BIOGRAPHICAL SKETCH

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NAME: William N. Green

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

POSITION TITLE: Professor

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 College, University of Toronto	B.Sc	06/1978	Physics & Zoology
Cornell Univ. Grad. School of Med. Sciences	Ph.D.	06/1986	Physiology & Biophysics
Yale University, Dept, Cell. & Molec. Physiology	Postdoctoral	06/1990	Physiology & Neurobiol.
Yale University, Dept, Cell. & Molec. Physiology	Res. Asst Prof.	12/1992	Physiology & Neurobiol.

A. Personal Statement:

I am interested in the cell biology of neurons, specifically, how synapses form, are maintained and change with activity and disease. We focus on the neurotransmitter receptors, nicotinic acetylcholine receptors (nAChRs) and NMDA- and AMPA-type glutamate receptors, which are responsible for the rapid postsynaptic excitatory responses. Our goal is to understand how neurons assemble these receptors, traffic them to and from synapses and how they are involved in synapse formation and plasticity. In collaboration with Dr. Tom Reese (NINDS), we are studying conformational changes in postsynaptic density scaffolding proteins (SAP97, PSD-95, SAP102) with NMDA- and AMPA-type glutamate receptor interactions using FRET and EM tomography. We also have developed techniques, acyl-biotin exchange (ABE), for assaying the protein post-translational modification palmitoylation. This work has led us to investigate neurodegenerative diseases and the palmitoylation of Huntingtin, Huntingtin interacting protein14, gamma-secretase and, most recently, SOD1 and mutant forms of SOD1 found in ALS as well as the palmitoylation of different synaptic receptors and scaffold proteins. In collaboration with Dr. Paul Selvin (University of Illinois), we are developing fluorescent single-molecule methods to characterize neurotransmitter receptor subunit composition, stoichiometry, the diffusion/trafficking of the receptors and super high-resolution measurements of the postsynaptic density and active zones at synapses.

A major goal of my research is to determine how nicotine alters the properties of nAChRs and the role of nAChRs in nicotine addiction. Recent work on nicotine upregulation has led to the discovery that the anti-smoking drug, varenicline (Chantix), is selectively trapped as a weak base within acidic vesicles in neurons and that its slow release causes nAChR desensitization at the plasma membrane. Our results provide a new paradigm for how varenicline causes smoking cessation and how nAChR weak base ligands are specifically distributed throughout neurons. The results of this research provide new insights into the cellular distribution of the nAChR weak base ligands used in PET imaging and new models of parameters involved in measuring nicotine addiction.

B. Positions and Honors

Positions and Employment:
1993-2000: Assistant Professor, Department of Neurobiology, Pharmacology & Physiology, University of Chicago
2000-2007: Associate Professor, Department of Neurobiology, Pharmacology & Physiology, University of Chicago
2003-present: Principle Investigator, Marine Biological Laboratory, Woods Hole, MA
2007-2009: Associate Professor, Department of Neurobiology, University of Chicago
2007-present: Member of the Yale University/NIDA Neuroproteomics Center.

2009-present: Professor, Department of Neurobiology, University of Chicago

Other Experience and Honors:
The Osserman/McClure Postdoctoral Fellowship, Myasthenia Gravis Foundation, 1989 - 1990.
Albert & Ellen Grass Faculty Award from the Grass Foundation, 2002 - 2005
Distinguished Research Visitor Award from the University of Auckland, 2006.
Stephen W. Kuffler Research Award from the Marine Biological Laboratory (MBL), 2010
Herbert W. Rand and the Colwin Endowed Summer Research Fellowship from the MBL, 2011
Member, *Journal of General Physiology* Editorial Board, 2000 – 2010
Member, NIH CNNT study section, 2001 – 2005
Member, NIH MNPS study section, 2006 – 2010
Member and Chair, NIH ZRG1 MDCN R15 study section, 2010 – 2015
Reviewing Editor, *Frontiers in Synaptic Neuroscience*, 2009 – present
Chair of the Whitman Center Summer Research Steering Committee at the MBL, 2011-16
Member of Science Council at the MBL, 2013-present, Chair 2017-present
Member, *Scientific Reports* Editorial Advisory Panel and Editorial Board (2017 – present)

C. Contribution to Science

1. My early publications from my Ph.D. thesis work addressing questions about the detailed workings of voltage-gated Na channels using single-channel methods. These studies began before the development of patch-clamp techniques and assayed Batrachotoxin-modified Na channels in planar lipid membranes.

a. Green, W. N., L. B. Weiss, and O. S. Andersen. 1987. Batrachotoxin-modified sodium channels in planar bilayers. Ion conduction and block. *Journal of General Physiology* **89**:841-872.

b. Green, W. N., L. B. Weiss, and O. S. Andersen. 1987. Batrachotoxin-modified sodium channels in planar bilayers. Characteristics of saxitoxin- and tetrodotoxin-induced channel closures. *Journal of General Physiology* **89**:873-903.

c. Chabala, L.D., B.W. Urban, L.B. Weiss, W. N. Green and Andersen, O.S. 1991. Steady-state activation properties of batrachotoxin-modified sodium channels in lipid bilayers. *Journal of General Physiology* **98**:197-224.

d. Green, W. N. and O. S. Andersen. 1991. Surface charge and ion channel function. *Annual Review of Physiology* **53:**341-359.

2. My publications from my postdoctoral work and after starting my faculty position addressed questions about the cell biology of the muscle-type nicotinic acetylcholine receptors (nAChRs). To study muscle-type nicotinic acetylcholine receptors, we were, for the first time able stably transfect a multi-subunit receptor into a mammalian cell line. Subsequent studies characterized the trafficking, phosphorylation and subunit assembly of muscle-type nAChRs.

a. Claudio, T., W. N. Green, D. S. Hartman, D. Hayden, H. L. Paulson, F. J. Sigworth, S. S. Sine, and A. Swedlund. 1987. Genetic reconstitution of functional acetylcholine receptor-channels in mouse fibroblasts. *Science* **238**:1688-1694.

b. Green, W. N., A. F. Ross and T. Claudio. 1991. Acetylcholine receptor assembly is stimulated by phosphorylation of its γ subunit. *Neuron* **7**:659-666.

c. Green, W. N. and T. Claudio. 1993. Acetylcholine receptor assembly: subunit folding and oligomerization occur sequentially. *Cell* **74**: 57-69.

d. Christianson, J. C. and W. N. Green. 2004. Regulation of Nicotinic Receptor Expression by the Ubiquitin-Proteasome System. *EMBO Journal* **23**:4156-65.

3. At the University of Chicago, ongoing studies have characterized $\alpha 7$- and $\alpha 4\beta 2$-type nAChRs in brain and links to nicotine addiction. These studies have established that $\alpha 7$ nAChRs are homomers of $\alpha 7$ subunits, that $\alpha 7$ nAChRs are palmitoylated as they assemble and that nicotine-induced upregulation of $\alpha 4\beta 2$

nAChRs occurs via multiple mechanisms.

a. Drisdel, R. C. and W.N. Green. 2000. Neuronal α-Bungarotoxin receptors are homomers composed of five α7 subunits. *Journal of Neuroscience* **20**: 133-139.

b. Vallejo, Y., B. Buisson, D. Bertrand and W. N. Green. 2005. Chronic Nicotine Exposure Upregulates Nicotinic Receptors by a Novel Mechanism. *Journal of Neuroscience* **25**:5563-5572.

c. Govind, A. P., H. Walsh, and W. N. Green. 2012. Nicotine-induced upregulation of native neuronal nicotinic receptors is caused by multiple mechanisms. *Journal of Neuroscience* **32**:2227-38. PMCID: PMC3286518.

d. Govind A.P., Y. Vallejo, J. R. Stolz, J. Z. Yan, G. T. Swanson and W. N. Green. 2017. Selective and regulated trapping of nicotinic receptor weak base ligands and relevance to smoking cessation. *Elife* 6:e25651. PMID:8718768.

4. At the University of Chicago, we have developed new methods to assay the posttranslational modification of palmitoylation, acyl-biotin exchange (ABE), which are quantitative and more sensitive than previous methods. We used these methods to develop proteomic tools and to assay nAChRs, PSD-95 and a number of proteins linked to neurodegenerative diseases.

a. Drisdel, R. C. and W.N. Green. 2004. Labeling and Quantifying Sites of Protein Palmitoylation. *BioTechniques*. **36**:276-285. PMID: 14989092.

b. Drisdel, R. C., E. Manzana and W.N. Green. 2004. The role of palmitoylation in functional expression of nicotinic α7 receptors. *Journal of Neuroscience* **24**:10502-10510. PMID: 15548665.

c. Kang, R., J. Wan, P. Arstikaitis, K. Huang, A. F. Roth, R, Drisdel, W. N. Green, J. R. Yates, N. G. Davis, A. El-Husseini. 2008. Neural palmitoyl-proteomics reveals dynamic synaptic palmitoylation. *Nature* 456:904-9. PMCID: PMC2610860.

d. Antinone, S. E., G. D. Ghadge, T. T. Lam, L. Wang, R. Roos and W. N. Green. 2013. Human superoxide dismutase 1 (SOD1) is palmitoylated and palmitoylation of familial ALS-linked SOD1 mutants is increased. *Journal of Biological Chemistry* 288:21606-17. PMID: 28120938.

5. At the University of Chicago, we are developing FRET-based, single-molecule and super-resolution techniques to characterize the trafficking of glutamate receptors and adaptor/scaffold proteins to and from excitatory synapses.

a. Jeyifous, O, M. Schubert, C. G. Specht, C. L. Waites, E. Lin, S. Fujisawa, J. Marshall, C. Aoki, J. M. Montgomery, C. C. Garner and W. N. Green. 2009. SAP97 and CASK mediate sorting of N-Methyl-D-Aspartate Receptors through a previously unknown secretory pathway. *Nature Neuroscience* **12**:10111019 PMCID: PMC2779056.
b.Cai, E., P. Ge, S. H. Lee, O. Jeyifous, Y. Wang, Y. Liu, K. M. Wilson, S. J. Lim, M. A. Baird, J. E. Stone, K. Y. Lee, M. W. Davidson, H. J. Chung, K. Schulten, A. M. Smith, W. N. Green, P. R. Selvin. 2014. Stable small quantum dots for synaptic receptor tracking on live neurons. *Angewandte Chemie.* 53:12484-8. PMCID: PMC4240739.

c. Zheng, N., O. Jeyifous, C. Munro, J. Montgomery and W. N. Green. 2015. Synaptic Activity Regulates AMPA Receptor Trafficking Through Different Recycling Pathways. *Elife*. 4:e06878.

d. Jeyifous, O., E. I. Lin, X. Chen, S. E. Antinone, R. Mastro, R. Drisdel, T. S. Reese and W. N. Green. 2016. Palmitoylation regulates glutamate receptor distributions in postsynaptic densities through control of PSD95 conformation and orientation. *Proceedings of the National Academy of Sciences* 113:8482–8491.

e. Lee, S. H., C. Jin, E. Cai, P. Ge, Y. Ishitsuka, K. W. Teng, A. A. de Thomaz, D. Nall, M. Baday, O. Jeyifous, D. Demonte, C. M. Dundas, S. Park, W. N. Green, P. R. Selvin. 2017. Super-resolution Imaging of Synaptic and Extrasynaptic Pools of Glutamate Receptors with Different-sized Fluorescent Probes. *Elife* 6: e25651.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40865882/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support:

1. R01NS100019-01A1 (Selvin-PI, Green-Co-I) 07/01/2017 - 06/30/2022 0.06 calendar
NIH
Super-Resolution Microscopy of Neuronal Synapses with Small Quantum Dots, UCNPs and Advanced Imaging Tools
The goals of my portion of the application are to help the Selvin Lab with applying the different nano-particles and microscope techniques they are developing to cultured neurons and synaptic proteins.

2. R01 DA044997-01 (Zhuang-PI, Green-Co-I) 09/01/2017-08/31/2022 0.60 Calendar
NIH/NIDA
"RNA methylation in synaptic plasticity and drug-seeking"
The primary objective of this research is to test in animal models and cell culture models the contribution of RNA methylation to synaptic protein translation, synaptic plasticity and drug seeking behavior.

3. R01 DA044760-01 (Green-PI, Chen/Mukherjee-Co-Is) 07/01/2017 - 06/30/2022 3.60 calendar
NIH
PET imaging of a4b2 nicotinic receptor upregulation and smoking cessation
The goals of this proposal are to examine how our discovery of the trapping of weak base $\alpha4\beta2$R ligands in acid vesicles affects the imaging of $\alpha4\beta2$Rs using PET probes and to use PET probe imaging to examine how nicotine causes $\alpha4\beta2$Rs upregulation and how varenicline alters upregulation.

OVERLAP: There is no overlap.

Completed Research Support:

1. R01DA035430-01 (William N. Green, PI) 8/01/2013 – 7/31/2018 4.00 calendar
NIH/NIDA
Different components of nicotine-induced upregulation of nicotinic receptors
This grant focuses on characterizing the different components of nicotine-induced upregulation of nicotinic receptors and the underlying mechanisms.

2. R56NS090903-01 (Paul Selvin PI, W. N. Green Co-PI) 10/01/2014 – 09/30/2016
NIH/NINDS
Organization and Dynamics of PSD-bound Glutamate Receptors at Super-resolution

3. RO1 NS043782 (William N. Green PI) 7/1/08 – 6/30/013
NIH/NINDS
The Neuronal α-Bungarotoxin Receptor

4. ALS Association (Ray Roos PI, William N. Green Co-PI) 04/01/2014 – 03/30/15
Palmitoylation of SOD1 and the pathogenesis of ALS