Prof. Larry Benowitz: the future of optic nerve regeneration and the difficulty of keeping retinal ganglion cells alive

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Editor's note

Guangzhou Glaucoma Forum (GZGF) was successfully held in the Zhongshan Ophthalmology Center on April 21–22, 2018. The forum gathered domestic and international experts from all over the world, including Prof. Larry Benowitz from Harvard Medical School, Prof. Leopold Schmetterer from Singapore Eye Research Institute, Prof. Anuj Chauhan from University of Florida, Prof. Shlomo Melamed from Israel, and Prof. Keith Barton from Moorfields Eye Hospital. AME editorial team had the honor to interview Prof. Benowitz.

Prof. Benowitz gave a lecture on the topic "Optic Nerve Regeneration". During the talk, he described some of the latest research progress of his group, highlighting Dr. Yiqing Li's work. Through Dr. Li's work, he found that Zn^{2+} chelation promotes RGC survival and axon regeneration after optic nerve injury. He mentioned how Zn^{2+}, which rises rapidly in the retina after optic nerve injury, is carried to RGCs after being released from synaptic vesicles in amacrine cells (where it accumulates due to the action of a zinc transporter protein, ZnT3). After Prof. Benowitz's talk, we are all excited about the future of optic nerve regeneration.

Expert introduction

Dr. Larry Benowitz (*Figure 1*) is Professor of Neurosurgery and Ophthalmology at Harvard Medical School and Director of the Laboratories for Neuroscience Research in Neurosurgery at Boston Children's Hospital. At Boston Children's Hospital, he is also appointed as Endowed Professor of Neurosurgical Innovation and Research. At Harvard Medical School, he is the Co-chair of the Committee on Awards and Honors and has taught in a number of courses.

Professor Benowitz joined Harvard Medical School in 1979. He has numerous outstanding research publications with a focus on brain rewiring after injury since early 70s.

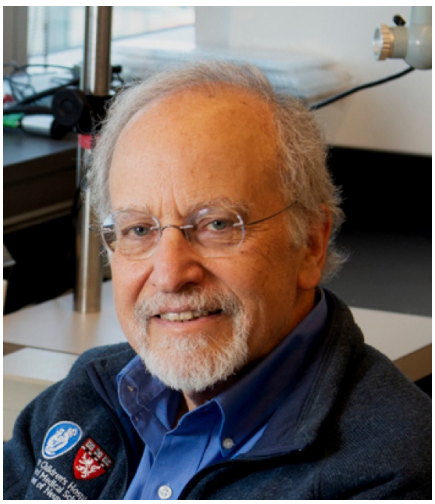

Figure 1 Prof. Larry Benowitz.

He and his lab have focused on recovery after central nervous system (CNS) injury, including stroke, spinal cord injury, and optic nerve injury. In 2006, he was named by *Scientific American* as one of the 50 leaders of the year in science and technology.

Interview

AES: Please introduce yourself to our readers.

Prof. Benowitz: I am Larry Benowitz, a professor of Neurosurgery and Ophthalmology at Harvard Medical School. I hold an endowed chair at Boston Children's Hospital where my laboratory is located. The general interest of our laboratory is to understand how to fix the central nervous system; how to fix connections in the brain, optic nerve and spinal cord after injury. Currently, most of our work is focused on the regeneration of the optic nerve and on preservation of the retinal ganglion cells (RGCs) after the optic nerve has been injured.

AES: We know the number of glaucoma patients is increasing these years. What do you think are the primary causes for glaucoma?

Prof. Benowitz: There are multiple factors. I think one area that should receive more attention is the role of inflammation. Many people are studying what happens directly to RGCs, but there is a lot of evidence showing that inflammation plays an important role.

In the past year, a very important paper was published showing that even after just injuring the optic nerve, there is a massive inflammatory reaction that contributes to the death of the RGCs. Importantly, if you block the inflammation, the survival rate of the RGCs remains high despite the axonal injury. We do not understand yet how the events that occur in retinal neurons activate inflammatory cells, but this will be an important area for investigation in the future. Likewise, in several mouse models of glaucoma, elevation of intraocular pressure leads to an inflammatory reaction at the optic nerve head (equivalent to the human lamina cribrosa) before RGCs begin to die, and blocking this inflammation protects RGCs despite a persistence of ocular hypertension.

Meanwhile, the work that Dr. Yiqing Li, an Instructor in Neurosurgery at Harvard Medical School, has done will continue to be an important part of this evolving story, because through his work we are learning that many cells in the retina participate in the death of the RGCs, and that post-injury changes are not just occurring in the RGCs themselves. We have to think about the reaction to injury as involving a complex set of interactions among several cell types.

AES: Since glaucoma is a neurodegenerative disease of the optic nerve and retina, could you share with us the commonly-used regenerative therapies?

Prof. Benowitz: This question is a bit difficult, but of course the most important thing is to make sure that RGCs remain alive. The first thing we have to do is to ensure that the cells stop dying. We currently are learning many things about why the cells die and how to prevent it.

Dr. Li's work has shown the role of ionic zinc in contributing to the death of RGCs, and we know from the work of other groups that there is a whole complex series of events that become triggered in the retina when RGC axons are injured.

So again, the important thing is to understand the interaction between what happens to the ganglion cells themselves and how multiple cell types in the retina contribute to RGC death. I think the future of glaucoma research will be to understand those multiple cellular and molecular events and going beyond just simply maintaining low intraocular pressure (IOP).

AES: What is your vision for optic nerve regeneration?

Prof. Benowitz: We are making progress. Our laboratory and others have learned many things about why RGCs fail to regenerate axons and how to reverse this situation, but we still have a long way to go. Although we have shown in principle that RGCs can be stimulated to regenerate damaged axons back to the brain, the number of RGCs that do so is probably about 1% of the total. I think the future is in collaboration, bringing together the best ideas from multiple labs for the sake of patients. At this moment, several of the most prominent laboratories in this field are joining together to see what we can do to make regeneration much stronger than is currently possible. But again, the first thing is to keep the cells alive and we are trying hard to do that as well.

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Footnote

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