University at Buffalo
The State University of New York
Jacobs School of Medicine and Biomedical Sciences

Department of Ophthalmology
Ira G. Ross Eye Institute
Office of the Vice Chairman / Director of Research

January 15, 2024

Helen Keller Prize for Vision Research
Helen Keller Foundation
ATTN: Lara C. Beckwith, Executive Director
Email: lbeckwith@helenkellerfoundation.org

Dear Ms. Beckwith:

I am writing to nominate **Robert E. ("Gene") Anderson, MD, PhD** for the **2025 Helen Keller Prize for Vision Research**. [This nomination is supported also by a letter from John S. Penn, PhD (Vanderbilt University).] The majority of what we currently know regarding lipid biosynthesis and metabolism in the eye (especially in the retina) and their relationship to both the normal biology as well as pathobiology of the retina is largely due to the *foundational scientific contributions* emanating from the Anderson laboratory over the past 50 years. Arguably, Gene Anderson is **the world's leading authority on the biosynthesis and metabolism of lipids in the retina**. His and his coworkers' seminal discoveries have both fundamental as well as translational relevance for understanding the molecular etiology and the potential treatment of retinal degenerative disorders (as well as other neurodegenerative diseases) that stem from a variety of sources, both hereditary and traumatic.

Gene Anderson is the George Lynn Cross Research Professor *Emeritus* of Ophthalmology and Cell Biology at the University of Oklahoma Health Sciences Center (OUHSC) in Oklahoma City, OK (USA). Per Google Scholar, as of this writing, his **h-index=78, i10=321, with >21,988 citations** to his published work (>310 publications, plus 20 co-edited books); this is indicative of **highly prodigious and impactful scholarly productivity**. Some key discoveries from the Anderson lab include (but are not limited to) the following:

Demonstration of the essential role of *omega*-3 fatty acids in retinal function. Gene's laboratory was the first to show that docosahexaenoic acid (DHA; C22:6ω3)— an "essential" fatty acid (cannot be made *de novo*, so must come from the diet)— is not only the predominant fatty acid in retinal rod photoreceptor outer segment (ROS) membranes (as well as the retina, in general), but is also required for ROS membrane assembly, maintenance, and electrophysiological function as well as for the development of the retina and visual system. Their initial findings were published in two seminal papers in *Science* (1973 and 1975). These two papers were the first to demonstrate unequivocally an identified biological function for ω3 fatty acids in any animal tissue. For this discovery, Gene was inducted in 2016 into the inaugural class of ISSFAL Fellows of the International Society for the Study of Fatty Acids and Lipids. Gene's functional findings were confirmed in primates made deficient in DHA and ultimately in preterm human infants, whose formulas were deficient in omega-3 fatty acids. Later studies by several groups showed that DHA has beneficial effects on human preterm and neonatal retinal and cognitive development, which contributed to the body of information that ultimately lead to DHA being included in infant dietary formulas. Gene's lab was the first to demonstrate that DHA is conserved by the retina during omega-3 fatty acid deprivation— yet another indication of the importance of DHA to the retina.

Role of the phosphoinositide cascade in invertebrate retinal phototransduction. In collaboration with Joel Brown and others, Gene's lab was the first to show that light activates enzymes in the invertebrate retina that cause the release of inositol phosphate, which then causes release of calcium from intracellular stores. Calcium release is the signal for visual transduction in the invertebrate retina. Notably, this explained the mechanism by which light converts chemical energy into an electrical signal in the invertebrate retina. In their collaborative 1984 *Nature* paper, Gene's lab identified the inositol phosphate products produced by light activation of phospholipase C and Joel Brown's lab showed that injection of these products into ventral eyes of

Limulus (horseshoe crab) recapitulated the light effect. This study done almost four decades ago demonstrated the power of combining biochemistry and electrophysiology to studies on a living biological system.

Role of the insulin receptor/PI-3-kinase/Akt pathway in stress-induced retinal degenerations. Gene's lab discovered that the insulin receptor (IR) is present in rod and cone outer segment membranes and is activated by light, which sets in motion a series of reactions involving phosphoinositol-3-kinase (PI-3-K) and Akt (protein kinase B) that ultimately lead to neuroprotection of the retina from oxidative stress. Hence, the IR/PI-3-K/Akt pathway in rod and cone photoreceptors is one of the endogenous defense systems that protects the retina from oxidative stress and preserves visual function. Importantly, this pathway is "druggable"— *i.e*., it can be modulated by pharmaceuticals, so offers a potential therapeutic target for preserving remnant visual function under conditions of progressive degeneration.

Identification of the biosynthetic step catalyzed by ELOVL4, the enzyme that is mutated in autosomal dominant Stargardt-3 juvenile macular degeneration (STGD3). Genetic studies had identified mutations in *ELOVL4* (**ELO**ngation of **V**ery **L**ong chain fatty acids-**4**) as the cause of STGD3, although the specific biochemical reaction catalyzed by ELOVL4 was unknown. The Anderson lab solved this mystery by showing that ELOVL4 catalyzed the first (rate-limiting) step in the formation of very long chain polyunsaturated fatty acids (VLC-PUFAs; ≥ 28-carbons) in the retina. Gene worked with Martin-Paul Agbaga (one of his former PhD trainees, now an independent faculty member) to clone and express ELOVL4 in culture and unequivocally identify the products as VLC fatty acids. Importantly, they showed that retinal degeneration in a mouse model of STGD3 is caused by a dominant-negative effect of the mutant ELOVL4 on the wildtype protein, which results in further reducing VLC-PUFA levels in the retina. Later studies by another one of Gene's graduate students, Lea Bennett, showed that absence of VLC-PUFAs in the retina leads to photoreceptor cell death. This seminal discovery has led to current studies to determine if dietary supplementation with VLC-PUFAs can rescue degenerating or dying retinal cells. If so, this opens the possibility of a new, effective therapeutic avenue for treatment of humans with dominant Stargardt's macular degeneration.

Current research activities. Although "retired", Gene remains active in two areas of retinal research that may have significant impacts on treatment of blinding retinal diseases. He, along with Martin-Paul Agbaga, have recently obtained sufficient amounts of a VLC-PUFA (34:5n3) to carry out pharmacokinetic and rescue studies in their mouse model of STGD3. If VLC-PUFA are able to prevent retinal degeneration in this model, the next step will be to acquire sufficient amounts of these fatty acids to do a clinical trial in humans with STGD3. A broader implication of these findings could be clinical trial to treat AMD, since Paul Bernstein's laboratory has found that the levels of VLC-PUFAs are lower in the macula of AMD donor eyes than in age matched non-AMD donor eyes. In his second area of research, Gene and Martin-Paul are using a modified 22:6n3 that is less susceptible to lipid peroxidation to try to prevent retinal pathology that develops in the well-known oxidant stress mouse model of retinopathy of prematurity (ROP). Preliminary results are promising as they are able to replace over 90% of the 22:6n3 in the mouse retinas with the less susceptible form. The clinical implications of a successful study are enormous as there is currently no medical treatment for retinopathy of prematurity (ROP).

In summary, the studies performed in the Anderson lab have resulted in a series of fundamental and profoundly impactful discoveries, including the elucidation of novel mechanisms that offer promising new avenues for the development of innovative translational approaches to treating retinal degenerative diseases. His life's cumulative work has markedly enlightened our understanding of fundamental molecular and cellular mechanisms by which photoreceptor/RPE functional integrity is promoted and sustained— an essential prerequisite for vision. [On a personal note: I consider myself to be most fortunate to be one of his many former trainees. He was the best mentor I've ever had, and that relationship has continued over the course of my entire career. **Gene Anderson is truly a *mensch* and is an exemplar of not only what a *scientist* should be, but what a *human being* should be**.] Hence, **it is with my highest enthusiasm** that I nominate Dr. Robert E. Anderson for the 2025 Helen Keller Prize for Vision Research.

Sincerely,

Steven J. Fliesler, PhD
SUNY Distinguished Professor
Meyer H. Riwchun Endowed Chair Professor of Ophthalmology
Vice-Chairman & Director of Research, Department of Ophthalmology, and
Professor, Department of Biochemistry and the Neuroscience Graduate Program
and Research Career Scientist, VA Western NY Healthcare System

VANDERBILT UNIVERSITY

MEDICAL CENTER

John S. Penn, Ph.D.
KTEF Endowed Director and Professor
Vice Chairman
Vanderbilt Eye Institute

January 16, 2024

Helen Keller Prize for Vision Research
Helen Keller Foundation for Research and Education
1201 11th Avenue South, Suite 300
Birmingham, Alabama, USA 35205

ATTN: Laura C. Beckwith, Executive Director

Dear Ms. Beckwith,

I am writing to support the nomination of Robert E. "Gene" Anderson, M.D., Ph.D., for the 2025 Helen Keller Prize for Vision Research, widely viewed as the most prestigious award in the field of vision research. I am fully confident that Dr. Anderson's collective contributions to the field of retinal lipid biochemistry warrant this singular recognition. Spanning nearly half a century, Dr. Anderson's many seminal contributions have achieved several important goals: his studies have been of critical importance to our fundamental understanding of lipid metabolism in the retina, they have provided the foundation for many discoveries by other investigators that would have been otherwise impossible, and they have led to the consideration and development of several novel therapeutic strategies for a number of clinically significant eye diseases.

By way of introduction to the members of your selection committee, I am an endowed professor and vice chairman of Ophthalmology and Visual Sciences and serve as Associate Dean for Faculty Affairs in the Vanderbilt University School of Medicine. I have secondary appointments in Cell & Developmental Biology, Molecular Physiology & Biophysics, Pharmacology, and Medical Education & Administration. I have known Gene Anderson for 40 years and have both personal and professional perspectives from which to draw in evaluating his suitability for the distinction of Helen Keller Laureate. I joined Gene's lab at Baylor College of Medicine as a postdoctoral fellow in 1984, was promoted under his mentorship to instructor, then assistant professor, and eventually left Baylor after five years under his expert training to further develop my own research program. Gene has remained my active mentor ever since.

Dr. Anderson is the Dean A. McGee Professor Emeritus of Ophthalmology, Professor Emeritus of Cell Biology, George Lynn Cross Research Professor Emeritus, and Adjunct Professor Emeritus of Biochemistry & Molecular Biology and Geriatric Medicine at the University of Oklahoma Health Sciences Center (OUHSC). He served as both the chairman of Cell Biology and the Research Director at Dean McGee during his many years of service at OUHSC. Over the course of his career, he also has served both the International Society for Eye Research (ISER) and the Association for Research in Vision and Ophthalmology (ARVO) in multiple elected governance roles, including Councilor and President of ISER and founding Trustee (Biochemistry section) and Vice President of ARVO. He has won major

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awards from both organizations, including the Kayser Award from ISER in 2012 and the Proctor Medal from ARVO in the same year.

Laying a solid foundation for all future studies in the field of retinal lipid biology, Gene first described the lipid composition of mammalian photoreceptor outer segment membranes and retinas, and he played a principal role in defining the importance of docosahexaenoic acid (22:6n3, DHA) in photoreceptor function. Extending this line of investigation, Gene showed that oxidation of polyunsaturated fatty acids like DHA is an important component of environmentally induced retinal degenerations, and he tested the protective activity of DHA supplementation, elucidating its therapeutic effects. This approach illustrates an important theme of Gene's work; he first investigated and characterized a fundamental aspect of retinal lipid biology, and he then applied his newly acquired knowledge to therapeutic development and testing. This is the very definition of translational (and, in the case of Gene's work, transformative) science.

Furthermore, Dr. Anderson and his co-workers made the seminal discovery that light activates the production of the phosphoinositide PIP_3 from PIP_2 in both rod and cone outer segments through the insulin receptor activation of PI 3-kinase. This was the first biochemical demonstration of an insulin receptor in photoreceptor outer segment membranes and the first indication that the receptor was activated *in situ* by light, rather than by insulin. The product of these events, PIP_3, is a signaling molecule with multiple intracellular targets. In the retina, Gene discovered that PIP_3 activates an endogenous neuroprotective pathway that protects the retina from stress-induced degeneration. Later, he discovered that insulin receptor activation of PI 3-kinase also serves to regulate glucose metabolism in rods and cones at steps in the glycolytic pathway that lead to shunting of more glucose into the hexose monophosphate pathway, an important source of reducing equivalents like NADPH.

Additionally, Dr. Anderson identified the catalytic function of the enzyme, ELOVL4 (elongation of very-long-chain fatty acids-4), that was known to be truncated in autosomal dominant Stargardt Disease. He demonstrated that activation of ELOVL4 is an early step in the formation of a class of previously unrecognized very long chain polyunsaturated fatty acids (VLC-PUFAs) in the retina. Further, Gene showed that when retinal levels of these VLC-PUFAs are reduced below a certain threshold, photoreceptor death is triggered. This has spawned efforts to determine if exogenous administration of VLC-PUFAs is neuroprotective, potentially offering a novel approach to the treatment of Stargardt Disease.

There is no uncertainty among our community that Gene's published works represent landmark contributions to the field; his studies are directed at significant targets and are creative, impactful and paradigm-shifting. In my view, we have learned more about functional and dysfunctional retinal lipid biochemistry from Gene Anderson than any other scientist. Consistent with this claim, Gene is universally considered to be an extraordinarily patient and gifted teacher. Trust me, if he could teach lipid biochemistry to

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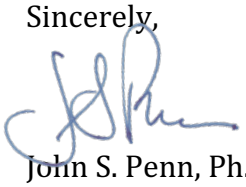
me, he can teach it to anyone. And Gene's tutelage went far beyond lipid biochemistry. Indeed, though I left his direct tutelage 35 years ago, to this day when I find myself in a challenging professional circumstance, I often reflect on Gene's strategies for successful outcomes.

Finally, over decades, Dr. Anderson has been a generous collaborator who shares his knowledge and resources freely; his many successful collaborations with scientists throughout the world attest to that. Moreover, his record of service to our most important professional organizations is exemplary and is an important part of his scientific legacy. His legacy is expanded by his training and mentoring of dozens of scientists who now contribute their own creative ideas to the goal of improving our understanding of the visual system in health and disease. Indeed, his record of training scientists who go on to develop their own impactful vision research programs is unparalleled, and it would not surprise me if, following in Gene's footsteps, one or more of them is nominated for this prestigious award in the future. In these additional ways, Gene's impact on our research community and the field is vastly amplified beyond his own highly significant scientific contributions.

For the reasons detailed above and others too numerous to elaborate here, I unequivocally and enthusiastically endorse this nomination and urge your strong consideration of Dr. Gene Anderson for the 2025 Helen Keller Prize for Vision Research. It would be quite a challenge for me to identify a more worthy recipient.

Sincerely,



John S. Penn, Ph.D.
Associate Dean, Endowed Professor and Vice Chairman

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Robert Eugene Anderson**

eRA COMMONS USER NAME (credential, e.g., agency login): ROBERTANDERSON

POSITION TITLE: George Lynn Cross Research Professor *Emeritus* of Cell Biology and Ophthalmology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M Univ, College Station, TX	BA	06/1963	Mathematics
Texas A&M Univ, College Station, TX	MS	06/1965	Biochemistry
Texas A&M Univ, College Station, TX	PhD	06/1968	Biochemistry
Oak Ridge (TN) Associated Universities	Postdoc	06/1969	Biochemistry
Baylor College of Medicine, Houston, TX	MD	05/1975	Medicine

A. Personal Statement

I have studied lipid metabolism in the normal and diseased retinas for the last 55 years. During this time, we made a number of discoveries regarding the role of lipids in retinal structure and function, including 1) demonstrating the importance of docosahexaenoic acid (DHA, 22:6n3) in retina function in human infants and rats, 2) showing that PIP_2 hydrolysis generated the light-driven second messengers necessary for visual excitation in the invertebrate retina, 3) describing the plasticity of retinal photoreceptors to up-regulate endogenous neuroprotective pathways in response to stress (now called pre-conditioning), 4) identifying lipid peroxidation as a major risk-factor in retinal degenerations, 5) identifying the light-driven insulin receptor-PI 3-kinase-Akt pathway as a major neuroprotective pathway in the retina, 6) identifying the product of the gene that is mutated in AD Stargardt-like macular dystrophy (STGD3) as a very long chain fatty acid elongase (ELOVL4), and most recently 7) demonstrating that very long saturated and polyunsaturated fatty acids (≥ 28 carbons) are essential for life and play major roles in vision, brain function, skin permeability, and male fertility.

Although I am officially retired from the University of Oklahoma Health Sciences Center and the Dean McGee Eye Institute, I maintain an emeritus appointment as George Lynn Cross Research Professor *Emeritus* of Cell Biology and Ophthalmology and remain actively involved in two ongoing research projects. The first is focused on determining the role of very long chain polyunsaturated fatty acids (VLC-PUFA) in age related macular degeneration and Stargardt-like Macular Dystrophy (STGD3). We now have deuterated VLC-PUFA and are testing their efficacy in preventing retinal degeneration in our animal models of retinal degeneration where absence of these fatty acids in photoreceptor membranes leads to loss of retinal structure and function.

We are also actively engaged in studies using deuterated 22:6n3 and 20:4n6 to prevent retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) in retinas and lungs, resp., of newborn mice using a well-known oxygen exposure paradigm. If successful, we will propose clinical trials in preterm human infants. Currently, there is no medical treatment for ROP and BPD in preterm human infants exposed to high levels of oxygen in the NICU.

B. Positions, Scientific Appointments, and Honors

RESEARCH AND/OR PROFESSIONAL EXPERIENCE:

1968-1969	Postdoctoral fellow, Oak Ridge Assoc. Univ., Medical Div., Oak Ridge, TN
1969-1976	Assistant Professor, Depts. Ophthalmology and Biochem., Baylor College of Medicine, Houston, TX
1976-1981	Associate Professor, Depts. Ophthalmology and Biochem., Baylor College of Medicine, Houston, TX
1977-1989	Faculty, Program in Neuroscience, Baylor College of Medicine, Houston, TX
1981-1995	Professor, Depts. Ophthalmology and Biochemistry and Div Neuroscience (1989), Baylor College of Medicine, Houston, TX
1995-1999	Director, Oklahoma Center for Neuroscience, Univ. Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK
1995-1998	Professor, Dept. Ophthalmology; Adjunct Professor, Dept. Biochemistry & Molecular Biology, OUHSC, Oklahoma City, OK
1998-2020	Professor, Department of Cell Biology; Dean A. McGee Professor of Ophthalmology; Adjunct Professor of Geriatric Medicine, OUHSC, Oklahoma City, OK
1998-2007	Chair, Department of Cell Biology, OUHSC, Oklahoma City, OK
2005-2020	George Lynn Cross Research Professor, OUHSC, Oklahoma City, OK
2007-2019	Director of Research, Department of Ophthalmology and the Dean A. McGee Eye Institute, Oklahoma City, OK
2018-2020	Interim Chair, Department of Cell Biology, OUHSC, Oklahoma City, OK
2020-present	George Lynn Cross Research Professor *Emeritus* of Ophthalmology and Cell Biology, OUHSC, Oklahoma City, OK

SPECIAL HONORS AND POSITIONS (selected):

Board of Scientific Counselors, National Eye Institute, NIH, 1983-87; Chair, 1985-87
Scientific Advisory Board, The Foundation Fighting Blindness, 1985 – 2014
Alcon Research Institute Award for Outstanding Contributions in the Field of Vision Research, 1985
Counselor, International Society for Eye Research, 1988-91
Trustee, ARVO, Biochemistry & Molecular Biology Section, 1991-97; Vice-President, 1996-97
Treasurer, International Society for Eye Research, 1992-96
Senior Scientific Investigators Award, Research to Prevent Blindness, Inc., 1997
Dean A. McGee Professor of Ophthalmology, 1998-2019
Anne Gibson Memorial Lecture, Institute of Brain Chemistry and Human Nutrition, London- July 6, 2004
President, International Society for Eye Research, January 2004-December 2007
Scientific Advisory Panel, Research to Prevent Blindness, 2005 – 2015
George Lynn Cross Research Professor, OUHSC, 2005-2020.
Study Section, BrightFocus Foundation, 2006-2021.
Past-President, International Society for Eye Research, January, 2008 – December, 2009
Fellow (Gold level, inaugural class), Association for Research in Vision and Ophthalmology (ARVO), 2009
Llura Liggett Gund Lifetime Achievement Award, Foundation Fighting Blindness, June 23, 2011
Proctor Medal, Association for Research in Vision and Ophthalmology (ARVO), May 2, 2011
Paul A. Kayser International Award, Retina Research Foundation, Houston, TX, July 24, 2012
Special Recognition Award, ARVO Foundation, April 30, 2016
Fellow (Inaugural class), International Society for the Study of Fatty Acids and Lipids (ISSFAL), Sept, 2016
Robert E. Anderson Endowed Lectureship, Dept. Ophthalmol, OUHSC, established September 8, 2016
Oklahoma Chemist of the Year, ACS Pentasectional meeting, April 21, 2018
James P. Luton Professor of Ophthalmology, 2019-2020
Dean's Award for Distinguished Medical Service, OU College of Medicine Alumni Association, Jan. 23, 2020

RESEARCH PROJECTS I would like to highlight:

Presbyterian Health Foundation Collaborative Grant. Vitiello (PI); Anderson (MPI) Jul 1, 2020 – Jun 30, 2023
Treatment of retinopathy of prematurity and bronchopulmonary dysplasia with deuterated polyunsaturated fatty acids.

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Harrington Discovery Institute Award. Anderson (PI). Jan 1, 2019-Dec. 31, 2020
Treating systemic diseases/conditions with very long chain (VLC) fatty acids.

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P20 GM125528-01/05 Sonntag (Contact PI), Anderson (MPI) 2/01/19 – 12/31/23
Cellular and Molecular Geroscience CoBRE
The major goal is to provide support and mentoring for Promising Junior Investigators that will enable them to obtain NIH R01 grant support to launch their independent research careers.
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R01 EY00871-41/45 Rajala (PI); Anderson (Co-I) 4/1/16 – 3/31/21
Second Messengers in the Retina
The retina is one of the most susceptible tissues to oxidant stress. To survive daily stress challenges, the retina has developed remarkable protective mechanisms, among them the IR/PI3K/Akt pathway. Our long-term goal is to understand these mechanisms as a foundation on which novel drug therapies can be designed to protect retinal function in patients who suffer from retinal degenerations.
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U54 GM104938p Judith James (PI) 09/01/18 – 06/30/23
Role: Pilot Program KCA Co-Director
The OSCTR will provide clinical and translational research infrastructure which fosters clinically relevant discoveries translates findings into improved health and launches the careers of junior investigators. As KCA Co-Director, I will help set solicit applications, establish review protocols, set up review panels and help JPIs find alternate funding sources for their applications
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Growth Fund, OU Office of Technology Development Award. Anderson (PI) Jan 1 – Dec 31, 2020
VLC-FA Treatment of Male Infertility, Skin Disorders, and Neural Development.
==========
Presbyterian Health Foundation. Team Science Grant. Anderson (PI). July 1, 2018 – June 30, 2020
Treatment of infertility in mice with very long chain polyunsaturated fatty acids.

(My role in several of these grant-funded projects ended when I retired 07/01/2020)

C. Contributions to Science

My laboratory has investigated lipid metabolism in the retina for over 50 years. During this time, we made a number of discoveries regarding the role of lipids in neuronal structure and function, including:

1. **The importance of docosahexaenoic acid (DHA, 22:6n3) in retina function**. The retina contains the highest levels of DHA of any tissue in the body. We performed the first studies that showed that n3 polyunsaturated fatty acids (PUFA) played a functional role in the nervous system. I was a new assistant professor with my first R01 grant (EY00871) and collaborated with a senior neurophysiologist (Benolken) and his graduate student (Wheeler). These early studies contributed to the body of knowledge that ultimately led to the inclusion of DHA in human infant formulas.

- Benolken, R.M., **R.E. Anderson**, and T.G. Wheeler (1973). Membrane fatty acids associated with the electrical response in visual excitation. *Science* **182**:1253-1254. PMID: 4752217
- Wheeler, T.G., R.M. Benolken, and **R.E. Anderson** (1975). Visual membranes: Specificity of fatty acid precursors for the electrical response to illumination. *Science* **188**:1312-1314. PMID: 1145197

2. **The "PI Cycle" in the retina**. We showed that the PI cycle was activated by light in vertebrate and invertebrate retinas. In collaboration with a neurophysiologist (Joel Brown), we showed in *Limulus* ventral photoreceptors that light stimulated PIP_2 hydrolysis, which generated 1,4,5-IP_3 that caused release of intracellular calcium. This experiment provided a molecular explanation for visual excitation in the invertebrate retina. Brown did the intracellular recordings and I did the biochemistry. Although light stimulated the PI cycle in vertebrate retinas, PI metabolism was not directly involved with visual transduction. We later learned that light activates the PI 3-kinase pathway in vertebrate retinas (see #4 below)

- Brown, J.E., L.J. Rubin, A.J. Ghalayini, A.P. Tarver, R.F. Irvine, M.J. Berridge, and **R.E. Anderson** (1984). *Myo*-inositol polyphosphate may be a messenger for visual excitation in *Limulus* photoreceptors. *Nature* (London) **311**:160-163. PMID: 6472474

- Ghalayini, A.J. and **R.E. Anderson** (1984). Phosphatidylinositol 4,5-bisphosphate: Light-mediated breakdown in the vertebrate retina. *Biochem. Biophys. Res. Comm.* **124**:503-506. PMID: 6093803

3. **Discovery of the plasticity of retinal photoreceptors to up-regulate specific endogenous neuroprotective pathways in response to stress (now called "pre-conditioning").** John Penn, who was then a graduate student in Ted Williams' laboratory Florida State University, discovered that albino rats adapted to their habitat illuminance so that their retinas captured the same number of photons each day. Those raised in brighter cyclic light were protected from light stress-induced retinal degeneration. Penn came to my laboratory to try to identify the mechanism. We found that rats raised in bright (sub-lethal) cyclic light up-regulated retinal anti-oxidant defenses, both specific proteins and small molecules, and down-regulated polyunsaturated fatty acid substrates. Their retinal photoreceptor membranes also became disorganized, which reduced their efficiency of photon capture. Returning the rats to dim cyclic light reversed the molecular and structural adaptive changes. These studies were among the first to convincingly demonstrate the amazing plasticity of the nervous system to adapt to stress.

- Penn, J.S., M.I. Naash, and **R.E. Anderson** (1987). Effect of light history on retinal antioxidants and light damage susceptibility in the rat. *Exp. Eye Res*. **44**:779-788. PMID: 3653273
- Penn, J.S. and **R.E. Anderson** (1987). Effect of light history on rod outer segment membrane composition in the rat. *Exp. Eye Res*. **44**:767-778. PMID: 3653272
- Penn, J.S. and **R.E. Anderson** (1992). Effects of light history on the rat retina. In *Progress in Retinal Research*, Vol. 11, edited by N. Osborne and G. Chader, Pergamon Press (New York), pp. 75-98.
- Li, F., Cao, W., and **Anderson, R.E**. (2001). Protection of photoreceptor cells in adult rats from light-induced degeneration by adaptation to bright cyclic light. *Exp. Eye Res*. **73**:569-577. PMID: 11825027

4. **Identified the light-driven insulin receptor-PI 3-kinase-Akt pathway as a major neuroprotective pathway in the retina**. We had found that the retina had high levels of PI 3-kinase (PI3K) activity, which can lead to many different intracellular effects, including cytoprotection in post-mitotic cells. We showed that PI3K activity was enhanced by light and protein tyrosine phosphorylation. Raju Rajala joined my laboratory in 2000 and immediately identified the insulin receptor as the membrane binding partner for PI3K. Over the last 17 years, we have shown that activation of this pathway protects rods and cones from degeneration. Additionally, our most recent studies have shown that the IR/PI3K/Akt pathway also controls intermediary metabolism (glucose phosphorylation and pyruvate kinase activity) to shunt glucose to the pentose phosphate pathway for NADPH and ribose production.

- Rajala, R.VS., McClellan, M.E., Ash, J.D., and **Anderson, R.E**. (2002). In vivo regulation of phosphoinositide 3-kinase in retina through light induced tyrosine phosphorylation of the insulin receptor β-subunit. J. Biol. Chem. 277:43319-43326. PMID: 12213821
- Rajala, A., **Anderson, R.E**., Ma, J-X., Al-Ubaidi, M.R., Lem, J., and Rajala, R.VS. (2007). G protein-coupled receptor rhodopsin regulates the phosphorylation of retinal insulin receptor. J. Biol. Chem. 282:9865-9873. PMID: 17272282
- Rajala A, Gupta, VK, **Anderson RE**, Rajala RVS. (2013). Insulin-phosphoinositide 3-kinase pathway regulates hexokinase-mitochondria interaction in the retina. *Mitochondrion* **13**:566-576. PMC3818532
- Rajala A, Dighe R, Agbaga, M-P, **Anderson RE**, Rajala RVS. (2013). Insulin receptor signaling in cones. *J Biol Chem*, **288**:19503-19515. PMC3707652
- Rajala RVS, Rajala A, Kooker C, Wang Y **Anderson RE** (2016). The Warburg Effect mediator pyruvate kinase M2 expression and regulation in the retina. *Scientific Reports*, **6**:37727. PMID: 27883057
- Rajala A, Wang Y, Brush RS, Tsantilas K, Jankowski CSR, Lindsay KJ, Linton JD, Hurley JB, **Anderson RE**, Rajala RVS (2018). Pyruvate kinase M2 regulates photoreceptor structure, function, and viability. *Cell Death and Disease* **9**:240, DOI 10.1038/s41419-018-0296-4. PMID: 29445082

5. **Discovered that the gene mutated in AD Stargardt-like macular dystrophy encodes a very long chain fatty acid elongase (*ELOVL4*).** We found that ELOVL4 catalyzed the rate-limiting condensation step in the biosynthesis of VLC-PUFA and showed that the retinal phenotype was caused by loss of product rather than expression of the truncated protein.

- Agbaga, M.-P., Brush, R.S., Mandal, M.N.A., Henry, K., Elliott, M.H., and **Anderson, R.E**. (2008) Role of Stargardt-3 macular dystrophy protein (ELOVL4) in the biosynthesis of very long chain fatty acids. Proc. Natl. Acad. Sci. USA 105:12843-12848. PMID: 18728184, PMC2525561
- Logan S, Agbaga, M-P, Chan, M.D., Kabir, N, Mandal, N.A., Brush, R.S., **Anderson, R.E**. (2013). Deciphering mutant ELOVL4 activity in autosomal dominant Stargardt Macular Dystrophy. Proc. Natl. Acad. Sci. USA, 110:5446-51. PMC3619277
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6. **Discovered the essentiality of very long chain fatty acids (VLC-FA, ≥ C-28) in the brain**. Dr. Agbaga in my group generated transgenic mice that express *ELOVL4* in the skin under control of the K-14 promoter. This prevented neonatal death, but to our great surprise, all TG mice at P19 became hyperactive and developed seizures, and died by P21. This is the first report of an essential function for VLC-SFA in brain function and survival.

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