BIOGRAPHICAL SKETCH

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NAME Stephen J Smith	POSITION TITLE Professor of Molecular & Cellular Physiology Stanford University School of Medicine Stanford, CA 94305
eRA COMMONS USER NAME SMITH.STEPHEN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, & include postdoctoral training.)*

INSTITUTION & LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Reed College, Portland Oregon	B.A.	1970	Psychology
University of Washington, Seattle WA	Ph.D.	1977	Physiology/Psychology
University of California, Berkeley, CA	Postdoc	1977-1980	Physiology

A. Personal Statement

I have explored neural calcium signaling, synapses, synaptogenesis and neural circuit structure through scholarship, instrument invention, experimental work, laboratory leadership and teaching. My lab has invented numerous novel physiological optics methods and used them to advance neuroscience and cell biology. These optical inventions (with years of initial publication) include:

- *Novel calcium-sensing spectrometers,* enabling the first quantitative modeling of neuronal calcium transients (1980), the first quantitative measurements of presynaptic Ca transients (1982), the first measurements of calcium transients in vertebrate neurons (1983), and the discovery of calcium ion influx through NMDA receptor channels[15] (1986).
- *Novel digital video microscopy methods,* used to pioneer imaging measurement and modeling of presynaptic calcium (1988) and retinal calcium waves (1995), and *to discover* retrograde actin flow in growth cones (1988), *intracellular Ca waves in astrocytes*[14] *(1990)*, *active filipodial responses of neurons and glia to glutamate (1990)*, dynamic interactions of microtubules and trans-Golgi cisternae (1990), dendritic filopodial activities during synaptogenesis (1992), and actin activities in host-pathogen interaction (1993).
- *Novel laser-based fluorescent chip readers,* enabling early development of cDNA microarray methods for RNA transcript measurement[13] (1996).
- *Novel laser scanning microscopy methods,* used to make the *first optical measurements of astrocytic Ca responses to neural activity in brain slices* (1992), presynaptic function in single mammalian synapses (1993), and cadherin dynamics during cell-cell junction (1996) and synapse formation (2004); to discover synaptic protein transport packets (2000), retrograde regulation of presynaptic PIP_2 (2001), and to make the first optical measurements of single synaptic vesicle release events[11] (1997), the first live cell[12] (1996) and *in vivo* (2000) time-lapse observations of dendritic filopodia driving synaptogenesis and synaptotropic dendrite growth (2004), and the first *in vivo* functional imaging measurements of visual receptive field development[10] (2005).
- *Array tomography*, a novel high-resolution proteometric imaging method, now emerging as a uniquely powerful tool for structural neuroscience[1-9] (2007).

The Smith laboratory is now concentrating on array tomography technology development and applications to research on memory, gray matter myelin and neurodegenerative disorders. The lab has a very strong record of high-impact collaborative applications of its novel imaging methodologies. Please visit smithlab.stanford.edu for more.

B. Positions & Honors

1981- 1984 Assistant Professor of Physiology, Yale Medical School
1984- 1987 Assistant Professor of Molecular Neurobiology, Yale Medical School
1986- 1987 Assistant Investigator, Howard Hughes Medical Institute
1987- 1989 Associate Professor of Molecular Neurobiology, Yale Medical School
1987- 1989 Associate Investigator Howard Hughes Medical Institute
1989- 1994 Associate Professor of Molecular & Cellular Physiology, Stanford Medical School
1989- Pres NIH Study Sections, *ad hoc* and Chartered Service
1989- Pres NIH Site Visit Teams
1994- Pres Professor of Molecular & Cellular Physiology, Stanford Medical School
1994- Pres External Advisory Panel, *National Center for Microscopy & Imaging Research*, La Jolla
1994- 1995 Course Director, *Imaging Neuronal Structure & Function*, Cold Spring Harbor
1996- 1999 Director of Imaging Section, *Neurobiology*, Woods Hole
1999- 2004 Board of Scientific Counselors, National Institute of Child Health & Human Development, NIH
2000- 2004 Scientific Advisory Board, Max Planck Institute, Heidelberg, Germany
2000- Pres Faculty, Imaging Section, *Neurobiology*, Woods Hole

C. Selected peer-reviewed publications. (Selected from 122 total).

Selected recent publications introducing and making use of array tomography:

1. Allen, N.J, Howe, M.L., Foo, L.C., Wang, G.X., Chakraborty, C., **Smith, S.J** and Barres, B.A. (2012) Astrocyte-derived glypicans 4 and 6 promote the formation of excitatory synapses containing GluA1 AMPA glutamate receptors. *Nature* 486:410-4.
2. Wang, G.X. and **Smith S.J** (2012) Sub-diffraction Limit Localization of Proteins in Volumetric Space Using Bayesian Restoration of Fluorescence Images from Ultrathin Specimens. *PLoS Comput Biol.* 8(8):e1002671.
3. O'Rourke, N.A., Weiler, N.C., Micheva, K.D. and **Smith, S.J** (2012) Deep molecular diversity of mammalian synapses: Why it matters and how to measure it. *Nature Reviews Neuroscience* 13:365-79.
4. Micheva, K.D., Busse, B.L., Weiler, N.C., O'Rourke, N., **Smith, S.J** (2010) Single-synapse analysis of a diverse synapse population: Proteomic imaging methods and markers. *Neuron* 68(4):639-53.
5. Appelbaum, L., Wang, G., Yokogawa, T., Skariah, G.M., **Smith, S.J**, Mourrain, P. and Mignot, E. (2010) Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. *Neuron* 68:87-98.
6. Eroglu, C., Allen, N.J., Susman, MW, O'Rourke, N.A., Park, C.Y., Ozkan, E., Chakraborty, C., Mulinyawe, S.B., Annis, D.S., Huberman, A.D., Green, E.M., Lawler, J., Dolmetsch, R., Garcia, K.C., **Smith, S.J**, Luo, Z.D., Rosenthal, A., Mosher, D.F. and Barres, B.A. (2009) Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. *Cell* 139:380-92.
7. Datwani, A., McConnell, M.J., Kanold, P.O., Micheva, K.D., Busse, B., Shamloo, M., **Smith, S.J** and Shatz, C.J. (2009) Classical MHCI molecules regulate retinogeniculate refinement and limit ocular dominance plasticity. *Neuron* 64:463-70.
8. Stevens, B., Allen, N.J., Vazquez, L.E,. Howell, G.R.,Christopherson, K.S., Nouri, N., Micheva, K.D., Mehalow, A., Huberman, A.D., Stafford, B., Sher, A., Litke, A.M., Lambris, J.D., Smith, S.J., John, S.W.M., & Barres, B.A. (2007) The classical complement cascade mediates CNS synapse elimination. *Cell* 131:1164-78.
9. Micheva, K.D., & Smith, S.J (2007) Array tomography: A new tool for imaging the molecular architecture & ultrastructure of neural circuits. *Neuron* 55:25-36.

Other relevant publications:

10. Niell, C.M. & Smith, S.J (2005) Functional imaging reveals rapid development of visual response properties in the zebrafish tectum. *Neuron* 45: 941-951.

11. Ryan, T.A., Reuter, H. & S.J Smith (1997) Optical detection of quantal presynaptic membrane turnover. *Nature* 388: 478-482.

12. Ziv. N.E. & Smith, S.J (1996) Evidence for a role of dendritic filopodia in synaptogenesis & spine formation. *Neuron* 17: 91-102.

13. Shalon, D., Smith, S. J and Brown, P.O. (1996) A DNA micro-array system for analyzing complex DNA samples using two-color fluorescent probe hybridization. *Genome Research* **6**:639-645.

14. Cornell-Bell, A.H., Finkbeiner, S.M., Cooper, M.S. & Smith, S.J (1990) Glutamate induces calcium waves in cultured astrocytes: Long-range glial signalling. *Science* 247: 470-473.

15. MacDermott, A.B., Mayer, M.L., Westbrook, G.L., Smith, S.J., & Barker, J.L. (1986) NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. *Nature* 321: 519-522.

Extras:

16. Dani, J.W., Chernjavsky, A, and Smith, S.J. (1992) Neuronal activity triggers Ca waves in hippocampal astrocyte networks. *Neuron*, 8: 429-440.

D. Research Support.

ONGOING

1R21MH099797 Smith, Stephen J (PI) 09/12/2012 – 07/31/2014
National Institutes of Health
"A Fast Proteometric Synapse Census Platform"
Major Goal: Develop and disseminate a hew, high-speed hardware and software platform for in situ array tomographic analysis of large and diverse synapse populations.

1R01NS075252 Smith, Stephen J (PI) 07/01/11 – 04/30/15
National Institutes of Health
"Single-Synapse Analysis of Neocortical Circuit Plasticity"
Major Goal: Discover subsets of synapses in mouse whisker somatosensory cortex that participate differentially in use-dependent cortical plasticity using array tomography.

1R01NS077601 Smith, Stephen (Co-PI) 07/01/11 - 05/31/14
National Institutes of Health
"CRCNS: Collaboration on high-resolution maps of synapses on hippocampal neurons"
Major Goal: Explore mechanisms of dendritic integration in hippocampus using array tomography.

Research Grant (Consortium: Lichtman, Sanes, Zhuang, Smith, Seung) 10/1/08 – 9/30/13
Gatsby Charitable Trust
"Connectomics: Wiring Diagrams of the Mammalian Brain."
Major Goal: Develop & apply new technologies for imaging mouse brain circuit architecture.
Smith Role: Co-PI (Harvard-MIT-Stanford Consortium)

Collaborative Innovation Award (Zhuang, Harvard, PI) (in NCX) 09/01/08 - 08/31/13
Howard Hughes Medical Institute
"Wiring Diagrams of Mammalian Brain"
Smith Role: Non-HHMI PI, Stanford University performance site

COMPLETED LAST THREE YEARS

Development Fund Smith, Stephen J (PI) 1/1/08 – 12/31/12
Stanford BioX Program
“Stanford Array Tomography Resource”
Major Goal: Develop & apply new array tomography imaging methods & resources for collaborations & services designed to advance the understanding, prevention & treatment of neurodegenerative disease conditions.

Foundation Award (Lichtman, Harvard, PI) 9/1/08 – 8/31/11
“Wiring Diagrams of Mammalian Brain“
Major Goal: Develop & apply new technologies for imaging mouse brain circuit architecture.
Role: Co-PI (Harvard-MIT-Stanford Consortium)

1R21 NS063210 Smith, Stephen J (PI) 8/1/08 – 6/30/11
National Institutes of Health
“Array Tomographic Single-Synapse Analysis of Normal & Disordered Cortex”
Major Goal: Develop & apply new array tomography imaging methods for collaborations designed to advance the understanding, prevention & treatment of neurodegenerative disease conditions.

1 R01 NS054252 (Subcontract to Choe, PI, Texas A&M) 9/1/05 – 5/31/10
National Institutes of Health
“Multiscale Imaging, Modeling and Integration of Brain Networks”
Major Goal: Development new imaging and computational tools for mapping central nervous system circuitry at high resolution.
Role: Co-PI (Stanford Subcontract to Texas A&M)