Remodeling barriers to retinal transplant therapies
Many forms of blindness arise from genetic defects that lead to the death of rod and cone photoreceptors. Four classes of intercession have been proposed to ameliorate these diseases: gene therapy, molecular therapy, cell therapy and bionic implants. This blue paper addresses the barriers to cell therapies.

1. Cell transplant therapies presume substantial survival of retinal outflow channel architectures. The retina is complex and forms ≈ 14 patterned outflow channels, realized as ganglion cells. The mammalian retinal parts list 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 14 ganglion cells. Thus, ≈ 60 cellular devices form the outflow channels. Our next challenge will be to trace the wirings that create outflow channels; resolve synaptic transduction assemblies in terms of molecular signaling and electromorphology; reconcile wiring models with physiological data; and produce a complete, validated model of retinal vision.

There are four broad classes of cell-based retinal degeneration therapies: (1) RPE or RPE-surrogate transplants; (2) photoreceptor transplants; (3) embryonic retina transplants; (4) stem cell transplants. RPE and RPE/surrogate transplants are designed to replace failed RPE or provide survival factor delivery. These are the simplest and most promising therapies, but must be introduced prior to cone loss and remodeling onset. All other therapies depend explicitly upon the survival of normal architecture in the neural retina and proper synaptic patterning of all transplanted elements. Rod transplants are a popular model system, but have poor prospects for restoring photopic vision. Embryonic systems represent large-scale replacements that must serially connect with ganglion cells or replace them. Finally, injections of naïve stem cells require an unknown guidance to activate proper transcriptions of coordinate gene arrays, morphing extrinsic cells into phenotypes proper for retinal function.

2. Photoreceptor degenerations trigger negative remodeling of retinal outflow channel architectures. The retina is a bilaminar device. The sensory retina is composed of photoreceptors and is the photon transducer layer. The neural retina, composed of the remaining neuron classes is the image processor layer. It has long been claimed that the neural retina remains unchanged after the death of the sensory retina. This is incorrect. The neural retina enters a protracted tertiary phase of remodeling characterized by (1) disruption of topography by glial hypertrophy and neuronal migration, (2) neuronal cell death; and (3) extensive rewiring.

2.1 Neural retinal topology is corrupted in retinal degenerations. After loss of the cones, all Müller cells enter a hypertrophic response phase where the perikarya migrate throughout the retina and their processes hypertrophy to form distal and proximal seals, as well and columns or walls of glia that transect the neural retina. The distal glial seal obliterates the subretinal space and there is no place to transplant new cells without creating traumas that trigger further remodeling. All glial surfaces appear to be guides for unregulated neuronal migration and transplanted cells will also migrate. Spatial patterning is key to visual processing, and no control of de-patterning is offered by any transplant design to date.

2.2 Neuronal cell death is extensive in retinal degenerations. Though many neurons persist after death of the sensory retina, all classes are susceptible to cell death in varying fractions and patterns. Focal regions of complete inner nuclear layer depletion are common and some genetic forms can lead to complete loss of ganglion cells in large patches of retina. There is no evidence that transplanted cells are better survivors or can delay intrinsic death events. So far, it appears that transplantation triggers more death and remodeling.

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2.3 Aberrant rewiring attends retinal degenerations.
The most dramatic changes in remodeling retinas include the elaboration of new neurite fascicles and
the formation of new circuitry in microneuromas across the retina, next to the distal glial seal. New circuitry includes aberrant re-entrant bipolar cell circuits and extensive changes in synaptic architecture. Modeling of new circuits shows that all are corruptive and many form resonant circuits. Thus, the remnant neural retina is no longer an effective image processor. Insertion of any transplant system into this architecture offers no basis for recovery of proper wiring.

3. Cell fusion, improper rewiring, and co-opting prevent restoration of a normal retina. 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 is not a viable strategy for most human disease. Further, transplantation studies often do not report failure rates or study transplant fate properly. It is likely that the outcomes of most transplants will be impacted by cell fusion, improper rewiring, and co-opting of transplanted cells into defective or non-functional forms by resident neurons and glia.

3.1 Fusion.
Many reports of transplanted stem cells assuming phenotypes of host cells are now known to be instances of cell fusion. When sufficient trauma attends the delivery of exogenous cells, aberrant protein and DNA uptake can also alter host and guest phenotypes, confounding analysis.

3.2 Improper rewiring
Remodeling retinas engage in corruptive local and global rewiring and have lost patterning restrictions as well. Naïve cells do not carry this developmentally proffered structuring and cannot 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.

3.3 Co-opting
What phenotype should an uncommitted stem cell assume and how will it be transcriptionally guided in forming that phenotype? Published data demonstrate that most transplant studies fail to properly phenotype cells; that any emergent phenotypes, if informed by local signaling from negatively remodeling cells, will most likely be co-opted into an aberrant phenotype; and that most cells slowly lose their own mature phenotypes after transplantation. The key error in transplant designs is a belief that the neural retina is normal. It is not – there is hardly a cell type that evinces normality.

4. Summary: 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 are baseless and, as yet, untested.

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