BIOGRAPHICAL SKETCH

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NAME: David S. Lawrence

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

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, microscopy, and *in vivo* preclinical studies. 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. In the field of education, Professor Lawrence has developed several graduate level courses that promote ties between the Department of Chemistry and the Division of Chemical Biology & Medicinal Chemistry (CBMC) in the School of Pharmacy, including an Introduction to Laboratory Safety course that is required of all first-year graduate students in the Department of Chemistry and CBMC. This course has been the subject of a recent publication and subsequently, a series of virtual reality safety exercises have been developed that authentically recapitulate the research laboratory experience.

a. Ding, S., O'Banion, C. P., Welfare, J. G., and Lawrence, D. S. "Cellular Cyborgs: On the Precipice of a Drug Delivery Revolution" *Cell Chem. Biol.* **2018**, *25*, 648 - 58. PMID: 29628434. PMCID: In process.
b. O'Banion, C. P., Vickerman, B. M., Haar, L., Lawrence, D. S. "Compartmentalized cAMP Generation by Engineered Photoactivated Adenylyl Cyclases", *Cell Chem. Biol.*, **2019**, *26*, 1393 - 1406. PMCID: PMC680063.
c. Marvin, C. M., Ding, S., White, R. E., Orlova, N., Wang, Q., Zywot, E. M., Vickerman, B. M., Haar, L, Tarrant, T. K., Dayton, P. A., and Lawrence, D. S. (2019). On Command Drug Delivery via Cell-Conveyed Phototherapeutics. *Small*, **2019**, *15*, 1901442. PMCID: PMC6739139.
d. Hill, D. J., Williams, O. F., Mizzy, D. P., Triumph, T. F., Brennan, C. R., Mason, D. C. and Lawrence, D. S. "Introduction to Laboratory Safety for Graduate Students: An Active Learning Endeavor", *J. Chem. Ed.*, **2019**, *96*, 652 – 9.

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, Division of 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 A 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. Design and Application of Optogenetic Constructs. Optogenetics is a powerful light-triggered technology that, via control of biochemical activity, enables spatiotemporal manipulation of cellular and organismal behavior. Neurobiologists, who have been the chief end-users of this technology, have inserted light-gated ion channels (obtained from lower organisms) into the nervous system of higher organisms, including mammals. In addition to exogenous light-gated ion channels, cell and molecular biologists have turned their attention toward the construction of light-responsive analogs of endogenous mammalian proteins. We have developed a straightforward strategy that overcomes the challenges associated with the preparation of optogenetic proteins and have employed these engineered species to explore the relationships between compartmentalized signaling activity and cell behavior.

a. Ghosh, M., Song, X., Mouneimne, G., Sidani, M., Lawrence, D. S., and Condeelis, J. S. "Cofilin Generates Barbed Ends for Actin Polymerization and Defines the Direction of Protrusion and Locomotion *in vivo*", *Science*, **2004**, *303*, 743-746. PMID: 15118165.
b. Hughes R. M. and Lawrence D. S. "Optogenetic Engineering: Light-Directed Cell Motility" *Angew. Chem. Intl. Ed.* **2014**, *53*, 10904 - 7. PMCID: PMC4196877.
c. 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", *Angew. Chem. Intl. Ed.*, **2015**, *54*, 12064 - 8. PMCID: PMC4819321.
d. O'Banion, C. P., Priestman, M. A., Hughes, R. M., Herring, L. E., Capuzzi, S. J., and Lawrence, D. S. "Design and Profiling of a Subcellular Targeted Optogenetic cAMP-Dependent Protein Kinase", *Cell Chem. Biol.*, **2018**, *25*, 100 - 9. PMCID: PMC5777159.

2. Probing and Perturbing Intracellular Behavior with Light-Responsive Compounds. 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. We've identified the "steering wheel" of the cell during chemotaxis, probed intracellular enzymatic activity during the stages of cell division, and revealed the mechanism of gene transcription in single cells.

a. 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.*, **2013**, *52*, 9936 - 9. PMCID: PMC3840492. *Designated as a Very Important Paper (VIP).*
b. Shell, T. A., Lawrence, D. S. "Vitamin B12: A Tunable, Long Wavelength, Light-Responsive Platform for Launching Therapeutic Agents" *Accts. Chem. Res.* **2015**, *48*, 2866-74. PMCID: PMC5240631.
c. 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.*, **2014**, *53*, 875 - 8. PMID: 24285381. PMCID: PMC4036634. *Designated as a Very Important Paper (VIP).*
d. Hughes, R.M., Marvin, C.M., Rodgers, Z.L., Ding, S., Oien, N.P., Smith, W.J., and Lawrence, D.S. (2016). Phototriggered Secretion of Membrane Compartmentalized Bioactive Agents. *Angew. Chem. Intl. Ed. Engl.*, **2016**, *55*, 16080 - 3. PMCID: PMC5177521. *Designated as a Hot Paper.*

3. Chemical Cytometry. 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. 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. Turner A. H., Lebhar M. S., Proctor A., Wang Q., Lawrence D. S., and Allbritton N. L. "Rational Design of a Dephosphorylation-Resistant Reporter Enables Single-Cell Measurement of Tyrosine Kinase Activity", *ACS Chem. Biol.*, **2016**, *11*, 355 - 62. PMID: 26587880.
b. Mainz E. R., Wang Q., Lawrence D. S., and Allbritton N. L. "An Integrated Chemical Cytometry Method: Shining a Light on Akt Activity in Single Cells", *Angew Chem. Intl. Ed.* **2016**, *55*, 13095 - 8. PMCID: PMC5149395.
c. Vickerman, B. M., Anttila, M. M., Petersen, B. V., Allbritton, N. E., and Lawrence, D. S. "Design and Application of Sensors for Chemical Cytometry" *ACS Chem. Biol.*, **2018**, *13*, 1741 - 51. PMCID: PMC6061971.
d. Cann, M. L., Herring, L. E., Haar, L. L., Gilbert, T. S. K., Goldfarb, D., Richards, K. L., Graves, L. M., and Lawrence, D. S. "Dasatinib Is Preferentially Active in the Activated B-Cell Subtype of Diffuse Large B-Cell Lymphoma" *J. Proteome Res.* **2019**, *18*, 522 - 34. PMID: 30540191; PMCID: In process.

4. 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.* has been cited ~350 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 developed 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 protein-tyrosine phosphatase 1B: 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.

5. 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 PKCα Inhibitor Generated Via Combinatorial Modification of a Peptide Scaffold”, *J. Amer. Chem. Soc.,* **2004**, *126*, 3394 - 5.

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

D. Research Support

ACTIVE

1R01CA203032 12/01/2015 - 11/30/2020 1.8 Cal
NIH/NCI (PI: Lawrence; Co-I: Allbritton, Carey, Gallagher)
Single Cell Sampling of Signaling Activity in Triple Negative Breast Cancer.
The advent of effective pharmacologic kinase inhibitors for clinical applications has created a critical need for assessing kinase activity, and therefore inhibitor efficacy, in disease models and in-patient samples. Biochemical analyses of aberrant signaling pathways are informative in terms of identifying the best treatment option and assessing therapeutic effectiveness in individual patients. One of the most critical issues in preclinical and clinical drug discovery is the ability to accurately monitor drug action and patient responsiveness. Indeed, it has been noted in a recent review: “As the age of precision medicine evolves, the heterogeneity of breast cancers continues to challenge the research community, emphasizing the need for robust patient selection strategies to guide the future clinical development of RTK (receptor tyrosine kinase) inhibitors.” Others have pointed out that “understanding tumor heterogeneity - the differences between individual cells in the same tumor - is one of the biggest challenges in cancer research today. The ability to describe tumors at the resolution of single cells would enhance our ability to determine the best treatment

options and to anticipate disease outcome." The goal of this collaborative multidisciplinary research program is to create instrumentation and chemical tools that rapidly and directly assess the intracellular catalytic activity of protein kinases in individual single cells from disease models and malignant tissue from cancer patients.

5 R01 NS103486 06/15/2018 - 03/31/2023 3.0 Cal
NIH/NINDS (PI: Lawrence)
Spatiotemporal Control of Migratory Cellular Behavior.
There is keen interest in identifying the biochemical pathways that mediate cytoskeletal remodeling, motility, migration, and phenotype switching since members of these pathways serve as potential therapeutic targets. Unfortunately, the spatiotemporal nature of these pathways renders the application of conventional tools (over/under-expression of the proteins of interest, inhibitory compounds, etc.) inadequate for studying dynamic cell behavior. We seek to engineer and evaluate optogenetic analogs of cofilin, cofilin's upstream activators (slingshot and chronophin), and cofilin's upstream negative regulators (LIM protein kinase, the cAMP-dependent protein kinase, the p21 activated protein kinase, and rho-associated protein kinase). These species offer a means to correlate spatially focused biochemical activity with dynamic cellular behavior including F-actin remodeling activity as well as migratory aptitude.

1R01CA224763-01 04/01/2018 - 03/31/2023 1.0 Cal
NIH (MPI: Allbritton/Lawrence)
Profiling signaling activity and gene expression in single, pancreatic adenocarcinoma cells using CE-RNA-Seq.
Strategies to molecularly profile aberrant pancreatic tissue and inform targeted therapeutic decisions would be of immense value in patient treatment. A multidisciplinary research team proposes to develop a state-of-the-art, single-cell, platform technology to measure the catalytic activity of sentinel serine/threonine protein kinases within the KRAS pathway and gene expression through RNA sequencing.

1R01DK112939-01A1 06/15/2018 – 05/31/2023 0.5 Cal
NIH (P.I.: Z. Gu. Consortium P.I.: J. Buse. Co-I: D. S. Lawrence)
Towards Glucose Transporter-Mediated Glucose-Responsive Insulin Delivery with Fast Response. Glucose-responsive delivery of insulin mimicking the function of pancreatic β-cells to achieve meticulous control of blood glucose (BG) would revolutionize type 1 and advanced type 2 diabetes care. However, it is extremely challenging to demonstrate a system which would combine fast response, reversible activation, ease of administration and excellent biocompatibility. We aim to establish an innovative glucose-responsive insulin delivery system based on the interaction between the glucose derivative- modified insulin (Glu-insulin) and glucose transporters (GLUTs) on red blood cells (RBCs). This binding interaction is reversible in the setting of hyperglycemia, resulting in fast release of insulin and subsequent drop of blood glucose levels. We will exploit two conjugation formulations of Glu-insulin and glucose transporters (GIGTer): 1) polymeric nanoparticles (NPs; ~100 nm in diameter) coated with the RBC membrane (with GLUTs) and loaded with Glu-insulin; and 2) liposomal NPs integrated with exogenously expressed glucose transporters and Glu-insulin. The proposed goal, when successfully realized, will be a significant upgrade over the current insulin-dependent diabetes therapy options and have a profound impact to improve health and quality of life of diabetic patients.

R1040 RX03712116 06/01/2017 - 05/31/2020
Intramural Award (PI: Lawrence)
Eshelman Institute for Innovation
Optogenetic Manipulation of Striatal Neurons.
The primary goal of the proposed research program is the introduction of previously prepared optogenetic constructs developed in the Lawrence Lab (cAMP-dependent protein kinase and adenylate cyclase analogs) into neuronal D1R-triggered signaling pathways. These constructs will be used to correlate intracellular neuronal biochemical activity with reward behavior and motor control.

R1040 RX03912129 11/01/2019 - 10/31/2020
Intramural Award (PI: Lawrence)
Eshelman Institute for Innovation
Optogenetic Manipulation of Striatal Neurons.
The Lead Innovator (Lawrence) has developed a full-semester safety course (CHEM 701) required of all first-year graduate students in the Division of Chemical Biology and Medicinal Chemistry and the Department of

Chemistry. Although the students appreciate the case study-based nature of the course, evaluations at the semester's end revealed a desire to introduce practical exercises into the class. However, exposure to authentic laboratory conditions in all fields of the Pharmaceutical and Chemical Sciences for 60+ first-year graduate students is not realistic. We have developed a first-in-its-kind, proof-of-concept, virtual laboratory experience for (1) the laptop and (2) a virtual reality headset. We now seek to dramatically extend this concept by creating a suite of laboratory experiences that provide entering graduate students with virtual, yet practical, exposure to various subdisciplines in the general fields of Pharmaceutical and Chemical Sciences. These modules are designed to provide an immersive lab environment for active learning.