Kai Kaarniranta

Kai Kaarniranta lab, Department of Ophthalmology Kuopio University Hospital/University of Eastern Finland.

In the Middle of (K)nowhere

where **Medicine, Science,** and **Discovery** come **Together**

*It is remarkable how **AMD therapy** went from being **a field with poor prognoses to a field where we have relative success and safety** thanks to **deep translational research** around the world.*

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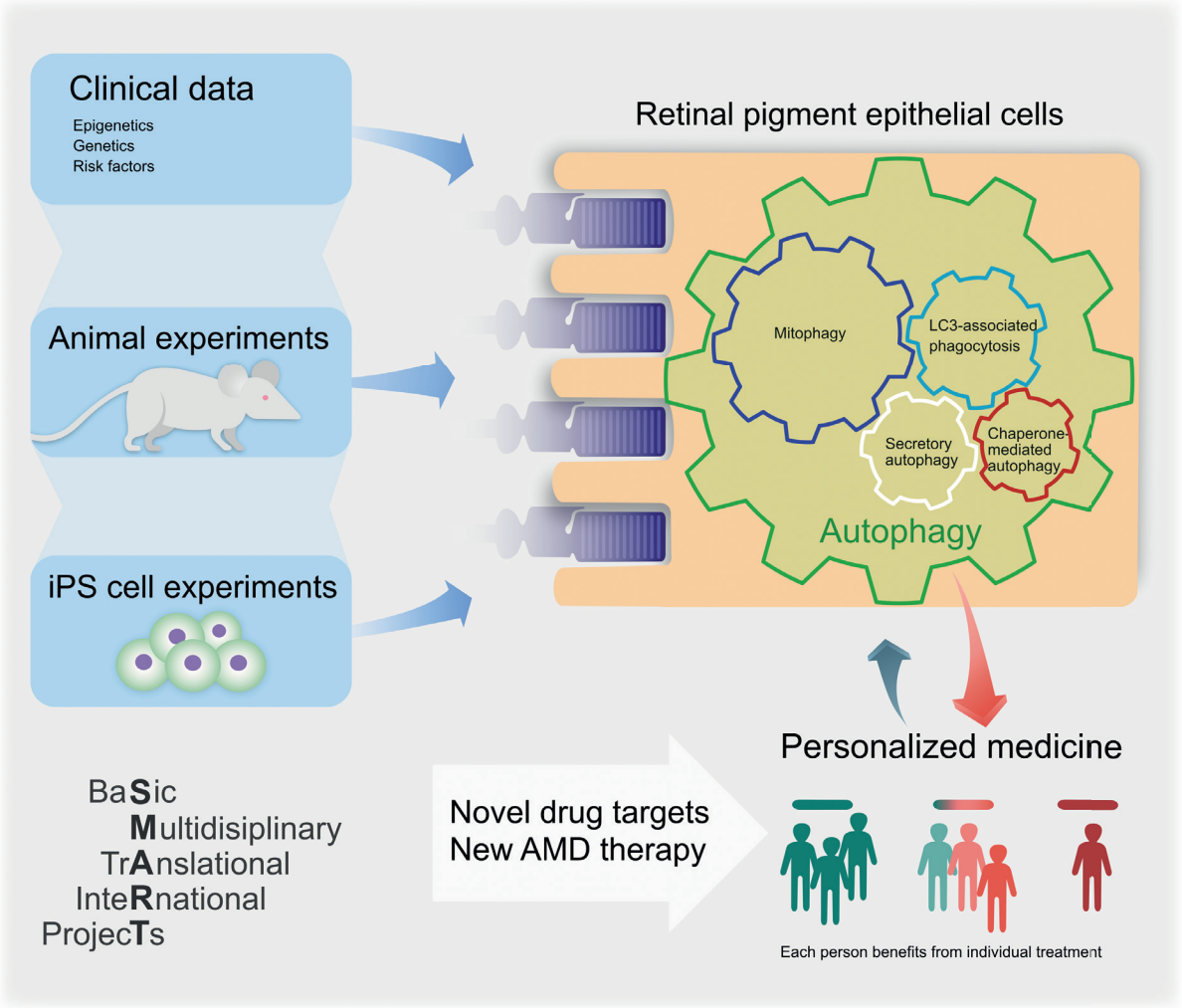
Age-related macular degeneration (AMD) is a complex eye disease with a multifactorial background. In addition to a strong genetic component, cardiovascular diseases and environmental risk factors such as smoking and unhealthy diet are associated with AMD pathology. Since increased accumulation of lipofuscin



Autophagy as a therapy target in age-related macular degeneration

The Nobel Assembly at Karolinska Institute awarded the 2016 Prize in Physiology or Medicine to the cell biologist Yoshinori Ohsumi for his early identification and characterization of the autophagy machinery, in particular, AuTophaGy-related (Atg) genes, in yeast (Tsukada & Ohsumi, 1993). Since early 90s our understanding of autophagy has expanded considerably, on both mechanistic and pathophysiological grounds of the mechanisms in the maintenance of cellular balance and the disposal of unwanted material by autophagy. Reduced autophagic clearance in RPE has been proposed to be linked with the development and progression of AMD (Kaarniranta et al., 2020). This manifests as impaired cargo transport, disturbed waste clearance, and increased accumulation of lipofuscin that all increase oxidative stress in RPE. Degeneration of RPE cells is one of the most important clinical hallmarks of AMD. However, the lack of good *in vitro* and *in vivo* models has hindered the full understanding of the molecular mechanisms behind AMD pathogenesis. By using physiologically relevant animal models that develop RPE degeneration and protein aggregation we aim to understand cross-talk between genetic, environmental risk factors and molecular mechanisms behind AMD. In doing so, we aim to provide new tools for better AMD diagnostics and risk-based personalized prevention strategies for the healthcare system as well as for the benefit of individual patients.

Our major projects are shown on the left side of the illustration: 1) Investigation of the role of autophagy in the novel AMD iPSC RPE cell models, derived from our well-characterized human clinical cohort. 2) Study and comparison of the regulation of heterophagy and autophagy in human iPSC RPE cells and the primary RPE cells derived from Nrf2/PGC1 double knockout mice. 3) Determination of the clinical parameters and autophagy function in Nrf2 and PGC1 single and double knockout mice.

We aim to provide information that has wide scientific impact and will help scientists to improve technologies for studying not only AMD but also other neurodegenerative diseases such as Alzheimer´s disease. This research strategy is ambitious and would not be possible without multidisciplinary and multinational expertise, which combines modern cell and molecular biology, patient material and top ophthalmology clinic.

Abbreviations: AMD = age-related macular degeneration, RPE = retinal pigment epithelium, iPSC = induced pluripotent stem cells, Nrf2 = nuclear factor (erythroid-derived 2)-like 2, PGC-1 = peroxisome proliferator-activated receptor-gamma coactivator 1.

and drusen at the cellular level are key factors in AMD, Kaarniranta's team studies the molecular mechanisms of the formation and clearance of those detrimental components.

Prof. Kaarniranta and his team focus on the regulatory pathways of protein aggregation, as well as proteasomal and autophagy clearance in the retinal pigment epithelium (RPE) cells in AMD patients and models. They also aim to understand oxidative stress in the retina: the molecular mechanisms of its origin, its triggers, its effects, and what signaling pathways it encompasses.

Kaarniranta's team's main clinical focus is AMD. More widely, they have an interest in evidence-based translational ophthalmology. He and his team have repeatedly been granted sizeable research funds, which shows that their hard work has not gone unnoticed. The number of peer reviewed publications professor Kaarniranta has been part of exceeds 300, with more than 25 000 citations.

Missions and Goals

Search for novel AMD autophagy mechanisms and add to the existing knowledge.

Model normal and diseased states to elucidate basic scientific concepts for personalized medicine.

Apply state of the art translational science for the advancement of AMD research.

Robust experiments to identify new drug targets to inhibit AMD development and progression.

Train the next generation of scientists and physicians through involvement in mentoring of graduates and residents.

Kaarniranta's worldwide network of top-notch researchers

The team is also very keen to know more about the role of energy metabolism and autophagy and theirs interactions with cellular degeneration, as they have become increasingly important topics in AMD.

Kaarniranta emphasizes that "to develop personalized AMD care is the billion-dollar question in AMD research for scientists around the globe today. We are super excited to find new methods in translational science that may significantly reduce AMD treatment burden. We believe that human data and cell cultures together with new animal models, which mimic features of human dry AMD, could potentially be useful for high-throughput personalized drug screening to find molecules that slow or prevent the development of the more severe forms of AMD."

Kaarniranta`s AMD laboratory is one of the main research arms of the Department of Ophthalmology at the University of Eastern Finland (UEF). The AMD team is comprised of scientists

Professor Kaarniranta, his researchers and staff, as well as their top-notch collaborators around the globe, are all united by shared commitment to new scientific discovery related to AMD.

They seek to uncover and answer key questions in basic and preclinical research, allowing them to find novel therapies and cures for AMD.

Their vision is to connect talented young scientists with world-class leaders in AMD research and thereby promote discoveries that impact AMD care for the benefit of all.

representing distinct basic science and clinical disciplines.

Their research combines modern, multi-disciplinary approaches, including molecular, cellular, biochemical, genomic, and *in vitro* and *in vivo* imaging techniques. The AMD team also provides integrated training to numerous undergraduate, graduate, and postdoctoral students within a collaborative and interdisciplinary training environment.

The team has a special advantage in being able to design, construct, and apply its research results at a preclinical level (translational research).

Every manuscript is celebrated appropriately

The Home of Kaarniranta's Lab.
The Canthia building of the University of Eastern Finland (www.uef.fi). For more on Kai Kaarniranta's research and his AMD research group, please go to https://uefconnect.uef.fi/en/group/kaarniranta-amd-lab/ https://www.kaarnirantalab.fi

Major projects:

- Studying of induced pluripotent stem cells (iPSC) using RPE cells from severe AMD patients.
- Determination of the clinical parameters and clearance mechanisms in Nrf2 and PGC1 single and double knockout mice.
- Role of genetic and epigenetic markers focused on energy metabolism and autophagy from cell culture models to patients.