OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Sondek, John

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-1127-8310

Position Title: Professor

Organization and Location: Department of Pharmacology, UNC Chapel Hill, Chapel Hill, North Carolina, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Yale University, New Haven, Connecticut, United States	Postdoctoral Fellow	05/1992	10/1996	Structural Biology
The Johns Hopkins University, Baltimore, Maryland, United States	Doctor of Philosophy (PHD)	05/1985	05/1992	Biochemistry
University of Rochester, Rochester, New York, United States	Bachelor of Science (BS)	09/1981	05/1985	Biochemistry

Appointments and Positions

2006 - present	Professor, Department of Pharmacology, UNC Chapel Hill, Chapel Hill, North Carolina, United States
2014 - present	Faculty Director, Center for Structural Biology, UNC Chapel Hill, Chapel Hill, North Carolina, United States
2006 - present	Professor, Department of Biochemsitry & Biophysics, UNC Chapel Hill, Chapel Hill, North Carolina, United States
2002 - 2006	Associate Professor, Department of Biochemsitry & Biophysics, UNC Chapel Hill, Chapel Hill, North Carolina, United States
2002 - 2006	Associate Professor, Department of Pharmacology, UNC Chapel Hill, Chapel Hill, North Carolina, United States
1998 - present	Member, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States
1996 - 2002	Assistant Professor, Department of Biochemistry & Biophysics, UNC Chapel Hill, Chapel Hill, North Carolina, United States
1996 - 2002	Assistant Professor, Department of Pharmacology, UNC Chapel Hill, Chapel Hill, North Carolina, United States

Products

Products Closely Related to the Proposed Project

1. Carr AJ, Hajicek N, Tsai AP, Acharya PP, Hardy PB, Meyer E, Wyss-Coray T, Pearce KH, Sondek J, Zhang Q. A high-throughput assay platform to discover small molecule activators of the phospholipase PLC-γ2 to treat Alzheimer's disease. J Biol Chem. 2025 Apr;301(4):108356. PubMed Central PMCID: PMC12131191.
2. Zeng L, Zhang X, Xiong Y, Sato K, Hajicek N, Kogure Y, Kataoka K, Ogawa S, Sondek J, Su X. Hyperactive PLCG1 induces cell-autonomous and bystander T cell activation and drug resistance. EMBO Rep. 2025 Sep;26(18):4563-4586. PubMed Central PMCID: PMC12457681.
3. Siraliev-Perez E, Stariha JTB, Hoffmann RM, Temple BRS, Zhang Q, Hajicek N, Jenkins ML, Burke JE, Sondek J. Dynamics of allosteric regulation of the phospholipase C-γ isozymes upon recruitment to membranes. Elife. 2022 Jun 16;11 PubMed Central PMCID: PMC9203054.
4. Hajicek N, Keith NC, Siraliev-Perez E, Temple BR, Huang W, Zhang Q, Harden TK, Sondek J. Structural basis for the activation of PLC-γ isozymes by phosphorylation and cancer-associated mutations. Elife. 2019 Dec 31;8 PubMed Central PMCID: PMC7004563.
5. Waldo GL, Ricks TK, Hicks SN, Cheever ML, Kawano T, Tsuboi K, Wang X, Montell C, Kozasa T, Sondek J, Harden TK. Kinetic scaffolding mediated by a phospholipase C-beta and Gq signaling complex. Science. 2010 Nov 12;330(6006):974-80. PubMed Central PMCID: PMC3046049.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Sondek, John

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-1127-8310

Position Title: Professor

Organization and Location: Department of Pharmacology, UNC Chapel Hill, Chapel Hill, North Carolina, United States

Personal Statement

I am focused on understanding signal transduction cascades controlled by heterotrimeric G proteins, small GTPases related to Ras, and the phospholipase C (PLC) isozymes. I primarily use biochemical and biophysical methods to dissect these cascades at atomic and molecular resolution to understand and manipulate associated cellular processes. I contributed to the determination of the first atomic-resolution structures of a heterotrimeric G protein. Additional, impactful works include our studies on: i) R7-family RGS proteins, ii) guanine nucleotide exchange factors (GEFs) that active Rho-family GTPases, and iii) phospholipase C isozymes that are directly activated by heterotrimeric G proteins and small GTPases. Active programs include distinct drug discovery campaigns to identify inhibitors and activators of the PLC-gamma isozymes. These campaigns arise from our on-going research to understand the regulation of the PLC-gamma isozymes downstream of growth factor receptors and immune receptors that are dysregulated in certain cancers, immune disorders, and neurodegenerative diseases.

I am committed to training our next generation of scientists. In the past ten years, I have trained three graduate students as well as seven post-doctoral associates. In the past, I have served as the Director of Graduate Studies for the Molecular and Cellular Biophysics Training Program at UNC-Chapel Hill. I currently serve on the Internal Steering Committee for the Carolina Cancer Nanotechnology T32 Training Program.

Structural biology is a mainstay of my research. This research requires extensive infrastructure that is best supported through multi-user facilities. To support these facilities, I currently serve as a member of the UNC Core Facilities Advisory Committee and Director of the UNC Center for Structural Biology. My research has led to over 100 research papers in peer-reviewed journals.

Honors

2013 - 2013	Winner, GlaxoSmithKline Discovery Fast Track Competition, GlaxoSmithKline
2009 - 2011	Chair, GRC Mechanisms of Cell Signaling, Gordon Research Conferences
1999 - 2003	Pew Scholar in the Biomedical Sciences, The Pew Charitable Trusts
1993 - 1996	Damon Runyon - Walter Winchell Fellowship, Damon Runyon Cancer Research Foundation
1991 - 1992	Institutional Research Grant, The Johns Hopkins University
1989 - 1992	Institute for Biophysical Research Predoctoral Fellowship, The Johns Hopkins University
1985 - 1986	NIH Predoctoral Fellowship, The Johns Hopkins University
1981 - 1985	Regents Scholarship, State of New York
1981 - 1985	Centennial Prize Scholarship, University of Rochester

Contributions to Science

1. Regulation of phospholipase C isozymes. I started as an Assistant Professor at UNC-Chapel Hill in 1996 and immediately began a collaboration with Dr. Ken Harden (UNC-Chapel Hill) to understand the biology of phospholipase C (PLC) isozymes and their activation by heterotrimeric G proteins. Our collaboration lasted until 2014 when Dr. Harden retired. During this period, we published 25 papers together describing the regulation of PLC isozymes. PLCs hydrolyze phosphatidylinositol 4,5-bisphospate (PIP2) to produce the second messengers inositol 1,4,5-trisphosphate and diacylglycerol. PIP2 as well as its second messengers control a plethora of downstream events including levels of intracellular calcium and the activation of PKC isozymes. Furthermore, humans possess 13 distinct PLC isozymes that are activated by a myriad of inputs including Ras- and Rho-family GTPases, heterotrimeric G proteins and receptor tyrosine kinases. Therefore, PLCs occupy an important nexus between extracellular stimuli and intracellular responses including migration and proliferation. Our work focused on understanding the regulation of PLCs isozymes and in 2008, we formulated a coherent framework that explained the near-universal autoinhibition of PLC isozymes as well as the capacity of diverse inputs to activate these phospholipases. This framework has withstood the test of time and continues to be used by many researchers in this field. More recently, this framework has been used to explain activating mutations in PLC-gamma isozymes that contribute to inflammatory diseases and cancer.

2. New targets to treat cancer and neurodegenerative diseases. Our structural and biophysical studies often require us to develop new methods to produce and assay pure proteins. Consequently, these methods and reagents are often easily adaptable to high-throughput screens. In recent years, we have developed and patented high-throughput screens to identify chemical modulators of: i) the Ras superfamily of GTPases, ii) phospholipase C isozymes, and iii) G-alpha subunits of heterotrimeric G proteins. The identification of drug-like modulators to any of these proteins have immediate ramifications for the treatment of cancer as well as many other human diseases. For example, the aberrant activation of Rac1 GTPase is implicated in most cutaneous melanomas. Similarly, mutated and constitutively active G-alpha-q or G-alpha-11 drive about 90% of uveal melanomas while constitutively active PLC-gamma1 contributes to ~40% of adult T cell leukemias/lymphomas. Other potential therapeutic areas include asthma that can be controlled by inhibition of G-alpha-q and rheumatoid arthritis that is exacerbated by active PLC-gamma2. More recently a natural variant of PLC-gamma2 has been shown to control immune responses that protect against cognitive decline associates with Alzheimer's disease and several other neurodegenerative diseases. We have enlisted the help of several large screening operations: GlaxoSmithKline, AstraZeneca, HitGen, and the NIH-funded Molecular Libraries Production Centers Network to screen these targets. In addition, I co-founded a biotech firm to commercialize these technologies.

3. Activation of Rho GTPases. He was not even a graduate student in my lab, but Mr. Kent Rossman asked me so many questions about the purification and structural biology of Dbl-family proteins that we would eventually collaborate on over twenty papers related to these proteins. Dbl-family proteins comprise the major set of activators of Rho GTPases in humans and together with Dr. David Worthylake, Kent and I described the first atomic-resolution complex of a Dbl-family protein in complex with a Rho-family GTPases. This work was essential for understanding how Dbl-family proteins directly activate Rho GTPases and was published in Nature in 2000. Our subsequent work in this field would detail how Dbl-family protein are regulated by membranes where they operate. We would also go on to explain the structural rules that dictate the specific pairings between the 70 human Dbl-family proteins and the three major Rho-family GTPases: RhoA, Rac1 and Cdc42.

   Our review of this field in 2005 has been cited over 1,000 times based on Thomson Reuters' Web of Science, placing it in the top 1% of cited papers in the field of cell biology and indicative of our major impact in this area.

   I continue to study Dbl-family proteins and our most recent work is focused on the creation of FRET-based biosensor of Dbl-family proteins using general design principles based on core regulation of these proteins. These biosensors are being used to map the spatiotemporal activation of Dbl-family proteins in cells to be correlated with similar work monitoring Rho GTPases.

4. Signaling by G proteins. Dr. Heidi Hamm was an excellent biochemist at the University of Illinois at Chicago with expertise studying vision while Dr. Paul Sigler was an established crystallographer at the University of Chicago when they established a collaboration to understand visual signal transduction. This collaboration led to the first atomic-resolution structure of a heterotrimeric G protein alpha subunit when Dr. Joe Noel determined the structure of active transducin in 1994. David Lambright and I quickly followed this initial work with a series of papers in Nature describing structures of additional states of transducin including the intact heterotrimer. These papers provided an extensive understanding of the regulatory cycle of heterotrimeric G proteins at atomic resolution. This work and similar studies by the groups of Drs. Alfred Gilman and Stephen Sprang at the University of Texas Southwestern Medical Center were foundational in establishing our current understanding of signaling by G proteins.

   I continue to study signaling by G proteins. My early work at UNC Chapel Hill included a detailed study of inhibition of G-alpha subunits by GoLoco motif-containing proteins and the first structural description of the unconventional G-beta subunit, G-beta5, bound to an essentially full-length RGS9.

5. Protein plasticity and humanized antibodies. For my Ph.D. work with Dr. David Shortle at Johns Hopkins University, I sought to quantify the energetic and structural effects of one to two amino acid insertions or deletions in proteins. This work was initially motivated by earlier indications that the natural process of somatic hypermutation incorporated insertions and deletions during the directed evolution of mature antibodies. In a systematic analysis of dozens of mutant proteins, we found that insertions and deletions were remarkably well tolerated in model proteins; changes in stability were comparable to the equivalent substitution at flanking sites. Indeed, insertions into secondary structural elements often led to register shifts or bulges as determined by protein crystallography and we coined the phrase, “alpha-aneurysm” for the first identification of the structural equivalent of a beta-bulge in alpha-helices. Additional work led us to conclude that the most common mutation, deletion of Phe508, in the cystic fibrosis conductance regulator (CFTR) protein contributes to cystic fibrosis through localized rearrangements of the surrounding beta-sheets that reduce stability but not function. It has since become clear that deletion of Phe508 results in misfolding and poor intracellular trafficking of the CFTR protein due to lack of stability, but once trafficked correctly, will function normally.

   Our work in this field also produced more facile methods for the creation of large numbers of mutant proteins using site-directed mutagenesis. Indeed, this work led to an international patent that was licensed to the publicly traded, mid-cap biotechnology company, Morphosys AG, to produce humanized antibodies. Royalties are estimated to be more than one million dollars and emphasize the importance of this work to the pharmaceutical industry.

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