Keeping an eye on visual loss through retinal oedema

Professor Francine Behar-Cohen, Director of a team at the French National Institute of Health and Medical Research in Paris, and Professor of Ophthalmology at Hôtel-Dieu / Cochin Hospital in Paris, has identified crossover targets between the cardiovascular and ocular systems. These innovations may provide more effective treatments for diabetic macular oedema and other retinal diseases.

Professor Behar-Cohen is an experienced research director, holding positions in universities, hospitals and industry in both France and Switzerland. Having received numerous awards for her research, her interests include the development of innovative treatments and methods of administration for drugs in the eye. Her particular focus has been on the mechanism of action of steroids and its relation to retinal diseases, and it is here that she has uncovered a largely overlooked issue in ophthalmology.

A GOOD PAIR OF EYES

The retina (the light-sensing area of the eye) starts life in the embryo as an outgrowth of the brain, meaning that the retina is neural tissue and part of the central nervous system. It is composed of layers of different cell types, which support and protect the light-sensing rods and cones. These cells gain nourishment from the epithelia (tightly packed cells which form a border or barrier) and the choroid blood vessels, which line the back of the eye. It is this mechanism of layers of cells transmitting a cascade of signals, via the ocular nerve to the visual centres of the brain, which produces vision.

The correct functioning of the retina is dependent on the fluid balance in the eye and surrounding tissues. Retinal oedema (the build-up of fluid in the tissues making up the retina) is caused by a breakdown in the barrier between the blood and those tissues, poor regulation of fluid withdrawal by glial cells (the nervous system's protective cells) and retinal pigment epithelium, or other fluid movements in and around this sensitive area of layered cell types.

IDENTIFYING THE ISSUES

Current treatments focus on the use of high doses of corticosteroids (steroid hormones), particularly glucocorticoids (GC), which are not well tolerated in long-term use. Corticosteroids are involved in a wide range of physiological processes including the immune response and control of inflammation. Mineralocorticoids (MC) are mostly involved in the regulation of electrolyte balance, via epithelia in the tubules of the kidney. Glucocorticoids are important in the regulation of carbohydrate, fat and protein metabolism, as well as their vasoconstrictive (constriction of blood vessels) and anti-inflammatory effects, which are utilised in retinal oedema treatment.

These two classes of corticosteroids have different effects, mediated by their own class of receptors (protein molecules that receive signals and initiate a response) on the epithelial cell surface (glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) respectively). However, glucocorticoids in particular are known to have activity at both types of receptor. It was this off-target activity, coupled with the successful use of MC antagonists (blocking drugs) to prevent overstimulation of MR in cardiovascular diseases, that led Prof Behar-Cohen to consider their use in the treatment of retinal disease.

A FRESH PAIR OF EYES

In recent research, Prof Behar-Cohen and her colleagues have shown that several retinal cell types express the MR, and that activating these by direct injection of aldosterone (a corticosteroid specific for this receptor class) produces effects similar to the symptoms of retinal diseases. Interested to uncover the mechanism underlying these observations,

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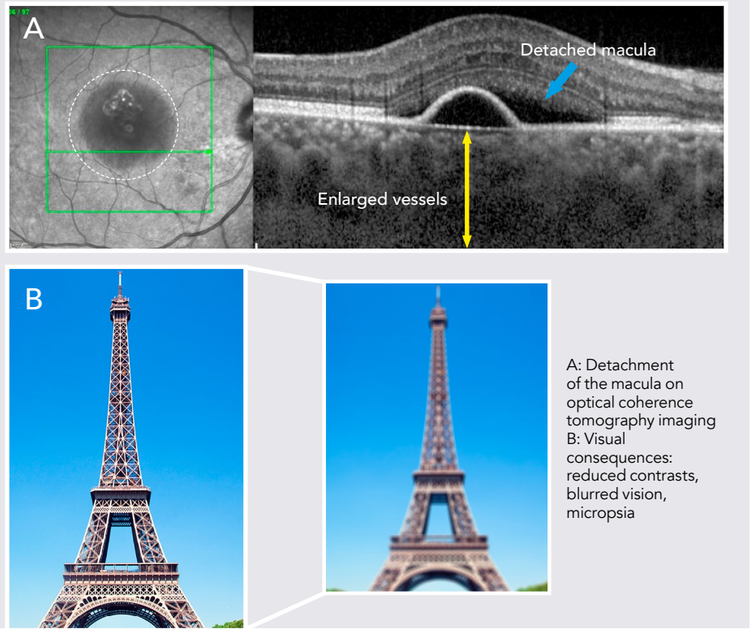
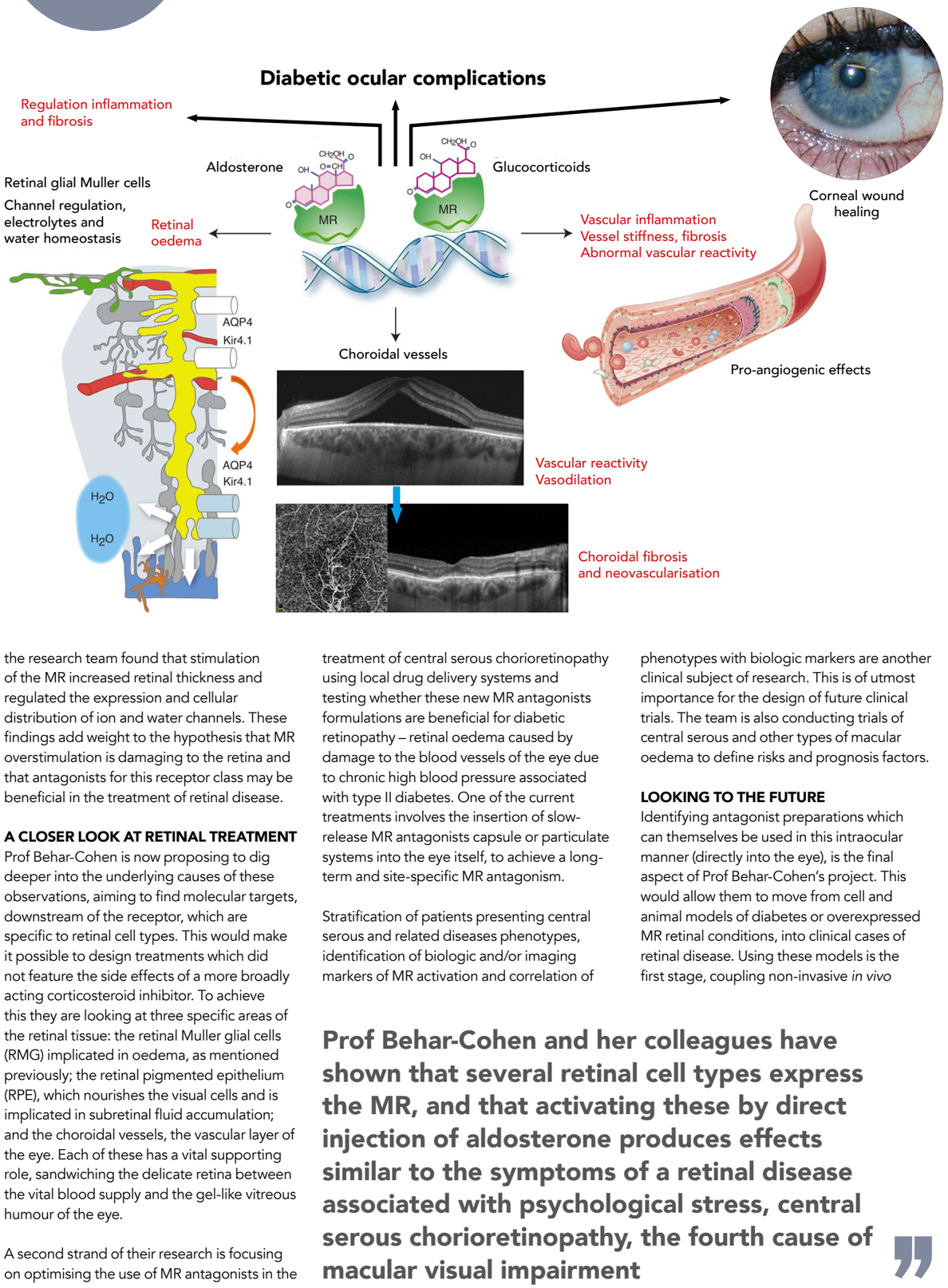


A: Detachment of the macula on optical coherence tomography imaging
B: Visual consequences: reduced contrasts, blurred vision, micropsia



the research team found that stimulation of the MR increased retinal thickness and regulated the expression and cellular distribution of ion and water channels. These findings add weight to the hypothesis that MR overstimulation is damaging to the retina and that antagonists for this receptor class may be beneficial in the treatment of retinal disease.

A CLOSER LOOK AT RETINAL TREATMENT

Prof Behar-Cohen is now proposing to dig deeper into the underlying causes of these observations, aiming to find molecular targets, downstream of the receptor, which are specific to retinal cell types. This would make it possible to design treatments which did not feature the side effects of a more broadly acting corticosteroid inhibitor. To achieve this they are looking at three specific areas of the retinal tissue: the retinal Muller glial cells (RMG) implicated in oedema, as mentioned previously; the retinal pigmented epithelium (RPE), which nourishes the visual cells and is implicated in subretinal fluid accumulation; and the choroidal vessels, the vascular layer of the eye. Each of these has a vital supporting role, sandwiching the delicate retina between the vital blood supply and the gel-like vitreous humour of the eye.

A second strand of their research is focusing on optimising the use of MR antagonists in the treatment of central serous chorioretinopathy using local drug delivery systems and testing whether these new MR antagonists formulations are beneficial for diabetic retinopathy – retinal oedema caused by damage to the blood vessels of the eye due to chronic high blood pressure associated with type II diabetes. One of the current treatments involves the insertion of slow-release MR antagonists capsule or particulate systems into the eye itself, to achieve a long-term and site-specific MR antagonism.

Stratification of patients presenting central serous and related diseases phenotypes, identification of biologic and/or imaging markers of MR activation and correlation of phenotypes with biologic markers are another clinical subject of research. This is of utmost importance for the design of future clinical trials. The team is also conducting trials of central serous and other types of macular oedema to define risks and prognosis factors.

LOOKING TO THE FUTURE

Identifying antagonist preparations which can themselves be used in this intraocular manner (directly into the eye), is the final aspect of Prof Behar-Cohen's project. This would allow them to move from cell and animal models of diabetes or overexpressed MR retinal conditions, into clinical cases of retinal disease. Using these models is the first stage, coupling non-invasive *in vivo* measurements of retinal function with cell biology and molecular approaches; this will assess the tolerance and bioavailability of the preparations.

Utilising techniques such as transcriptomics and proteomics (the analysis of all transcribed genetic material in a specific cell population), the team will uncover the specific genes and gene products associated with the aldosterone/MR pathway, in both normal physiological circumstances and those found in retinal disease states, in animal models and in patients. Improving the range of knowledge in this area, which has been lacking to date, will provide the bedrock for further advances in the treatment of these debilitating and life-changing conditions. The goal is specific biomarker identification and the development of well-tolerated and effective treatments for patients.

It could be concluded that this project is repurposing and reformulating known drugs, widely used in cardiovascular and kidney fields, allowing for quick translation to clinical application. Dr Behar-Cohen's work is also opening new avenues in the field of the role of stress hormones and ocular diseases.

Prof Behar-Cohen and her colleagues have shown that several retinal cell types express the MR, and that activating these by direct injection of aldosterone produces effects similar to the symptoms of a retinal disease associated with psychological stress, central serous chorioretinopathy, the fourth cause of macular visual impairment

Q&A

What is it that you find particularly fascinating about eye research?

Going from patient observation, to basic animal and *in vitro, in silico* study, and back to clinical application. This translation can be much more rapid due to the fact that we aim at repurposing known drugs. The role of steroids on ocular diseases links stress, environment, immunity and inflammation with retinal diseases.

Why has finding effective and well-tolerated treatments for retinal disorders proved so difficult?

The eye is an isolated organ, which like the brain is protected by barriers, thus ocular drug delivery to the retina is a challenge that limits treatment options. Nevertheless, in the last 15 years, major advances have been made using therapeutic proteins injected into the eye.

What led you to examine the mineralocorticoid receptor as a possible therapeutic target?

Glucocorticoids are found in higher levels in the eye than in the circulation, suggesting that they play major and specific roles in the eye but how they act on the retina is incompletely understood.

My interest in MR came from the clinical observations that after glucocorticoids treatment the anti edematous is extremely rapid (less than one hour) suggesting an effect on hydro ionic mechanisms rather than simply on inflammation. The other observation is that retinal oedema is usually ameliorated by glucocorticoids except in the case of central serous, suggesting that those patients may have over activity of MR. Indeed, in patients treated with glucocorticoids, illicit MR occupancy induces hydro-ionic retention by the kidney and oedema. I suspect that similar mechanisms may exist in the eye and this is what we have demonstrated.

How do you envisage being able to target just those receptors in the eye without inducing systemic effects?

When administered into the eye, we do not find circulating steroids elsewhere in the body, demonstrating that local effects are expected.

What is needed to bring effective MR treatments for retinal disease into clinical practice?

Since our first paper in 2012, more than 15 papers have reported use of the mineralocorticoid receptor for the treatment of central serous and associated diseases.

To optimise MR treatment for other ocular diseases and to get approval, we need now to conduct studies on well phenotyped patients with our new formulations. This should be achieved within the next three years. Patents have been granted and pre clinical publications will come soon. Regulation of downstream targets should be possible in the next five years.

Detail

RESEARCH OBJECTIVES

Prof Behar-Cohen's research interests include the development of innovative treatments and methods of administration for drugs in the eye, particularly for diseases of the retina, and mechanisms of action of steroids and anti-VEGFs in the retina. She has introduced the use of mineralocorticoid receptor antagonists for the treatment of central serous chorioretinopathy.

FUNDING

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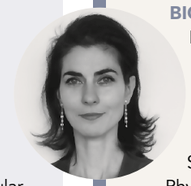
COLLABORATORS

Nicolette Farman and Frederic Jaisser (Inserm), Min Zhao, a close collaborator on this project



BIO

Professor Francine Behar-Cohen is full professor in Ophthalmology at the University of Lausanne and at the Paris Descartes University. She is also the director of the Physiopathology of Ocular Diseases: Therapeutic Innovations Team, based in the French National Institute of Health and Medical Research at the Cordeliers Research Centre in Paris.

Prof Behar-Cohen founded the start-up companies Optis France, now Eyegate Pharma and Eyevensys S.A.S. As well as her medical degree, she has gained a diploma of advanced studies in cell biology, a diploma of specialised studies in ophthalmology and a PhD in biology at the Paris Descartes University. Prof Behar-Cohen was awarded by Oseo-Anvar, Fondation de l'Avenir, Euretina.

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