Chapter 3: Retinal remodeling and visual prosthetics

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Introduction:

Our understanding of retinal structure and function has been a 150 year journey through biological science with the goal of understanding precisely how the retina is anatomically composed and how that structure interacts physiologically. Unfortunately this goal while close to completion in some areas, remains woefully lacking in complete detail of development, participants, connectivity, physiology and pathology, particularly in disease processes. This chapter examines the retina in disease and will attempt to clarify some of the long misunderstood aspects of retinal pathology, discussing how those pathologies impact bionic and/or biological strategies in the rescue of vision.

Other chapters in this book will discuss bionic and biological approaches to delaying or "curing" vision loss using various prosthetics, leaving this chapter to function as a biological primer of sorts to introduce some of the biological realities that any therapeutic intervention will have to deal with as all of the inherited retinal degenerations studied to date reveal a biological moving target that must be considered prior to therapy.

The question of whether or not the neural retina is receptive to bionic or biological intervention is one that historically has been investigated without consideration of the actual disease process neural systems proceed through when they experience loss of photoreceptors. Though the neural retina grossly appears to survive photoreceptor loss in diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), the reality is that the retina is no different from other CNS pathways when their afferent inputs are lost. When photoreceptor inputs are lost, the retina engages in a wide variety of remodeling events driven by loss of signaling inputs. These transformations include glial hypertrophy and possible hyperplasia, neuronal translocations, neuronal loss and the emergence of retinal circuit alteration with the

formation of novel synaptically active neuronal processes. These new processes are perhaps the most significant impediment to prosthetic retinal rescue through bionic or biological interventions as the disease process corrupts and modifies the normal visual information processing so as to make it indecipherable by the visual cortex. If we are to proceed, vision rescue strategies need to contend with the biological realities of retinal remodeling.

Background:

The effort to build, design and implement neuroprosthetic devices has been challenging due to not just the complexity of the retina, but also the difficulty of dealing with a complex, reactive biological tissue that changes its fundamental connectivity in disease processes. Efforts from a variety of labs now make it clear that the neural retina does not adopt a passive role with respect to photoreceptor degenerations and that extensive alterations and remodeling occur from the molecular scale up through the synaptic, cellular and tissue levels (Kolb and Gouras, 1974; Li et al., 1995; de Raad et al., 1996; Fletcher and Kalloniatis, 1996; Fariss et al., 2000; Machida et al., 2000; Strettoi and Pignatelli, 2000; Strettoi et al., 2002; Jones et al., 2003; Marc and Jones, 2003; Marc et al., 2003; Strettoi et al., 2003; Cuenca et al., 2004; Cuenca et al., 2005; Jones and Marc, 2005; Jones et al., 2005; Pu et al., 2006; Aleman et al., 2007; Marc et al., 2007; Specht et al., 2007; Sullivan et al., 2007; Marc et al., 2008; Stasheff, 2008). Regardless of whether the intervention is survival factor delivery (Faktorovich et al., 1990, 1992), genetic (Bainbridge et al., 2008; Maguire et al., 2008), cellular (Young et al., 2000; Gias et al., 2007; Vugler et al., 2007) or bionic (Humayun et al., 1996; Zrenner, 2002b, a; Lakhanpal et al., 2003; Eckhorn et al., 2006; Yanai et al., 2007), approaches will have to address the ongoing process of neuronal death, alterations to gene expression, neuronal circuit rewiring and migration and the elaboration of novel glial barriers. While these prospects may appear daunting, prosthetic devices may in fact be the ideal intervention with which to rescue and reconfigure neural retinas altered by disease.

Retinal Disease and its Diversity:

Retinal disease including the well characterized retinitis pigmentosa (Figure 1) with an incidence of 1-4000 (Bunker et al., 1984) and the less well understood, yet far more prevalent age related macular degeneration affect millions of people world wide. While RP affects a significant portion of the population, AMD is far more common with an incidence in the United States alone estimated to reach 3 million by 2020 (Friedman et al., 2004). Indeed, it has been estimated that AMD is the leading cause of new cases of blindness in Americans over 60 with an estimated 18% of Americans between 65 and 74 and 30% of Americans older than 74 showing signs of early AMD (Zarbin, 2004).

Regardless of the form retinal degenerative disease takes, the final common pathway of photoreceptor loss followed by downstream reactive biological processes results in a system that has proven difficult to rescue. While rescues of vision targeted towards the

anterior eye have been possible for a great many years due to the accessibility and amenability of the tissues involved to pharmacological and surgical interventions, retinal disease presents a significantly larger challenge that has proven more difficult to combat due to its complex and progressive nature and the number of potential gene loci involved. These diverse pathological insults currently number close to 200 gene defects associated associated with various retinal diseases http://www.sph.uth.tmc.edu/RetNet/ including AMD, RP, diabetic retinopathy and glaucoma. These disease loci are located on 23 different genes in addition to mitochondrial gene loci and result in vision loss through diverse mechanisms including defects in retinal pigment epithelium cells seen in recessive Leber congenital amaurosis (Gu et al., 1997; Aguirre et al., 1998; Morimura et al., 1998), defects in the ATP binding cassette transporter seen in recessive Stargardt disease (Allikmets, 1997; Allikmets et al., 1997a; Allikmets et al., 1997b; Cremers et al., 1998; Allikmets, 2000) , the c-mer protooncogene receptor tyrosine kinase (D'Cruz et al., 2000; Gal et al., 2000; Duncan et al., 2003), alterations in cilia function and intraflagellar transport (Li et al., 2004; Yen et al., 2006), arrestin (Sommer et al., 2005; Sommer and Farrens, 2006), and transducin defects (Dryja et al., 1993; Zeitz et al., 2008), rod cGMP phosphodiesterase defects (McLaughlin et al., 1993; Huang et al., 1995; McLaughlin et al., 1995), metabotropic glutamate receptor defects (Dryja et al., 2005; Zeitz et al., 2005), peripherin defects (Clarke et al., 2000), fatty acid biosynthetic enzymes (Zhang et al., 2001; Vasireddy et al., 2007), and a diverse assortment of other gene loci encoding proteins responsible for signaling (Chen et al., 2000; Hu and Wensel, 2002; Hu et al., 2003; Wensel, 2008).

Defects for AMD are likely as numerous and complex as the RP causes, (Kaplan et al., 1993; Allikmets et al., 1997a; Cremers et al., 1998; Molday et al., 2000; Stone et al., 2004; Wang et al., 2004; Edwards et al., 2005; Hageman et al., 2005; Jakobsdottir et al., 2005; Dewan et al., 2006; Gold et al., 2006; Cameron et al., 2007; Maller et al., 2007; Yates et al., 2007; Boon et al., 2008; Chen et al., 2008), yet are dependent upon a number of potential gene defect interactions that over time and with the accumulation of other risk factors result in retinal degeneration of the central portion of the retina responsible for high acuity vision (Yates et al., 2007). Additionally, because no one specific cause of AMD has been identified, there is some difficulty defining a precise definition complicated by significant overlap of clinical manifestations. Indeed there is even some degree of controversy over whether or not the pathophysiological processes responsible for many of the sequelae of AMD including drusen accumulation, geographic atrophy, pigmentary changes and alterations in the vascular network are even directly related. Whatever the mechanism(s) involved, the end result of AMD is likely the same; photoreceptor cell death followed by retinal remodeling.

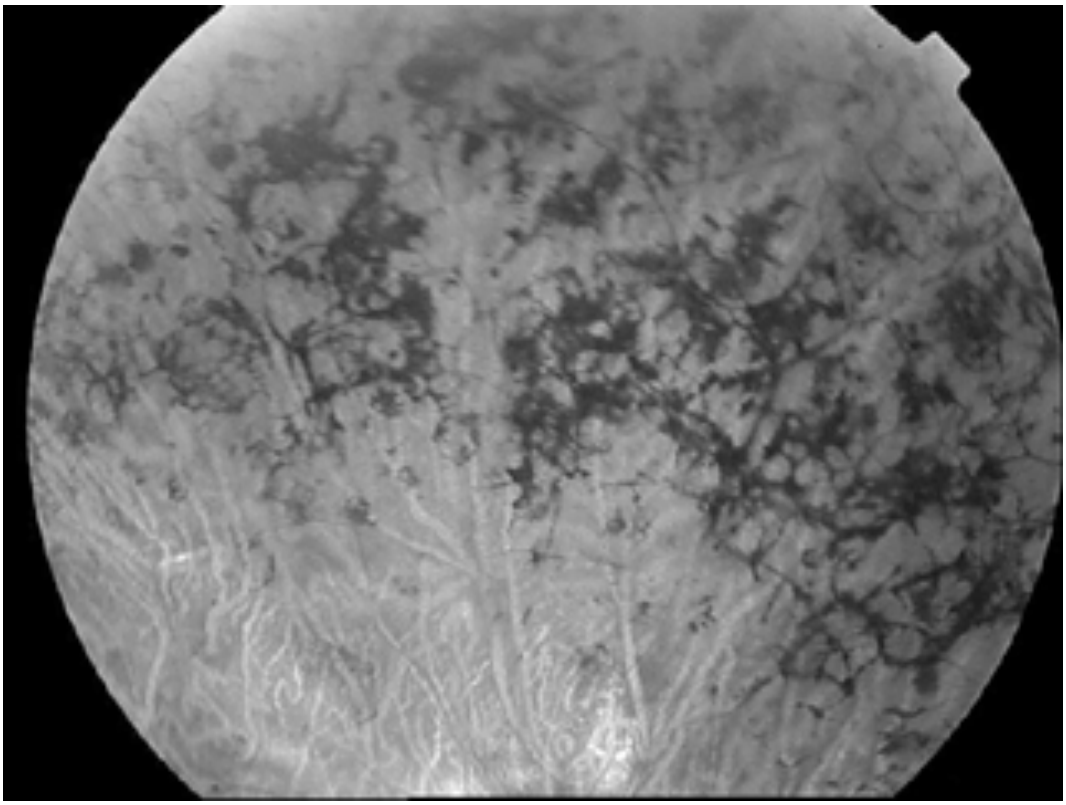

Figure 1: Fundascopic image from 46 year old male with a diagnosis of X-linked retinitis pigmentosa, showing 'pigmented bone spicules', accumulations of pigment epithelium that are formed by migration of the pigment epithelium into the neural retina along glial columns. These clinically pathologic findings are often seen in the peripheral retina in patients with RP.

Retinal remodeling:

While work prior to the last decade assumed that retinal degenerative disease only affected the sensory retina, it is now commonly understood that these diseases also involve the neural retina to dramatic fashion (Jones et al., 2003; Strettoi et al., 2003; Sullivan et al., 2003; Jones and Marc, 2005; Jones et al., 2005; Aleman et al., 2007; Marc et al., 2007; Specht et al., 2007; Sullivan et al., 2007; Marc et al., 2008). The reality of retinal degenerative disease and the subsequent changes that occur to the anatomy and physiology of the retina present profound difficulties to prospects of rescue, whether that rescue is biologically based or bionic in nature. Retinas that have lost their principal inputs, the photoreceptors, have been effectively deafferented and undergo changes to their circuitry early and likely initially clinically occult. Regardless of the initial molecular or environmental insult, the proverb *omnes viae Romam ducunt* or all roads lead to Rome summarizes where these mechanisms take us with respect to retinal remodeling. All defects resulting in loss of photoreceptor input to the neural retina initiate a series of events that change the fundamental ground truth of the retinal neural circuitry. This alteration in how the retina processes signals presents a

significant challenge to retinal rescue through bionic prosthetic devices or biological interventions and it can be argued that most approaches to intervention have waited far too long in the degenerative process to hope for any substantiative visual rescue. By the time photoreceptors are gone (Figure 1), the changes to wiring are well underway.

Most implant strategies presume substantial survival of retinal outflow architectures and while it has long been claimed that the neural retina remains unchanged after the death of the sensory retina, this perspective is incorrect. In retinal degenerations, the neural retina undergoes a series of phases initiated by a period of photoreceptor or retinal pigment epithelial cell stress (Figure 2). The standard metabolic phenotypes of some cells (Müller cells) becomes altered possibly indicating fundamental changes in the abilities of these cells to maintain their function and viability, but neuronal metabolic profiles appear to be maintained until cell death. Initially clinically occult changes also occur to the circuitry of the neural retina as well in even early stages of retinal degeneration. Subsequent to phase one, the neural retina enters into a phase of outer nuclear layer modification that includes photoreceptor cell death, apparent death of bystander neurons, phagocytic consumption of dying neurons and the walling off or entombment of the remnant neural retina beneath Müller cell processes. The final tertiary phase of retinal degeneration occurs as the retina enters a protracted period of remodeling characterized by disruption of topology by glial hypertrophy and continued neuronal migration, continued neuronal cell death and extensive rewiring with elaboration of de novo neurite and synaptic formation (Jones et al., 2003; Marc et al., 2003; Jones and Marc, 2005; Jones et al., 2005). Late in the course of retinal degeneration, neuronal death becomes extensive. Though many neurons persist after death of the sensory retina, all are susceptible to cell death in varying fractions and patterns. Focal depletion of the inner nuclear layer is common and some genetic types of photoreceptor degenerations express massive ganglion cell loss in large patches of retina. In the most extreme cases, the Müller cell seal breaks down and neurons do in fact emigrate from the retina into the remnant choroid (Jones et al., 2006).

These three phases of retinal remodeling culminate in the rewiring of all cell classes and essentially reprogram the retina rendering the circuitry incapable of processing visual data and delivering those data to visual cortex (Marc et al., 2007). It should be noted that even though the first report of aberrant circuity in the human RP retina goes back to 1974 (Kolb and Gouras, 1974), the concept of neural remodeling events are abundant in the epilepsy literature (Pollard et al., 1994; Sutula, 2002; Koyama et al., 2004) and the vision community is coming late to the game. These alterations in retinal morphology and physiology are seen across the spectrum of retinal degenerations from inherited (Fletcher and Kalloniatis, 1996) to engineered (Jones et al., 2003) and induced photoreceptor degenerations (de Raad et al., 1996) with changes occurring relatively early after photoreceptor cell stress and death (Marc et al., 2007).

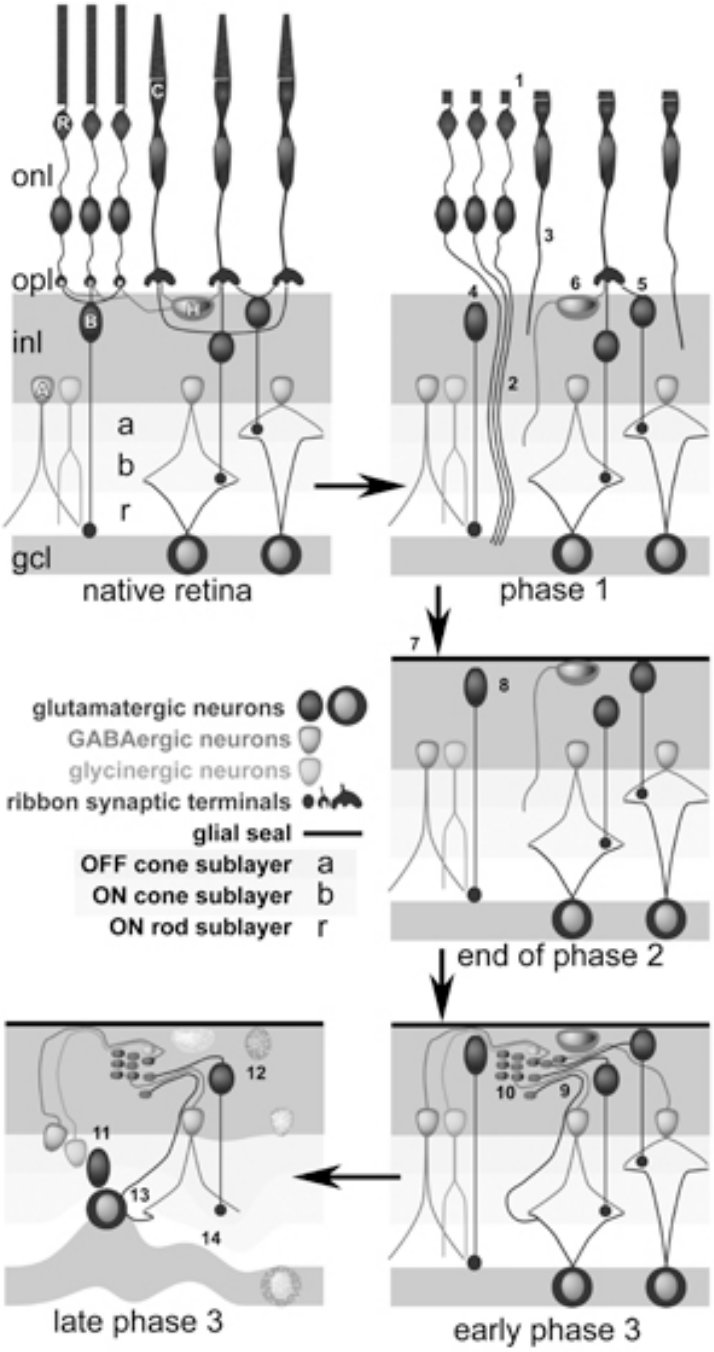

Figure 2:

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A schematic representation of the three stages of retinal degeneration showing both rod and cone photoreceptors, rod and cone bipolar cells, ganglion cells, a horizontal cell, GABAergic amacrine and glycinergic amacrine cells. The two nuclear layers are illustrated as horizontal bands. The first frame, native retina shows normal lamination and connectivity of cell classes in the retina. Phase 1 reveals early photoreceptor stress and outer segment shortening (1) along with rod and cone neurite extensions projecting down into inner nuclear layer and ganglion cell layer (2, 3). Horizontal cells are also seen contributing to the neurite projections (6) along with rod and cone bipolar cells undergoing dendrite retraction (4,5). Müller cells

may also begin to hypertrophy in this stage. By the end of phase 2 there is a complete loss of photoreceptors and elaboration of a Müller cell seal over the neural retina (7), sealing it-off away from the remnant choroid. Neuronal phenotypic revisions are underway or complete at this time (8). Early phase 3 events ensue with the elaboration of neurite extensions from glycinergic and GABAergic amacrine cells along with contributions from bipolar cells and ganglion cells forming complex tangles of processes called microneuromas (9, 10) that form outside the normal lamination of the inner plexiform layer, sometimes merging with the inner plexiform layer. These microneuromas possess active synaptic elements corruptive of normal signaling. By late phase 3, retinal degeneration is advanced with neuronal migration or translocation events occurring in a bi-directional fashion (11) along with neuronal death of many cell classes (12). IPL rewiring and laminar deformation of the plexiform layers can also be observed.

Retinal circuitry:

Though analysis of the neural retina and its circuitry goes back over 100 years ago to Ramón y Cajal's work, most work examining the anatomy of circuitry in retinal disease is more recent, encompassing efforts in the last three decades to understand the components and their function. This work has revealed the retina to be a bi-laminar device with sensory and computational layers.

The sensory retina is composed of photoreceptors and is the photon transduction layer, while the neural retina is composed of the remaining neuron classes that comprise the image-processing layer. Even in a simple retina like the mammalian, the retinal circuitry is complex, comprising approximately 14 patterned outflow channels, realized as ganglion cells. The number of cell classes in the mammalian retina includes 1 rod class, 1 rod horizontal cell, 1 rod bipolar cell, 2-3 cone classes, 1-3 cone horizontal cells, 9+ cone bipolar cells, 27 amacrine cells, and about 15-20 ganglion cells. Thus, about 60-70 cellular devices form the outflow channels (Masland, 2001b, a; Wässle, 2004; Marc, 2008). These outflow channels involve the flow of information through a set of stereotypical circuits from photoreceptors to bipolar cells to ganglion and amacrine cells with amacrine cells providing both feedback and feedforward control (Masland, 2001b, a; Marc, 2004; Wässle, 2004). It should be noted however that even two bipolar cells providing input to two separate ganglion cells, interconnected by a single amacrine cell provides a combinatorial 90 distinct and separate motifs assuming lumped-parameter circuitry. Assuming distributed parameter circuitry (Weiss, 1996) expands the number of combinatorials to over 2000 potential motifs. This approximation of a circuit diagram does not include any weightings for differential synaptic strength, cell class diversity, and coupling by gap junctions. Nor does this approximation include the most common form of synaptic connection in the retina between cells, the amacrine-amacrine cell serial synaptic chain. However, we know that the outflow of signals from the mammalian retina is represented by only 15-20 ganglion cell classes (Marc and Jones, 2002; Rockhill et al., 2002), greatly simplifying the number of possible outputs, though we do not know what the total network topology is.

Even rich models (Hennig et al., 2002) that mimic physiologic data acquired over limited spatiotemporal domains predict little about network topology or emergent features. Despite a broad view of the bounds of biophysical performance provided by physiology, models derived from physiology are essentially degenerate: not unique to any one network topology. In addition, remodeling and reprogramming of neural networks in retinal disease strongly argues that network scrambling is a key pathology (Marc et al., 2007). Network motif diversity is analogous to genetic diversity: many connective motifs (gene sequences) are possible, but only a subset form good filters (proteins), and mutating motifs generates neural malfunction (genetic disease).

In theory, subretinal implants drive remnant circuits with cone-like inputs and epiretinal implants drive ganglion cell channels by mimicking bipolar-amacrine cell networks. Both schemes require survival of retinal neurons to drive perceptual and oculomotor systems, and presume no alterations in cell patterning or connectivity, nor any corruptive signal invasion into retinal networks. Subretinal strategies uniquely require positioning within the subretinal space. *These presumptions (preservation of topology, cell numbers and wiring) are false for most retinal degenerations.*

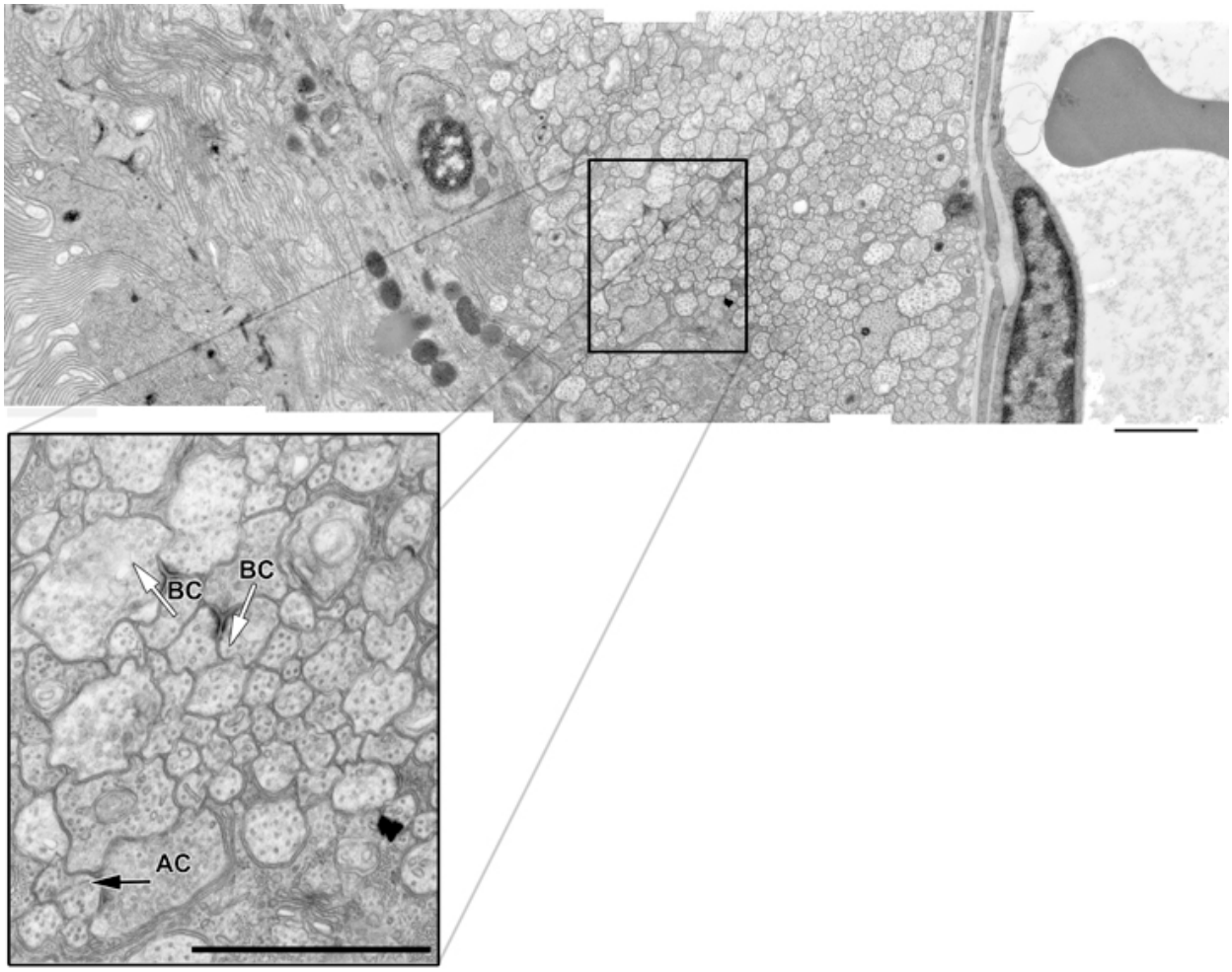

Figure 3: EM image of a microneuroma underneath a distal retinal Müller cell seal on the left with a blood vessel and portion of an erythrocyte on the right. 100-400nm diameter processes are running parallel together, perpendicularly through this plane of section comprised of five TEM images mosaiced together. Synaptic profiles are present in this microneuroma with apparent bipolar cell (BC) like synapses with dyads, yet bereft of ribbons as well as conventional synapses from amacrine cells (AC) shown in the inset indicating that microneuromas are potentially not passive structures with respect to circuitry. Efforts to reconstruct microneuromas are underway to define the pathology of circuitry in these retinas. Scale bars = 1 micrometer.

Retinal Circuitry revision:

Neuronal translocations in the remodeling retina are complex and do not just involve migrations of cell somata that leave their dendrites and axons in the original locations, preserving connectivity. The reality is far more insideous as the elaboration of new neurite, axonal, and synaptic structures occurs before gross cellular migration ensues

Figures 3 and 4). These structures occur individually and may assemble into fascicles and microneuromas that may run for many microns underneath the Müller cell seal, forever changing and corrupting completely the neuronal circuitry of the retina (Jones et al., 2003; Marc and Jones, 2003; Marc et al., 2003; Jones and Marc, 2005; Jones et al., 2005; Jones et al., 2006; Marc et al., 2007; Marc et al., 2008). Modeling of new circuits demonstrates that all observed circuits are corruptive and many form resonant circuits, rendering the remnant neural retina no longer effective as an image processor (Jones et al., 2003; Jones and Marc, 2005; Marc et al., 2007).

While most analyses of retinal degeneration have focused on events surrounding phase 2 and photoreceptor death, rewiring of the neural retina occurs in all phases of retinal degeneration, and likely begins prior to photoreceptor death during the stress phase (Marc et al., 2003; Marc et al., 2007). Early in phase 2, ganglion cell light responses are altered, resulting in the loss of ON responses with the simultaneous preservation of OFF responses (Pu et al., 2006). Once the photoreceptors are completely lost, ganglion cells spike throughout the retina of the Pde6b^{rd1} mouse retina (Stasheff, 2008), possibly providing a mechanism behind the scintillating scotomas reported by many patients with RP (Delbeke et al., 2001).

Therefore, passive anatomy alone does not reveal the scope of neural change in response to retinal degenerative disease. The growing evidence supports retinal rewiring as a common feature in retinal degenerations that involve photoreceptor loss and recent work (Marc et al., 2007) indicates profound changes in physiology through the use of excitation mapping (Marc, 1999a, b) and mapping cellular identity across disease states with single-cell resolution (Marc and Jones, 2002) along with *in vivo* and *in vitro* ligand activation in wild-type mice and rdcl and hrhoG mutant mice exhibiting rapid photoreceptor degeneration. In addition, the Marc 2007 study included *in vitro* excitation mapping in a sample of human RP retina revealing reprogramming events in bipolar cells that likely impact all forms of proposed retinal rescue strategies as the remodeling goes beyond rewiring and morphological change to include molecular reprogramming.

These findings are perhaps not surprising in that changes in circuitry have been documented in the literature for years. Other than the previously noted 1974 study by Kolb, some of the earliest indications of retinal rewiring or connectivity defects can be seen in a paper by Li et al in 1995 (Li et al., 1995) where the authors documented aberrantly sprouting rod photoreceptors. Fei in 2002 (Fei, 2002) documented sprouting cones, Machida et. al. (Machida et al., 2000) found abnormal sprouting of photoreceptors and horizontal cells in the degenerating retinas of the P23H transgenic rat and Fariss (Fariss et al., 2000) documented anomalous extension of rod, horizontal and amacrine cell neurites throughout the neural retina while Gregory-Evans et. al. identified abnormal cone synapses in human cone-rod dystrophy (Gregory-Evans et al., 1998). Peng et. al. identified ectopic synapses in the RCS rat (Peng et al., 2003) while other investigators working concurrently in mouse models of RP identified some of the earliest changes in the second order neurons, with dendritic retraction of rod bipolar and horizontal cells after photoreceptor cell loss (Strettoi and Pignatelli, 2000; Strettoi et al.,

2002; Varela et al., 2003). Documentation of neuronal migration (Jones et al., 2003; Marc et al., 2003; Jones and Marc, 2005; Jones et al., 2005), the identification of corruptive synaptic machinery in rod and cone bipolar cells as well as horizontal cells (Cuenca et al., 2004; Cuenca et al., 2005) and most significantly, formation of new neuronal connectivities and reprogramming (Marc et al., 2007) have made for a compelling literature that will absolutely impact the implementation and success of rescues designed to preserve or restore vision.

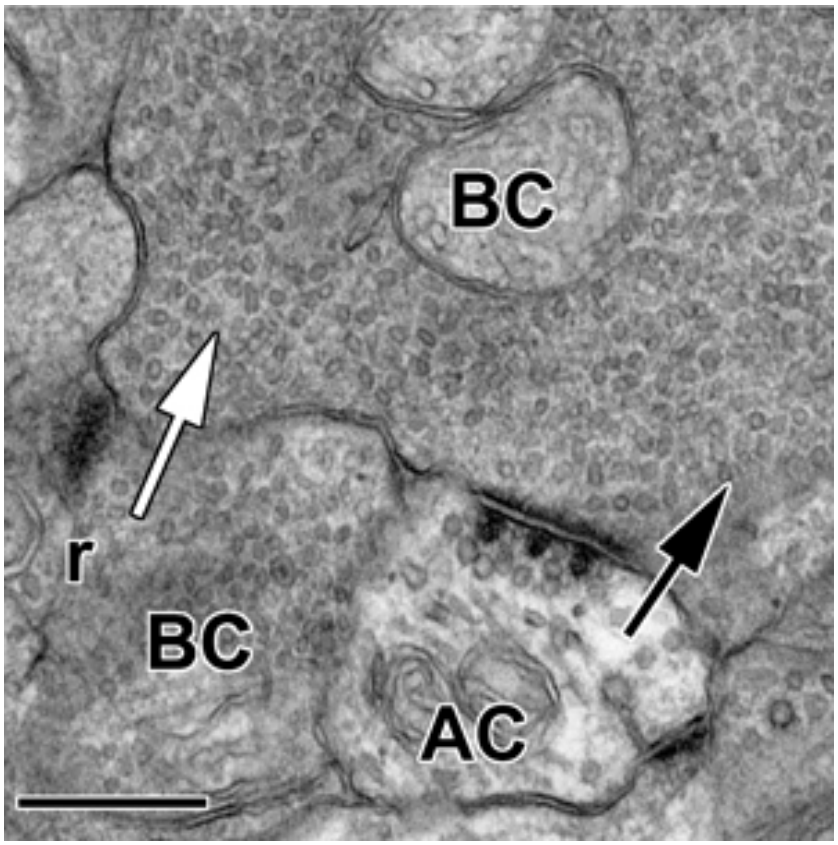

Figure 4: Additional synaptic structures often present in microneuromas, though with immature forms. This example shows a aberrant presynaptic multi-projection amacrine cell (AC) making synaptic contact onto a bipolar cell in parallel with another bipolar cell (BC) profile making a simultaneous synapse complete with synaptic ribbon, onto the same bipolar cell profile. Scale bar = 200 nanometers.

Implications for bionic rescue:

Because of the vast diversity of potential insults in both RP and AMD, any one, targeted intervention will be useful for only a small percentage of potential individuals. Therefore, approaches designed to replace entire systems with bionic and biological solutions may appear attractive. However, as noted all retinal degenerations lead to problems of access and alterations to the fundamental image processing circuitry. The problem of how to rescue vision is further compounded by the issue of when to intervene. Current therapies or interventions are limited to those patients who have lost a considerable portion of their vision and are legally blind. These patients often present at late stage with advanced retinal degeneration (Figure 1) and already likely exhibit profound alterations to the retinal circuitry that corrupt any surrogate inputs.

While modern engineering has allowed significant advancements in miniaturization of circuitry combined with the ability to power potentially prosthetic devices (Asher et al., 2007; Loudin et al., 2007), we still are lacking in our development and implementation of visual system interfaces to those devices. Additionally, the design and implementation will depend upon where in the visual system we intend to attempt an intervention and at what stage of retinal degeneration the subject might be in. Specifically, intervening in a degenerative retina will present an entirely different set of engineering difficulties than intervening at the optic nerve or the visual cortex and it could be argued that until we understand how each component of the visual system processes information, we will not be successful in the implementation of vision rescue prosthetics that attempt a simulation of the retinotopically organized flow of information to the visual cortex where properly patterned inputs result in spatiotemporally correct percepts.

Furthermore, how to actually stimulate the retina is one consideration, but unless one knows the circuitry, or can model the circuitry, there is no predicting the possible output of the neural retina. Additionally, given that neurons in the retina appear to be relatively promiscuous with respect to contacts on cell classes they make during the degenerative process and that those contacts appear to be impoverished, predicting the output of the retina irrespective of the type or methodology of stimulus will be difficult at best. Some modeling (Marc et al., 2007) predicts that circuits may “ring” for many seconds, essentially leaving the visual cortex no option but to filter these inputs out. Additionally, since retinal degeneration is a progressive disease, one might suspect that the neural retina will continue to remodel, possibly even recruiting and corrupting interventions or rescues into a continued degenerative process.

Implications for biological rescue:

These critiques and findings can also be applied to biological rescues in that certain transplantation schemes may slow some forms of retinal degeneration when implemented before degeneration of the sensory retina is complete and remodeling

becomes dominant. This however, is not a viable strategy for most human disease. Further, it is likely that the outcomes of most transplants will be impacted by at least three factors including cell fusion, improper rewiring, and co-opting of transplanted cells into defective or non-functional forms by resident neurons and glia. Many reports of transplanted stem cells assuming phenotypes of host cells are now known to be instances of cell fusion (Terada et al., 2002). It is also a distinct possibility that when delivery of exogenous cells induces trauma from the surgery, aberrant protein and DNA uptake can also alter host and guest phenotypes, confounding analysis.

In addition to the corruptive local and global rewiring that occurs in retinal remodeling, retinas appear to have lost patterning restrictions as well. Naïve cells do not carry the normally present developmental structuring that occurs during retinal maturation and do not induce re-patterning. Moreover, transplanted photoreceptors or any other fragments of retina will certainly engage in wide-area neurite extensions if they survive, and degenerating retinas already engage in profuse generation of aberrant neurites. There is no evidence that any of these processes make proper connections.

This of course also begs the question: What phenotype should an uncommitted stem cell assume and how will it be transcriptionally guided in forming that phenotype? Additionally, properly phenotyping transplanted cells (Canola et al., 2007) is critical and most transplant studies fail in this regard. Any emergent phenotypes, if informed by local signaling from negatively remodeling cells, will most likely be co-opted into an aberrant phenotype. Additionally, most transplanted cells are rejected (Bull et al., 2008) or slowly lose their own mature phenotypes after transplantation. In short, the key error in transplant designs is a belief that the neural retina is normal. It is not normal and in the degenerate retina, there is hardly a cell type that demonstrates normality. The basic assumptions of transplant technologies (intactness, receptivity and instructional capacity of the host neural retina) are false for most retinal degenerations. Moreover, expectations that cells transplanted into negatively remodeling environments will restore normalcy to host cells, maintain mature phenotypes or assume proper phenotypes seem baseless and are as yet, untested.

It should be noted that biological approaches should not necessarily be thought of as impossible as there are a number of “lower” organisms that possess retinas far more complex than mammalian retinas. Yet, these organisms with more complex retinas are able to restore or repair to some extent damage incurred to their retinas through stem cell dedifferentiation and recapitulation of an approximate structure and function of the retina (Raymond et al., 2006). However, these appraisals are gross as there have been no efforts that these authors are aware of that describes the nature of the circuitry in repair zones.

Final:

The diversity of potential defects is impressive because of the complex specialization and highly optimized function of the mammalian retina. Because of this complexity, it may seem tempting to attempt a rescue or target a solution that would bypass all of the potential defects through a straightforward bionic approach, solving all potential blinding diseases with a single solution. Fifty years from now, this may in fact be how history records a cure for vision loss, but any intervention, bionic or otherwise is going to have to deal with a progressive disease that exhibits a plastic, reactive neural retina with likely downstream visual alterations in the circuitry of visual elements in cortex that display their own ability to adapt (Gutnisky and Dragoi, 2008) and potentially remodel in response to retinal deafferentation or alteration in efferent retinal signals resulting from retinal rewiring. These diseases are not focal and will spread, possibly even involving interventions designed to rescue the retina.

FIGURES:

Figure 1: Fundascopic image from 46 year old male with a diagnosis of X-linked retinitis pigmentosa, showing 'pigmented bone spicules', accumulations of pigment epithelium that are formed by migration of the pigment epithelium into the neural retina along glial columns. These clinically pathologic findings are often seen in the peripheral retina in patients with RP.

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illustrated as horizontal bands. The first frame, native retina shows normal lamination and connectivity of cell classes in the retina. Phase 1 reveals early photoreceptor stress and outer segment shortening (1) along with rod and cone neurite extensions projecting down into inner nuclear layer and ganglion cell layer (2, 3). Horizontal cells are also seen contributing to the neurite projections (6) along with rod and cone bipolar cells undergoing dendrite retraction (4,5). Müller cells may also begin to hypertrophy in this stage. By the end of phase 2 there is a complete loss of photoreceptors and elaboration of a Müller cell seal over the neural retina (7), sealing it-off away from the remnant choroid. Neuronal phenotypic revisions are underway or complete at this time (8). Early phase 3 events ensue with the elaboration of neurite extensions from glycinergic and GABAergic amacrine cells along with contributions from bipolar cells and ganglion cells forming complex tangles of processes called microneuromas (9, 10) that form outside the normal lamination of the inner plexiform layer, sometimes merging with the inner plexiform layer. These microneuromas possess active synaptic elements corruptive of normal signaling. By late phase 3, retinal degeneration is advanced with neuronal migration or translocation events occurring in a bi-directional fashion (11) along with neuronal death of many cell classes (12). IPL rewiring and laminar deformation of the plexiform layers can also be observed.

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Funding:
Supported in part by an Unrestricted Grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology & Visual Sciences, University of Utah. Dr. Bryan William Jones Is a recipient of a Research to Prevent Blindness Career Development Award (BWJ). NEI R01 EY02576, R01 EY015128, P01 EY014800 (REM); support from the Cal and JeNeal Hatch Presidential Endowed Chair (REM).

Competing Interests:
Robert E. Marc is a principal of Signature Immunologics. All other authors declare no other competing interests.

Bibliography:

Aguirre GD, Baldwin V, Pearce-Kelling S, Narfstrom K, Ray K, Acland GM (1998) Congenital stationary night blindness in the dog: common mutation in the RPE65 gene indicates founder effect. Mol Vis 4:23.

Aleman TS, Cideciyan AV, Sumaroka A, Schwartz SB, Roman AJ, Windsor EA, Steinberg JD, Branham K, Othman M, Swaroop A, Jacobson SG (2007) Inner retinal abnormalities in X-linked retinitis pigmentosa with RPGR mutations. Invest Ophthalmol Vis Sci 48:4759-4765.

Allikmets R (1997) A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet 17:122.

Allikmets R (2000) Simple and complex ABCR: genetic predisposition to retinal disease. Am J Hum Genet 67:793-799.

Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, Peiffer A, Zabriskie NA, Li Y, Hutchinson A, Dean M, Lupski JR, Leppert M (1997a) Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science 277:1805-1807.

Allikmets R, Singh N, Sun H, Shroyer NF, Hutchinson A, Chidambaram A, Gerrard B, Baird L, Stauffer D, Peiffer A, Rattner A, Smallwood P, Li Y, Anderson KL, Lewis RA, Nathans J, Leppert M, Dean M, Lupski JR (1997b) A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet 15:236-246.

Asher A, Segal WA, Baccus SA, Yaroslavsky LP, Palanker DV (2007) Image processing for a high-resolution optoelectronic retinal prosthesis. IEEE Trans Biomed Eng 54:993-1004.

Bainbridge JW, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K, Viswanathan A, Holder GE, Stockman A, Tyler N, Petersen-Jones S, Bhattacharya SS, Thrasher AJ, Fitzke FW, Carter BJ, Rubin GS, Moore AT, Ali RR (2008) Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med 358:2231-2239.

Boon CJ, Klevering BJ, Hoyng CB, Zonneveld-Vrieling MN, Nabuurs SB, Blokland E, Cremers FP, den Hollander AI (2008) Basal laminar drusen caused by compound heterozygous variants in the CFH gene. Am J Hum Genet 82:516-523.

Bull ND, Limb GA, Martin K (2008) Human Muller stem cell (MIO-M1) transplantation in a rat model of glaucoma: survival, differentiation and integration. Invest Ophthalmol Vis Sci.

Bunker CH, Berson EL, Bromley WC, Hayes RP, Roderick TH (1984) Prevalence of retinitis pigmentosa in Maine. Am J Ophthalmol 97:357-365.

Cameron DJ, Yang Z, Gibbs D, Chen H, Kaminoh Y, Jorgensen A, Zeng J, Luo L, Brinton E, Brinton G, Brand JM, Bernstein PS, Zabriskie NA, Tang S, Constantine R, Tong Z, Zhang K (2007) HTRA1 variant confers similar risks to geographic atrophy and neovascular age-related macular degeneration. Cell Cycle 6:1122-1125.

Canola K, Angenieux B, Tekaya M, Quiambao A, Naash MI, Munier FL, Schorderet DF, Arsenijevic Y (2007) Retinal stem cells transplanted into models of late stages of retinitis pigmentosa preferentially adopt a glial or a retinal ganglion cell fate. Invest Ophthalmol Vis Sci 48:446-454.

Chen CK, Burns ME, He W, Wensel TG, Baylor DA, Simon MI (2000) Slowed recovery of rod photoresponse in mice lacking the GTPase accelerating protein RGS9-1. Nature 403:557-560.

Chen H, Yang Z, Gibbs D, Yang X, Hau V, Zhao P, Ma X, Zeng J, Luo L, Pearson E, Constantine R, Kaminoh Y, Harmon J, Tong Z, Stratton CA, Cameron DJ, Tang S, Zhang K (2008) Association of HTRA1 polymorphism and bilaterality in advanced age-related macular degeneration. Vision Res 48:690-694.

Clarke G, Goldberg AF, Vidgen D, Collins L, Ploder L, Schwarz L, Molday LL, Rossant J, Szel A, Molday RS, Birch DG, McInnes RR (2000) Rom-1 is required for rod photoreceptor viability and the regulation of disk morphogenesis. Nat Genet 25:67-73.

Cremers FP, van de Pol DJ, van Driel M, den Hollander AI, van Haren FJ, Knoers NV, Tijmes N, Bergen AA, Rohrschneider K, Blankenagel A, Pinckers AJ, Deutman AF, Hoyng CB (1998) Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. Hum Mol Genet 7:355-362.

Cuenca N, Pinilla I, Sauve Y, Lund R (2005) Early changes in synaptic connectivity following progressive photoreceptor degeneration in RCS rats. Eur J Neurosci 22:1057-1072.

Cuenca N, Pinilla I, Sauve Y, Lu B, Wang S, Lund RD (2004) Regressive and reactive changes in the connectivity patterns of rod and cone pathways of P23H transgenic rat retina. Neuroscience 127:301-317.

D'Cruz PM, Yasumura D, Weir J, Matthes MT, Abderrahim H, LaVail MM, Vollrath D (2000) Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. Hum Mol Genet 9:645-651.

de Raad S, Szczesny PJ, Munz K, Reme CE (1996) Light damage in the rat retina: glial fibrillary acidic protein accumulates in Muller cells in correlation with photoreceptor damage. Ophthalmic Res 28:99-107.

Delbeke J, Pins D, Michaux G, Wanet-Defalque MC, Parrini S, Veraart C (2001) Electrical stimulation of anterior visual pathways in retinitis pigmentosa. Invest Ophthalmol Vis Sci 42:291-297.

Dewan A, Liu M, Hartman S, Zhang SS, Liu DT, Zhao C, Tam PO, Chan WM, Lam DS, Snyder M, Barnstable C, Pang CP, Hoh J (2006) HTRA1 promoter polymorphism in wet age-related macular degeneration. Science 314:989-992.

Dryja TP, Berson EL, Rao VR, Oprian DD (1993) Heterozygous missense mutation in the rhodopsin gene as a cause of congenital stationary night blindness. Nat Genet 4:280-283.

Dryja TP, McGee TL, Berson EL, Fishman GA, Sandberg MA, Alexander KR, Derlacki DJ, Rajagopalan AS (2005) Night blindness and abnormal cone electroretinogram ON responses in patients with mutations in the GRM6 gene encoding mGluR6. Proc Natl Acad Sci U S A 102:4884-4889.

Duncan JL, Yang H, Vollrath D, Yasumura D, Matthes MT, Trautmann N, Chappelow AV, Feng W, Earp HS, Matsushima GK, LaVail MM (2003) Inherited retinal dystrophy in Mer knockout mice. Adv Exp Med Biol 533:165-172.

Eckhorn R, Wilms M, Schanze T, Eger M, Hesse L, Eysel UT, Kisvarday ZF, Zrenner E, Gekeler F, Schwahn H, Shinoda K, Sachs H, Walter P (2006) Visual resolution with retinal implants estimated from recordings in cat visual cortex. Vision Res 46:2675-2690.

Edwards AO, Ritter R, 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA (2005) Complement factor H polymorphism and age-related macular degeneration. Science 308:421-424.

Faktorovich EG, Steinberg RH, Yasumura D, Matthes MT, LaVail MM (1990) Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor. Nature 347:83-86.

Faktorovich EG, Steinberg RH, Yasumura D, Matthes MT, LaVail MM (1992) Basic fibroblast growth factor and local injury protect photoreceptors from light damage in the rat. J Neurosci 12:3554-3567.

Fariss RN, Li ZY, Milam AH (2000) Abnormalities in rod photoreceptors, amacrine cells, and horizontal cells in human retinas with retinitis pigmentosa. Am J Ophthalmol 129:215-223.

Fei Y (2002) Cone neurite sprouting: an early onset abnormality of the cone photoreceptors in the retinal degeneration mouse. Mol Vis 8:306-314.

Fletcher EL, Kalloniatis M (1996) Neurochemical architecture of the normal and degenerating rat retina. J Comp Neurol 376:343-360.

Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, de Jong PT, Nemesure B, Mitchell P, Kempen J (2004) Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 122:564-572.

Gal A, Li Y, Thompson DA, Weir J, Orth U, Jacobson SG, Apfelstedt-Sylla E, Vollrath D (2000) Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. Nat Genet 26:270-271.

Gias C, Jones M, Keegan D, Adamson P, Greenwood J, Lund R, Martindale J, Johnston D, Berwick J, Mayhew J, Coffey P (2007) Preservation of visual cortical function following retinal pigment epithelium transplantation in the RCS rat using optical imaging techniques. Eur J Neurosci 25:1940-1948.

Gold B, Merriam JE, Zernant J, Hancox LS, Taiber AJ, Gehrs K, Cramer K, Neel J, Bergeron J, Barile GR, Smith RT, Hageman GS, Dean M, Allikmets R (2006) Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet 38:458-462.

Gregory-Evans K, Fariss RN, Possin DE, Gregory-Evans CY, Milam AH (1998) Abnormal cone synapses in human cone-rod dystrophy. Ophthalmology 105:2306-2312.

Gu SM, Thompson DA, Srikumari CR, Lorenz B, Finckh U, Nicoletti A, Murthy KR, Rathmann M, Kumaramanickavel G, Denton MJ, Gal A (1997) Mutations in RPE65 cause autosomal recessive childhood-onset severe retinal dystrophy. Nat Genet 17:194-197.

Gutnisky DA, Dragoi V (2008) Adaptive coding of visual information in neural populations. Nature 452:220-224.

Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, Stockman HA, Borchardt JD, Gehrs KM, Smith RJ, Silvestri G, Russell SR, Klaver CC, Barbazetto I, Chang S, Yannuzzi LA, Barile GR, Merriam JC, Smith RT, Olsh AK, Bergeron J, Zernant J, Merriam JE, Gold B, Dean M, Allikmets R (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A 102:7227-7232.

Hennig MH, Funke K, Worgotter F (2002) The influence of different retinal subcircuits on the nonlinearity of ganglion cell behavior. J Neurosci 22:8726-8738.

Hu G, Wensel TG (2002) R9AP, a membrane anchor for the photoreceptor GTPase accelerating protein, RGS9-1. Proc Natl Acad Sci U S A 99:9755-9760.

Hu G, Zhang Z, Wensel TG (2003) Activation of RGS9-1GTPase acceleration by its membrane anchor, R9AP. J Biol Chem 278:14550-14554.

Huang SH, Pittler SJ, Huang X, Oliveira L, Berson EL, Dryja TP (1995) Autosomal recessive retinitis pigmentosa caused by mutations in the alpha subunit of rod cGMP phosphodiesterase. Nat Genet 11:468-471.

Humayun MS, de Juan E, Jr., Dagnelie G, Greenberg RJ, Propst RH, Phillips DH (1996) Visual perception elicited by electrical stimulation of retina in blind humans. Arch Ophthalmol 114:40-46.

Jakobsdottir J, Conley YP, Weeks DE, Mah TS, Ferrell RE, Gorin MB (2005) Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet 77:389-407.

Jones BW, Marc RE (2005) Retinal remodeling during retinal degeneration. Exp Eye Res 81:123-137.

Jones BW, Watt CB, Marc RE (2005) Retinal remodelling. Clin Exp Optom 88:282-291.

Jones BW, Marc RE, Watt CB, Vaughan DK, Organisciak DT (2006) Neural plasticity revealed by light-induced photoreceptor lesions. Adv Exp Med Biol 572:405-410.

Jones BW, Watt CB, Frederick JM, Baehr W, Chen CK, Levine EM, Milam AH, Lavail MM, Marc RE (2003) Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol 464:1-16.

Kaplan J, Gerber S, Larget-Piet D, Rozet JM, Dollfus H, Dufier JL, Odent S, Postel-Vinay A, Janin N, Briard ML, et al. (1993) A gene for Stargardt's disease (fundus flavimaculatus) maps to the short arm of chromosome 1. Nat Genet 5:308-311.

Kolb H, Gouras P (1974) Electron microscopic observations of human retinitis pigmentosa, dominantly inherited. Invest Ophthalmol 13:487-498.
Koyama R, Yamada MK, Fujisawa S, Katoh-Semba R, Matsuki N, Ikegaya Y (2004) Brain-derived neurotrophic factor induces hyperexcitable reentrant circuits in the dentate gyrus. J Neurosci 24:7215-7224.
Lakhanpal RR, Yanai D, Weiland JD, Fujii GY, Caffey S, Greenberg RJ, de Juan E, Jr., Humayun MS (2003) Advances in the development of visual prostheses. Curr Opin Ophthalmol 14:122-127.
Li JB, Gerdes JM, Haycraft CJ, Fan Y, Teslovich TM, May-Simera H, Li H, Blacque OE, Li L, Leitch CC, Lewis RA, Green JS, Parfrey PS, Leroux MR, Davidson WS, Beales PL, Guay-Woodford LM, Yoder BK, Stormo GD, Katsanis N, Dutcher SK (2004) Comparative genomics identifies a flagellar and basal body proteome that includes the BBS5 human disease gene. Cell 117:541-552.
Li ZY, Kljavin IJ, Milam AH (1995) Rod photoreceptor neurite sprouting in retinitis pigmentosa. J Neurosci 15:5429-5438.
Loudin JD, Simanovskii DM, Vijayraghavan K, Sramek CK, Butterwick AF, Huie P, McLean GY, Palanker DV (2007) Optoelectronic retinal prosthesis: system design and performance. J Neural Eng 4:S72-84.
Machida S, Kondo M, Jamison JA, Khan NW, Kononen LT, Sugawara T, Bush RA, Sieving PA (2000) P23H rhodopsin transgenic rat: correlation of retinal function with histopathology. Invest Ophthalmol Vis Sci 41:3200-3209.
Maguire AM, Simonelli F, Pierce EA, Pugh EN, Jr., Mingozzi F, Bennicelli J, Banfi S, Marshall KA, Testa F, Surace EM, Rossi S, Lyubarsky A, Arruda VR, Konkle B, Stone E, Sun J, Jacobs J, Dell'Osso L, Hertle R, Ma JX, Redmond TM, Zhu X, Hauck B, Zelenaia O, Shindler KS, Maguire MG, Wright JF, Volpe NJ, McDonnell JW, Auricchio A, High KA, Bennett J (2008) Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med 358:2240-2248.
Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM (2007) Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet 39:1200-1201.
Marc RE (1999a) Mapping glutamatergic drive in the vertebrate retina with a channel-permeant organic cation. J Comp Neurol 407:47-64.
Marc RE (1999b) Kainate activation of horizontal, bipolar, amacrine, and ganglion cells in the rabbit retina. J Comp Neurol 407:65-76.
Marc RE (2004) Retinal Neurotransmitters. In: Chalupa LM, Werner J, editors. The Visual Neurosciences.:315-330.
Marc RE (2008) Functional Neuroanatomy of the Retina in Albert and Jakobiec's Principles and Practice of Ophthalmology, 3rd edition (Eds Albert and Miller). Elsivier 1565-1592.
Marc RE, Jones BW (2002) Molecular phenotyping of retinal ganglion cells. J Neurosci 22:413-427.
Marc RE, Jones BW (2003) Retinal remodeling in inherited photoreceptor degenerations. Mol Neurobiol 28:139-147.
Marc RE, Jones BW, Watt CB, Strettoi E (2003) Neural remodeling in retinal degeneration. Prog Retin Eye Res 22:607-655.

Marc RE, Jones BW, Watt CB, Vazquez-Chona F, Vaughan DK, Organisciak DT (2008) Extreme retinal remodeling triggered by light damage: implications for age related macular degeneration. Mol Vis 14:782-806.
Marc RE, Jones BW, Anderson JR, Kinard K, Marshak DW, Wilson JH, Wensel T, Lucas RJ (2007) Neural reprogramming in retinal degeneration. Invest Ophthalmol Vis Sci 48:3364-3371.
Masland RH (2001a) Neuronal diversity in the retina. Curr Opin Neurobiol 11:431-436.
Masland RH (2001b) The fundamental plan of the retina. Nat Neurosci 4:877-886.
McLaughlin ME, Sandberg MA, Berson EL, Dryja TP (1993) Recessive mutations in the gene encoding the beta-subunit of rod phosphodiesterase in patients with retinitis pigmentosa. Nat Genet 4:130-134.
McLaughlin ME, Ehrhart TL, Berson EL, Dryja TP (1995) Mutation spectrum of the gene encoding the beta subunit of rod phosphodiesterase among patients with autosomal recessive retinitis pigmentosa. Proc Natl Acad Sci U S A 92:3249-3253.
Molday LL, Rabin AR, Molday RS (2000) ABCR expression in foveal cone photoreceptors and its role in Stargardt macular dystrophy. Nat Genet 25:257-258.
Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP (1998) Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. Proc Natl Acad Sci U S A 95:3088-3093.
Peng YW, Senda T, Hao Y, Matsuno K, Wong F (2003) Ectopic synaptogenesis during retinal degeneration in the royal college of surgeons rat. Neuroscience 119:813-820.
Pollard H, Khrestchatisky M, Moreau J, Ben-Ari Y, Represa A (1994) Correlation between reactive sprouting and microtubule protein expression in epileptic hippocampus. Neuroscience 61:773-787.
Pu M, Xu L, Zhang H (2006) Visual response properties of retinal ganglion cells in the royal college of surgeons dystrophic rat. Invest Ophthalmol Vis Sci 47:3579-3585.
Raymond PA, Barthel LK, Bernardos RL, Perkowski JJ (2006) Molecular characterization of retinal stem cells and their niches in adult zebrafish. BMC Dev Biol 6:36.
Rockhill RL, Daly FJ, MacNeil MA, Brown SP, Masland RH (2002) The diversity of ganglion cells in a mammalian retina. J Neurosci 22:3831-3843.
Sommer ME, Farrens DL (2006) Arrestin can act as a regulator of rhodopsin photochemistry. Vision Res 46:4532-4546.
Sommer ME, Smith WC, Farrens DL (2005) Dynamics of arrestin-rhodopsin interactions: arrestin and retinal release are directly linked events. J Biol Chem 280:6861-6871.
Specht D, Tom Dieck S, Ammermuller J, Regus-Leidig H, Gundelfinger ED, Brandstatter JH (2007) Structural and functional remodeling in the retina of a mouse with a photoreceptor synaptopathy: plasticity in the rod and degeneration in the cone system. Eur J Neurosci 26:2506-2515.

Stasheff SF (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.
Stone EM, Braun TA, Russell SR, Kuehn MH, Lotery AJ, Moore PA, Eastman CG, Casavant TL, Sheffield VC (2004) Missense variations in the fibulin 5 gene and age-related macular degeneration. N Engl J Med 351:346-353.
Strettoi E, Pignatelli V (2000) Modifications of retinal neurons in a mouse model of retinitis pigmentosa. Proc Natl Acad Sci U S A 97:11020-11025.
Strettoi E, Porciatti V, Falsini B, Pignatelli V, Rossi C (2002) Morphological and functional abnormalities in the inner retina of the rd/rd mouse. J Neurosci 22:5492-5504.
Strettoi E, Pignatelli V, Rossi C, Porciatti V, Falsini B (2003) Remodeling of second-order neurons in the retina of rd/rd mutant mice. Vision Res 43:867-877.
Sullivan R, Penfold P, Pow DV (2003) Neuronal migration and glial remodeling in degenerating retinas of aged rats and in nonneovascular AMD. Invest Ophthalmol Vis Sci 44:856-865.
Sullivan RK, Woldemussie E, Pow DV (2007) Dendritic and synaptic plasticity of neurons in the human age-related macular degeneration retina. Invest Ophthalmol Vis Sci 48:2782-2791.
Sutula T (2002) Seizure-Induced Axonal Sprouting: Assessing Connections Between Injury, Local Circuits, and Epileptogenesis. Epilepsy Curr 2:86-91.
Terada N, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, Meyer EM, Morel L, Petersen BE, Scott EW (2002) Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Nature 416:542-545.
Varela C, Igartua I, De la Rosa EJ, De la Villa P (2003) Functional modifications in rod bipolar cells in a mouse model of retinitis pigmentosa. Vision Res 43:879-885.
Vasireddy V, Uchida Y, Salem N, Jr., Kim SY, Mandal MN, Reddy GB, Bodepudi R, Alderson NL, Brown JC, Hama H, Dlugosz A, Elias PM, Holleran WM, Ayyagari R (2007) Loss of functional ELOVL4 depletes very long-chain fatty acids (> or =C28) and the unique omega-O-acylceramides in skin leading to neonatal death. Hum Mol Genet 16:471-482.
Vugler A, Lawrence J, Walsh J, Carr A, Gias C, Semo M, Ahmado A, da Cruz L, Andrews P, Coffey P (2007) Embryonic stem cells and retinal repair. Mech Dev 124:807-829.
Wang QL, Chen S, Esumi N, Swain PK, Haines HS, Peng G, Melia BM, McIntosh I, Heckenlively JR, Jacobson SG, Stone EM, Swaroop A, Zack DJ (2004) QRX, a novel homeobox gene, modulates photoreceptor gene expression. Hum Mol Genet 13:1025-1040.
Wässle H (2004) Parallel processing in the mammalian retina. Nat Rev Neurosci 5:747-757.
Weiss T (1996) Cellular Biophysics: Electrical Properties. Cambridge, MA: MIT Press: 557.
Wensel TG (2008) Signal transducing membrane complexes of photoreceptor outer segments. Vision Res.

Yanai D, Weiland JD, Mahadevappa M, Greenberg RJ, Fine I, Humayun MS (2007) Visual performance using a retinal prosthesis in three subjects with retinitis pigmentosa. Am J Ophthalmol 143:820-827.

Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, Clayton DG, Hayward C, Morgan J, Wright AF, Armbrecht AM, Dhillon B, Deary IJ, Redmond E, Bird AC, Moore AT (2007) Complement C3 variant and the risk of age-related macular degeneration. N Engl J Med 357:553-561.

Yen HJ, Tayeh MK, Mullins RF, Stone EM, Sheffield VC, Slusarski DC (2006) Bardet-Biedl syndrome genes are important in retrograde intracellular trafficking and Kupffer's vesicle cilia function. Hum Mol Genet 15:667-677.

Young MJ, Ray J, Whiteley SJ, Klassen H, Gage FH (2000) Neuronal differentiation and morphological integration of hippocampal progenitor cells transplanted to the retina of immature and mature dystrophic rats. Mol Cell Neurosci 16:197-205.

Zarbin MA (2004) Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 122:598-614.

Zeitz C, Gross AK, Leifert D, Kloeckener-Gruissem B, McAlear SD, Lemke J, Neidhardt J, Berger W (2008) A novel constitutively active rhodopsin mutation (p.Ala295Val) causes autosomal dominant CSNB. Invest Ophthalmol Vis Sci.

Zeitz C, van Genderen M, Neidhardt J, Luhmann UF, Hoeben F, Forster U, Wycisk K, Matyas G, Hoyng CB, Riemslag F, Meire F, Cremers FP, Berger W (2005) Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a distinctive scotopic 15-Hz flicker electroretinogram. Invest Ophthalmol Vis Sci 46:4328-4335.

Zhang K, Kniazeva M, Han M, Li W, Yu Z, Yang Z, Li Y, Metzker ML, Allikmets R, Zack DJ, Kakuk LE, Lagali PS, Wong PW, MacDonald IM, Sieving PA, Figueroa DJ, Austin CP, Gould RJ, Ayyagari R, Petrukhin K (2001) A 5-bp deletion in ELOVL4 is associated with two related forms of autosomal dominant macular dystrophy. Nat Genet 27:89-93.

Zrenner E (2002a) Will retinal implants restore vision? Science 295:1022-1025.

Zrenner E (2002b) The subretinal implant: can microphotodiode arrays replace degenerated retinal photoreceptors to restore vision? Ophthalmologica 216 Suppl 1:8-20; discussion 52-23.