the presence of ingrowing blood vessels into the RPE cell layer, causing RPE and photoreceptor cell death. Treatment for wet AMD centres on suppression of neovascularisation, mainly through inhibition of vascular endothelial growth factor (VEGF). However, for dry AMD, despite its prevalence, no treatment options are available.

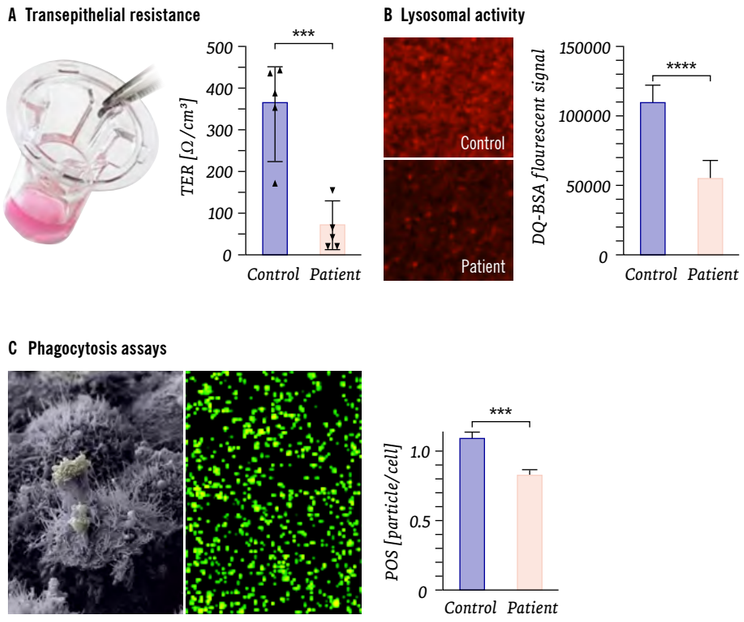
This is also due to the lack of identified causative gene mutations, as the risk of developing AMD is currently determined by environmental factors, aging, family history, and the presence of genetic risk associated single nucleotide polymorphisms (SNPs). Many potentially pathologic mechanisms have been proposed, including inflammation, oxidative stress and build-up of potentially toxic intra- and extracellular material. Current *in vitro* models to study AMD rely heavily on external stimuli to induce cellular phenotypes, reminiscent of AMD. This approach therefore creates an artificial system, which superficially may appear to model aspects of AMD pathology, but does not necessarily trigger relevant disease pathways. To gain a better understanding of the underlying disease mechanisms of AMD, we derive iPSC-RPE cells from a range of AMD patients and from patients with different, genetic retinal diseases, such as Best1 and MerTK, which have overlapping pathological features with AMD. These patient iPSC-RPE cells do not require external stimuli to exhibit disease phenotypes, which enables us to focus on cellular features that are relevant for the pathology and have not been induced artificially. This allows us to enhance our understanding of individual, mutation-specific disease pathways, but we also gain insights into shared pathways, common to these different genetic

retinopathies and AMD. Therefore, we aim to approximate AMD disease pathology through studying individual, overlapping functional and morphological changes from different genetic patient iPSC-RPE cells and ultimately use this approach to unravel complex AMD disease phenotypes.

We were able to show the utility of the Target*RD* platform by analysing iPSC-RPE cells carrying a patient mutation for a lysosomal storage disorder. Patients with this type of mutation develop, amongst other symptoms, severe retinal degeneration, leading to complete blindness early in life. Using the various phenotypic and functional assays that we have established, we were able to show impaired transepithelial resistance in patient cells. This indicates that patient RPE cells are not able to form the tight monolayer required for normal RPE cell function. Furthermore, patient RPE cells have, as expected, impaired lysosomal activity, but are also not able to phagocytose photoreceptor outer segments (POS) at the same rate as control RPE cells. Since all our assays are high-throughput capable, we can use the Target*RD* platform to identify phenotypic and functional disease phenotypes from patient cells and enable novel drug discovery approaches.



Proof of concept study of the Target*RD* platform. *iPSCs carrying a patient mutation for a lysosomal storage disorder were differentiated into RPE cells and analysed for their phenotype and function.* **(A)** *Patient iPS-RPE cells show impaired transepithelial resistance. In addition, patient RPE cells have reduced lysosomal activity* **(B)** *and have significant less phagocytic capacity* **(C)**.



CHAPTER 05

TARGET*RD:* 4 QUESTIONS

TO DR NELE SCHWARZ

SHORT SUMMARY OF SCIENTIFIC CAREER

Dr Nele Schwarz received her PhD in molecular endocrinology from Queen Mary College London, University of London, UK focusing on the role of endocrine receptors and accessory proteins in the adrenal gland.

In 2006, Nele joined the Institute of Ophthalmology, University College London, UK as a postdoc to investigate the at that point unknown function of an important protein in retinal disease. Nele helped unravel the function of several retinal disease proteins by developing iPSC-derived retina cell models and testing therapeutic approaches. Her proven track record in the iPSC field includes research papers in Human Molecular Genetics, Cell Stem Cell and the American Journal for Human Genetics.

In 2016, Nele was awarded a senior research fellowship from the eye charity Fight for Sight where she investigated the role of cilia proteins in retinal disease. Since joining Evotec Göttingen in 2017 as a research scientist, Nele has taken on the project lead for NEPLEX, as well as for the Target*RD* project.

1 What are the challenges for developing new therapies for retinal degeneration?

One of the major challenges in the development of therapeutic compounds for patients with retinal disease is the lack of predictive *in vitro* and *in vivo* models. With better models, disease mechanisms can be studied and unravelled, which would enable us to identify disease biomarkers, molecular pathways and assess feasibility of potential drug targets. However, suitable *in vitro* cell models are either not available, for example for photoreceptors, or they lack significant phenotypic and functional features of their *in vivo* counterparts. Similarly, the architecture of the retina in animal models, especially the commonly used rodents, is different to that in humans. Translating observations made in cells or animal models to the human patient situations is therefore a huge hurdle and many clinical trials fail because molecules that showed impressive activity in animal models were not efficacious in patients.

The retina is a complex cell layer with many different cell types and the contribution of each cell type to the disease is not always clear. For example, RPE cell death which leads to subsequent photoreceptor loss, but when patients present with visual problems to an ophthalmologist, it is not easily distinguishable, in which cell type the degeneration originated.

An additional challenge is that retinal dystrophies are highly heterogeneous, even within families. Here mutations in the same gene can give rise to different patient phenotypes. However, similar patient phenotypes can also arise from mutations in different genes. Mutations in some genes can lead to syndromic disease, involving a multitude of organs, in some patients, while others only present with a retinal phenotype. This diversity adds to the challenge to identify relevant disease pathways and drug targets. Therefore, a better understanding of disease mechanisms to develop novel drug candidates, but also the selection of the right patient population is important, to develop new therapies.

2 How can iPSC-derived RPE cells contribute to disease understanding and aid the discovery of new compounds?

Patient derived iPSCs offer new chances to model a plethora of diseases *in vitro* with a relevant genetic and epigenetic background. This is especially important in areas where suitable, predictive *in vitro* and/or *in vivo* models are lacking, such as neurodegenerative diseases and retinal degenerations. Evotec has a very robust, efficient protocol to differentiate iPSCs into RPE cells, which allows us to generate a limitless supply of cells to study disease mechanisms and use these cells for drug screening. RPE cells are the main cell type impacted by several retinal degenerations, including the highly prevalent AMD. Patient-derived RPE cells enable us to mimic as closely as possible the *in vivo* situation, which enables us to replicate retinal disease phenotypes with more accuracy than ever before. With a better understanding of disease phenotypes and processes, we have a higher chance of developing disease relevant assays for drug screening to develop therapies for patients.

3 What are the specific challenges of using iPSC-derived cells?

A general challenge working with iPSCs is the difficulty of differentiating the cells into the desired, disease relevant cell type. Even when differentiation protocols have been published, replicating them can be challenging, especially if the cell population at the end of the differentiation is heterogeneous. Therefore, Evotec places a high value on robust, reproducible iPSC differentiation protocols to enable the generation of meaningful cellular assays. Through Evotec's longstanding expertise in the iPSC field, we have implemented thorough quality controls, both for the iPSCs, as well as for the final differentiated cell types. Batches of differentiated iPSC-RPE cells for example are routinely analysed for specific gene and protein expression, as well as for functional capacities, such as phagocytosis and VEGF secretion.

An additional challenge is the difficulty of modelling late onset diseases using iPSCs, such as AMD. Here, patient-derived iPSC-RPE represent RPE cells at a young age, but when disease manifests in patients only with older age, it can be challenging to uncover disease relevant pathways in these young cells.

4 What is the long-term vision in retinal disease?

In recent years, efforts have increased significantly to improve therapeutic options for patients with retinal disease. For example, new retinal implants are being developed, which contain photodiodes that convert light into electrical stimuli, which are received by the brain as an optic signal. However, the current chips improve vision only minimally, allowing patients to see mainly contours without optic clarity. Another potential approach to treat retinal disease is gene therapy. Here, small clinical trials with few patients have been conducted with varying results. One of the downsides of this approach is that it is only currently suitable for a small subset of patients. Recent progress has also been made in iPSC-RPE transplantation where a small patch with healthy RPE cells is transplanted onto the macular region of the retina. This approach has so far only been tested on a few patients and is not a widely available therapeutic option. Whether this approach is suitable for the majority of patients, as well as the long-term efficacy of this therapy is currently not clear.

Currently, no small molecule-based therapy is available for any of the approximately 200 million patients with retinal disease. Owing to advances in technology, such as iPSC-based research, treatment of retinal conditions can improve significantly. Evotec's thorough understanding of stem cell research, coupled with long-standing expertise in drug development will significantly contribute to establish practical therapies for patients with retinal degeneration.

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