BIOGRAPHICAL SKETCH

Michael Z. Lin	Assistant Professor Departments of Pediatrics and Bioengineering Stanford University
eRA COMMONS USER NAME Lin.Michael	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, Massachusetts	A.B. *summa cum laude*	1990-1994	Biochemistry
Harvard Medical School, Boston, Massachusetts	Ph.D.	1996-2002	Biological and Biomedical Sciences
UCLA School of Medicine, Los Angeles, California	M.D.	1994-1996, 2002-2004	Medicine
UCSD School of Medicine, La Jolla, California		2004-2009	Pharmacology and Neuroscience

A. Personal Statement

My research interests are at the interface of protein engineering, molecular imaging, and molecular therapy. I received training with Dr. Michael Greenberg on the biochemistry of signal transduction, and with Dr. Roger Tsien, the late Nobel Laureate in Chemistry, on protein engineering. My laboratory specializes in deveoping new protein reporters for visualizing molecular processes and protein control switches for controlling gene and cellular therapies in living organisms. Our general approach is create synthetic protein architectures that link input and output domains in useful ways, proceeding stepwise through structural biology, computational biology, high-throughput screening, biochemistry, cell biology, and *in vivo* experiments.

My lab has a long-standing interest in applying protein engineering to detecting and controlling cell signals. In particular, we pioneered the use of sequence-specific viral proteases to detect and control protein activity in living cells, beginning with a 2008 paper in *PNAS*, and continuing with studies published in 2015 in *Nature Chemical Biology* and 2018 in *Nature Methods*. Since 2010 we have been developing the RASER system, as described in this proposal, using NS3 to specifically rewire oncogenic signals that drive breast cancer to therapeutic outputs. RASER is the first treatment that is limited to cancerous states via intracellular signaling and thus highly novel. It is also highly effective, as we demonstrated it was superior to standard of care in specificity and efficacy on breast cancer cells. The RASER work is now in press at *Science*. We are excited to use the RASER system as the basis for engineering viruses with exquisite specificity for diseased cancer cells and the ability to amplify in tumors, with the goal of more complete and lasting treatments for breast cancer.

B. Positions and Honors

Positions

- 1996-2002: PhD student, Laboratory of Dr. Michael E. Greenberg, Division of Neuroscience, Children's Hospital, Boston, Massachusetts
- 1994-1996, 2002-2004: Medical student, UCLA School of Medicine, Los Angeles, California
- 2004-2009: Postdoctoral research fellow, Laboratory of Dr. Roger Y. Tsien, Dept. of Pharmacology and Howard Hughes Medical Institute, University of California at San Diego, La Jolla, California
- 2009-2016: Assistant Professor of Pediatrics and Bioengineering, Stanford University School of Medicine, Palo Alto, California
- 2016-current: Associate Professor of Neurobiology and Bioengineering and by courtesy Pediatrics and Chemical and Systems Biology, Member of Bio-X and Molecular Imaging Programs and Chem-H Faculty Fellow, Stanford University School of Medicine, Palo Alto, California

Honors

- NIH Pioneer Award, 2013
- Rising Star Award, Biomedical Engineering Society, Cellular and Molecular Bioengineering Interest Group, 2013
- Damon Runyon-Rachleff Innovation Award, 2012
- Rita Allen Scholar Award, 2011
- Young Investigator Award, Alliance for Cancer Gene Therapy, 2010
- Burroughs Wellcome Career Award for Medical Scientists, 2007
- Jane Coffin Childs Memorial Fund for Medical Research Fellowship, 2005
- Western Student Medical Research Forum Award, 2004
- United States Department of Defense Graduate Fellowship, 1996
- NIH Medical Scholars Training Program Scholarship, 1994
- Harvard University Phi Beta Kappa, 1994

Other Experience, Professional Memberships and Certifications

- 2009-2012: Cancer Prevention and Research Institute of Texas, Interfaces Study Section, member
- 2009-current: Member, American Society for Gene and Cell Therapy
- 2009-current: Member, Protein Society
- 2008-current: Member, Biophysical Society
- 2007-current: Member, Society for Neuroscience
- USMLE Step I and II certified

C. Contribution to Science

1. A major contribution of my research has been the development and application of new protease-based reporters to enable unique insights into and control over protein turnover. These include TimeSTAMP tags, which allow visualization of copies of proteins of interest that are synthesized within specific time windows defined by application of a drug, and SMASh tags, which allow drug-induced shutoff of protein synthesis.

Chung HK, Zou X, Bajar BT, Brand BR, Huo Y, Alcudia JF, Ferrell JE, **Lin MZ**. **2019.** Rewiring aberrant cancer signaling to therapeutic effector release with a synthetic two-component system. ***Science***, in press.

Jacobs CL, Badiee RK, **Lin MZ. 2018.** StaPLs: versatile genetically encoded modules for engineering drug-inducible proteins. 2018. ***Nature Methods*****,** 15:523. http://doi.org/10.1038/s41592-018-0041-z. PMID 29967496.

Chung HK, Jacobs CL, Huo Y, Yang J, Krumm SA, Plemper RK, Tsien RY, **Lin MZ**. **2015**. Tunable and reversible drug control of protein production via a self-excising degron. ***Nature Chemical Biology*** 11:713-720. http://dx.doi.org/10.1038/nchembio.1869. PMID 26214256. PMCID PMC4543534.

Lin MZ, Glenn JS, Tsien RY. **2008**. A drug-controllable tag for specific labeling of newly synthesized proteins in cells and whole animals. ***Proc Natl Acad Sci U S A***. 105:7744-9. doi: 10.1073/pnas.0803060105. Epub 2008 May 29. PMID: 18511556. (Cover article.)

2. Another major ongoing scientific contribution of my work has been the development of the first generalizable method for making light-regulatable proteins, which I believe will allow optical regulation of biology (optobiology) to become a commonplace experimental approach. As part of this work, we discovered that the oligomerization state of an engineered photoswitching fluorescence protein can be controlled by light, in the first example of a light-regulatable protein-protein interaction outside of natural light-regulated signal transduction pathways. We then used this behavior to create a generalizable design for light-controllable proteins in which a protein is caged by fusion to fluorescent protein domains and uncaged by light.

Zhou XX, Fan LZ, Li P, Shen K, Lin MZ. **2017**. Optical control of cell signaling by single-chain photoswitchable kinases. ***Science*** 355:836-842. http://dx.doi.org/10.1126/science.aah3604. PMID: 28232577.

Zhou XX, Zou X, **Lin MZ**. **2017**. A single-chain photoswitchable Cas9 architecture for inducible gene editing and transcription. ***ACS Chem Biol*** 13:443. http://dx.doi.org/10.1021/acschembio.7b00603. PMID: 28938067.

Kim B, **Lin MZ**. **2013**. Optobiology: optical control of biological processes via protein engineering. ***Biochem Soc Trans.*** 2013 Oct;41(5):1183-8. doi: 10.1042/BST20130150. Review. PMID: 24059506. PMCID PMC4076147.

Zhou XX, Chung HK, Lam AJ, **Lin MZ**. **2012**. Optical control of protein activity by fluorescent protein domains. ***Science***. 2012 Nov 9;338(6108):810-4. doi: 10.1126/science.1226854. PMID: 23139335; PMCID: PMC3702057.

3. Another of my major contributions has been the engineering of new optical reporters to enable dynamic real-time imaging of biochemical processes in cells and animals. For example, my lab created a specific fluorescent sensor of the S-G2 transition, which together allowed the reporting of all four cell cycle stages. We also created the first bioluminescent indicator of calcium bright enough to visualize organ-wide calcium signaling in mice completely non-invasively (through the body wall, without surgery).

Oh Y, Park Y, Cho, JH, Wu H, Paulk NK, Liu LX, Kim N, Kay MA, Wu JC, **Lin MZ. 2019**. An orange calcium-modulated bioluminescent indicator for non-invasive activity imaging. ***Nature Chemical Biology,*** in press.

Bajar BT*, Lam AJ*, Badiee R, Oh YH, Chu J, Zhou XX, Kim N, Kim BB, Chung M, Yabonovitch AL, Cruz BF, Kulalert K, Tao JJ, Meyer T, Su XD, **Lin MZ**. **2016**. Fluorescent indicators for simultaneous reporting of all four cell cycle phases. ***Nature Methods*** 13:989. PMID 27798610. PMCID PMC5548384.

Chu J, Oh YH, Sens A, Ataie N, Dana H, Macklin J, Laviv T, Welf ES, Dean KM, Zhang F, Kim BB, Tang CT, Hu M, Baird MA, Davidson MW, Fioka F, Kay M, Fiolka R, Yasuda R, Kim DS, Ng H-L, **Lin MZ**. **2016**. A bright cyan-excitable orange fluorescent protein enables dual-emission microscopy and highly sensitive bioluminescence imaging *in vivo*. ***Nature Biotechnology*** 34:760. PMID 27240196. PMCID PMC4942401.

Lam AJ, St-Pierre F, Gong Y, Marshall JD, Cranfill PJ, Baird MA, McKeown MR, Wiedenmann J, Davidson MW, Schnitzer MJ, Tsien RY, **Lin MZ**. **2012**. Improving FRET dynamic range with bright green and red fluorescent proteins. ***Nature Methods*** 9:1005-12. doi: 10.1038/nmeth.2171. PMID: 22961245; PMCID: PMC3461113.

4. Another of my major contributions has been the engineering of improved fluorescent proteins for use in optical reporters or as cell trackers. For example, my lab also engineered the brightest monomeric far-red fluorescent protein, and demonstrated that it was superior to other fluorescent proteins for non-invasive longitudinal imaging of stem cell differentiation in living mice.

Laviv T*, Kim BB*, Chu J, **Lin MZ**, Yasuda R. **2016**. Simultaneous dual-color fluorescence lifetime imaging with novel red-shifted fluorophores. ***Nature Methods*** 13:989**.** doi:10.1038/nmeth.4045. PMID 27798609. PMCID PMC5322478. *co-first authors.

Bajar BT, Wang ES, Lam AJ, Kim BB, Jacobs CL, Howe ES, Davidson MW, **Lin MZ***, Chu J*. **2016**. Improving brightness and photostability of green and red fluorescent proteins for live cell imaging and FRET reporting. ***Scientific Reports*** 6:20889. http://dx.doi.org/10.1038/srep20889. PMID 26879144. PMCID PMC4754705. *corresponding authors.

Chu J, Haynes RD, Corbel SY, Li P, González-González E, Burg JS, Ataie NJ, Lam AJ, Cranfill PJ, Baird MA, Davidson MW, Ng HL, Garcia KC, Contag CH, Shen K, Blau HM, **Lin MZ. 2014**. Non-invasive intravital imaging of cellular differentiation with a bright red-excitable fluorescent protein. ***Nature Methods.*** 2014 May;11(5):572-8. doi: 10.1038/nmeth.2888. PMID: 24633408; PMCID: PMC4008650.

Lin MZ, McKeown MR, Aguilera T, Shaner NC, Campbell RE, Adams SR, Tsien RY. **2009**. Autofluorescent proteins with excitation in the optical window for intravital imaging in mammals. ***Chem Biol***. 2009 Nov 25;16(11):1169-79. doi: 10.1016/j.chembiol.2009.10.009. PMID: 19942140.

5. In earlier work, I elucidated signaling pathways controlling morphological and structural aspects of neuronal differentiation. This included the discovery of ephexin-family signaling proteins linking Eph-family receptors to the actin cytoskeleton during axon guidance in mammalian neurons and of regulatory proteins involved in the suppression of the cell cycle in differentiating neurons in the fly.

Cowan CW, Shao YR, Sahin M, Shamah SM, **Lin MZ**, Greer PL, Gao S, Griffith EC, Brugge JS, Greenberg ME. **2005**. Vav family GEFs link activated Ephs to endocytosis and axon guidance. ***Neuron***. 46:205-17. PMID: 15848800.

Sahin M*, Greer PL*, **Lin MZ***, Poucher H, Eberhart J, Schmidt S, Wright TM, Shamah SM, O'connell S, Cowan CW, Hu L, Goldberg JL, Debant A, Corfas G, Krull CE, Greenberg ME. **2005**. Eph-dependent tyrosine phosphorylation of ephexin1 modulates growth cone collapse. ***Neuron***. 46:191-204. PMID: 15848799. *Equal authorship.

Shamah SM*, **Lin MZ***, Goldberg JL, Estrach S, Sahin M, Hu L, Bazalakova M, Neve RL, Corfas G, Debant A, Greenberg ME. **2001**. EphA receptors regulate growth cone dynamics through the novel guanine nucleotide exchange factor ephexin. ***Cell***. 105:233-44. PMID: 11336673. *Equal authorship.

Dalva MB, Takasu MA, **Lin MZ**, Shamah SM, Hu L, Gale NW, Greenberg ME. **2000**. EphB receptors interact with NMDA receptors and regulate excitatory synapse formation. ***Cell***. 103:945-56. PMID: 11136979.

A complete list of published work is available at http://tinyurl.com/michaelzlinbibliography

D. Research Support

Completed Research Support

Damon Runyon-Rachleff Innovation Award 1/1/2013 – 12/31/2015
"Building the magic bullet: protein switches for sensing oncogenic signals and executing therapeutic programs"
Major goal: Designing protein switches that sense and respond to intracellular oncogenic pathways.
Responsibility: PI

Young Investigator Award, Alliance for Cancer Gene Therapy 4/1/2011 – 3/31/2013
"Designing protein switches to control oncolytic RNA virus replication"
Major goal: to create protein switches to control viral replication in cancer cells.
Responsibility: PI

NIH 5DP1GM111003-02 10/1/2013 – 9/30/2018
"Generalizing Optogenetics: Universal Designs for Light-Inducible Proteins"
Major goal: To improve a generalizable strategy for the creation of light-dependent proteins and extend its applications across protein classes and experimental contexts
Responsibility: PI

AHA 15IRG23290018 1/1/2015 – 12/31/2016
"Breaking the Brightness Barrier: Intensely luminescent proteins for tracking stem cell survival and function"
Major goals: (1) To image cardiac stem cell survival with an improved bioluminescent reporter, and (2) To develop a red bioluminescent calcium sensor for imaging cardiomyocyte activity in vivo
Responsibility: PI

NIH/NIGMS R01GM098734 9/30/2011 – 9/29/2015
"A molecular tag for drug-regulated synthesis of specific proteins"
Major goal: To characterize and extend a new method for rapidly controlling production of proteins.
Responsibility: PI