BIOGRAPHICAL SKETCH

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NAME: David S. Lawrence

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POSITION TITLE: Fred Eshelman Distinguished Professor, Professor of Chemistry, Medicine, and Pharmacy

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 at Irvine	BS	06/1976	Biological Sciences
University of California at Los Angeles	PhD	01/1982	Organic Synthesis
University of Chicago/Rockefeller University	Postdoc	1985	Bioorganic Chemistry

A. Personal Statement

The Lawrence research program is multifaceted; encompassing the fields of organic and peptide synthesis, photochemistry, enzymology, cell and molecular biology, and microscopy. The research group's expertise lies in the design, synthesis, characterization, and application of light-responsive agents, including sensors, inhibitors, activators, proteins, gene-expression, and drug delivery systems. The technology developed for the latter, in particular, is notable since drug photo-release is easily tuned to any wavelength in the visible and near IR, enabling multiple drugs to be either simultaneously or sequentially discharged from cell-based carriers. Photoresponsive agents in the Lawrence Lab have been used to probe, perturb, and reengineer biological systems.

1. Nguyen L. T., Oien N. P., Allbritton N. L., and Lawrence D. S. "Lipid Pools As Photolabile 'Protecting Groups': Design of Light-Activatable Bioagents" *Angew. Chem. Intl. Ed. Engl.*, **2013**, *52*, 9936-9. PMCID: PMC3840492. *Designated as a very important paper (VIP).*
2. Shell T. A., Shell J. R., Rodgers Z. L., and Lawrence D. S. "Tunable Visible and Near-IR Photoactivation of Light-Responsive Compounds by Using Fluorophores as Light-Capturing Antennas" *Angew. Chem. Intl. Ed. Engl.*, **2014**, *53*, 875-8. PMID: 24285381. PMCID: PMC4036634. *Designated as a very important paper (VIP).*
3. Smith W. J., Oien N. P., Hughes R. M., Marvin C. M., Rodgers Z. L., Lee J., and Lawrence D. S. "CellMediated Assembly of Phototherapeutics" *Angew. Chem. Intl. Ed. Engl.*, **2014**, *53*, 10945 - 8. PMCID: PMC4209249.
4. Rodgers Z. L., Hughes R. M., Doherty L. M., Shell J. R., Molesky B. P., Brugh A. M., Forbes M. D., Moran A. M., and Lawrence D. S. "B_{12}-Mediated, Long Wavelength Photopolymerization of Hydrogels" *J. Amer. Chem. Soc.* **2015**, *137*, 3372 - 8. PMID: 25697508 [PubMed - in process].

B. Positions and Honors

1976 - 1982 Graduate Student, UCLA with R. V. Stevens
1982 - 1985 Postdoctoral Fellow, University of Chicago and Rockefeller University with E. T. Kaiser
1985 - 1991 Assistant Professor of Chemistry, SUNY at Buffalo
1991 - 1994 Associate Professor of Chemistry/Medicinal Chemistry, SUNY at Buffalo

1995	Professor of Chemistry, SUNY at Buffalo
1996 - 2007	Professor of Biochemistry, Albert Einstein College of Medicine; Albert Einstein Comprehensive Cancer Center
2007-	Fred Eshelman Distinguished Professor, University of North Carolina; Professor of Chemical Biology & Medicinal Chemistry (Pharmacy), Chemistry (Arts & Sciences), and Pharmacology (Medicine); Member, Lineberger Comprehensive Cancer Center
2011-	Chair, Chemical Biology & Medicinal Chemistry, UNC Eshelman School of Pharmacy

Scientific Advisory Committee on Cancer Drug Development, American Cancer Society (1996 - 97); Chemical and Related Sciences Special Emphasis Study Section, National Institutes of Health (1994); Clinical and Experimental Therapeutics Study Section, The USAMRMC Breast Cancer Research Program (1997); Chemical and Related Sciences Special Emphasis Study Section, NIH (1997); International Advisory Board, The International Conference on Inhibitors of Protein Kinases, Warsaw, Poland (1998); Organizer of the symposium on "Biosensors: Visualizing the Chemistry of Living Cells", American Chemical Society Western Regional Meeting (1999); Biochemistry Study Section, NIH (1999); Bio-Organic and Natural Products Chemistry Study Section, NIH (2000-04); Samuel M. Rosen Award (2000); Leo M. Davidoff Society (2000); Olympia Dukakis Award/Grant in A-T Research (2000); Scientific Advisory Board, Keryx Biopharmaceuticals (2000 - 02), International Advisory Board, The 2nd International Conference on Inhibitors of Protein Kinases, Warsaw, Poland (2001); Guest Editor, Accounts of Chemical Research Special Issue on Signal Transduction (2003); International Advisory Board, The 3rd International Conference on Inhibitors of Protein Kinases, Warsaw, Poland (2003); Scientific Advisory Board, Panomics (2003 - 09); Editorial Advisory Board, *Current Organic Synthesis* (2003 - 08); Editorial Advisory Board, *Accounts Chemical Research* (2004 - present); Scientific Co-founder, OnSetThera Pharmaceuticals (2004); Member, The Harvey Society (2005 - 07); AAAS Fellow (2005); Member, American Society for Cell Biology (2006 - 08); Consultant, Sigma-Aldrich (2006 - 07); International Advisory Board, The 6th International Conference on Inhibitors of Protein Kinases, Warsaw, Poland (2009); Macromolecular Structure and Function E Study Section, National Institutes of Health (2010 and 2012 - 18); External Reviewer, Department of Medicinal Chemistry, University of Utah (2011); External Reviewer, Purdue University Cancer Center (2011); International Advisory Board, The 7th International Conference on Inhibitors of Protein Kinases, Warsaw, Poland (2012); Member, du Vigneaud Award Committee (2013); Co-Organizer, 23rd American Peptide Symposium and the 6th International Peptide Symposium (2013); Scientific Founder, Iris BioMed, LLC (2015); American Peptide Society Council (2015 – 2021).

C. Contributions to Science

1. Multicolor Monitoring of Enzyme Action. Conventional strategies for identifying the biochemical basis of tumorigenesis and metastasis rely upon the search for up- (or down-) regulated genes and proteins. However, the complexity and heterogeneity of many forms of cancer make it clear that this approach alone is not sufficient for extracting the information necessary to generate diagnostic and prognostic biomarkers. This biomedical imperative dictates the development of a series of new cellular and molecular strategies to tackle, what is admittedly, a devilishly difficult problem. We've developed an array of fluorescent sensors of protein remodeling enzymes (kinases, phosphatases, demininases, proteases) that furnish robust readouts of catalytic activity (>100 fold) across the visible spectrum and into the near infrared. Furthermore, these sensors are photophysically distinct, enabling multiple enzymatic activities to be simultaneously monitored. For example, we've employed multicolor sensing of catalytic activity to identify aberrant tyrosine kinase activity in drug resistant cells, identified a key protein kinase responsible for promoting the transition from prophase to metaphase, and demonstrated that the proteasome's three protease activities constitute a characteristic "catalytic signature" that varies as a function of species, cell type, and disease. Sensors have been used to correlate signaling activity with prostate cancer invasiveness, distinguish between signaling activity in the individual compartments of organelles, monitor allosteric crosstalk between active sites within multi-subunit complexes, and visualize epigenetic enzymatic activity.

a. Wang Q., Zimmerman E. I., Toutchkine A., Martin T. D., Graves L. M., and Lawrence, D. S. "Multicolor Monitoring of Dysregulated Protein Kinases in Chronic Myelogenous Leukemia", *ACS Chemical Biology,* **2010**, *5,* 887 - 95. PMCID: PMC2943031.

b. Wang Q., Priestman M. A., and Lawrence D. S. “Monitoring of Protein Arginine Deiminase Activity by Using Fluorescence Quenching: Multicolor Visualization of Citrullination” *Angew. Chem. Intl. Ed. Engl.* **2013**, *52*, 2323 – 5. PMCID: PMC3752692.
c. Oien N. P., Nguyen L. T., Jernigan F. E., Priestman M. A., and Lawrence D. S. “Long-Wavelength Fluorescent Reporters for Monitoring Protein Kinase Activity” *Angew. Chem. Intl. Ed. Engl.* **2014**, *53*, 3975 – 8. PMCID: PMC4036623.
d. Priestman M. A., Wang Q., Jernigan F. E., Chowdhury R., Schmidt M., and Lawrence D. S. “Multicolor Monitoring of the Proteasome's Catalytic Signature” *ACS Chem. Biol.* **2015**, *10*, 433 - 40. PMCID: PMC4340355.

2. Acquisition and Application of Potent and Selective Protein Tyrosine Phosphatase (PTPase) Inhibitors. In collaboration with Zhong-Yin Zhang, we’ve constructed an array of highly selective inhibitors of PTPases. We developed a paradigm for inhibitor design that has been replicated by many other research groups (Puius *et al.* below has been cited 270 times). We were also the first group to create sub-μM inhibitors of these enzymes. We demonstrated that an inhibitor of PTP1B serves as an insulin sensitizer, an insulin mimetic, and an appetite suppressant. We’ve identified inhibitors for other PTPases as well, including YopH, the essential virulent factor of Yersinia pestis (plague).

a. Puius Y. A., Zhao Y., Sullivan M., Lawrence D. S., Almo S. C., and Zhang Z.-Y. “Identification of a Second Aryl Phosphate-Binding Site in PTP1B: A Paradigm for Inhibitor Design”. *Proc. Natl. Acad. Sci. USA,* **1997**, *94:* 13420 - 5. PMID: 9391040.
b. Shen K., Keng Y.-F., Wu L., Guo X.-L., Lawrence D. S., and Zhang Z.-Y. "Acquisition of A Specific and Potent PTP1B Inhibitor from a Novel Combinatorial Library and Screening Procedure" *J. Biol. Chem.,* **2001**, *276*, 47311 - 9. PMID: 11584002.
c. Xie L., Lee S.-Y., Andersen J. N., Waters S., Shen K., Guo X.-L., Moller N. P. H., Olefsky J. M., Lawrence D. S., and Zhang Z.-Y. “Cellular Effects of Small Molecule PTP1B Inhibitors on Insulin Signaling” *Biochemistry*, **2003**, *42*, 12792 - 804. PMID: 14596593.
d. Morrison C. D., White C., Wang Z., Lee S.-Y., Lawrence D. S., Cefalu W. T., Zhang Z.-Y., and Gettys T. W. “Increased Hypothalamic PTP1B Contributes to Leptin Resistance with Age”, *Endocrinology*, **2007**, *148*, 433 - 40. PMID: 17038557.

3. Probing and Perturbing Intracellular Behavior with Light-Responsive Constructs. We’ve employed a combination of organic photochemistry, organic and peptide synthesis, protein design, cell biology and microscopy to control and manipulate dynamic biological phenomena. Our molecular constructs have been used to identify the “steering wheel” of the cell during chemotaxis, to probe intracellular enzymatic activity during the stages of cell division, and to reveal the mechanisms of gene transcription in single cells. In the last decade, the field of optogenetics has received a great deal of attention. The vast majority of studies have used light responsive proteins appropriated from microorganisms. Unfortunately, protein engineering challenges have hindered the ready acquisition of optogenetic analogs of endogenous mammalian proteins. Recently, we developed an optogenetic engineering strategy that is straightforward and potentially applicable to a wide variety of proteins.

a. Dai Z., Dulyaninova N. G., Kumar S., Bresnick A. R., and Lawrence D. S. “Visual Snapshots of Intracellular Kinase Activity At The Onset of Mitosis”, *Chemistry & Biology*, **2007**, *14*, 1254 - 60.
b. Larson D. R., Fritzsch C., Sun L., Meng X., Condeelis J., Lawrence D. S., and Singer R. H. “Direct Observation of Frequency Modulated Transcription in Single Cells using Light-Activation” *eLife* **2013**, *2*, E00750. PMCID: PMC3780543.
c. Hughes R. M. and Lawrence D. S. “Optogenetic Engineering: Light-Directed Cell Motility” *Angew. Chem. Intl. Ed. Engl.* **2014**, *53*, 10904 - 7. PMCID: PMC4196877.
d. Hughes R. M., Freeman D. J., Lamb K. M., Pollet R. M., Smith W. J., and Lawrence D. S. “Optogenetic Apoptosis: Light-Triggered Cell Death”, *Angewandte Chemie International Edition in English*, **2015**, *54*, *in press*. PMCID: in process.

4. The Active Site Specificities of Protein Kinases. We've developed library-based strategies that combine peptide frameworks with non-natural small molecules to create hybrids that perturb, sense, or inhibit signaling enzyme activity. We discovered that even closely related protein kinases can be distinguished based on active site activities toward unnatural amino acid residues, an observation that ultimately lead to the acquisition of highly selective protein kinase inhibitors. This work was performed at a time (the early-to-mid 90s) when scientists still questioned whether it was possible to develop selective active site-targeted protein kinase inhibitors. Our studies demonstrated that selective protein kinase inhibitors could be identified and these findings have, of course, been subsequent validated in a host of clinically relevant studies. Our inhibitory agents have been used in a variety of applications, including the exploration of the molecular basis of memory with Roger Tsien (UCSD) and Bob Hawkins (Columbia).

a. Kwon Y. G., Mendelow M., and Lawrence D. S. "The Active Site Substrate Specificity of Protein Kinase C". *J. Biol. Chem.* **1994**, *269*, 4839 - 44.
b. Lee T. R., Niu J., and Lawrence D. S. "The Extraordinary Active Site Substrate Specificity of $pp60^{c\text{-}src}$: A Multiple Specificity Protein Kinase". *J. Biol. Chem.*, **1995**, *270*, 5375 - 80.
c. Lev-Ram V., Jiang T., Wood J., Lawrence D. S., and Tsien R. Y. "Synergies and Coincidence Requirements Between NO, cGMP, and Ca^{2+} in the Induction of Cerebellar Long-Term Depression" *Neuron*, **1997**, *18*, 1025 - 38.
d. Lee J. H., Nandy S. K., and Lawrence D. S. "A Highly Potent and Selective PKCa Inhibitor Generated Via Combinatorial Modification of A Peptide Scaffold", *J. Amer. Chem. Soc.,* **2004**, *126*, 3394 - 5.

5. Self-Assembling Supramolecular Complexes. Although we no longer work in the area of self-assembly, our papers from the early 1990s are highly cited and form the basis for many of the studies that are ongoing today. For example, stimuli-responsive supramolecular complexes are of intense interest in a wide variety of endeavors (materials science, biomedical devices, etc.). We devised a series of strategies that furnished highly organized structurally well-defined entities, such as the rotaxane described in *Rao et al.* (which subsequently served as a basis for the field of "molecular electronics") and the porphyrin-cyclodextrin complex in Manka *et al*, which is still cited in a wide variety of applications.

a. Manka J. S. and Lawrence D. S. "The Template-Driven Self-Assembly of a Heme-Containing Supramolecular Complex". J*. Amer. Chem. Soc.* **1990**, *112*, 2440 - 2.
b. Rao T. V. S. and Lawrence D. S. "The Template-Driven Self-Assembly of a Threaded-Molecular Loop". *J. Amer. Chem. Soc.* **1990**, *112*, 3614 - 5.
c. Dick D., Rao T. V. S., Sukumaran D., and Lawrence D. S. "Molecular Encapsulation: CyclodextrinBased Analogs of Heme-Containing Proteins", *J. Amer. Chem. Soc.* **1992**, *114*, 2664 - 9.
d. Jiang T., Levett M., and Lawrence D. S. "Self-Assembling Supramolecular Complexes", *Chemical Reviews*, **1995**, *95*, 2229 - 60.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/david.lawrence.1/bibliography/41144279/public/?sort=date&direction=ascending