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► **To cite this version:**

Valérie Fradot, Sébastien Augustin, Valérie Fontaine, Katia Marazova, Xavier Guillonneau, et al.. Rodent Models of Retinal Degeneration: From Purified Cells in Culture to Living Animals. Cold Spring Harbor Perspectives in Medicine, 2023, pp.a041311. 10.1101/cshperspect.a041311 . inserm-04250159

HAL Id: inserm-04250159

<https://inserm.hal.science/inserm-04250159>

Submitted on 19 Oct 2023

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Rodent Models of Retinal Degeneration: From Purified Cells in Culture to Living Animals

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Abstract

Rodent models of retinal degeneration are essential for the development of therapeutic strategies. In addition to living animal models, we here also discuss models based on rodent cell cultures, such as purified retinal ganglion cells and retinal explants. These *ex vivo* models extend the possibilities for investigating pathological mechanisms and assessing the neuroprotective effect of pharmacological agents by eliminating questions on drug pharmacokinetics and bioavailability. The number of living rodent models has greatly increased with the possibilities to achieve transgenic modifications in animals for knocking in and out genes and mutations. The cre-lox system has further enabled investigators to target specific genes or mutations in specific cells at specific stages. However, chemically or physically induced models can provide alternatives to such targeted gene modifications. The increased diversity of rodent models has widened our possibility to address most ocular pathologies for providing initial proof of concept of innovative therapeutic strategies.

Introduction

The ultimate goal of vision research is to understand the underlying mechanisms of vision as well as visual pathologies, prevent vision loss and restore sight in blind patients. Inherited retinal degenerations that lead to blindness are as yet mostly untreatable, apart from one approved gene augmentation therapy for retinal disease associated with mutations in the RPE65 gene. Additional examples of highly prevalent retinal degenerative diseases that are currently an unmet need include the non-neovascular (dry) form of age-related macular degeneration as well as the loss of retinal ganglion cells (RGCs) in glaucoma that often occurs despite available treatments. The need for novel treatments is urged by the high number of blind patients worldwide rising above 30 million (Bourne *et al.*, 2017; Blindness *et al.*, 2021) with an expected doubling of blind and tripling of visually impaired patients, respectively, due mostly to population aging at the 2050 horizon (Bourne *et al.*, 2017).

In order to develop treatments for the prevention of retinal diseases, there is a clear need to develop models that will allow better understanding of normal processes of vision as well as pathological mechanisms leading to blindness or severe visual impairment. In addition to naturally occurring rodent animal models of retinal diseases, the recent development of transgenic animals has transformed the analysis of normal and pathological mechanisms of vision. Transgenic animals have not only provided living models of retinal diseases, they also allowed the production of animals containing the green fluorescent protein (GFP) in different cell types. Via fluorescent-activated cell sorting (FACS), this permits generation of purified cell cultures as well as analysis of gene expression patterns in specific cell types. In addition to the culture of purified rodent retinal cells, culture of the whole retina has also provided interesting models to assess molecular mechanisms in a fully wired structure with the ease to apply various pharmacological agents in the medium, either toxic or therapeutic. Recently, the development of retinal organoids from stem cells or induced pluripotent stem cells (iPSCs) from control or patient cells further expand the potential of these *in vitro* approaches to develop therapeutic strategies (Reichman *et al.*, 2014; Reichman *et al.*, 2017). These *in vitro* models of retinal diseases also carry an additional benefit in that they adhere to the 3 R objectives of reduction, refinement and replacement of animal experimentation.

We therefore propose here to review different rodent models, ranging from single cell types in culture to living animals, as tools for the development of novel therapeutic strategies for retinal degenerative diseases.

A) Rodent monolayer cell cultures

Culture of rodent retinal cells was obtained with different cell types, from retinal pigment epithelium cells (RPE) to retinal neurons including photoreceptors and retinal ganglion cells (Hicks & Courtois, 1990; 1992; Malecaze *et al.*, 1993; Heidinger *et al.*, 1998). Several methods are available to separate retinal pigmented epithelium cells from the retina and obtain a pure preparation for seeding in culture dishes (Hicks *et al.* 1990). These cells can divide until confluence, reconstituting in a layer similar to that seen *in vivo*. However, for large studies on retinal pigment epithelium such as light toxicity, we recently preferred porcine eyes available in large quantities to obtain more cells (Arnault *et al.*, 2013; Fontaine *et al.*, 2016; Marie *et al.*, 2018; Fontaine *et al.*, 2021). This method is also relevant for primates, including human eyes under condition of a reduced post-mortem delay. Using freshly removed Macaque eyes, we were able to apply trypsin in the eyecup and harvest RPE cells that survived for several weeks. With opportunity to get human donor eyes, we established that a post-mortem delay of less than 10 hours is the key for success of the purification protocol. Glial cells were also prepared and cultured from overnight incubated rat eyes following mere retinal dissociation (Hicks & Courtois, 1990; Heidinger *et al.*, 1998) or from dissociated porcine retina on a density gradient (Guidry, 1996).

Rat retinal ganglion cells were also purified by a technique named “immunopanning” using thy1 antibody (Barres *et al.*, 1988) to then assess the effect of different trophic factors on their survival *in vitro* (Meyer-Franke *et al.*, 1995). This approach was also used to investigate axonal growth and myelination (Watkins *et al.*, 2008). While these postnatal day 5 (P5) retinal ganglion cells required a combination of BDNF, CNTF and components like forskolin to survive (Watkins *et al.*, 2008), we found that adult rat retinal ganglion cells prepared in the same manner did not require these factors although conditioning media from Müller cells or mesenchymal cells were neuroprotective (Fuchs *et al.*, 2005; Roubéix *et al.*, 2015). We also demonstrated that these retinal ganglion cells were sensitive to TNF α through NF- κ B activation (Fuchs *et al.*, 2005). Furthermore, we showed that VEGF is an autocrine/paracrine trophic factor for these adult retinal ganglion cells in culture (Froger *et al.*, 2020). Taurine was also found to support their survival *in vitro* (Froger *et al.*, 2012).

Photoreceptor cells were also purified from the rodent retina by cutting the tissue in its thickness at the level of the outer plexiform layer to then investigate the photoreceptor sensitivity to factors such as FGF (Fontaine *et al.*, 1998). However, these isolated photoreceptors, mainly rods, did not survive for very long in culture beyond P10. Adult porcine photoreceptors purified similarly were found to survive on a glial feeder layer for weeks (Picaud *et al.*, 1998). For the analysis of cone

survival, other species such as chick and pig have been used to test survival medium and factors, due to the very low number of mouse cone photoreceptors (Leveillard *et al.*, 2004; Balse *et al.*, 2005). Porcine cones were purified by lectinpanning (Balse *et al.*, 2005) with a survival effect promoted by a glial conditioned medium (Balse *et al.*, 2005). Such purified cone photoreceptor cells enabled us to identify blue violet light as the most toxic to cone cells even at intensities which the retina is exposed to during the summer time in France (Marie *et al.*, 2020).

B) Retinal explants

To preserve the retinal architecture with original synaptic connections, the whole retina was kept in culture with great success at the water/air interface first on small rafts and then on insert wells (Caffe *et al.*, 1993; Soderpalm *et al.*, 1994; Pinzon-Duarte *et al.*, 2000; Vallazza-Deschamps *et al.*, 2005) allowing to assess retinal cell development while controlling the extracellular medium (Caffe *et al.*, 1993; Soderpalm *et al.*, 1994; Pinzon-Duarte *et al.*, 2000). These explant cultures offer the advantage of very precisely controlling the extracellular medium for application of toxic molecules for modeling neuronal degeneration or to assess the efficacy of pharmacological agents for neuroprotection (Vallazza-Deschamps *et al.*, 2005; Froger *et al.*, 2013). Depending on the cell of interest, the retinal pigment epithelium can be kept in contact with the retina for investigating photoreceptor survival (Vallazza-Deschamps *et al.*, 2005) whereas assessing retinal ganglion cell survival does not require its presence (Froger *et al.*, 2012). For instance, phosphodiesterase blockers were applied to model photoreceptor degeneration (Vallazza-Deschamps *et al.*, 2005) whereas retinal ganglion cell loss was induced by application of a glutamate receptor agonist, MK801 (Froger *et al.*, 2013). Retinas from various animal models of photoreceptor degeneration (e.g., rd1, P23H Rhodopsin) were also used in such studies to screen for neuroprotective molecules because these explants bypass all problems of molecule bioavailability that may exist in-vivo via application directly in the culture medium (Vallazza-Deschamps *et al.*, 2005; Sen *et al.*, 2021a; Sen *et al.*, 2021b). Reverse magnetofection was even applied to deliver siRNA in rodent retinal explant (Bassetto *et al.*, 2021). These ex vivo retinal explant cultures can thus provide an interesting modality to limit in vivo animal experimentation while demonstrating efficacy of a drug, such as in neuroprotection. Since these early studies in rodents, retinal explants were further developed with other species like the bovine retina (Peynshaert *et al.*, 2017) or even with postmortem human retina (Buskamp *et al.*, 2010; Fradot *et al.*, 2011) to investigate retinal gene delivery.

C) Living animals

Retinal function and structure including effects of degenerative processes as well as various treatments can be documented in living rodents using a wide range of non-invasive technologies that

are also applied in humans. These include monitoring visual behavior and assessing acuity through the optomotor response (Jellali et al., 2005), quantifying rod and cone-derived retinal function by electroretinography (Orhan et al., 2015) and documenting retinal structure by fundus color and autofluorescence eye fundus (Paques et al., 2007), optical coherence tomography (OCT) (Orhan et al., 2015) and scanning laser ophthalmoscope (Paques *et al.*, 2006). Isolating the retina allows recording the ex-vivo activity in retinal ganglion cells using a multielectrode array to further characterize the functional change in the diseased tissue. Waves of activity were thus observed in the degenerating retina with features highly reminiscent to those described during development (Stasheff, 2008; Kolomiets *et al.*, 2010). Then, histopathology provides access to cell counting in both sections or retinal flatmounts (Clerin *et al.*, 2011) while investigating the degree of reactive gliosis with increased expression of the glial fibrillary acidic protein in Muller cells at or around the lesion area (Picaud *et al.*, 1993) or the transformation and migration of microglial cells from stellate cells to an amoeboid morphology (Gaucher *et al.*, 2007).

1) Increase intraocular pressure

Increase of intraocular pressure (IOP) is a main risk factor in the development of glaucoma and animal models of glaucoma can be created by increasing the IOP in the eye through different strategies. Thus, the disease was modelled by increasing transiently the intraocular pressure for a limited period (1hour) in the anterior chamber (Mohand-Said *et al.*, 1997). In addition, increase of IOP can be induced by cauterization of episcleral veins (Froger *et al.*, 2012). A similar result was obtained by laser photocoagulation of episcleral and limbal veins (Salinas-Navarro *et al.*, 2010). Injection of polystyrene or magnetic beads in the anterior chamber was also used to block the mouse trabecular meshwork thereby raising the IOP (Cone *et al.*, 2010; Mao *et al.*, 2013). In clinical practice, many different topical treatments that lower IOP, have proved efficient in attenuating disease progression toward blindness. However, unfortunately, even when controlling the pressure, some patients still experience retinal ganglion cell loss and additional effective treatments for this highly prevalent disease are sorely needed.

2) Light damage

Light damage models are widely used to investigate intracellular mechanisms that lead to photoreceptor cell death, a common feature in retinitis pigmentosa and age-related macular degeneration. Photochemical damage to the retina occurs after short or prolonged exposures of mild or intense light in mice and rats. The “white light damage” model targets photoreceptors whereas the “blue light damage” model (excitation peak 440 nm) induces primarily RPE cell photosensitization. These models have been shown to have a major impact on photoreceptor and

RPE function, inducing photochemical damage and leading to cell death (Wu *et al.*, 2006). It is also possible to couple transgenic models sharing cellular features of AMD with light damage. Thus, transgenic *Abca4*^{-/-} or *Abca4*^{-/-}*Rdh8*^{-/-} mice that accumulate RPE lipofuscin at increased levels are more susceptible to retinal light damage than wild-type mice (Maeda *et al.*, 2008; Maeda *et al.*, 2009; Wu *et al.*, 2014; Fontaine *et al.*, 2016).

3) Laser-induced subretinal inflammation

Laser treatments were applied to generate choroidal neovascularization (CNV) as a model of such complications in the neovascular (“wet”) form of age-related macular degeneration (Combadiere *et al.*, 2007). This model allowed analysis of different treatment modalities including anti-VEGF treatments and studying the role of inflammation in CNV formation. It involves the induction of CNV using laser photocoagulation, which mimics the pathological processes seen in diseases such as age-related macular degeneration (AMD) (Grossniklaus *et al.*, 2010). Subretinal inflammation is induced in pigmented mice with a laser mounted on a slit lamp. The injury induces a neutrophil and macrophage (macrophage/microglial cell) infiltration that can be quantified using Ly-6G and IBA-1 immunostainings on retinal and choroidal flatmounts or by FACS analysis at different time points after laser-injury. Ly-6G⁺ neutrophils are significantly recruited to the injury site, reaching their maximum at 10h and being cleared at day 3. IBA-1⁺ MPs are recruited at day 3, reach a maximum at day 4 and diminish thereafter. Agonists and antagonists can be administered at different time points after laser-injury by intravitreal injection (Camelo *et al.*, 2012; Levy *et al.*, 2015) or systemic treatment (Lavalette *et al.*, 2011). Even sizeable molecules (such as antibodies) penetrate the post-laser injury retina and can affect subretinal inflammation. Choroidal neovascularization is evaluated by angiography or by OCT *in vivo* and by immunostained flatmounts post mortem. Although the trigger to induce neovascularization is very different from the human disease, mechanisms of downstream subretinal inflammation and neo-angiogenesis are likely similar. For instance, Aflibercept, which blocks murine as well as human VEGF, inhibits CNV in this model similar to its effect in humans (Ma *et al.*, 2016).

4) Oxygen-induced retinopathy

Ischemic retinopathies, including retinopathy of prematurity (ROP), vein occlusion and diabetic retinopathy (DR) are all characterized by primary retinal ischemia. If left untreated, they can progress to neuronal dysfunction and proliferative forms of retinopathies causing rapid and irreversible vision loss. Unlike humans, adult rodents do not develop a proliferative response to experimental ischemic situations even following laser-induced vein occlusion or diabetes induction. To address the mechanisms of proliferative retinopathies, L. Smith *et al.* described a model of oxygen-induced

retinopathy in newborn mice (Smith *et al.*, 1994). The treatment relies on alternating periods of high and low oxygen levels on neonatal mice. It results in retinal vascular abnormalities resembling those observed in human retinopathy of prematurity and diabetic retinopathy. As a consequence, it has since become a widely used model for studying the pathophysiology and potential treatments of ischemic retinopathies.

Beside the vascular abnormalities observed in human retinopathy of prematurity, persistent rod photoreceptor dysfunction is observed in adulthood despite the clinical resolution of vascular abnormalities (Fulton *et al.*, 2009). A similar observation is made in the mouse and rat oxygen-induced retinopathy model (Liu *et al.*, 2006; Vessey *et al.*, 2011). This long-term loss of rod photoreceptor function, while cone function remains intact, has been attributed to differential metabolic adaptation of rods and cones to ischemic stress (Fulton *et al.*, 2009). Overall, while the oxygen-induced retinopathy model is widely used to study pathological neovascularization, it also allows for the investigation of rod photoreceptor responses to acute ischemia as well as long-term modifications of rod photoreceptor activity.

5) Pharmacological models

Different pharmacological treatments were shown to induce retinal degeneration. For instance, treatments limiting taurine transport by introducing β -alanine or guanidinoethane sulfonate in the diet were first reported to induce photoreceptor degeneration (Pasantes-Morales *et al.*, 1983). More recently, similar treatments were shown to preferentially affect cone photoreceptors and retinal ganglion cells (Gaucher *et al.*, 2012; Garcia-Ayuso *et al.*, 2019). This more precise description of the damaging effect of taurine deficiency resulted from the investigation of the retinal toxicity of Vigabatrin, an antiepileptic drug, still prescribed in infantile spasms, which was shown to induce taurine deficiency in rodents and patients (Jammoul *et al.*, 2009). It was first reported to generate a destruction of the outer nuclear layer in albino animals (Butler *et al.*, 1987) and we showed that the earlier cone and retinal ganglion cell degeneration is related to taurine deficiency associated with phototoxicity (Duboc *et al.*, 2004; Jammoul *et al.*, 2009; Jammoul *et al.*, 2010).

In glaucoma, the loss of retinal ganglion cells was often attributed to a glutamate excitotoxicity (Lipton, 2003). Supporting this hypothesis, memantine, a NMDA receptor antagonist was found to be neuroprotective in different animal models of glaucoma (WoldeMussie *et al.*, 2002). As a consequence, glaucomatous conditions are often modelled by intraocular injection of a glutamate NMDA receptor agonist (Torero Ibad *et al.*, 2011). However, memantine was not proved efficient in glaucomatous patients (Danesh-Meyer & Levin, 2009).

Pharmacological treatments with streptozotocin or alloxan were also applied to induce diabetes in rodents (Barber *et al.*, 1998; Park *et al.*, 2003; Martin *et al.*, 2004; Gaucher *et al.*, 2007). These treatments allowed to demonstrate neuronal apoptosis or a microglial reaction in the treated animals. The neurodegenerative process in these animal models was very variable from photoreceptors to retinal ganglion cells. These models also showed some alterations of the vascular system occurring with time (Song *et al.*, 2004).

6) Naturally occurring models

Many mice display spontaneous phenotypes of retinal degeneration in the photoreceptor layer, and they were named numerically in the order that they were identified- rd1, rd2, rd10, etc. (Chang *et al.*, 2002). The rd1 mouse (*Pde6b*^{rd1}, also known as the rd mouse) was described in 1924 by C. Keller as “leading to absence of the visual cells (rods), the external nuclear layer, and the external molecular layer” (Keeler, 1924). Subsequently, it was found that that the phenotype results from a spontaneous recessive mutation in the β -subunit of the rod-phosphodiesterase (PDE) gene *Pde6b*^{rd1} (Bowes *et al.*, 1990). The model is associated with massive death of rods in the first weeks of postnatal life, followed by the death of cones, thus mimicking an early onset severe retinal degeneration as in patients affected by retinitis pigmentosa, who can in some cases have a mutation in the homologue human gene (Farber, 1995). rd10 mice carry a different recessive mutation in the same rod-PDE gene, leading to a similar but slower degeneration profile with slower rod loss (between P20 and P25) and slower secondary cone degeneration (Chang *et al.*, 2002). The rd1 mouse was used in the lab of Jean Bennett to demonstrate the therapeutic potential of subretinal injection of a recombinant replication-defective adenovirus that contained the murine eDNA for wild-type β PDE, Ad.CMV β PDE (Bennett *et al.*, 1996).

Other naturally occurring mouse models of retinal degeneration include the rds (retinal degeneration slow) mouse, due to a mutation in the *Prph* gene (rd2). The retinal phenotype of *Prph2* *Rd2/Rd2* mouse consists of a complete failure to develop photoreceptor outer segments and apoptotic loss of photoreceptor cells. This model allowed for demonstration of successful reversal of the retinal degeneration by gene augmentation therapy using a recombinant adeno-associated virus (AAV) vector encoding a *Prph2* transgene, showing stable generation of normal outer segments (Ali *et al.*, 2000). The RD3 protein was reported to negatively modulate the activity of guanylate cyclase (Chen *et al.*, 2022). The rd5 or tubby mouse (tub) displays not only retinal degeneration but also maturity-onset obesity, insulin resistance, and hearing deficits (Noben-Trauth *et al.*, 1996). The rd6 phenotype is due to a mutation in the membrane-type frizzled related protein (MFRP), which is normally expressed in the retinal pigment epithelium and ciliary body (Fogerty & Besharse, 2011).

The retinal degeneration 7 (rd7) is related to a mutation in the transcription factor Nr2e3, the mutation of which results in the production of photoreceptors with a hybrid rod and cone cell type responsible for enhanced S-cone syndrome phenotype (Corbo & Cepko, 2005). The rd8 mutation in the *CrB1* gene is often discovered in different lines of C57BL/6N or embryonic stem cells such that it can generate confusing retinal phenotypes in transgenic animals and should be actively screened for (Mattapallil *et al.*, 2012). The rd9 mouse carries a base-pair duplication in the purine reach domain (ORF) of the retinitis pigmentosa GTPase regulator (*RPGR*) providing thereby an appropriate model of X-linked retinitis pigmentosa (Thompson *et al.*, 2012). The rd11 is caused by mutation in the lysophosphatidylcholine acyltransferase-1 (*LPCAT1*) gene coding for a phospholipid biosynthesis/remodeling enzyme (Friedman *et al.*, 2010). The rd12 mouse, which represent a model for Leber congenital amaurosis (Redmond & Hamel, 2000), was used to demonstrate efficacy of gene therapy when reintroducing the correct gene sequence of *RPE65* (Pang *et al.*, 2006). Similarly, the rd16 mouse, which represents a model for *CEP290*-elicited ciliogenesis defect, was used to assess a possible therapeutic intervention (Mookherjee *et al.*, 2018).

Apart from these mouse models, a very common animal model in many research laboratories is the Royal College of Surgeon rat (RCS rat), which shows an accumulation of debris below the retina. The retinal degeneration in this model is caused by a recessive mutation in the *Mertk* gene (D'Cruz *et al.*, 2000; Nandrot *et al.*, 2000), which is expressed in RPE cells, and plays an important role in phagocytosis of photoreceptor outer segments, as part of their natural turnover (Vollrath *et al.*, 2001). The failure of phagocytosis leads to accumulation of debris under the retina, leading to secondary degeneration of the photoreceptors. As such, it is often considered as a model of age-related macular degeneration, since photoreceptor loss follows upon primary dysfunction of the RPE. However, it is actually an inherited retinal disorder, and in humans, mutations in the *Mertk* gene cause an early and severe form of retinitis pigmentosa or Leber Congenital Amaurosis. Gene augmentation therapy was shown to attenuate the course of disease in the RCS rat (Vollrath *et al.*, 2001). Later, washout of the debris by subretinal surgery was also shown to prolong the survival of photoreceptors in this model (Lorach *et al.*, 2018).

Finally, the *DBA2/2J* mouse serves as a common model for glaucoma because pigment dispersion in the anterior chamber and trabecular meshwork induces a major increase in intraocular pressure. Despite the high variability of this model, it was used to demonstrate efficacy of different molecules for the prevention of glaucoma such as memantine, timolol or taurine (Schuettauf *et al.*, 2002; Froger *et al.*, 2012).

7) Electroporation for gene transfer

The Paris Vision Institute has been a pioneer in the preclinical and clinical development of gene therapy for a severe pathology, Leber's hereditary optic neuropathy (LHON) (Carelli *et al.*, 2023). To study the pathological background of this blinding disease, an animal model was created through the introduction of the human *ND4* gene harboring the *G11778A* mutation (responsible for 60% of LHON cases) to rat eyes by *in vivo* electroporation (Ellouze *et al.*, 2008). The treatment induced morphological and functional characteristics of human LHON with degeneration of retinal ganglion cells, a deleterious effect that was also confirmed in primary cell culture. Importantly, retinal ganglion cell loss was clearly associated with a decline in visual performance. Subsequent electroporation with wild-type *ND4* prevented both retinal ganglion cell loss and the impairment of visual function, providing proof-of-principle that optimized allotopic expression can be an effective treatment for LHON, thus opening the way to clinical studies on other devastating mitochondrial disorders. Following these discoveries, we have created the biotech company GenSight Biologics, which initiated the GS010 gene therapy clinical trial for *G11778A*-associated LHON (NCT02652780, NCT03406104). The study confirmed the clinical benefit of LUMEVOQ® (lenadogene nolparvovec) for retinal ganglion cell preservation and bilateral improvement in visual acuity after unilateral injection in patients with LHON (Newman *et al.*, 2021). Long-term follow-up demonstrated that the gene therapy is well tolerated in the short as well as long term (currently for a minimum of five years) (Vignal *et al.*, 2018; Vignal-Clermont *et al.*, 2021; Carelli *et al.*, 2023; Newman *et al.*, 2023).

8) Induced Genetic models

To increase the frequency of mutagenesis in mouse colonies, N-ethyl-N-nitrosourea-induced (ENU) mutagenesis was applied and then followed by screening for mouse models of diseases. This approach was applied with great success to generate animals with clear eye phenotypes including retinal degeneration (Thaung *et al.*, 2002). However, recent advances in molecular genetic techniques now allow to manipulate the genome with high precision and provide the ability to generate specific models of retinal diseases, especially models of rare diseases. These include gene knockouts but also knock in model in which specific mutations can be introduced into specific genes. The list of these transgenic animal models is not exhaustive as they have increased exponentially, and cannot be fully reviewed here. A major example is the P23H rat and mouse, which reproduce a highly prevalent human mutation in the rhodopsin gene (Machida *et al.*, 2000; Chrysostomou *et al.*, 2009; Kolomiets *et al.*, 2010; Orhan *et al.*, 2015). This animal model was used to assess different therapeutic strategies such as the effect of the rod-derived cone viability factor RdCVF on cone survival (Yang *et al.*, 2009). Similarly, the *Abca4-KO* mouse model has been largely utilized to understand the etiology of Stargardt disease or age-related macular degeneration (Weng *et al.*, 1999). For the large *ABCA4* gene which exceeds the loading capacity of AAV vectors, a lipid

nanoparticle-based approach has demonstrated effectiveness for in vivo delivery in *Abca4*^{-/-} mice (Sun *et al.*, 2020; Sun *et al.*, 2022). Development of therapies for Usher syndrome type 1 (USH1) -a major cause of combined inherited deafness-blindness in humans- has been hampered because mouse models only develop deafness but no retinal degeneration, as is the case in both harmonin (*Ush1c*^{-/-}) or sans (*Ush1g*^{-/-}) knock-out mice (Trouillet *et al.*, 2018). In fact, cone degeneration was observed only when transferring the transgene in an albino background (Trouillet *et al.*, 2018), thereby suggesting a role for light and oxidative stress in the degenerative process of Usher retinal disease. This result was consistent with a previous study showing vulnerability of photoreceptors in the shaker 1 mouse (*Ush1b* mutant) to moderate light exposure (Peng *et al.*, 2011).

The etiology of age-related macular degeneration is multifactorial and associated with various genetic and environmental factors. The need to develop effective treatments for AMD has led to the generation of multiple rodent models by expressing genetic mutations commonly associated with the disease (Pennesi *et al.*, 2012; Ratnapriya & Chew, 2013; Fletcher *et al.*, 2014; Veleri *et al.*, 2015). Although there is no model that fully recapitulates all of the features of human AMD (particularly in view of the fact that rodents and indeed most species except primates and certain types of birds do not possess a macular structure), these models have helped in the discovery of pathophysiological mechanisms underlying AMD, such as inflammation and immune dysregulation, chronic oxidative damage, and alteration in lipid and carbohydrate metabolism, among others (Calippe *et al.*, 2017; Beguier *et al.*, 2020). Polymorphisms in the gene for complement factor H (CFH) B, C2, C3, and C9 have been associated with either conferring protection or susceptibility to the development and progression of AMD. The *Cfh*^{-/-} mouse was used to study some aspects of the complement factor pathway in the pathogenesis of AMD, but one should bear in mind that the genetic variants associated with AMD do not lead to a downregulation of CFH. These mice also display systemic consumption of C3, deposition of C3a in the glomerular basement membrane and glomerulonephritis, contrary to the increase of C3 and C3a observed in AMD. In the retina, they develop mild loss of photoreceptors, reduced rod function and increased deposition of complement in the photoreceptor layer (Coffey *et al.*, 2007). Decreased visual acuity and reduction in rod-driven ERG a- and b-wave responses were found at two years of age, together with thinning of the Bruch's membrane (Coffey *et al.*, 2007), that is not typical of AMD. Transgenic *CFH* Y402H mice (*Cfh*^{-/-} mice expressing the human AMD-related polymorphism CFH 402H under control of the human ApoE promoter) show a large number of drusen-like deposits at age of 1 year, increased number of microglial and macrophages in the subretinal space, thickening of Bruch's membrane and basement membrane deposition of C3d as compared to wildtype mice (Ufret-Vincenty *et al.*, 2010). However, they did not show photoreceptor atrophy even under high fat diet but they showed clear differences

with mice expressing the “wildtype” CFH 402Y protein (Landowski *et al.*, 2019). Transgenic mice overexpressing C3 show several features of AMD such as proliferation and migration of endothelial cells within the retina, disruption of the RPE with migration of pigmented cells into the retina, complement deposition and atrophy of the photoreceptor outer segments. However, the C3-overexpressing animals demonstrate increased incidence of retinal detachments that is not consistent with AMD (reviewed in (Pennesi *et al.*, 2012)). These *cfh* mouse models of AMD developed by Bowes Rickman and collaborators have enabled the unveiling of novel mechanisms contributing to AMD pathophysiology, including correlation between CFH levels and retinal integrity (Ding *et al.*, 2015) and a link between the complement system and lipid pathways (Ding *et al.*, 2015; Toomey *et al.*, 2015; Landowski *et al.*, 2019; Landowski & Bowes Rickman, 2022). Importantly, they serve as tools for validation of potential therapeutic targets in AMD (for review (Kelly *et al.*, 2020; Landowski & Bowes Rickman, 2022)).

Our research in the field of AMD showed that under physiological conditions, the subretinal space is immunosuppressive and devoid of mononuclear phagocytes, a family of cells that includes monocytes and infiltrating and resident macrophages (reviewed in (Guillonneau *et al.*, 2017)). A common feature of early and advanced dry and neovascular forms of AMD is the activation of macrophages in the inner retina and the chronic accumulation of subretinal mononuclear phagocytes. We showed that the homeostatic elimination of mononuclear phagocytes that infiltrate the photoreceptor cell layer depends on Thrombospondin 1 (TSP1)-mediated activation of their CD47 receptor. Accordingly, *Thbs1*^{-/-} and *Cd47*^{-/-}-mice develop age-related subretinal mononuclear phagocyte accumulation similar to AMD patients. Importantly, we demonstrated that both major genetic AMD risk factors, the CFH H402 variant and 10q26 risk-haplotype, inhibit TSP1-mediated CD47 activation and MP elimination, promoting chronic pathogenic inflammation (Calippe *et al.*, 2017; Beguier *et al.*, 2020). Our findings described a comprehensive mechanism of how these two prominent AMD-risk haplotypes, the variant of the complement factor H and a minor haplotype of the chromosome 10q26, account for most of the genetic risk for AMD and promotes AMD pathogenesis. This work provides a rationale for therapeutic restoration of immune privilege in the subretinal space to induce the resolution of subretinal chronic inflammation that promotes photoreceptor destruction and blindness in AMD. In agreement with these results, several mouse models targeting the inflammatory mediators and Apoelipoproteins have been generated and reported to partially replicate AMD features, including subretinal drusen-like accumulations, thickening of Bruch's membrane, and an increase in autofluorescence and lipofuscin granules and photoreceptor degeneration (Combadiere *et al.*, 2007). However, the Rd8 mutation of the *Crb1* gene present in many mouse strains appears sufficient to generate most of these ocular phenotypes

(Mattapallil *et al.*, 2012). Unless explicitly excluding the rd8 mutation, it is therefore impossible to conclude which genetic alteration truly provokes AMD-like features. Alternatively, different models of oxidative damage leading to inflammation have been developed based on the particular susceptibility of the retina to oxidative injury associated with its high metabolic demand, high concentration of oxidizable polyunsaturated fatty acids and presence of photosensitive molecules (such as rhodopsin or lipofuscin). Among them, ceruloplasmin/hephaestin^{-/-} mice, *Sod1*^{-/-} mice, *Sod2*^{-/-} and *Sod2* knockdown mice and OXYS rat are commonly used models allowing to evaluate the role of oxidative stress in the pathogenesis of AMD (Fletcher *et al.*, 2014). Exposure to cigarette smoke, hydroquinone, high fat diet and blue light also produced many of the AMD-like features (see light damage model above).

Myopia can also have a genetic origin (Tedja *et al.*, 2018) such that many mutated mouse models were found to develop or to have increased susceptibility to develop myopia under application of different optical devices (Zeitz *et al.*, 2023). For instance, mutations causing complete congenital stationary night blindness (cCSNB) in patients and animal models were often found to induce myopia (Zeitz *et al.*, 2023). For instance, a substantial increase of the myopic shift was reported in *Gpr179*^{-/-} mice compared to wild-type littermates following a 3-week-long lens-induced myopia protocol (Wilmet *et al.*, 2022). The adult *Gpr179*^{-/-} mice have a significant decrease in both retinal dopamine and 3,4-dihydroxyphenylacetic acid, in agreement with previous observations that an alteration of the dopaminergic system correlated with an increased susceptibility to lens-induced myopia (Schwahn *et al.*, 2000; Feldkaemper & Schaeffel, 2013; Landis *et al.*, 2020).

9) Cre/Lox gene targeting

The Cre/*lox* system is a genetic tool permitting efficient and accurate control over the location and timing of gene expression and generation of mouse strains in which a transgene is either inducible or expressed only in certain tissues (Sauer & Henderson, 1990; Lakso *et al.*, 1992). A pioneering work of Botond Roska's group described ~100 mouse lines with either defined strata or, more specifically, retinal cell types marked with GFP allowing stratification-based screening for characterizing neuronal circuitry (Siegert *et al.*, 2009). This strategy not only allowed to sort specific cell types for genetic analysis, but also to optically target cells for recording and functional characterization. For the anatomical analysis of the circuit, the approach can be combined with the Brainbow technology (Livet *et al.*, 2007). This transgenic system allows for stochastic expression of multiple fluorescent protein genes through Cre/*lox* recombination (Livet *et al.*, 2007; Dumas *et al.*, 2015; Dumas *et al.*, 2022).

This strategy to selectively ablate gene expression in a specific cell type was applied to demonstrate expression of the nucleoredoxin-like-1 (*Nxn1*) gene in cone photoreceptors (Mei *et al.*, 2016). Indeed, when using a transgenic line expressing Cre recombinase under the control of a cone opsin promoter, cones of these mice were dysfunctional and degenerated by 8 months of age. Similarly, silencing the expression of RdCVFL in cone-enriched culture resulted in reduced cell viability. These experiments indicated that the *Nxn1* gene protects cones by two distinct pathways, by RdCVFL produced by cones themselves and by RdCVF released from rods (Leveillard *et al.*, 2004; Ait-Ali *et al.*, 2015). These results have provided the rationale for a future therapy combining both RdCVF and RdCVFL expression by gene therapy.

Concluding remarks

Demonstrating “proof of principle” in one or more animal models opens the road to moving a candidate therapy toward human clinical trials. Considering that today the potential to translate novel therapies for retinal diseases to the clinic increases, there is a strong need of relevant animal models that can provide information about the natural history of the disease and its pathogenic pathways and genetic background. Among mammals, large animal models, particularly non-human primates that have a macula, can most faithfully reproduce the human conditions for assessing a treatment efficacy and safety (Picaud *et al.*, 2019). Furthermore, the cell sizes, the cell types, the eye sizes, the eye architectures, the immune responses are all very different between species and especially between rodents and primates. Gene isoforms and redundancy may also easily differ in the different species. All these differences justify the need to assess the safety and efficiency of therapeutic strategies in primates prior to the clinical trials for increasing their final success rate as we intended for retinal prostheses (Prevot *et al.*, 2020), optogenetic therapy (Gauvain *et al.*, 2021; Sahel *et al.*, 2021), or cell therapy (Ben M'Barek *et al.*, 2020). Developing an AMD model in non-human primates will thus become critical for the development of an efficient therapeutic treatment for dry AMD because no one of the multiple rodent models fully recapitulates the features of the human disease. However, non-human primates are difficult to manage and manipulate genetically, and are expensive to maintain.

The limited number of spontaneously-arising large animal models of retinal degeneration and ethical concerns are additional points to consider. This is why rodents, particularly mice, are most widely used for modeling of human disease and have helped to reveal the roles of oxidative damage, inflammation, immune dysregulation, and lipid metabolism in the development of AMD. The adaptation of human clinical eye examination technologies for assessment of retinal function and structure also in rodent eyes helped to enhance translational investigations of novel therapeutic

approaches in relevant models. Today, the principle of the 3Rs—replacement (avoid/replace the use of animals), reduction (minimize the number of animals used), and refinement (minimize animal suffering and improve welfare)—is widely considered and wherever possible at early stage of translational research, a significant reduction in animal studies is achieved by alternative cellular and organotypic methods *in vitro*, *in vivo*, and *in silico* mathematical models for disease modeling and outcome prediction.

Acknowledgments

This work was supported by: the French state funds managed by the Agence Nationale de la Recherche (ANR) within Programme Investissements d'Avenir: Laboratoire d'Excellence (LABEX) LIFESENSES (ANR-10-LABX-0065) and Institut Hospitalo-Universitaire FOReSIGHT (ANR-18-IAHU-0001), by Optic 2000, the City of Paris and Région Ile de France, by NIH CORE Grant P30 EY08098 to the Department of Ophthalmology, the Eye and Ear Foundation of Pittsburgh, and from an unrestricted grant from Research to Prevent Blindness, New York, NY.

References

- Ait-Ali, N., Fridlich, R., Millet-Puel, G., Clerin, E., Delalande, F., Jaillard, C., Blond, F., Perrocheau, L., Reichman, S., Byrne, L.C., Olivier-Bandini, A., Bellalou, J., Moyse, E., Bouillaud, F., Nicol, X., Dalkara, D., van Dorsselaer, A., Sahel, J.A. & Leveillard, T. (2015) Rod-derived cone viability factor promotes cone survival by stimulating aerobic glycolysis. *Cell*, **161**, 817-832.
- Ali, R.R., Sarra, G.M., Stephens, C., Alwis, M.D., Bainbridge, J.W., Munro, P.M., Fauser, S., Reichel, M.B., Kinnon, C., Hunt, D.M., Bhattacharya, S.S. & Thrasher, A.J. (2000) Restoration of photoreceptor ultrastructure and function in retinal degeneration slow mice by gene therapy. *Nat Genet*, **25**, 306-310.
- Arnault, E., Barrau, C., Nanteau, C., Gondouin, P., Bigot, K., Vienot, F., Gutman, E., Fontaine, V., Villette, T., Cohen-Tannoudji, D., Sahel, J.A. & Picaud, S. (2013) Phototoxic action spectrum on a retinal pigment epithelium model of age-related macular degeneration exposed to sunlight normalized conditions. *PLoS One*, **8**, e71398.
- Balse, E., Tessier, L.H., Fuchs, C., Forster, V., Sahel, J.A. & Picaud, S. (2005) Purification of mammalian cone photoreceptors by lectin panning and the enhancement of their survival in glia-conditioned medium. *Invest Ophthalmol Vis Sci*, **46**, 367-374.
- Barber, A.J., Lieth, E., Khin, S.A., Antonetti, D.A., Buchanan, A.G. & Gardner, T.W. (1998) Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. *J Clin Invest*, **102**, 783-791.
- Barres, B.A., Silverstein, B.E., Corey, D.P. & Chun, L.L. (1988) Immunological, morphological, and electrophysiological variation among retinal ganglion cells purified by panning. *Neuron*, **1**, 791-803.
- Bassetto, M., Sen, M., Poulhes, F., Arango-Gonzalez, B., Bonvin, E., Sapet, C., Ueffing, M. & Zelphati, O. (2021) New Method for Efficient siRNA Delivery in Retina Explants: Reverse Magnetofection. *Bioconjug Chem*, **32**, 1078-1093.

- Beguier, F., Housset, M., Roubéix, C., Augustin, S., Zagar, Y., Nous, C., Mathis, T., Eandi, C., Benchaboune, M., Drame-Maigne, A., Carpentier, W., Chardonnet, S., Touhami, S., Blot, G., Conart, J.B., Charles-Messance, H., Potey, A., Girmens, J.F., Paques, M., Blond, F., Leveillard, T., Koertvely, E., Roger, J.E., Sahel, J.A., Sapiéha, P., Delarasse, C., Guillonéau, X. & Sennlaub, F. (2020) The 10q26 Risk Haplotype of Age-Related Macular Degeneration Aggravates Subretinal Inflammation by Impairing Monocyte Elimination. *Immunity*, **53**, 429-441 e428.
- Ben M'Barek, K., Bertin, S., Brazhnikova, E., Jaillard, C., Habeler, W., Plancheron, A., Fovet, C.M., Demilly, J., Jarraya, M., Bejanariu, A., Sahel, J.A., Peschanski, M., Goureau, O. & Monville, C. (2020) Clinical-grade production and safe delivery of human ESC derived RPE sheets in primates and rodents. *Biomaterials*, **230**, 119603.
- Bennett, J., Tanabe, T., Sun, D., Zeng, Y., Kjeldbye, H., Gouras, P. & Maguire, A.M. (1996) Photoreceptor cell rescue in retinal degeneration (rd) mice by in vivo gene therapy. *Nat Med*, **2**, 649-654.
- Blindness, G.B.D., Vision Impairment, C. & Vision Loss Expert Group of the Global Burden of Disease, S. (2021) Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*, **9**, e144-e160.
- Bourne, R.R.A., Flaxman, S.R., Braithwaite, T., Cicinelli, M.V., Das, A., Jonas, J.B., Keeffe, J., Kempen, J.H., Leasher, J., Limburg, H., Naidoo, K., Pesudovs, K., Resnikoff, S., Silvester, A., Stevens, G.A., Tahhan, N., Wong, T.Y., Taylor, H.R. & Vision Loss Expert, G. (2017) Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Glob Health*, **5**, e888-e897.
- Bowes, C., Li, T., Danciger, M., Baxter, L.C., Applebury, M.L. & Farber, D.B. (1990) Retinal degeneration in the rd mouse is caused by a defect in the beta subunit of rod cGMP-phosphodiesterase. *Nature*, **347**, 677-680.
- Buskamp, V., Duebel, J., Balya, D., Fradot, M., Viney, T.J., Siegert, S., Groner, A.C., Cabuy, E., Forster, V., Seeliger, M., Biel, M., Humphries, P., Paques, M., Mohand-Said, S., Trono, D., Deisseroth, K., Sahel, J.A., Picaud, S. & Roska, B. (2010) Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. *Science*, **329**, 413-417.
- Butler, W.H., Ford, G.P. & Newberne, J.W. (1987) A study of the effects of vigabatrin on the central nervous system and retina of Sprague Dawley and Lister-Hooded rats. *Toxicol Pathol*, **15**, 143-148.
- Caffe, A.R., Soderpalm, A. & van Veen, T. (1993) Photoreceptor-specific protein expression of mouse retina in organ culture and retardation of rd degeneration in vitro by a combination of basic fibroblast and nerve growth factors. *Curr Eye Res*, **12**, 719-726.

- Calippe, B., Augustin, S., Beguier, F., Charles-Messance, H., Poupel, L., Conart, J.B., Hu, S.J., Lavalette, S., Fauvet, A., Rayes, J., Levy, O., Raoul, W., Fitting, C., Deneffe, T., Pickering, M.C., Harris, C., Jorieux, S., Sullivan, P.M., Sahel, J.A., Karoyan, P., Sapieha, P., Guillonneau, X., Gautier, E.L. & Sennlaub, F. (2017) Complement Factor H Inhibits CD47-Mediated Resolution of Inflammation. *Immunity*, **46**, 261-272.
- Camelo, S., Raoul, W., Lavalette, S., Calippe, B., Cristofaro, B., Levy, O., Houssier, M., Sulpice, E., Jonet, L., Klein, C., Deevre, E., Thuret, G., Duarte, A., Eichmann, A., Leconte, L., Guillonneau, X. & Sennlaub, F. (2012) Delta-like 4 inhibits choroidal neovascularization despite opposing effects on vascular endothelium and macrophages. *Angiogenesis*, **15**, 609-622.
- Carelli, V., Newman, N.J., Yu-Wai-Man, P., Biousse, V., Moster, M.L., Subramanian, P.S., Vignal-Clermont, C., Wang, A.G., Donahue, S.P., Leroy, B.P., Sergott, R.C., Klopstock, T., Sadun, A.A., Rebolleda Fernandez, G., Chwalisz, B.K., Banik, R., Girmens, J.F., La Morgia, C., DeBusk, A.A., Jurkute, N., Priglinger, C., Karanjia, R., Josse, C., Salzmann, J., Montestruc, F., Roux, M., Taiel, M., Sahel, J.A. & the, L.S.G. (2023) Indirect Comparison of Lenadogene Nolparvovec Gene Therapy Versus Natural History in Patients with Leber Hereditary Optic Neuropathy Carrying the m.11778G>A MT-ND4 Mutation. *Ophthalmol Ther*, **12**, 401-429.
- Chang, B., Hawes, N.L., Hurd, R.E., Davisson, M.T., Nusinowitz, S. & Heckenlively, J.R. (2002) Retinal degeneration mutants in the mouse. *Vision Res*, **42**, 517-525.
- Chen, Y., Brauer, A.U. & Koch, K.W. (2022) Retinal degeneration protein 3 controls membrane guanylate cyclase activities in brain tissue. *Front Mol Neurosci*, **15**, 1076430.
- Chrysostomou, V., Stone, J. & Valter, K. (2009) Life history of cones in the rhodopsin-mutant P23H-3 rat: evidence of long-term survival. *Invest Ophthalmol Vis Sci*, **50**, 2407-2416.
- Clerin, E., Wicker, N., Mohand-Said, S., Poch, O., Sahel, J.A. & Leveillard, T. (2011) -conome: an automated tissue counting platform of cone photoreceptors for rodent models of retinitis pigmentosa. *BMC Ophthalmol*, **11**, 38.
- Coffey, P.J., Gias, C., McDermott, C.J., Lundh, P., Pickering, M.C., Sethi, C., Bird, A., Fitzke, F.W., Maass, A., Chen, L.L., Holder, G.E., Luthert, P.J., Salt, T.E., Moss, S.E. & Greenwood, J. (2007) Complement factor H deficiency in aged mice causes retinal abnormalities and visual dysfunction. *Proc Natl Acad Sci U S A*, **104**, 16651-16656.
- Combadiere, C., Feumi, C., Raoul, W., Keller, N., Rodero, M., Pezard, A., Lavalette, S., Houssier, M., Jonet, L., Picard, E., Debre, P., Sirinyan, M., Deterre, P., Ferroukhi, T., Cohen, S.Y., Chauvaud, D., Jeanny, J.C., Chemtob, S., Behar-Cohen, F. & Sennlaub, F. (2007) CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. *J Clin Invest*, **117**, 2920-2928.

- Cone, F.E., Gelman, S.E., Son, J.L., Pease, M.E. & Quigley, H.A. (2010) Differential susceptibility to experimental glaucoma among 3 mouse strains using bead and viscoelastic injection. *Exp Eye Res*, **91**, 415-424.
- Corbo, J.C. & Cepko, C.L. (2005) A hybrid photoreceptor expressing both rod and cone genes in a mouse model of enhanced S-cone syndrome. *PLoS Genet*, **1**, e11.
- D'Cruz, P.M., Yasumura, D., Weir, J., Matthes, M.T., Abderrahim, H., LaVail, M.M. & Vollrath, D. (2000) Mutation of the receptor tyrosine kinase gene *Mertk* in the retinal dystrophic RCS rat. *Hum Mol Genet*, **9**, 645-651.
- Danesh-Meyer, H.V. & Levin, L.A. (2009) Neuroprotection: extrapolating from neurologic diseases to the eye. *Am J Ophthalmol*, **148**, 186-191 e182.
- Ding, J.D., Kelly, U., Landowski, M., Toomey, C.B., Groelle, M., Miller, C., Smith, S.G., Klingeborn, M., Singhapricha, T., Jiang, H., Frank, M.M. & Bowes Rickman, C. (2015) Expression of human complement factor H prevents age-related macular degeneration-like retina damage and kidney abnormalities in aged *Cfh* knockout mice. *Am J Pathol*, **185**, 29-42.
- Duboc, A., Hanoteau, N., Simonutti, M., Rudolf, G., Nehlig, A., Sahel, J.A. & Picaud, S. (2004) Vigabatrin, the GABA-transaminase inhibitor, damages cone photoreceptors in rats. *Ann Neurol*, **55**, 695-705.
- Dumas, L., Clavreul, S., Michon, F. & Loulier, K. (2022) Multicolor strategies for investigating clonal expansion and tissue plasticity. *Cell Mol Life Sci*, **79**, 141.
- Dumas, L., Heitz-Marchaland, C., Fouquet, S., Suter, U., Livet, J., Moreau-Fauvarque, C. & Chedotal, A. (2015) Multicolor analysis of oligodendrocyte morphology, interactions, and development with Brainbow. *Glia*, **63**, 699-717.
- Ellouze, S., Augustin, S., Bouaita, A., Bonnet, C., Simonutti, M., Forster, V., Picaud, S., Sahel, J.A. & Corral-Debrinski, M. (2008) Optimized allotopic expression of the human mitochondrial ND4 prevents blindness in a rat model of mitochondrial dysfunction. *Am J Hum Genet*, **83**, 373-387.
- Farber, D.B. (1995) From mice to men: the cyclic GMP phosphodiesterase gene in vision and disease. The Proctor Lecture. *Invest Ophthalmol Vis Sci*, **36**, 263-275.
- Feldkaemper, M. & Schaeffel, F. (2013) An updated view on the role of dopamine in myopia. *Exp Eye Res*, **114**, 106-119.

- Fletcher, E.L., Jobling, A.I., Greferath, U., Mills, S.A., Waugh, M., Ho, T., de longh, R.U., Phipps, J.A. & Vessey, K.A. (2014) Studying age-related macular degeneration using animal models. *Optom Vis Sci*, **91**, 878-886.
- Fogerty, J. & Besharse, J.C. (2011) 174delG mutation in mouse MFRP causes photoreceptor degeneration and RPE atrophy. *Invest Ophthalmol Vis Sci*, **52**, 7256-7266.
- Fontaine, V., Fournie, M., Monteiro, E., Boumedine, T., Balducci, C., Guibout, L., Latil, M., Sahel, J.A., Veillet, S., Dilda, P.J., Lafont, R. & Camelo, S. (2021) A2E-induced inflammation and angiogenesis in RPE cells in vitro are modulated by PPAR-alpha, -beta/delta, -gamma, and RXR antagonists and by norbixin. *Aging (Albany NY)*, **13**, 22040-22058.
- Fontaine, V., Kinkl, N., Sahel, J., Dreyfus, H. & Hicks, D. (1998) Survival of purified rat photoreceptors in vitro is stimulated directly by fibroblast growth factor-2. *J Neurosci*, **18**, 9662-9672.
- Fontaine, V., Monteiro, E., Brazhnikova, E., Lesage, L., Balducci, C., Guibout, L., Feraille, L., Elena, P.P., Sahel, J.A., Veillet, S. & Lafont, R. (2016) Norbixin Protects Retinal Pigmented Epithelium Cells and Photoreceptors against A2E-Mediated Phototoxicity In Vitro and In Vivo. *PLoS One*, **11**, e0167793.
- Fradot, M., Busskamp, V., Forster, V., Cronin, T., Leveillard, T., Bennett, J., Sahel, J.A., Roska, B. & Picaud, S. (2011) Gene therapy in ophthalmology: validation on cultured retinal cells and explants from postmortem human eyes. *Hum Gene Ther*, **22**, 587-593.
- Friedman, J.S., Chang, B., Krauth, D.S., Lopez, I., Waseem, N.H., Hurd, R.E., Feathers, K.L., Branham, K.E., Shaw, M., Thomas, G.E., Brooks, M.J., Liu, C., Bakeri, H.A., Campos, M.M., Maubaret, C., Webster, A.R., Rodriguez, I.R., Thompson, D.A., Bhattacharya, S.S., Koenekoop, R.K., Heckenlively, J.R. & Swaroop, A. (2010) Loss of lysophosphatidylcholine acyltransferase 1 leads to photoreceptor degeneration in rd11 mice. *Proc Natl Acad Sci U S A*, **107**, 15523-15528.
- Froger, N., Cadetti, L., Lorach, H., Martins, J., Bemelmans, A.P., Dubus, E., Degardin, J., Pain, D., Forster, V., Chicaud, L., Ivkovic, I., Simonutti, M., Fouquet, S., Jammoul, F., Leveillard, T., Benosman, R., Sahel, J.A. & Picaud, S. (2012) Taurine provides neuroprotection against retinal ganglion cell degeneration. *PLoS One*, **7**, e42017.
- Froger, N., Jammoul, F., Gaucher, D., Cadetti, L., Lorach, H., Degardin, J., Pain, D., Dubus, E., Forster, V., Ivkovic, I., Simonutti, M., Sahel, J.A. & Picaud, S. (2013) Taurine is a crucial factor to preserve retinal ganglion cell survival. *Adv Exp Med Biol*, **775**, 69-83.
- Froger, N., Matonti, F., Roubex, C., Forster, V., Ivkovic, I., Brunel, N., Baudouin, C., Sahel, J.A. & Picaud, S. (2020) VEGF is an autocrine/paracrine neuroprotective factor for injured retinal ganglion neurons. *Sci Rep*, **10**, 12409.

- Fuchs, C., Forster, V., Balse, E., Sahel, J.A., Picaud, S. & Tessier, L.H. (2005) Retinal-cell-conditioned medium prevents TNF-alpha-induced apoptosis of purified ganglion cells. *Invest Ophthalmol Vis Sci*, **46**, 2983-2991.
- Fulton, A.B., Hansen, R.M., Moskowitz, A. & Akula, J.D. (2009) The neurovascular retina in retinopathy of prematurity. *Prog Retin Eye Res*, **28**, 452-482.
- Garcia-Ayuso, D., Di Pierdomenico, J., Valiente-Soriano, F.J., Martinez-Vacas, A., Agudo-Barriuso, M., Vidal-Sanz, M., Picaud, S. & Villegas-Perez, M.P. (2019) beta-alanine supplementation induces taurine depletion and causes alterations of the retinal nerve fiber layer and axonal transport by retinal ganglion cells. *Exp Eye Res*, **188**, 107781.
- Gaucher, D., Arnault, E., Husson, Z., Froger, N., Dubus, E., Gondouin, P., Dherbecourt, D., Degardin, J., Simonutti, M., Fouquet, S., Benahmed, M.A., Elbayed, K., Namer, I.J., Massin, P., Sahel, J.A. & Picaud, S. (2012) Taurine deficiency damages retinal neurones: cone photoreceptors and retinal ganglion cells. *Amino Acids*, **43**, 1979-1993.
- Gaucher, D., Chiappore, J.A., Paques, M., Simonutti, M., Boitard, C., Sahel, J.A., Massin, P. & Picaud, S. (2007) Microglial changes occur without neural cell death in diabetic retinopathy. *Vision Res*, **47**, 612-623.
- Gauvain, G., Akolkar, H., Chaffiol, A., Arcizet, F., Khoei, M.A., Desrosiers, M., Jaillard, C., Caplette, R., Marre, O., Bertin, S., Fovet, C.M., Demilly, J., Forster, V., Brazhnikova, E., Hantraye, P., Pouget, P., Douar, A., Pruneau, D., Chavas, J., Sahel, J.A., Dalkara, D., Duebel, J., Benosman, R. & Picaud, S. (2021) Optogenetic therapy: high spatiotemporal resolution and pattern discrimination compatible with vision restoration in non-human primates. *Commun Biol*, **4**, 125.
- Grossniklaus, H.E., Kang, S.J. & Berglin, L. (2010) Animal models of choroidal and retinal neovascularization. *Prog Retin Eye Res*, **29**, 500-519.
- Guidry, C. (1996) Isolation and characterization of porcine Muller cells. Myofibroblastic dedifferentiation in culture. *Invest Ophthalmol Vis Sci*, **37**, 740-752.
- Guillonneau, X., Eandi, C.M., Paques, M., Sahel, J.A., Sapieha, P. & Sennlaub, F. (2017) On phagocytes and macular degeneration. *Prog Retin Eye Res*, **61**, 98-128.
- Heidinger, V., Dreyfus, H., Sahel, J., Christen, Y. & Hicks, D. (1998) Excitotoxic damage of retinal glial cells depends upon normal neuron-glial interactions. *Glia*, **23**, 146-155.
- Hicks, D. & Courtois, Y. (1990) The growth and behaviour of rat retinal Muller cells in vitro. 1. An improved method for isolation and culture. *Exp Eye Res*, **51**, 119-129.

- Hicks, D. & Courtois, Y. (1992) Fibroblast growth factor stimulates photoreceptor differentiation in vitro. *J Neurosci*, **12**, 2022-2033.
- Jammoul, F., Degardin, J., Pain, D., Gondouin, P., Simonutti, M., Dubus, E., Caplette, R., Fouquet, S., Craft, C.M., Sahel, J.A. & Picaud, S. (2010) Taurine deficiency damages photoreceptors and retinal ganglion cells in vigabatrin-treated neonatal rats. *Mol Cell Neurosci*, **43**, 414-421.
- Jammoul, F., Wang, Q., Nabbout, R., Coriat, C., Duboc, A., Simonutti, M., Dubus, E., Craft, C.M., Ye, W., Collins, S.D., Dulac, O., Chiron, C., Sahel, J.A. & Picaud, S. (2009) Taurine deficiency is a cause of vigabatrin-induced retinal phototoxicity. *Ann Neurol*, **65**, 98-107.
- Jellali, A., Hamid, M., Abdel-Mouttalib, O., Rousseau, S., Romand, R., Auwerx, J., Sahel, J., Chambon, P. & Picaud, S. (2005) The optomotor response: a robust first-line visual screening method for mice. *Vision Res*, **45**, 1439-1446.
- Keeler, C.E. (1924) The Inheritance of a Retinal Abnormality in White Mice. *Proc Natl Acad Sci U S A*, **10**, 329-333.
- Kelly, U.L., Grigsby, D., Cady, M.A., Landowski, M., Skiba, N.P., Liu, J., Remaley, A.T., Klingeborn, M. & Bowes Rickman, C. (2020) High-density lipoproteins are a potential therapeutic target for age-related macular degeneration. *J Biol Chem*, **295**, 13601-13616.
- Kolomiets, B., Dubus, E., Simonutti, M., Rosolen, S., Sahel, J.A. & Picaud, S. (2010) Late histological and functional changes in the P23H rat retina after photoreceptor loss. *Neurobiol Dis*, **38**, 47-58.
- Lakso, M., Sauer, B., Mosinger, B., Jr., Lee, E.J., Manning, R.W., Yu, S.H., Mulder, K.L. & Westphal, H. (1992) Targeted oncogene activation by site-specific recombination in transgenic mice. *Proc Natl Acad Sci U S A*, **89**, 6232-6236.
- Landis, E.G., Chrenek, M.A., Chakraborty, R., Strickland, R., Bergen, M., Yang, V., Iuvone, P.M. & Pardue, M.T. (2020) Increased endogenous dopamine prevents myopia in mice. *Exp Eye Res*, **193**, 107956.
- Landowski, M. & Bowes Rickman, C. (2022) Targeting Lipid Metabolism for the Treatment of Age-Related Macular Degeneration: Insights from Preclinical Mouse Models. *J Ocul Pharmacol Ther*, **38**, 3-32.
- Landowski, M., Kelly, U., Klingeborn, M., Groelle, M., Ding, J.D., Grigsby, D. & Bowes Rickman, C. (2019) Human complement factor H Y402H polymorphism causes an age-related macular degeneration phenotype and lipoprotein dysregulation in mice. *Proc Natl Acad Sci U S A*, **116**, 3703-3711.

- Lavalette, S., Raoul, W., Houssier, M., Camelo, S., Levy, O., Calippe, B., Jonet, L., Behar-Cohen, F., Chemtob, S., Guillonneau, X., Combadiere, C. & Sennlaub, F. (2011) Interleukin-1beta inhibition prevents choroidal neovascularization and does not exacerbate photoreceptor degeneration. *The American journal of pathology*, **178**, 2416-2423.
- Leveillard, T., Mohand-Said, S., Lorentz, O., Hicks, D., Fintz, A.C., Clerin, E., Simonutti, M., Forster, V., Cavusoglu, N., Chalmel, F., Dolle, P., Poch, O., Lambrou, G. & Sahel, J.A. (2004) Identification and characterization of rod-derived cone viability factor. *Nat Genet*, **36**, 755-759.
- Levy, O., Calippe, B., Lavalette, S., Hu, S.J., Raoul, W., Dominguez, E., Housset, M., Paques, M., Sahel, J.A., Bemelmans, A.P., Combadiere, C., Guillonneau, X. & Sennlaub, F. (2015) Apolipoprotein E promotes subretinal mononuclear phagocyte survival and chronic inflammation in age-related macular degeneration. *EMBO molecular medicine*, **7**, 211-226.
- Lipton, S.A. (2003) Possible role for memantine in protecting retinal ganglion cells from glaucomatous damage. *Surv Ophthalmol*, **48 Suppl 1**, S38-46.
- Liu, K., Akula, J.D., Falk, C., Hansen, R.M. & Fulton, A.B. (2006) The retinal vasculature and function of the neural retina in a rat model of retinopathy of prematurity. *Invest Ophthalmol Vis Sci*, **47**, 2639-2647.
- Livet, J., Weissman, T.A., Kang, H., Draft, R.W., Lu, J., Bennis, R.A., Sanes, J.R. & Lichtman, J.W. (2007) Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. *Nature*, **450**, 56-62.
- Lorach, H., Kang, S., Dalal, R., Bhuckory, M.B., Quan, Y. & Palanker, D. (2018) Long-term Rescue of Photoreceptors in a Rodent Model of Retinitis Pigmentosa Associated with MERTK Mutation. *Sci Rep*, **8**, 11312.
- Ma, J., Sun, Y., Lopez, F.J., Adamson, P., Kurali, E. & Lashkari, K. (2016) Blockage of PI3K/mTOR Pathways Inhibits Laser-Induced Choroidal Neovascularization and Improves Outcomes Relative to VEGF-A Suppression Alone. *Invest Ophthalmol Vis Sci*, **57**, 3138-3144.
- Machida, S., Kondo, M., Jamison, J.A., Khan, N.W., Kononen, L.T., Sugawara, T., Bush, R.A. & Sieving, P.A. (2000) P23H rhodopsin transgenic rat: correlation of retinal function with histopathology. *Invest Ophthalmol Vis Sci*, **41**, 3200-3209.
- Maeda, A., Maeda, T., Golczak, M., Chou, S., Desai, A., Hoppel, C.L., Matsuyama, S. & Palczewski, K. (2009) Involvement of all-trans-retinal in acute light-induced retinopathy of mice. *J Biol Chem*, **284**, 15173-15183.
- Maeda, A., Maeda, T., Golczak, M. & Palczewski, K. (2008) Retinopathy in mice induced by disrupted all-trans-retinal clearance. *J Biol Chem*, **283**, 26684-26693.

- Malecaze, F., Mascarelli, F., Bugra, K., Fuhrmann, G., Courtois, Y. & Hicks, D. (1993) Fibroblast growth factor receptor deficiency in dystrophic retinal pigmented epithelium. *J Cell Physiol*, **154**, 631-642.
- Mao, W., Liu, Y., Wordinger, R.J. & Clark, A.F. (2013) A magnetic bead-based method for mouse trabecular meshwork cell isolation. *Invest Ophthalmol Vis Sci*, **54**, 3600-3606.
- Marie, M., Bigot, K., Angebault, C., Barrau, C., Gondouin, P., Pagan, D., Fouquet, S., Villette, T., Sahel, J.A., Lenaers, G. & Picaud, S. (2018) Light action spectrum on oxidative stress and mitochondrial damage in A2E-loaded retinal pigment epithelium cells. *Cell Death Dis*, **9**, 287.
- Marie, M., Forster, V., Fouquet, S., Berto, P., Barrau, C., Ehrismann, C., Sahel, J.A., Tessier, G. & Picaud, S. (2020) Phototoxic damage to cone photoreceptors can be independent of the visual pigment: the porphyrin hypothesis. *Cell Death Dis*, **11**, 711.
- Martin, P.M., Roon, P., Van Ells, T.K., Ganapathy, V. & Smith, S.B. (2004) Death of retinal neurons in streptozotocin-induced diabetic mice. *Invest Ophthalmol Vis Sci*, **45**, 3330-3336.
- Mattapallil, M.J., Wawrousek, E.F., Chan, C.C., Zhao, H., Roychoudhury, J., Ferguson, T.A. & Caspi, R.R. (2012) The Rd8 mutation of the Crb1 gene is present in vendor lines of C57BL/6N mice and embryonic stem cells, and confounds ocular induced mutant phenotypes. *Invest Ophthalmol Vis Sci*, **53**, 2921-2927.
- Mei, X., Chaffiol, A., Kole, C., Yang, Y., Millet-Puel, G., Clerin, E., Ait-Ali, N., Bennett, J., Dalkara, D., Sahel, J.A., Duebel, J. & Leveillard, T. (2016) The Thioredoxin Encoded by the Rod-Derived Cone Viability Factor Gene Protects Cone Photoreceptors Against Oxidative Stress. *Antioxid Redox Signal*, **24**, 909-923.
- Meyer-Franke, A., Kaplan, M.R., Pfrieger, F.W. & Barres, B.A. (1995) Characterization of the signaling interactions that promote the survival and growth of developing retinal ganglion cells in culture. *Neuron*, **15**, 805-819.
- Mohand-Said, S., Weber, M., Hicks, D., Dreyfus, H. & Sahel, J.A. (1997) Intravitreal injection of ganglioside GM1 after ischemia reduces retinal damage in rats. *Stroke*, **28**, 617-621; discussion 622.
- Mookherjee, S., Chen, H.Y., Isgrig, K., Yu, W., Hiriyan, S., Levron, R., Li, T., Colosi, P., Chien, W., Swaroop, A. & Wu, Z. (2018) A CEP290 C-Terminal Domain Complements the Mutant CEP290 of Rd16 Mice In Trans and Rescues Retinal Degeneration. *Cell Rep*, **25**, 611-623 e616.
- Nandrot, E., Dufour, E.M., Provost, A.C., Pequignot, M.O., Bonnel, S., Gogat, K., Marchant, D., Rouillac, C., Sepulchre de Conde, B., Bihoreau, M.T., Shaver, C., Dufier, J.L., Marsac, C., Lathrop, M., Menasche, M. & Abitbol, M.M. (2000) Homozygous deletion in the coding

sequence of the c-mer gene in RCS rats unravels general mechanisms of physiological cell adhesion and apoptosis. *Neurobiol Dis*, **7**, 586-599.

Newman, N.J., Yu-Wai-Man, P., Carelli, V., Moster, M.L., Biousse, V., Vignal-Clermont, C., Sergott, R.C., Klopstock, T., Sadun, A.A., Barboni, P., DeBusk, A.A., Girmens, J.F., Rudolph, G., Karanjia, R., Tiel, M., Blouin, L., Smits, G., Katz, B., Sahel, J.A. & Group, L.S. (2021) Efficacy and Safety of Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy Treated within 6 Months of Disease Onset. *Ophthalmology*, **128**, 649-660.

Newman, N.J., Yu-Wai-Man, P., Subramanian, P.S., Moster, M.L., Wang, A.G., Donahue, S.P., Leroy, B.P., Carelli, V., Biousse, V., Vignal-Clermont, C., Sergott, R.C., Sadun, A.A., Rebolleda Fernandez, G., Chwalisz, B.K., Banik, R., Bazin, F., Roux, M., Cox, E.D., Tiel, M., Sahel, J.A. & Group, L.R.S. (2023) Randomized trial of bilateral gene therapy injection for m.11778G>A MT-ND4 Leber optic neuropathy. *Brain*, **146**, 1328-1341.

Noben-Trauth, K., Naggert, J.K., North, M.A. & Nishina, P.M. (1996) A candidate gene for the mouse mutation tubby. *Nature*, **380**, 534-538.

Orhan, E., Dalkara, D., Neuille, M., Lechauve, C., Michiels, C., Picaud, S., Leveillard, T., Sahel, J.A., Naash, M.I., Lavail, M.M., Zeitz, C. & Audo, I. (2015) Genotypic and phenotypic characterization of P23H line 1 rat model. *PLoS One*, **10**, e0127319.

Pang, J.J., Chang, B., Kumar, A., Nusinowitz, S., Noorwez, S.M., Li, J., Rani, A., Foster, T.C., Chiodo, V.A., Doyle, T., Li, H., Malhotra, R., Teusner, J.T., McDowell, J.H., Min, S.H., Li, Q., Kaushal, S. & Hauswirth, W.W. (2006) Gene therapy restores vision-dependent behavior as well as retinal structure and function in a mouse model of RPE65 Leber congenital amaurosis. *Mol Ther*, **13**, 565-572.

Paques, M., Guyomard, J.L., Simonutti, M., Roux, M.J., Picaud, S., Legargasson, J.F. & Sahel, J.A. (2007) Panretinal, high-resolution color photography of the mouse fundus. *Invest Ophthalmol Vis Sci*, **48**, 2769-2774.

Paques, M., Simonutti, M., Roux, M.J., Picaud, S., Levavasseur, E., Bellman, C. & Sahel, J.A. (2006) High resolution fundus imaging by confocal scanning laser ophthalmoscopy in the mouse. *Vision Res*, **46**, 1336-1345.

Park, S.H., Park, J.W., Park, S.J., Kim, K.Y., Chung, J.W., Chun, M.H. & Oh, S.J. (2003) Apoptotic death of photoreceptors in the streptozotocin-induced diabetic rat retina. *Diabetologia*, **46**, 1260-1268.

Pasantes-Morales, H., Quesada, O., Carabez, A. & Huxtable, R.J. (1983) Effects of the taurine transport antagonist, guanidinoethane sulfonate, and beta-alanine on the morphology of rat retina. *J Neurosci Res*, **9**, 135-143.

- Peng, Y.W., Zallocchi, M., Wang, W.M., Delimont, D. & Cosgrove, D. (2011) Moderate light-induced degeneration of rod photoreceptors with delayed transducin translocation in shaker1 mice. *Invest Ophthalmol Vis Sci*, **52**, 6421-6427.
- Pennesi, M.E., Neuringer, M. & Courtney, R.J. (2012) Animal models of age related macular degeneration. *Mol Aspects Med*, **33**, 487-509.
- Peynshaert, K., Devoldere, J., Forster, V., Picaud, S., Vanhove, C., De Smedt, S.C. & Remaut, K. (2017) Toward smart design of retinal drug carriers: a novel bovine retinal explant model to study the barrier role of the vitreoretinal interface. *Drug Deliv*, **24**, 1384-1394.
- Picaud, S., Dalkara, D., Marazova, K., Goureau, O., Roska, B. & Sahel, J.A. (2019) The primate model for understanding and restoring vision. *Proc Natl Acad Sci U S A*, **116**, 26280-26287.
- Picaud, S., Pattnaik, B., Hicks, D., Forster, V., Fontaine, V., Sahel, J. & Dreyfus, H. (1998) GABAA and GABAC receptors in adult porcine cones: evidence from a photoreceptor-glia co-culture model. *J Physiol*, **513 (Pt 1)**, 33-42.
- Picaud, S., Peichl, L. & Franceschini, N. (1993) Dye-induced photolesion in the mammalian retina: glial and neuronal reactions. *J Neurosci Res*, **35**, 629-642.
- Pinzon-Duarte, G., Kohler, K., Arango-Gonzalez, B. & Guenther, E. (2000) Cell differentiation, synaptogenesis, and influence of the retinal pigment epithelium in a rat neonatal organotypic retina culture. *Vision Res*, **40**, 3455-3465.
- Prevot, P.H., Gehere, K., Arcizet, F., Akolkar, H., Khoei, M.A., Blaize, K., Oubari, O., Daye, P., Lanoe, M., Valet, M., Dalouz, S., Langlois, P., Esposito, E., Forster, V., Dubus, E., Wattiez, N., Brazhnikova, E., Nouvel-Jaillard, C., LeMer, Y., Demilly, J., Fovet, C.M., Hantraye, P., Weissenburger, M., Lorach, H., Bouillet, E., Deterre, M., Hornig, R., Buc, G., Sahel, J.A., Chenegros, G., Pouget, P., Benosman, R. & Picaud, S. (2020) Behavioural responses to a photovoltaic subretinal prosthesis implanted in non-human primates. *Nat Biomed Eng*, **4**, 172-180.
- Ratnapriya, R. & Chew, E.Y. (2013) Age-related macular degeneration-clinical review and genetics update. *Clin Genet*, **84**, 160-166.
- Redmond, T.M. & Hamel, C.P. (2000) Genetic analysis of RPE65: from human disease to mouse model. *Methods Enzymol*, **316**, 705-724.
- Reichman, S., Slembrouck, A., Gagliardi, G., Chaffiol, A., Terray, A., Nanteau, C., Potey, A., Belle, M., Rabesandratana, O., Duebel, J., Orieux, G., Nandrot, E.F., Sahel, J.A. & Goureau, O. (2017) Generation of Storable Retinal Organoids and Retinal Pigmented Epithelium from Adherent Human iPSC Cells in Xeno-Free and Feeder-Free Conditions. *Stem Cells*, **35**, 1176-1188.

- Reichman, S., Terray, A., Slembrouck, A., Nanteau, C., Orieux, G., Habeler, W., Nandrot, E.F., Sahel, J.A., Monville, C. & Goureau, O. (2014) From confluent human iPS cells to self-forming neural retina and retinal pigmented epithelium. *Proc Natl Acad Sci U S A*, **111**, 8518-8523.
- Roubeix, C., Godefroy, D., Mias, C., Sapienza, A., Riancho, L., Degardin, J., Fradot, V., Ivkovic, I., Picaud, S., Sennlaub, F., Denoyer, A., Rostene, W., Sahel, J.A., Parsadaniantz, S.M., Brignole-Baudouin, F. & Baudouin, C. (2015) Intraocular pressure reduction and neuroprotection conferred by bone marrow-derived mesenchymal stem cells in an animal model of glaucoma. *Stem Cell Res Ther*, **6**, 177.
- Sahel, J.A., Boulanger-Scemama, E., Pagot, C., Arleo, A., Gallupi, F., Martel, J.N., Esposti, S.D., Delaux, A., de Saint Aubert, J.B., de Montleau, C., Gutman, E., Audo, I., Duebel, J., Picaud, S., Dalkara, D., Blouin, L., Tiel, M. & Roska, B. (2021) Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat Med*.
- Salinas-Navarro, M., Alarcon-Martinez, L., Valiente-Soriano, F.J., Jimenez-Lopez, M., Mayor-Torroglosa, S., Aviles-Trigueros, M., Villegas-Perez, M.P. & Vidal-Sanz, M. (2010) Ocular hypertension impairs optic nerve axonal transport leading to progressive retinal ganglion cell degeneration. *Exp Eye Res*, **90**, 168-183.
- Sauer, B. & Henderson, N. (1990) Targeted insertion of exogenous DNA into the eukaryotic genome by the Cre recombinase. *New Biol*, **2**, 441-449.
- Schuettauf, F., Quinto, K., Naskar, R. & Zurakowski, D. (2002) Effects of anti-glaucoma medications on ganglion cell survival: the DBA/2J mouse model. *Vision Res*, **42**, 2333-2337.
- Schwahn, H.N., Kaymak, H. & Schaeffel, F. (2000) Effects of atropine on refractive development, dopamine release, and slow retinal potentials in the chick. *Vis Neurosci*, **17**, 165-176.
- Sen, M., Al-Amin, M., Kickova, E., Sadeghi, A., Puranen, J., Urtti, A., Caliceti, P., Salmaso, S., Arango-Gonzalez, B. & Ueffing, M. (2021a) Retinal neuroprotection by controlled release of a VCP inhibitor from self-assembled nanoparticles. *J Control Release*, **339**, 307-320.
- Sen, M., Kutsyr, O., Cao, B., Bolz, S., Arango-Gonzalez, B. & Ueffing, M. (2021b) Pharmacological Inhibition of the VCP/Proteasome Axis Rescues Photoreceptor Degeneration in RHO(P23H) Rat Retinal Explants. *Biomolecules*, **11**.
- Siebert, S., Scherf, B.G., Del Punta, K., Didkovsky, N., Heintz, N. & Roska, B. (2009) Genetic address book for retinal cell types. *Nat Neurosci*, **12**, 1197-1204.
- Smith, L.E., Wesolowski, E., McLellan, A., Kostyk, S.K., D'Amato, R., Sullivan, R. & D'Amore, P.A. (1994) Oxygen-induced retinopathy in the mouse. *Invest Ophthalmol Vis Sci*, **35**, 101-111.

- Soderpalm, A., Szel, A., Caffè, A.R. & van Veen, T. (1994) Selective development of one cone photoreceptor type in retinal organ culture. *Invest Ophthalmol Vis Sci*, **35**, 3910-3921.
- Song, E., Dong, Y., Han, L.N., Sui, D.M., Xu, Q., Wang, X.R. & Wu, J.X. (2004) Diabetic retinopathy: VEGF, bFGF and retinal vascular pathology. *Chin Med J (Engl)*, **117**, 247-251.
- Stasheff, S.F. (2008) Emergence of sustained spontaneous hyperactivity and temporary preservation of OFF responses in ganglion cells of the retinal degeneration (rd1) mouse. *J Neurophysiol*, **99**, 1408-1421.
- Sun, D., Schur, R.M., Sears, A.E., Gao, S.Q., Vaidya, A., Sun, W., Maeda, A., Kern, T., Palczewski, K. & Lu, Z.R. (2020) Non-viral Gene Therapy for Stargardt Disease with ECO/pRHO-ABCA4 Self-Assembled Nanoparticles. *Mol Ther*, **28**, 293-303.
- Sun, D., Sun, W., Gao, S.Q., Lehrer, J., Naderi, A., Wei, C., Lee, S., Schilb, A.L., Scheidt, J., Hall, R.C., Traboulsi, E.I., Palczewski, K. & Lu, Z.R. (2022) Effective gene therapy of Stargardt disease with PEG-ECO/pGRK1-ABCA4-S/MAR nanoparticles. *Mol Ther Nucleic Acids*, **29**, 823-835.
- Tedja, M.S. & Wojciechowski, R. & Hysi, P.G. & Eriksson, N. & Furlotte, N.A. & Verhoeven, V.J.M. & Iglesias, A.I. & Meester-Smoor, M.A. & Tompson, S.W. & Fan, Q. & Khawaja, A.P. & Cheng, C.Y. & Hohn, R. & Yamashiro, K. & Wenocur, A. & Graza, C. & Haller, T. & Metspalu, A. & Wedenoja, J. & Jonas, J.B. & Wang, Y.X. & Xie, J. & Mitchell, P. & Foster, P.J. & Klein, B.E.K. & Klein, R. & Paterson, A.D. & Hosseini, S.M. & Shah, R.L. & Williams, C. & Teo, Y.Y. & Tham, Y.C. & Gupta, P. & Zhao, W. & Shi, Y. & Saw, W.Y. & Tai, E.S. & Sim, X.L. & Huffman, J.E. & Polasek, O. & Hayward, C. & Bencic, G. & Rudan, I. & Wilson, J.F. & Consortium, C. & andMe Research, T. & Eye, U.K.B. & Vision, C. & Joshi, P.K. & Tsujikawa, A. & Matsuda, F. & Whisenhunt, K.N. & Zeller, T. & van der Spek, P.J. & Haak, R. & Meijers-Heijboer, H. & van Leeuwen, E.M. & Iyengar, S.K. & Lass, J.H. & Hofman, A. & Rivadeneira, F. & Uitterlinden, A.G. & Vingerling, J.R. & Lehtimäki, T. & Raitakari, O.T. & Biino, G. & Concas, M.P. & Schwantes-An, T.H. & Igo, R.P., Jr. & Cuellar-Partida, G. & Martin, N.G. & Craig, J.E. & Gharahkhani, P. & Williams, K.M. & Nag, A. & Rahi, J.S. & Cumberland, P.M. & Delcourt, C. & Bellenguez, C. & Ried, J.S. & Bergen, A.A. & Meitinger, T. & Gieger, C. & Wong, T.Y. & Hewitt, A.W. & Mackey, D.A. & Simpson, C.L. & Pfeiffer, N. & Parssinen, O. & Baird, P.N. & Vitart, V. & Amin, N. & van Duijn, C.M. & Bailey-Wilson, J.E. & Young, T.L. & Saw, S.M. & Stambolian, D. & MacGregor, S. & Guggenheim, J.A. & Tung, J.Y. & Hammond, C.J. & Klaver, C.C.W. (2018) Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet*, **50**, 834-848.
- Thaung, C., West, K., Clark, B.J., McKie, L., Morgan, J.E., Arnold, K., Nolan, P.M., Peters, J., Hunter, A.J., Brown, S.D., Jackson, I.J. & Cross, S.H. (2002) Novel ENU-induced eye mutations in the mouse: models for human eye disease. *Hum Mol Genet*, **11**, 755-767.
- Thompson, D.A., Khan, N.W., Othman, M.I., Chang, B., Jia, L., Grahek, G., Wu, Z., Hiriyan, S., Nellisery, J., Li, T., Khanna, H., Colosi, P., Swaroop, A. & Heckenlively, J.R. (2012) Rd9 is a

naturally occurring mouse model of a common form of retinitis pigmentosa caused by mutations in RPGR-ORF15. *PLoS One*, **7**, e35865.

- Toomey, C.B., Kelly, U., Saban, D.R. & Bowes Rickman, C. (2015) Regulation of age-related macular degeneration-like pathology by complement factor H. *Proc Natl Acad Sci U S A*, **112**, E3040-3049.
- Torero Ibad, R., Rhee, J., Mrejen, S., Forster, V., Picaud, S., Prochiantz, A. & Moya, K.L. (2011) Otx2 promotes the survival of damaged adult retinal ganglion cells and protects against excitotoxic loss of visual acuity in vivo. *J Neurosci*, **31**, 5495-5503.
- Trouillet, A., Dubus, E., Degardin, J., Estivalet, A., Ivkovic, I., Godefroy, D., Garcia-Ayuso, D., Simonutti, M., Sahly, I., Sahel, J.A., El-Amraoui, A., Petit, C. & Picaud, S. (2018) Cone degeneration is triggered by the absence of USH1 proteins but prevented by antioxidant treatments. *Sci Rep*, **8**, 1968.
- Ufret-Vincenty, R.L., Aredo, B., Liu, X., McMahon, A., Chen, P.W., Sun, H., Niederkorn, J.Y. & Kedzierski, W. (2010) Transgenic mice expressing variants of complement factor H develop AMD-like retinal findings. *Invest Ophthalmol Vis Sci*, **51**, 5878-5887.
- Vallazza-Deschamps, G., Cia, D., Gong, J., Jellali, A., Duboc, A., Forster, V., Sahel, J.A., Tessier, L.H. & Picaud, S. (2005) Excessive activation of cyclic nucleotide-gated channels contributes to neuronal degeneration of photoreceptors. *Eur J Neurosci*, **22**, 1013-1022.
- Veleri, S., Lazar, C.H., Chang, B., Sieving, P.A., Banin, E. & Swaroop, A. (2015) Biology and therapy of inherited retinal degenerative disease: insights from mouse models. *Dis Model Mech*, **8**, 109-129.
- Vessey, K.A., Wilkinson-Berka, J.L. & Fletcher, E.L. (2011) Characterization of retinal function and glial cell response in a mouse model of oxygen-induced retinopathy. *J Comp Neurol*, **519**, 506-527.
- Vignal-Clermont, C., Girmens, J.F., Audo, I., Said, S.M., Errera, M.H., Plaine, L., O'Shaughnessy, D., Taiel, M. & Sahel, J.A. (2021) Safety of Intravitreal Gene Therapy for Treatment of Subjects with Leber Hereditary Optic Neuropathy due to Mutations in the Mitochondrial ND4 Gene: The REVEAL Study. *BioDrugs*, **35**, 201-214.
- Vignal, C., Uretsky, S., Fitoussi, S., Galy, A., Blouin, L., Girmens, J.F., Bidot, S., Thomasson, N., Bouquet, C., Valero, S., Meunier, S., Combal, J.P., Gilly, B., Katz, B. & Sahel, J.A. (2018) Safety of rAAV2/2-ND4 Gene Therapy for Leber Hereditary Optic Neuropathy. *Ophthalmology*, **125**, 945-947.
- Vollrath, D., Feng, W., Duncan, J.L., Yasumura, D., D'Cruz, P.M., Chappelow, A., Matthes, M.T., Kay, M.A. & LaVail, M.M. (2001) Correction of the retinal dystrophy phenotype of the RCS rat by viral gene transfer of Mertk. *Proc Natl Acad Sci U S A*, **98**, 12584-12589.

- Watkins, T.A., Emery, B., Mulinyawe, S. & Barres, B.A. (2008) Distinct stages of myelination regulated by gamma-secretase and astrocytes in a rapidly myelinating CNS coculture system. *Neuron*, **60**, 555-569.
- Weng, J., Mata, N.L., Azarian, S.M., Tzekov, R.T., Birch, D.G. & Travis, G.H. (1999) Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in *abcr* knockout mice. *Cell*, **98**, 13-23.
- Wilmet, B., Callebert, J., Duvoisin, R., Goulet, R., Tourain, C., Michiels, C., Frederiksen, H., Schaeffel, F., Marre, O., Sahel, J.A., Audo, I., Picaud, S. & Zeitz, C. (2022) Mice Lacking *Gpr179* with Complete Congenital Stationary Night Blindness Are a Good Model for Myopia. *Int J Mol Sci*, **24**.
- WoldeMussie, E., Yoles, E., Schwartz, M., Ruiz, G. & Wheeler, L.A. (2002) Neuroprotective effect of memantine in different retinal injury models in rats. *J Glaucoma*, **11**, 474-480.
- Wu, J., Seregard, S. & Algvere, P.V. (2006) Photochemical damage of the retina. *Surv Ophthalmol*, **51**, 461-481.
- Wu, L., Ueda, K., Nagasaki, T. & Sparrow, J.R. (2014) Light damage in *Abca4* and *Rpe65rd12* mice. *Invest Ophthalmol Vis Sci*, **55**, 1910-1918.
- Yang, Y., Mohand-Said, S., Danan, A., Simonutti, M., Fontaine, V., Clerin, E., Picaud, S., Leveillard, T. & Sahel, J.A. (2009) Functional cone rescue by RdCVF protein in a dominant model of retinitis pigmentosa. *Mol Ther*, **17**, 787-795.
- Zeitz, C., Roger, J.E., Audo, I., Michiels, C., Sanchez-Farias, N., Varin, J., Frederiksen, H., Wilmet, B., Callebert, J., Gimenez, M.L., Bouzidi, N., Blond, F., Guillonneau, X., Fouquet, S., Leveillard, T., Smirnov, V., Vincent, A., Heon, E., Sahel, J.A., Kloeckener-Gruissem, B., Sennlaub, F., Morgans, C.W., Duvoisin, R.M., Tkatchenko, A.V. & Picaud, S. (2023) Shedding light on myopia by studying complete congenital stationary night blindness. *Prog Retin Eye Res*, **93**, 101155.