BIOGRAPHICAL SKETCH

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NAME: John Clark Lagarias

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POSITION TITLE: Distinguished Professor Emeritus of Biochemistry

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
University of California, Berkeley CA	A.B.	06/1975	Chemistry/Botany
University of California, Berkeley CA	Ph.D.	06/1979	Chemistry
Michigan State University, East Lansing MI	Postdoc	1979-80	Photobiology

A. Personal Statement

The major focus of my laboratory's research has been to understand the structural basis of the wavelength selectivity and signal transduction of bilin-based sensors, phytochromes and cyanobacteriochromes, and to leverage this knowledge for crop improvement, biophotonic and optogenetic applications. Our research benefits from my training in organic chemistry and my long-standing interest in plant photobiology that enables us to pursue questions at the interface of chemistry and biology. In short, I urge my colleagues to make new reagents/protocols, to apply those techniques best suited to addressing the most important biological questions, and engage expert collaborators to address these questions. During previous studies to elucidate the linear tetrapyrrole (bilin) biosynthetic pathways of plants and cyanobacteria, we have developed widely used tools for expression and *in vivo* reconstitution of holophytochromes that have facilitated high-resolution structural analyses using x-ray crystallography, NMR and ultrafast spectroscopies by our collaborators and colleagues. Most recently, my laboratory has exploited these tools for discovery and characterization of the natural diversity and mechanisms of spectral tuning by cyanobacteriochromes, phytochrome-related photoswitches found in cyanobacteria that sense light throughout the visible spectrum (400-700 nm) and into the near ultraviolet (300-400) and the near infrared (up to 750 nm). Five US patents on bilin-based sensor technologies have issued, which range from applications for crop plant improvement to optogenetic actuator and fluorescent probe development.

B. Positions and Honors

Positions and Employment:

1980-1986 Assistant Professor of Biochemistry, Department of Biochemistry and Biophysics, University of California, Davis, CA

1986-1991 Associate Professor of Biochemistry, Department of Biochemistry and Biophysics, University of California, Davis, CA

1991-2013 Professor of Biochemistry, Department of Molecular and Cellular Biology, University of California, Davis, CA

2013-2020 Distinguished Professor of Biochemistry, Department of Molecular and Cellular Biology, University of California, Davis, CA

2020-present Distinguished Professor Emeritus of Biochemistry, Department of Molecular and Cellular Biology, University of California, Davis, CA

Other Experience and Professional Memberships:

1980-present	Member, American Society of Plant Biologists
1988-1994	Member of Reviewing Editorial Board, Peptide Research
1989	Panel Member, USDA Stratosphere Ozone Depletion and Crop Productivity
1990	Panel Member, DOE Energy Biosciences Proposal Evaluation
1996-1997	Panel Member, USDA Competitive Research Grants, Plant Growth and Development
1996-1999	Member of Reviewing Editorial Board, Journal of Plant Research
1999	Panel Manager, USDA Competitive Research Grants, Plant Growth and Development
1999	Program Review Panel Member, RIKEN Frontier Research Program, Laboratory for Photoperception and Signal Transduction
2001	Panel Member, NIH Study Section [ZRG1 SSS-2]
2006-present	Editorial Advisory Board, Molecular Plant
2007	Panel Member, USDA Competitive Research Grants, Plant Biochemistry
2007	Ad hoc Panel Member, NIH Study Section [MSFB]
2007	Program Review Committee Member, Academia Sinica Institute of Plant Biology
2008	DOE Site Reviewer Panel Member, MSU-DOE Plant Research Laboratory
2010-present	Member, American Chemical Society
2010	Panel Member, DOE Energy Biosciences Proposal Evaluation
2010	Chair, NSF Committee of Visitors, Plant Genome Research Division
2012	Panel Member, NSF
2013	Panel Member (teleconference), NIGMS
2014	Panel Member DOE
2015	Strategic Advisory Committee Member, DOE PARC EFRC
2016	Panel Member, NSF
2016	Strategic Advisory Committee Member, DOE PARC EFRC
2017	Panel Member (teleconference) DOE
2017	Strategic Advisory Committee Member, DOE PARC EFRC
2018	Panel Member (teleconference) DOE
2020	Panel Member (teleconference) DOE

Honors:

1975	Phi Beta Kappa (UC Berkeley)
1975	Achievement Rewards for College Scientists (UC Berkeley)
1999	Paul K. and Ruth R. Stumpf Professor of Plant Biochemistry
2001	Elected to The National Academy of Sciences (USA)
2010	Pollard Memorial Lecturer (Pennsylvania State University)
2013	Halocarbon Corporation Lecturer (Cornell University)
2016	Shang Fa-Yang Lecturer (Academia Sinica, Taipei Taiwan)
2017	Elected Fellow of American Society of Plant Biologists
2020	Pioneer Member of The American Society of Plant Biologists

C. Key Contributions to Science (168 total; 7 patents issued; h-index 69)

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/john.lagarias.1/bibliography/46025864/public/?sort=date&direction=descending

Complete list of published work in Google Scholar (Google “John Clark Lagarias”):
http://scholar.google.com/citations?user=n8Qg1cgAAAAJ&hl=en

1. **Light-regulated biochemistry of plant phytochromes.** In the mid-1980s, my laboratory was the first to define light-induced changes within plant phytochrome molecules using proteases and protein kinases as probes of protein conformation. Our studies also identified the intrinsic light-activated serine/threonine protein kinase activity of plant phytochromes, which we later confirmed to be an intrinsic property of phytochromes following development of *in vitro* assembly assays with recombinant apophytochromes.

a. Lagarias JC and Mercurio FM **1985** Identification of light-induced conformational changes in 124 kDa Avena phytochrome *in vitro*. *J Biol Chem 260*, 2415-2423.
b. Wong Y-S, Cheng H-C, Walsh DA, and Lagarias JC **1986** Phosphorylation of *Avena* phytochrome in vitro as a probe of light-induced conformational changes. *J Biol Chem 261*, 12089-12097.
c. Lagarias JC and Lagarias DM **1989** Self assembly of synthetic phytochrome holoprotein in vitro. *Proc Natl Acad Sci* (USA) *86*, 5778-5780.
d. Yeh, K-C and Lagarias JC **1998** Eukaryotic phytochromes: Light-regulated serine/threonine protein kinases with histidine kinase ancestry. *Proc Natl Acad Sci* (USA) *95*, 13976-13981.

2. **Bilin chromophore biosynthetic pathway.** Much of our current understanding of phytobilin biosynthesis stems from our seminal radioisotope and bilin analog labeling studies and *in vitro* assay development that enabled identification of the biochemical activities responsible for conversion of BV to phytochromobilin in plant plastids. This facilitated cloning of ferredoxin-dependent bilin reductase (FDBR) family and reconstitution of photoactive holophytochromes and phycobiliproteins in living cells.
    a. Elich TD, McDonagh AF, Palma LA and Lagarias JC **1989** Phytochrome chromophore biosynthesis. Treatment of tetrapyrrole-deficient *Avena* explants with natural and non-natural bilatrienes leads to formation of spectrally active holoproteins. *J Biol Chem 264*, 183-189.
    b. Kohchi T, Mukougawa K, Frankenberg N, Masuda M, Yokota A and Lagarias JC **2001** The Arabidopsis HY2 gene encodes phytochromobilin synthase, a ferredoxin-dependent biliverdin reductase. *Plant Cell 13*, 425-436.
    c. Frankenberg N, Mukougawa K, Kohchi T and Lagarias JC **2001** Functional genomic analysis of the HY2 family of ferredoxin-dependent bilin reductases from oxygenic photosynthetic organisms. *Plant Cell 13*, 965-978.
    d. Gambetta GA and Lagarias JC **2001** Genetic engineering of phytochrome biosynthesis in bacteria. *Proc Natl Acad Sci* (USA) *98*, 10566-10571.

3. **Phytochrome diversity.** Since the mid-1990s, our studies have leveraged the growing database of phytochrome-related genes available in the expanding genome databases. We were the first to identify phytochromes in cyanobacteria, established these to be light-repressed two component histidine kinases. Our studies have shed light on the profound spectral diversity of the cyanobacteriochromes family of phytochrome-related sensors that has proliferated in cyanobacteria. The broad spectral range from the near ultraviolet (350 nm) to the near infrared (750 nm) enables acclimation to a wide variety of light environments in water and on land. Most recently, our studies reveal that spectral tuning has occurred independently in eukaryote algae.
    a. Yeh K-C, Wu S-H, Murphy JT and Lagarias JC **1997** A cyanobacterial phytochrome two-component light sensory system. *Science 277***,** 1505-1508.
    b. Wu S-H and Lagarias JC **2000** Defining the bilin lyase domain: Lessons from the extended phytochrome superfamily. *Biochemistry 39*, 13487-13495.
    c. Rockwell NC, Martin SS, Feoktistova K and Lagarias JC **2011** Diverse two-cysteine photocycles in phytochromes and cyanobacteriochromes *Proc Natl Acad Sci* (USA) *108*, 11854-11859.
    d. Rockwell NC, Duanmu D, Martin SS, Bachy C, Price, DC, Bhattacharya D, Worden AZ and Lagarias JC **2014** Eukaryotic algal phytochromes span the visible spectrum *Proc Natl Acad Sci* (USA) *111*, 3871-3876.

4. **Phytochrome engineering.** The development of recombinant expression systems facilitated studies to engineer changes in both chromophore and protein that influence photoperception and signaling. Studies using chromophore analogs lead to the discovery of red fluorescent phytochromes, aka phytofluors, which are among the brightest genetic-encoded fluorescent proteins with quantum yields as high as 80%. Our directed evolution screen in 2004, led to isolation of a missense mutation that inhibits photochemistry and enhances red fluorescence. The unexpected light-independent constitutive signaling activity of this allele of plant phytochrome B has enabled studies of phytochrome signaling in the absence of photosynthesis.
    a. Murphy JT and Lagarias JC **1997** The phytofluors: A new class of fluorescent protein probes. *Curr Biol 7,* 870-876.
    b. Fischer AJ and Lagarias JC **2004** Harnessing phytochrome's glowing potential. *Proc Natl Acad Sci* (USA) *101,* 17334-17339.
    c. Su Y-S and Lagarias JC **2007** Light independent phytochrome signaling mediated by dominant GAF-domain tyrosine mutants of Arabidopsis phytochromes in transgenic plants, *Plant Cell* (USA) *19*, 2124–2139.

d. Hu, W, Franklin KA, Sharrock RA, Jones MA, Harmer SL and Lagarias JC **2013** Unanticipated regulatory roles for Arabidopsis phytochromes revealed by null mutant analysis. *Proc Natl Acad Sci* (USA) *110*, 1542-1547.

5. **Structure and biophysics of bilin-based sensors.** By combining photochemistry, transient absorption, solution NMR and x-ray crystallography with biochemical analysis of wild-type and mutant recombinant cyanobacteriochrome (CBCR) sensors, our studies have yielded new insight into how these sensors see specific colors of light, how chromophore-binding GAF domains transmit photophysical cues to biological outputs elsewhere in the same molecule, and how these molecules interface with the rest of the cell to trigger photobiological responses.
a. Kelly, J.M. and J.C. Lagarias **1985** Photochemistry of 124 kilodalton *Avena* phytochrome under constant illumination *in vitro*. *Biochemistry 24*, 6003-6010.
b. Blain-Hartung, M., Rockwell, N.C. and Lagarias, J.C. **2017** Light-regulated synthesis of cyclic-di-GMP by a bidomain construct of the cyanobacteriochrome Tlr0924 (SesA) without stable dimerization. *Biochemistry 56*, 6145-6154.
c. Lim, S., Yu, Q., Gottlieb, S. M., Chang, C.-W., Rockwell, N. C., Martin, S. S., Madsen, D., Lagarias, J. C., Larsen, D. S. and Ames, J. B. **2018** Correlating structural and photochemical heterogeneity in cyanobacteriochrome NpR6012g4. *Proc Natl Acad Sci* (USA) *115*, 4387-4392.
d. Moreno, M. V., Rockwell, N. C., Mora, M., Fisher, A. J. and Lagarias, J. C. **2020** A far-red cyanobacteriochrome lineage specific for verdins. *Proc Natl Acad Sci (USA) 117*, 27962-27970.

D. Ongoing Research Support

National Institute of General Medical Sciences, J. Clark Lagarias, Principal Investigator. NIH 1R35 GM139598 "Understanding and leveraging molecular diversity within the phytochrome superfamily", 1/1/2021-12/31/2025, $250,000 DC/y (51% effort)

This project examines the phytochromes, a superfamily of photoreceptors that can detect to a broad range of colors and can transmit that information to the cell to control many aspects of biology. Plant phytochromes are a major stumbling block in improving agricultural yield by mediating the shade avoidance response caused by competition for light among neighboring plants, while their bacterial relatives including the cyanobacteriochromes have proven a valuable source of imaging reagents for biomedical research and of photosensory reagents for synthetic control of cellular processes with light. Work under this project will provide new insight into color tuning, the usage of light energy, the integration of light with signals such as temperature and pH, and the transmission of information within these photoreceptors and to the rest of the cell.

Department of Energy (DE-FG02-09ER16117) Principal Investigator, J. Clark Lagarias; Co-PI Nathan C. Rockwell, "Diversification and function of bilin chromophores in oxygenic photosynthesis", 09/15/2021-09/14/2023, $400,000 TC (10% effort)

We seek to understand the roles played by linear tetrapyrroles (bilins) in oxygenic photosynthesis. Bilins are used for sensing light in phytochrome and cyanobacteriochrome photoreceptors, the previous focus of this grant. Some photosynthetic organisms also use bilins for harvesting light in phycobiliproteins. However, bilin biosynthesis pathways are found in all known oxygenic photosynthetic organisms, regardless of whether they contain phytochromes or phycobiliproteins. Our previous work in the model green alga *Chlamydomonas reinhardtii* demonstrated that this pathway synthesizes phycocyanobilin (PCB) and is required for photoautotrophic growth. We have now shown that PCB binds to GUN4 protein and stimulates magnesium chelatase (MgCh), the enzyme that carries out the first committed step in chlorophyll synthesis. Bilin biosynthesis and GUN4 are also both required for stabilization of CHLH1, the H-subunit of Chlamydomonas MgCh. Our overarching hypothesis is that bilin biosynthesis is ubiquitous in eukaryotic algae.