

How to stop early AMD turning into late AMD?

Action Against Age-Related Macular Degeneration (AAA)



Wellcome Genome Campus
Hinxton, Cambridge, UK

5-6 June 2017



WELLCOME
GENOME
CAMPUS

ADVANCED COURSES AND
SCIENTIFIC CONFERENCES

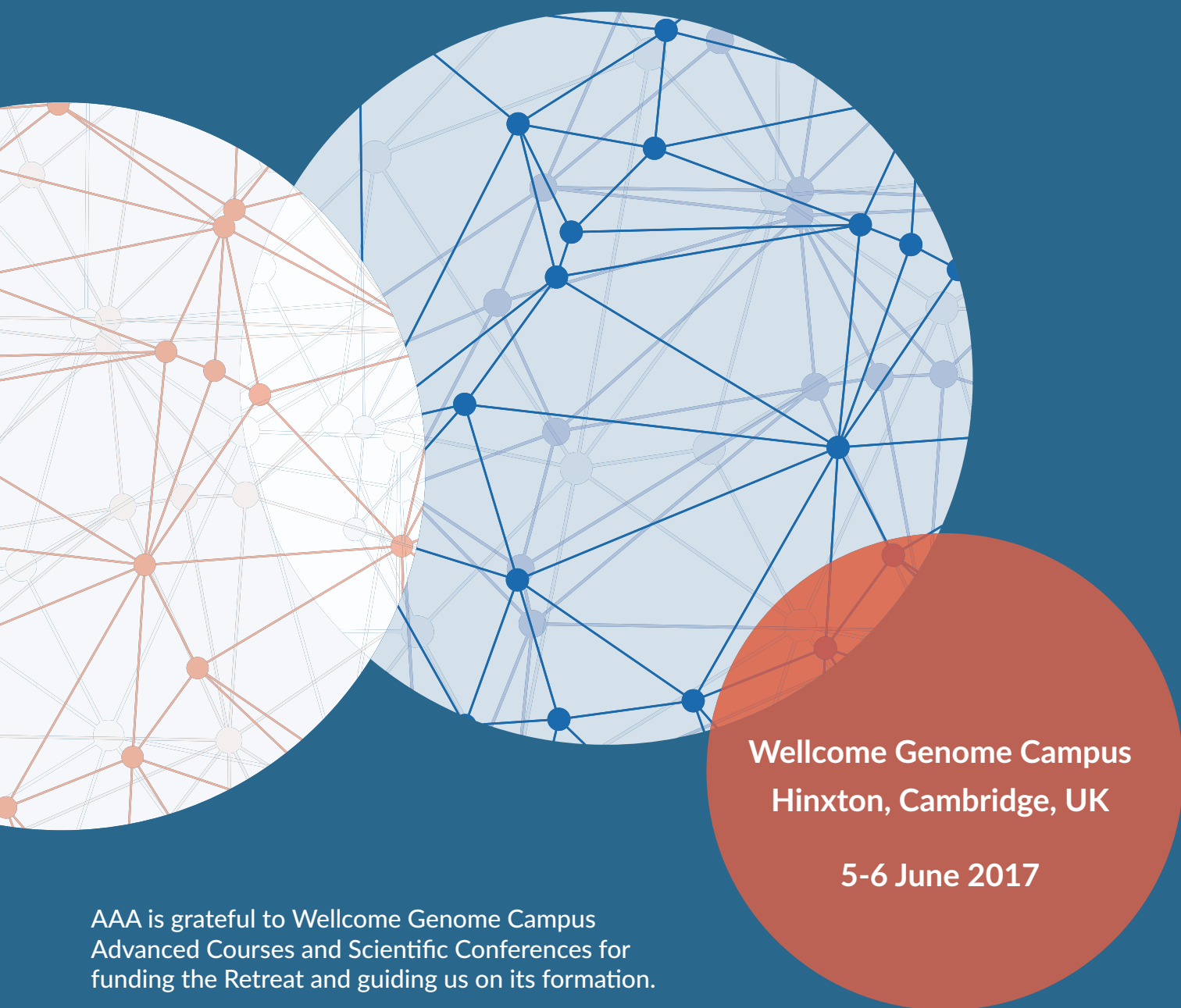
Executive summary

Christina Kiel ^{a,b} (christina.kiel@crg.eu) and Phil Luthert ^c (p.luthert@ucl.ac.uk)

a. EMBL/CRG Systems Biology Research Unit, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology, Dr. Aiguader 88, 08003 Barcelona, Spain

b. Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain

c. UCL Institute of Ophthalmology, and NIHR Biomedical Research Centre, University College London, 11-43 Bath Street, London EC1V 9EL, UK



AAA is grateful to Wellcome Genome Campus Advanced Courses and Scientific Conferences for funding the Retreat and guiding us on its formation.

Wellcome Genome Campus
Hinxton, Cambridge, UK

5-6 June 2017

The views expressed in this report are drawn from those of the participants and are not necessarily held by AAA, the three founding charities or Wellcome Genome Campus Advanced Courses and Scientific Conferences.

Abstract

The Wellcome Genome Campus Retreat entitled 'How to stop early AMD turning into late AMD?' was held in June 2017 at the Wellcome Genome Campus in Hinxton, UK. The Retreat was a gathering of experts in different areas of both basic and clinical research on age-related macular degeneration (AMD). AMD is the commonest cause of visual impairment in the developed world and, to date, there is no intervention that slows or prevents the early disease progressing to blinding neovascularization or geographic atrophy. The aim of this Retreat was to establish research priorities for the next few years to rapidly develop effective treatment(s) or strategies to help prevent individuals with early AMD progressing to late blinding disease.

Introduction

The challenge set by the charities: How to stop early AMD turning into late AMD?

Age-related macular degeneration (AMD) is the commonest cause of visual impairment in the developed world. Patients with early forms of AMD often have problems reading books and newspapers, and are also very much affected by the uncertainty of not knowing when onset late AMD may develop. Late AMD causes major visual impairment, which can interfere immensely with every day activities. People affected describe losing their sight as major deprivation. There is currently no cure for AMD and there is no intervention that slows or prevents early AMD disease progressing to late AMD, such as choroidal neovascularization (CNV) or geographic atrophy (GA).

The Priority Setting Partnership for Sight Loss and Vision, initiated by Fight for Sight and carried out with the James Lind Alliance, identified patient priorities for research. For AMD their top priority was: "Can a treatment to stop dry AMD progressing and/or developing into the wet form be devised?" Partly as a result of this clear imperative, three leading sight loss charities – Blind Veterans UK, Fight for Sight and the Macular Society – decided to launch a major program called Action Against Age-Related Macular Degeneration (AAA).

AAA's main objective is to facilitate the funding of medical research aimed at finding an effective treatment for early-stage age-related macular degeneration (AMD).

To reach its objective AAA will be:

- A catalyst for effective collaboration between industry, academia, government, research councils and foundations
- Instrumental in raising and coordinating the necessary research and development funding
- A sustainable partnership of equally-focused people and organisations
- Instrumental in building a pipeline of therapeutic approaches that will be in early-stage clinical trials by 2027
- An expert thought-leader in AMD patient need, research and development

The way forward: A truly collaborative approach

As a first step towards this goal, the three charities, together with Wellcome Genome Campus Advanced Courses and Scientific Conferences, brought together 42 international clinical and basic scientists, 16 members of eye charities and other funders, and two patients in a retreat-like workshop in June 2017. The scientific programme committee, formed by **Philip J Luthert** University College London, UK, **Paul Bishop** University of Manchester, UK, and **Luminita Paraoan** University of Liverpool, UK, set a retreat agenda that centred on establishing research priorities which will lead as rapidly as possible to effective treatment(s) to prevent individuals with early AMD progressing to late AMD.

Meeting highlights

Held at the Wellcome Genome Campus Conference Centre, this Retreat was a great opportunity for a leading group of AMD experts to discuss the future direction of AMD research. The Retreat was divided into six sessions: a welcome session, four sessions in which research priorities in different areas relevant to AMD were debated, and a closing session where the Retreat was summarised and priorities set.

Welcome and background session

The meeting started on Monday morning and included speeches from **Sir Colin Blakemore** (neuroscientist at the University of Oxford and member of the Board of Trustees of 'AAA'), **Sandie Pearce** (a patient with early AMD), **Phil Luthert** (eye pathologist at University College London), and **Greg Hageman** (vision scientist at the John A. Moran Eye Center, Salt Lake City, USA).

Sir Colin Blakemore emphasised the essential need to prevent early stages of AMD developing into the blinding forms. Because of an ageing population, AMD will soon become an urgent and enormous private and public health issue. He pointed out that worldwide, 288 million people are expected to be affected by AMD by 2040

(Wong et al., 2014), 20 million of whom will have sight loss, and he called for early and affordable intervention. Sandie Pearce provided the audience with a personal insight of what it means to be diagnosed and live with early AMD. She described the shocking experience of seeing people with advanced AMD and the fear of being dependent on another person. She also mentioned that one of the biggest challenges is that the onset to late, blinding AMD can happen any time and without any preceding symptoms, which gives her a feeling of dread that exists every day. Sandie reiterated the enormous achievement it would be if progression from early to late AMD could be prevented.

Phil Luthert reminded the audience about the challenge set by AAA, – solving the problem of the progression of early to late AMD. Phil pointed out that academia has an essential advantage over the pharmaceutical industry in that an army of expertise, excellence and talent is available. However, it will be essential to focus, integrate knowledge and work as a team. The next keynote lecture by Greg Hageman on AMD biology, pathogenesis and gene directed pathways was undoubtedly an influential and far-reaching highlight of the meeting. He has collected what is unquestionably the world's largest collection of human donor eyes (7,500 pairs of eyes) together with information from blood and urine, and detailed health records. Greg's main ambition is to find a cure for AMD and not necessarily to publish in scientific journals such as *Nature*, *Science* or *Cell*; yet his generosity in sharing the main research results obtained by means of his extraordinary resources was pivotal to the success of the meeting. Greg also emphasised that collaboration and teamwork is essential in achieving a breakthrough in the treatment of AMD.

Session 1 – The key challenges for finding an intervention for early AMD

This session was chaired by **Paul Bishop** (University of Manchester) and aimed to identify the key steps towards finding an intervention for early AMD.

Sub-group 1 discussed which in vitro (cell-based) and animal models (e.g. rodents or non-human primates) should be prioritised as the most informative for early AMD pathogenesis. While non-human primates have a retinal/macular anatomy that is closest to humans, they are costly to maintain, develop the phenotype slowly and are difficult to genetically modify. It was agreed that animal models should not be a priority. Instead, the aim should be novel and improved in vitro culture models. These have the advantage that they are defined systems which can be manipulated and tested under defined experimental conditions. Patient-derived induced pluripotent stem cells (iPSC) that can be differentiated to retinal pigmented epithelium (RPE) cells were discussed as a priority as they provide a link between the genetics (a particular genetic risk variant of a patient) and molecular phenotypes, such as energy metabolism, protein turnover and transport

across compartments. Importance was given to co-culture cell models, such as RPE with choriocapillaris (choroidal endothelial cells), RPE with neural retina, RPE with more authentic matrix substrates and RPE with Bruch's membrane.

Sub-group 2 discussed how an early diagnosis and assessment of risk can best be achieved. It is probable that whatever interventions are developed will come with associated costs and could also present a risk to the individual. It will therefore be essential to not only identify individuals with early AMD but also those with a high likelihood of progressing to significant visual impairment and a high likelihood of benefitting from a particular intervention. One of the problems that became immediately evident during the discussion was that it is not currently known what the earliest changes in AMD are and how they progress. The group concluded that to define early AMD, new patient cohorts are needed to define genetic markers, biomarkers, macroscopic phenotypes (imaging) and possibly functional biomarkers. One priority is to define cohorts of genetically-defined patients to be followed longitudinally by detailed phenotyping, ideally in association with existing or proposed studies.

Session 2: Complement pathways and AMD

The second afternoon session was chaired by **Paul Morgan** (Cardiff University). Because complement factor H (CFH) is a major risk factor, intervention in the complement pathway seems to be the most logical and quick route to a target, a drug candidate and then to the clinic.

Most of the discussion in **sub-group 1** was about where (in which retinal anatomical compartments) complement is activated (Sparrow et al., 2012). Unfortunately, very little is known about the location of complement activation and how complement-mediated damage happens. In order to fully map out where complement is activated as a main action point, it will be necessary to determine the localisation of all complement-related factors using antibodies in human post-mortem tissue.

In **sub-group 2** the issue of which part(s) of the complement pathway are best used as therapeutic targets was discussed. Anti-complement treatment has been proposed for many diseases so there is a great deal known about complement activation and its control. A number of drugs, including antibodies and small molecules, are currently under development for AMD and emerging clinical data supports a role for blocking complement in geographic atrophy. A number of drugs in development gives us the opportunity to intervene at different stages of the pathway (Morgan and Harris, 2015), although there was a general consensus in the group that a large volume of evidence pinpoints the alternative pathway as a key target for AMD. It was also noted that not only will selecting the right target be crucial to successfully develop anti-complement treatments in AMD, but getting the right drug to the right patient (stratifying) will be

critical. This might include understanding when disease in an individual is driven by complement (CFH) or by other factors such as ARMS2/HTRA1, or by a combination of these factors and other triggers. Preventing progression of early stage AMD to late stage disease was a key focus of discussion for the group as current intravitreal therapies can make access to treatment difficult for a large number of the patient population with early AMD. Better mechanistic understanding of the local versus systemic nature of disease is also likely to be essential for successful targeting of early stage disease. The lack of information on the exact disease-causing mechanism is potentially why only a few drugs have progressed to clinical trials so far. The group felt a major prerequisite (and therefore priority) for developing anti-complement drugs is a better mechanistic understanding of how complement drives AMD-associated pathology.

Session 3: From genetics to targets

The first morning session on Tuesday, chaired by **Andrew Lotery** (University of Southampton), started with a lecture by Alan Wright (University of Edinburgh). He reported on the latest high-confidence genome-wide association study (GWAS) on AMD (Fritsche et al., 2016). GWAS are useful for understanding the genetic cause of a disease, obtaining a molecular description of the disease and predicting the risk of disease progression.

Sub-group 1 then focused on the ARMS2/HTRA1 locus which is of great importance for understanding/assessing risk but surprisingly little is known about the pathogenesis. Therefore, an integrated approach that advances understanding about the ARMS2/HTRA1 locus was seen as a priority. This collaborative program would need to embrace the diagnosis and new imaging technologies, biomarkers, functional studies using in vitro models (iPSC) and human post-mortem tissues, in particular confirming the possible functional link and role in complement activation and extracellular matrix turnover.

Sub-group 2 discussed the role of lipids in AMD pathogenesis. It is known from genetics and epidemiology that lipid handling is likely to be an issue in AMD. Lipids/lipoprotein particles also accumulate in Bruch's membrane and there is a massive daily cycling of lipid from photoreceptors to RPE and back. The lipids consist of several structurally different classes that regulate a diverse set of processes at the cellular, tissue and systemic/organismal level (Magtanong et al., 2016) which makes understanding their role a major challenge. Thus, the question of what 'lipids' do in relation to AMD pathology is too general a question and needs to be much more refined (e.g. by asking what the role is of a certain class of lipids for retinal homeostasis and how perturbations in lipid-related function contribute to AMD progression). While some progress has been made in obtaining mechanistic insight about how sub-RPE deposits, a major feature of the ageing retina, are initiated and how they grow (Thompson et al., 2015), the general conclusion in this group was that we don't yet understand enough to know if lipids should be considered as a therapeutic target.

Session 4 – Other potential targets to slow the progression of early AMD

In session 4, chaired by **Alex Foss** (University of Nottingham), participants discussed other potential targets for the study of early pathogenesis, such as bioenergetics and extracellular matrix (ECM). Mitochondrial problems have been reported in several diseases and there is evidence of a mitochondrial problem in AMD. For example, functional defects caused by damage to mitochondrial DNA (mtDNA) increase with AMD progression and correlate with vision loss (Feher et al., 2006). Importantly, there is currently a Phase 1 study underway to assess a novel mitochondria-targeting peptide (elamipretide, MTP-131) in dry AMD (ReCLAIM study). Understanding the changes in the energy metabolism in RPE and photoreceptors, and the connection to choroidal blood flow were considered critical (e.g. the systems-level impact of a possible switch from oxidative phosphorylation to glycolysis in RPE cells). This could be done by combining computational network modelling and experimental validation in in vitro photoreceptor-RPE-choriocapillaris model systems.

It is obvious that ECM and Bruch's membrane are important in AMD; and several genes that encode ECM molecules have been associated with AMD. The ECM needs continuous rebuilding to maintain tissue homeostasis and the right level of synthesis, folding, degradation and transport is essential. Matrix components also regulate the adaptive and innate immune systems and matrix changes from age and disease may lead to immune dysfunction and localised inflammation. Currently however, these processes are not fully understood, which makes it hard to propose an ECM-based therapeutic. Therefore, how matrix ageing affects photoreceptor, RPE and choroidal cell function was identified as a research priority. As a more immediate therapeutic strategy, the cleaning of Bruch's membrane, e.g. by laser-based removal of debris, was also suggested as a priority.

Session 5 – Priority setting, Retreat summary and action

This final session was chaired by **Phil Luthert, Paul Bishop, Luminita Paraoan and Colin Blakemore**.

In order to get a sense of the participants' view of the relative priorities of the different research questions discussed, a Slido audience interaction voting app was used. Participants were able to vote on the importance of the research questions and issues discussed. At the end of the final session participants prioritised a number of research questions and from this a ranking was generated.

Whilst solely dependent on the views of the voting participants at the time, these rankings nevertheless provide an important starting point. They will help to develop a research strategy to find a way of preventing early AMD progressing to blinding disease.

The summary priorities:

- Cohorts for longitudinal studies of genetically-defined, highly-informative subject subsets.
- Ageing changes in the choroid-photoreceptor complex.
- Development of models of choriocapillaris endothelium and retinal pigment epithelium (RPE) ageing.
- Integrated approach to understanding how ARMS2/HTRA1 polymorphisms drive disease risk.
- Understand lipid and membrane handling in the choroid-photoreceptor complex.
- Approaches to revitalising Bruch's membrane.
- Support for a drug development programme and studies of therapeutic access to RPE-photoreceptor complex.
- Understanding mechanisms of impaired dark adaptation in early AMD (both to support appreciation of how early disease develops as well as developing a potential 'marker' of early disease).
- Work with other programmes to develop imaging/functional tests for early disease.
- Further our understanding of how the innate immune system drives disease.

Regarding infrastructure priorities, the participants considered seed corn funding to be most important, followed by the facilitation of academic and commercial partnerships, and non-clinical researcher capacity building.

Conclusion

The Retreat was a well-attended meeting with participants sharing many important insights. It was a valuable start for AAA to begin achieving its primary objective and be the catalyst organisation to facilitate the funding of medical research aimed at finding an effective treatment for early-stage AMD.

A more detailed report of the discussions, including ideas and thoughts confidential to the meeting participants has been prepared.

References

- Feher, J., Kovacs, I., Artico, M., Cavallotti, C., Papale, A., and Balacco Gabrieli, C. (2006). Mitochondrial alterations of retinal pigment epithelium in age-related macular degeneration. *Neurobiology of ageing* **27**, 983-993.
- Fritsche, L.G., Igl, W., Bailey, J.N., Grassmann, F., Sengupta, S., Bragg-Gresham, J.L., Burdon, K.P., Hebbaring, S.J., Wen, C., Gorski, M., et al. (2016). A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nature genetics* **48**, 134-143.
- Magtanong, L., Ko, P.J., and Dixon, S.J. (2016). Emerging roles for lipids in non-apoptotic cell death. *Cell death and differentiation* **23**, 1099-1109.
- Morgan, B.P., and Harris, C.L. (2015). Complement, a target for therapy in inflammatory and degenerative diseases. *Nature reviews. Drug discovery* **14**, 857-877.
- Sparrow, J.R., Ueda, K., and Zhou, J. (2012). Complement dysregulation in AMD: RPE-Bruch's membrane-choroid. *Molecular aspects of medicine* **33**, 436-445.
- Thompson, R.B., Reffatto, V., Bundy, J.G., Kortvely, E., Flinn, J.M., Lanzirotti, A., Jones, E.A., McPhail, D.S., Fearn, S., Boldt, K., et al. (2015). Identification of hydroxyapatite spherules provides new insight into subretinal pigment epithelial deposit formation in the aging eye. *Proceedings of the National Academy of Sciences of the United States of America* **112**, 1565-1570.
- Wong, W.L., Su, X., Li, X., Cheung, C.M., Klein, R., Cheng, C.Y., and Wong, T.Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet. Global health* **2**, e106-116.

“Protective-based therapeutics and the concept of treating early AMD are prudent.”

Greg Hageman, Steele Center for Translational Medicine



“We will not stop until we have solved AMD.”

Phil Luthert, University College London



“We need early and affordable intervention.”

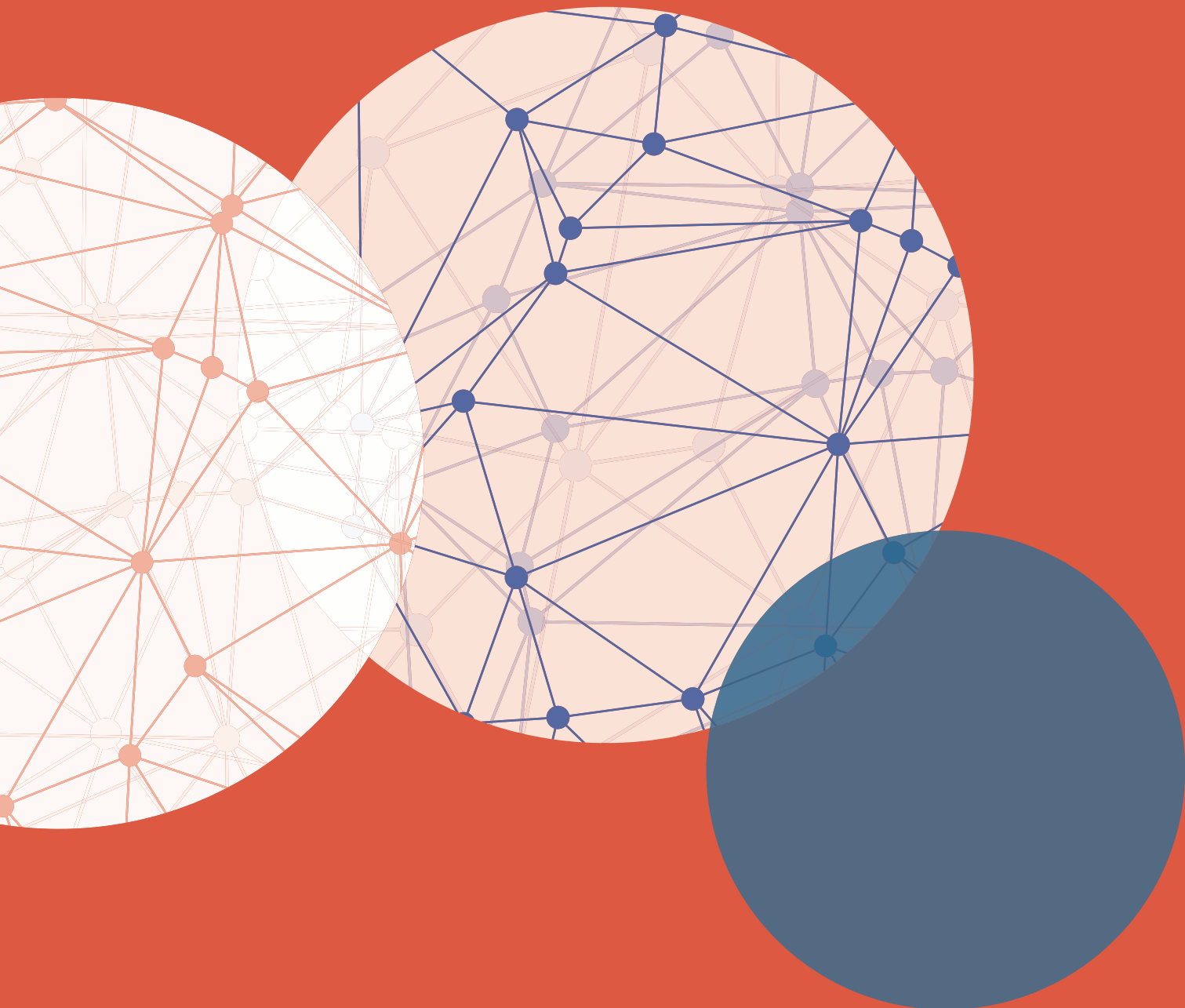
Sir Colin Blakemore,
Action Against Age-Related Macular Degeneration



“It would be an enormous achievement if we could prevent progression from early to late AMD.”

Sandie Pearce, patient with early AMD





Blind Veterans UK
www.blindveterans.org.uk

Fight for Sight
www.fightforsight.org.uk

Macular Society
www.macularsociety.org