
BIOGRAPHICAL SKETCH

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NAME Siderovski, David Peter	POSITION TITLE Associate Professor of Pharmacology; Co-Director of the UNC MD/PhD Program.		
eRA COMMONS USER NAME DSIDEROV			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Queen's University, Kingston, Ontario, Canada	B.Sc.(Hons)	1985-1989	Biochemistry
University of Toronto, Toronto, Ontario, Canada	Ph.D.	1989-1997	Medical Biophysics
AMGEN Research Institute, Toronto, Ontario	Industrial postdoc.	1997-1999	Molecular Pharmacology

A. Positions and Honors

Positions and Employment

1989 - 1994 Predoctoral Research Fellow, Department of Medical Biophysics, University of Toronto
1994 - 1997 Associate Scientist,
1997 - 1999 Research Scientist and Head,
Quantitative Biology Laboratory, AMGEN Research Institute, Toronto, Ontario, Canada
1999 - 2004 Assistant Professor (tenure-track), Department of Pharmacology,
University of North Carolina at Chapel Hill, Chapel Hill, NC
1999 - Member, Lineberger Comprehensive Cancer Center, UNC-Chapel Hill
2000 - Member, UNC Neuroscience Center & Neurobiology Curriculum, UNC-Chapel Hill
2003 - Member, UNC Biophysics Curriculum, UNC-Chapel Hill
2004 - Associate Professor (tenured), Department of Pharmacology, UNC-Chapel Hill
2006 - Co-Director of the UNC MD/PhD Program, UNC-Chapel Hill School of Medicine

Other Experience and Professional Memberships

1998 - Member, American Society for Pharmacology and Experimental Therapeutics
1998 - Member, American Society for Biochemistry and Molecular Biology
2001 - 2006 Associate Editor, *Molecule Pages*, Alliance for Cellular Signaling/NATURE Publishing
2002 Cell Development and Function 3 (CDF-3) Study Section, NIH/CSR
2004 Synapses, Cytoskeleton and Trafficking (SYN) Study Section, NIH/CSR
2005 - 2006 Allergy, Immunology & Transplantation (AITRC) review panel, NIH/NIAID
2005 - Member, Cell Biology Fellowship review panel (ZRG-1 F05), NIH/CSR
2006 - Member, K99/R00 Pathway to Independence (PI) award review panel, NIH/NIGMS

Academic Honors

2000 - 2003 Year 2000 Neuroscience Research Scholar, The EJLB Foundation, Montréal, PQ, Canada
2001 - 2004 New Investigator Award in the Pharmacological Sciences, Burroughs Wellcome Fund
2004 17th Charles W. Gowdey Distinguished Lecturer, Univ. of Western Ontario, London, Canada
2004 Co-chair, *Second RGS Protein Colloquium*, FASEB/Experimental Biology '04, Washington, D.C.
2004 John Jacob Abel Award to the Outstanding American Pharmacologist under 40,
American Society of Pharmacology and Experimental Therapeutics
2006 UNC's Philip and Ruth Hettleman Prize for Artistic and Scholarly Achievement

Patents

1998 "Methods of Inhibiting Syp Binding to a CTLA-4 Receptor"
United States Patent 5,786,152. Marengere, Siderovski, & Mak.
2004 "Apoptosis-Inducing Factor"
United States Patent 6,773,911. Penninger, Kroemer, Siderovski, Zamzami, Susin, & Snow.

B. Publications

Original research (selected from >85 peer-reviewed publications)

- Ingi T, Krumins AM, Chidiac P, Brothers GM, Chung S, Snow BE, Barnes CA, Lanahan AA, Siderovski DP, Ross EM, Gilman AG, Worley PF. (1998) Dynamic regulation of RGS2 suggests a novel mechanism in G-protein signaling and neuronal plasticity. *J. Neurosci.* 18, 7178-7188.
- Snow BE, Betts L, Mangion J, Sondek J, Siderovski DP. (1999) Fidelity of G protein β -subunit association by the G protein γ -subunit-like domains of RGS6, RGS7, and RGS11. *Proc. Natl Acad. Sci. USA* 96, 6489-94.
- Oliveira-dos-Santos AJ, Matsumoto G, Snow BE, Bai D, Houston FP, Whishaw IQ, Mariathasan S, Sasaki T, Wakeham A, Ohashi PS, Roder JC, Barnes CA, Siderovski DP, Penninger JM. (2000) Regulation of T cell activation, anxiety and male aggression by RGS2. *Proc. Natl Acad. Sci. USA* 97, 12272-12277.
- Schiff ML, Siderovski DP, Jordan J, Brothers G, Snow B, DeVries L, Ortiz D, Diversé-Pierluissi, M. (2000) Tyrosine-kinase-dependent recruitment of RGS12 to the N-type calcium channel. *Nature* 408, 723-727.
- Kimple RJ, De Vries L, Tronchère H, Behe CI, Morris RA, Farquhar MG, Siderovski, D.P. (2001) RGS12 and RGS14 GoLoco motifs are $G\alpha i$ interaction sites with guanine nucleotide dissociation inhibitor activity. *J. Biol. Chem.* 276, 29275-29281.
- Kimple RJ, Kimple ME, Betts L, Sondek J, Siderovski DP. (2002) Structural determinants of GoLoco-induced inhibition of nucleotide release by Galpha subunits. *Nature* 416, 878-881.
- Colombo K, Grill SW, Kimple RJ, Willard FS, Siderovski DP, Gönczy P. (2003) Translation of polarity cues into asymmetric spindle positioning in *Caenorhabditis elegans* embryos. *Science* 300, 1957-1961.
- Chen J-G, Willard FS, Huang J, Liang J, Chasse SA, Jones AM, Siderovski DP. (2003) A seven trans-membrane RGS protein that modulates plant cell proliferation. *Science*, 301, 1728-1731.
- Tang M, Wang G, Lu P, Karas RH, Aronovitz M, Heximer SP, Kaltenbronn KM, Blumer KJ, Siderovski DP, Zhu Y, Mendelsohn ME. (2003) Regulator of G-protein signaling-2 mediates vascular smooth muscle relaxation and blood pressure. *Nature Medicine*, 9, 1506-1512.
- Afshar K, Willard FS, Colombo K, Johnston CA, McCudden CR, Siderovski DP, Gonczy P. (2004) RIC-8 is required for GPR-1/2-dependent G-alpha function during asymmetric division of *C. elegans* embryos. *Cell*, 119, 219-230.
- Martin-McCaffrey L, Willard FS, Oliveria-dos-Santos AJ, Natale DR, Snow BE, Kimple RJ, Pajak A, Watson AJ, Dagnino L, Penninger JM, Siderovski DP, D'Souza SJ. (2004) RGS14 is a mitotic spindle protein essential from the first division of the mammalian zygote. *Dev. Cell*, 7, 763-769
- Webb CK, McCudden CR, Willard FS, Kimple RJ, Siderovski DP, Oxford GS. (2005) D2 dopamine receptor activation of potassium channels is selectively decoupled by $G\alpha i$ -specific GoLoco motif peptides. *J. Neurochem.*, 92, 1408-1418.
- Willard FS, Kimple AJ, Johnston CA, Siderovski DP. (2005) A direct fluorescence-based assay for RGS domain GTPase accelerating activity. *Anal. Biochem.*, 340, 341-351.
- Johnston CA, Willard FS, Jezyk MR, Fredericks Z, Bodor ET, Jones MB, Blaesius R, Watts VJ, Harden TK, Sondek J, Ramer JK, Siderovski DP. (2005) Structure of Galpha(i1) bound to a GDP-selective peptide provides insight into guanine nucleotide exchange. *Structure*, 13, 1069-1080.
- Afshar K, Willard FS, Colombo K, Siderovski DP, Gonczy P. (2005) Cortical localization of the $G\alpha$ protein GPA-16 requires RIC-8 function during *C. elegans* asymmetric cell division. *Development*, 132, 4449-4459.
- Martin-McCaffrey L, Hains MD, Pritchard GA, Pajak A, Dagnino L, Siderovski DP, D'Souza SJ. (2005) Differential expression of regulator of G-protein signaling R12 subfamily members during mouse development. *Dev. Dyn.*, 234, 438-444.
- Zigman M, Cayouette M, Charalambous C, Schleiffer A, Hoeller O, Dunican D, McCudden CR, Firnberg N, Barres BA, Siderovski DP, Knoblich JA. (2005) Mammalian Inscuteable regulates spindle orientation and cell fate in the developing retina. *Neuron*, 48, 539-545.
- Wang H, Ng KH, Qian H, Siderovski DP, Chia W, Yu F. (2005) Ric-8 controls *Drosophila* neural progenitor asymmetric division by regulating heterotrimeric G proteins. *Nature Cell Biol.*, 7, 1091-1098.
- Sambi BS, Hains MD, Waters CM, Connell MC, Willard FS, Kimple AJ, Pyne S, Siderovski DP, Pyne NJ. (2006) The effect of RGS12 on PDGFbeta receptor signalling to p42/p44 mitogen activated protein kinase in mammalian cells. *Cell Signal.*, 18, 971-981.
- Willard FS, McCudden CR, Siderovski DP. (2006) G-protein alpha subunit interaction and guanine nucleotide dissociation inhibitor activity of the dual GoLoco motif protein PCP-2 (Purkinje cell protein-2). *Cell Signal.*, 18, 1226-1234.
- Willard FS, Siderovski DP. (2006) Covalent immobilization of histidine-tagged proteins for surface plasmon resonance. *Anal. Biochem.* 353, 147-149.

- Fatemi SH, Reutiman TJ, Folsom TD, Bell C, Nos L, Fried P, Pearce DA, Singh S, Siderovski DP, Willard FS, Fukuda M. (2006) Chronic olanzapine treatment causes differential expression of genes in frontal cortex of rats as revealed by DNA microarray technique. *Neuropsychopharmacology* 31, 1888-1899.
- Hains M, Wing M, Maddileti S, Siderovski DP, Harden TK. (2006) G α 12/13- and Rho-dependent activation of phospholipase C- ϵ by lysophosphatidic acid and thrombin receptors. *Mol. Pharmacol.* 69, 2068-2075.
- Paing MM, Johnston CA, Siderovski DP, Trejo J. (2006) Clathrin adaptor AP2 regulates thrombin receptor constitutive internalization and endothelial cell resensitization. *Mol. Cell Biol.* 26, 3231-3242.
- Dho SE, Trejo J, Siderovski DP, McGlade CJ. (2006) Dynamic regulation of mammalian Numb by GPCR and PKC activation: structural determinants of Numb association with the cortical membrane. *Mol. Biol. Cell.* 17, 4142-4155.
- Johnston CA, Lobanova ES, Shavkunov AS, Low J, Ramer JK, Blaesius R, Fredericks Z, Willard FS, Kuhlman B, Arshavsky VY, Siderovski DP. (2006) Minimal determinants for binding activated G-alpha from the structure of a G-alpha-i1/peptide dimer. *Biochemistry* 45, 11390-11400.
- Liu H, Suresh A, Willard FS, Siderovski DP, Lu S, Naqvi NI. (2007) Rgs1 regulates multiple G α subunits in *Magnaporthe* pathogenesis, asexual growth and thigmotropism. *EMBO J.*, 26, 690-700.
- Johnston CA, Siderovski DP. (2007) A structural basis for nucleotide exchange on G α i subunits and receptor coupling specificity. *Proc. Natl Acad. Sci. USA*, 104, 2001-2006.
- Willard MD, Willard FS, Li X, Cappell SD, Snider WD, Siderovski DP. (2007) Selective role for RGS12 as a Ras/Raf/MEK scaffold in nerve growth factor-mediated differentiation. *EMBO J.*, 26, 2029-2040.
- Sammond DW, Eletr ZM, Purbeck C, Kimple RJ, Siderovski DP, Kuhlman B. (2007) Structure-based protocol for identifying mutations that enhance protein-protein binding affinities. *J. Mol. Biol.*, [in press]

Selected reviews and book chapters:

- Sondek J, Siderovski DP. (2001) Ggamma-like (GGL) domains: new frontiers in G-protein signaling and beta-propeller scaffolding. *Biochem. Pharmacol.* 61, 1329-1337.
- Neubig RR, Siderovski DP. (2002) Regulators of G-protein signalling as new central nervous system drug targets. *Nat. Rev. Drug Discov.* 1, 187-197.
- Kimple RJ, Jones MB, Shutes A, Yerxa BR, Siderovski DP, Willard FS. (2003) Established and emerging fluorescence-based assays for G-protein function: heterotrimeric G-protein alpha subunits and regulator of G-protein signaling (RGS) proteins. *Comb. Chem. High Throughput Screen.* 6, 399-407.
- Siderovski DP, Harden TK. (2003) "The RGS Protein Superfamily" in *Handbook of Cell Signalling, vol. 2* (Bradshaw RA and Dennis EA, eds.), pp. 631-638, Elsevier Press, San Diego.
- Willard FS, Kimple RJ, Siderovski DP. (2004) Return of the GDI: the GoLoco motif in cell division. *Annu. Rev. Biochem.*, 73, 925-951.
- Willard FS, Kimple RJ, Kimple AJ, Johnston CA, Siderovski DP. (2004) Fluorescence-based assays for RGS box function. *Methods Enzymol.*, 389, 56-71.
- Hains MD, Siderovski DP, Harden TK. (2004) Application of RGS box proteins to evaluate G-protein selectivity in receptor-promoted signaling. *Methods Enzymol.*, 389, 71-88.
- Uhlik MT, Temple B, Bencharit S, Kimple AJ, Siderovski DP, Johnson GL. (2005) Structural and evolutionary division of phosphotyrosine binding (PTB) domains. *J. Mol. Biol.*, 345, 1-20.
- McCudden CR, Hains MD, Kimple RJ, Siderovski DP, Willard FS. (2005) G-protein signaling: back to the future. *Cell Mol. Life Sci.*, 62, 551-577.
- Johnston CA, Siderovski DP. (2007) Receptor-mediated activation of heterotrimeric G-proteins: Current structural insights. *Mol. Pharmacol.*, [in press].

Books:

- Siderovski DP, ed. (2004) Regulators of G-Protein Signaling, Parts A & B. Volumes 389 & 390 of *Methods in Enzymology*. Elsevier Press, San Diego.

C. Research Support

Ongoing Research Support

5 R01 GM062338-07 Siderovski (PI) 2/01/01 – 1/31/10
NIH/NIGMS

G-protein signal coordination by RGS12

The major goals of this study are to define the specific roles that RGS12 partakes in signal transduction modulation in dorsal root ganglion neurons and thus illuminate the potential for RGS12 as a drug discovery target for novel pharmacotherapies for neuropathic pain, spasticity, and adult neuron regeneration. This project involves biochemical/biophysical and cell-biological analyses of RGS12-mediated protein/protein and protein/lipid interactions with multiple independent signal transduction components downstream of G protein-coupled receptors and growth factor receptor tyrosine kinases. Role: PI

5 R01 GM074268-02 Siderovski (PI) 7/01/06 – 6/30/10
NIH/NIGMS

Mechanistic Studies of a Novel G-alpha Nucleotide Cycle

The major goals of this project are to (a) to define the structural determinants and functional interplay between novel G α regulators (including RIC-8, RGS-7, and GPR-1/-2) of the model organism *Caenorhabditis elegans* that control G α subunit activity in the process of asymmetric cell division, (b) develop new peptide-based fluorescence biosensors to assess the spatiotemporal dynamics of G α nucleotide state in live cells during cell division, and (c) to define the structural features and combined biochemical actions of mammalian G α_i proteins, essential regulators of their nucleotide cycle, and the cell-cycle kinase Cdk1 in modulating microtubule dynamics during mitosis. Role: PI

1 R03 NS053754-01 Siderovski (PI) 9/30/05 – 8/31/08 (currently in N.C.E.)
NIH/NINDS

Real-time fluorescence assays of RGS domain GAP activity

The major goal of this one-year study is to modify and validate one of three novel, real-time, fluorescence-based assay of RGS protein function for automated high-throughput molecular screening: (i) a fluorescence resonance energy transfer (FRET)-based binding assay that employs cyan fluorescent protein-labelled G-alpha subunits and yellow fluorescent protein-labeled RGS proteins, (ii) a single-turnover GTP hydrolysis assay using a fluorescent sensor for inorganic phosphate, and (iii) an assay of G α nucleotide binding and hydrolysis that employs the fluor-modified nucleotide BODIPY FL guanosine 5'-triphosphate. Role: PI

5 R01 GM073960-03 Kuhlman (PI) 5/01/05 – 4/30/10
NIH/NIGMS

Designing affinity and specificity at protein interfaces

The major goal is to develop new technology for the computational design of protein-protein interfaces. A new flexible side chain model will be tested on the design of altered specificity protein interfaces, and design with full backbone flexibility will be used to extend protein interfaces and increase affinity. Two model systems will be used: the interaction between the GoLoco motif and G-alpha-i, and the interaction between the ubiquitin conjugating enzyme UbcH7 and the ubiquitin ligase E6AP.

Role: Collaborating investigator on one Specific Aim (salary support only).

Completed Research Support

Sponsored Research Siderovski (PI) 7/01/02 – 6/30/04
Karo*Bio USA

A structural determination of peptide interaction with G-alpha proteins

This industrially-sponsored research was focused on characterizing the interactions of phage-display peptides with G α proteins by crystallography and determining the effects of these peptides on G α function in vitro.

Role: PI

New Investigator Award Siderovski (PI) 7/01/01 – 6/30/04
Burroughs Wellcome Fund

GoLoco motif-derived peptides as selective G-protein "perturbagens"

The major goal of this project was to test the hypothesis that the GoLoco motifs of G α -binding proteins can be developed into cell membrane-permeant peptides to enable intracellular delivery of guanine-nucleotide dissociation inhibitor (GDI) activity directed toward select G α subunits. Role: PI