New Imaging Modalities for Monitoring Retinal Disease

- Steven Becker, PhD

OBJECTIVE Functional imaging technologies can enable noninvasive, in vivo monitoring of activity of individual retinal neurons.

PURPOSE The National Eye Institute (NEI) is catalyzing the translation of ocular stem cell therapies with its Audacious Goals Initiative for Regenerative Medicine (AGI). For the past five years, NEI funded five imaging projects to increase the sensitivity and resolution of a variety of imaging modalities. The goal of these projects is to allow the noninvasive monitoring of retinal neurons in patients.

METHODS Advances in imaging will enable researchers to study retinal cell death and monitor cell replacement therapies. Some projects are developing eye tracking systems to compensate for eye movement, enabling high-resolution optical coherence tomography (OCT) and adaptive optics scanning laser ophthalmoscopy (AOSLO). One project is developing magnetic resonance imaging (MRI) techniques to noninvasively assess the structure and function of regenerating axons in the optic nerve. These technologies will give clinicians the tools to better assess disease progression and the effects of treatment.

RESULTS Alfredo Dubra at Stanford is developing a suite of technologies that includes real-time eye motion stabilization, a tunable lens to improve the focusing of all colors of light, and high-throughput methods for the functional testing of cells. These imaging technologies will advance the usability of next-generation retinal cameras and microscopes and will compensate for involuntary eye movements. Krzysztof Palczewski's team at UC-Irvine has developed a two-photon microscope that measures the metabolism and distribution of vitamin A derivatives within photoreceptors via their autofluorescent properties. This technology will enable the monitoring of disease progression and response to future regenerative therapies. David Williams at the University of Rochester has designed an optical system to image the light responses of individual retinal cells in macaques. The system utilizes fluorescent calcium indicators to image nerve cell firing and infrared two-photon microscopy.

CONCLUSION The imaging modalities supported by the NEI AGI will enable approaches that can determine when and where retinal cells are dying as well as image and probe the physiology of replacement cells. These noninvasive functional imaging technologies that will improve the ability of eye care professionals to help people with vision loss.

HUMAN RESEARCH No: Study does not involve human research

Barriers facing cell replacement therapies

- Russell Van Gelder, MD, PhD

OBJECTIVE Several challenges need to be overcome in order for neuronal cell replacement therapies for retinal diseases to be translated to the clinic.

PURPOSE In the fall of 2018 the National Eye Institute convened a workshop bringing researchers, clinicians, regulators, and company representatives to discuss how to translate cell replacement therapies as part of its Audacious Goals Initiative for Regenerative Medicine. That meeting identified several preclinical and clinical challenges that need to be addressed in order to bring treatments to patients.

METHODS Brief presentations and discussion from leading experts identified the need of better preclinical animal models, improved cell characterization, advances in manufacturing, early engagement with regulators, guidance for clinicians about when and how to treat patients with cell therapies, and developing outcome measures that are clinically meaningful and readily measured. Regulators expressed the challenges with keeping up with the fast-moving field and businesses voiced their struggle to create new funding and reimbursement strategies.

RESULTS Attendees provided a number of recommendations to the NEI. Some needs are being pursued by current AGI consortia such as advanced imaging technologies, understanding the biology of regeneration, and the development of better animal models. Dissemination of the tools, techniques, and informational resources coming out of AGI to the broader research community is now being planned. Engaging clinicians to figure out what retinal diseases are optimally suited to cell therapy and determining the conditions to intervene with a cell replacement therapy are also important next steps. Training retina surgeons with the latest techniques such as intraoperative OCT and centralizing training for multicenter trials to minimize site to site variation were some practical suggestions that would aid in the NEI effort. Immunosuppression regimens need to be optimized and outcomes from various RPE clinical trials will be informative. Lessons from the spinal cord injury and face transplantation fields were also shared.

CONCLUSION Replacing the cells lost in retinal diseases remains a daunting goal, but 5 years into the endeavor the NEI has laid a foundation that can support the translation of this promising strategy in the next 10 years. Retinal cell replacement trials currently being planned as well as other neuroprotective strategies offer hope that debilitating ocular conditions can be treated in new ways in the coming years.

HUMAN RESEARCH No: Study does not involve human research