Profile of Krzysztof Palczewski

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As a child growing up in Poland, Krzysztof Palczewski was attracted to chemistry. By the time he was in high school, Palczewski had decided to pursue a research career in chemistry, specifically studying vision. “I really thought that my future job would be related to the chemistry of vision because I found this so fascinating,” he says. After receiving a doctorate in biochemistry at the Technical University of Wroclaw in Poland in 1986, he pursued postdoctoral research with Paul Hargrave at the University of Florida, Gainesville, a move that initiated Palczewski’s dedication to vision research.

Palczewski’s decades-long research has helped explain many biological and chemical processes underlying vertebrate vision. His team solved the crystal structure of rhodopsin, the light-responsive pigment in the retina that is a prototypical G protein-coupled receptor (GPCR), and characterized other important proteins of the visual system, advancing understanding of the visual process and providing insights into GPCR signaling (1). Palczewski’s laboratory has also developed mouse models of retinal diseases for enabling discovery of potential treatments for human blinding disorders. His research has provided a template for the development of both pharmacological and genome-editing therapeutics for such disorders (2–4).

Now director of the Center for Translational Vision Research and a professor of ophthalmology at the University of California, Irvine, Palczewski continues to work on deciphering the fundamental biochemical processes operating in the visual system. Palczewski, a member of both the National Academy of Sciences and the National Academy of Medicine, describes some of his latest discoveries in his Inaugural Article (5).

Introduction to Vision Signaling

In 1986, Palczewski joined Hargrave’s laboratory and took his first concrete steps toward a biochemical description of visual signaling. He successfully purified and biochemically characterized rhodopsin kinase, the enzyme that deactivates rhodopsin and renders it competent for binding the protein arrestin, thus terminating the light-activated signaling cascade of the visual cycle (6). “This was the beginning of understanding of signaling by rhodopsin,” he says. Before long, he purified and biochemically characterized arrestin.

In 1992, Palczewski started his own laboratory at the University of Washington in Seattle. “I never changed the topic. I always stuck to phototransduction and processes that sustain vision. In Seattle, with my collaborators, we were lucky to crystallize rhodopsin in [the year] 2000,” he says (1). “This was a major breakthrough in GPCR signaling, and through the work of very talented post-docs and technicians and many collaborators, the structure was determined.”

Palczewski. His studies revealed how rhodopsin dimerizes and is folded in the membrane. They also showed how rhodopsin binds to other members of the phototransduction cascade, such as arrestin, and provided animal models and leads for combating retinal diseases.

In 2005, Palczewski became a professor and chair of the Pharmacology Department at Case Western Reserve University. Over the next 13 years, he continued to decipher many aspects of signaling within the visual system, including crystallization of the RPE65 protein with his collaborator and friend Philip Kiser (7).

Understanding Disease-Related Processes

Throughout his career, Palczewski has sought to understand the key chemical and biological processes of vision. “It’s not magic that happens in our eyes. What happens is an extremely precise photochemistry,” he says. “We wanted to understand these processes and how to apply that knowledge to treat blinding diseases.”

In 2018, Palczewski joined the University of California, Irvine as a professor and director of the Center for Translational Vision Research. “We need to focus on innovative treatments for blinding diseases and to combine a basic understanding of vision with developing those treatments,” he says.

Palczewski has used classical pharmacology to override or repair mutations in genes involved in the visual system. “With classical pharmacology, we have been quite successful at better understanding the function of the mutated genes,” he says. Palczewski has also used systems pharmacology, which aims to address the same physiological process from many

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directions in parallel. “Systems pharmacology applies multiple ligands that affect the same network of signaling in cells, and the beauty is that they act synergistically,” he says. That could mean having to use much less of a drug to get a therapeutic effect, potentially improving the drug’s safety profile.

More recently, Palczewski has been interested in using genome editing to repair disease-causing mutations in DNA. “We can direct molecular editors to a spot in DNA and restore its native sequence, and that could be a permanent cure for that blinding disease,” says Palczewski.

The foundation of Palczewski’s translational research continues to be his studies of the basic chemical processes of vision. “Biology is an example of relatively restricted chemistry that has to happen at body temperature, in the presence of membranes that are highly unsaturated, and with water,” he says. “It is not like chemistry that is done in organic solvents, we have all these restrictions so it’s only a subset of chemistry, and understanding those processes is extremely important at the chemical level,” says Palczewski.

In his Inaugural Article (5), Palczewski provides an overview of his recent studies on the chemistry of vision. “I think there is still a lot of mystery in how our visual system operates, and there are still a lot of chemical questions that need to be answered,” he says.

**Rhodopsin Cycling**

For his Inaugural Article (5), Palczewski focused on a previously little-explored but critical step in vision. “When the absorption of light happens, the chromophore has to be released and, then, a fresh, newly synthesized active chromophore needs to replace it to make the retina lightsensitive again and to enable visual transduction,” he says. To sustain vision after absorption of a photon—which, at first, results in the isomerization of the 11-cis-retinalidene chromophore and formation of all-trans-retinylidene—all-trans-retinylidene is hydrolyzed and all-trans-retinal is released from opsin. Following these steps, a fresh molecule of 11-cis-retinal is bound covalently to regenerate rhodopsin in preparation for the absorption of the next photon for continued vision.

To better understand this process, Palczewski and his MD/PhD student, John Hong, investigated how this system operates at the chemical level, using precise methods to reveal details of the isomerization and energetics of the hydrolysis occurring during this process. “What this work shows is that the rate of hydrolysis follows a specific energetic profile, and a specific conformation of rhodopsin allows the chromophore to be released. So, it’s like rhodopsin releasing the chromophore has its own timing mechanism that is unaffected by other reactions,” says Palczewski, adding, “There is a specific stepwise manner in how rhodopsin activates and deactivates. In other words, it is like a very smart micromachine.”

The results uncover the process of rhodopsin cycling and chromophore regeneration, a crucial process in vision that, when disrupted, can lead to retinopathies. Palczewski plans to further study these chemical processes in vivo. “This was a major step, but now we would like to use mice to study this process in a living organism,” he says. “We will be able to employ genetically modified knockouts, knockins, etc... to improve our understanding of how chromophore release and regeneration are affected under different genetic conditions, and that...will be relevant to understanding the etiology of blinding diseases,” says Palczewski.

The methodology developed for this project could also be applied to examine other photopigments. “It will enable studies of other visual pigments like those in red, green, and blue cones, and melanopsin that regulates circadian rhythm,” says Palczewski. “The methodology could also help monitor the pharmacokinetics and pharmacodynamics of novel analogs of retinal that are being developed as therapeutics,” he adds.

For his contributions to vision research, Palczewski has won many distinctions. He especially cherishes the 1996 Cogan Award of the Association for Research in Vision and Ophthalmology (ARVO) that is given to promising young investigators. “It was like saying, ‘You’re doing well. Here is recognition because you are a young person and you may change the world, hopefully you will continue,’” says Palczewski. “I felt that it was very critical in my career because you have to prove that you deserve it, that you will really make a contribution.” For his continued noteworthy contributions, Palczewski also won the ARVO’s Friedenwald Award in 2014, an award recognizing sustained outstanding research in the basic or clinical sciences as applied to ophthalmology.

Palczewski also attaches special significance to the Knight’s Cross of the Order of Merit of the Republic of Poland that he was awarded in 2011. “It is a highly ranked award, but it was also recognition of my roots in Poland, so this was a very special recognition for me,” says Palczewski.

Having published more than 500 scientific articles, many of high impact, Palczewski is quick to credit his laboratory members and collaborators for his prodigious output. “I have been blessed with over 150 people training in my lab, many of them now having independent careers in research institutions across the world,” he says. “Science is not an activity that occurs in isolation, and the beauty of life sciences is the richness of different approaches, different ideas, and different talents. That diversity is perhaps the biggest contribution to my success and the success of current and future generations.”

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