BIOGRAPHICAL SKETCH

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NAME: Field, Seth Joel

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

POSITION TITLE: Professor of Medicine

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
Massachusetts Institute of Technology Cambridge, MA	B.S.	06/1987	Biology
Harvard Medical School Boston, MA	M.D.	06/1997	Medicine
Harvard Medical School Boston, MA	Ph.D.	06/1997	Genetics (thesis with Michael Greenberg)
Hospital of the University of Pennsylvania Philadelphia, PA	Intern/Resident	06/1999	Internal Medicine
Massachusetts General Hospital Boston, MA	Clinical Fellow	06/2001	Endocrinology
Harvard Medical School Boston, MA	Postdoctoral Fellow	06/2002	Cell Biology and Systems Biology (with Lewis Cantley)

A. **Personal Statement**

The Field laboratory works at the intersection of signal transduction and membrane trafficking, with a focus on understanding the functions of phosphoinositide lipids. We discovered that protein PX domains function to bind to phosphoinositides. This discovery enabled us to identify the mechanism of a gene mutation that causes the rare immunodeficiency syndrome, chronic granulomatous disease. Subsequently, we discovered part of the cellular machinery involved in Golgi function. In particular, we discovered the protein GOLPH3 as a novel phosphoinositide binding protein with specificity for PtdIns(4)P , serving to bridge the PtdIns(4)P-rich *trans*-Golgi membrane and an unconventional myosin, MYO18A. This complex applies a tensile force to the membrane to participate in the process of vesicle budding for forward trafficking, and also gives the Golgi its characteristic shape. Since then, our discovery of the GOLPH3 pathway and innovative studies of the Golgi have revealed surprising connections with the DNA damage response, cell migration, growth factor signaling, and cancer. The extensive evidence that the GOLPH3 pathway plays an important role in human cancer, and our insight and progress toward developing small molecule inhibitors of the GOLPH3 pathway create the tantalizing prospect of a unique approach to cancer therapeutics, which we are pursuing. In addition, I now serve as the Director of Physician Scientist Programs at the Harrington Discovery Institute with a mission to "accelerate promising discoveries into medicines for unmet needs."

A key aspect of my career has been, and continues to be, dedication to training the next generation of physicians, scientists, and, especially, physician-scientists. I do so both through leadership positions in graduate and physician-scientist training, and through mentoring of students and trainees. I maintain an open-door policy, to allow comfortable and easy communication with trainees to provide advice and assistance, as needed, to help them to advance their careers and achieve their goals.

B. Positions, Scientific Appointments, and Honors

2021- Director, Physician Scientist Programs, Harrington Discovery Institute
(Harrington Scholar Innovator Program, ASCI Harrington Prize, Harrington Symposium)
2020- Investigator, Harrington Discovery Institute
2020- Professor of Medicine, Case Western Reserve University School of Medicine
2020- Senior Attending Physician, Division of Endocrinology, University Hospitals
2020- Member, Case Comprehensive Cancer Center
2022-2023 Interim Director, Harrington UK Rare Disease Program
2015-2020 MSTP Steering Committee, University of California, San Diego
2010-2014 Director, MSTP Physician-Scientist Colloquia, University of California, San Diego
2007-2020 Biomedical Sciences Graduate Program Student Standing, Promotion, and Advisory Committee, University of California, San Diego
2005-2020 Assistant, Associate (with tenure in 2010), Professor (2016) of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego
2005-2020 UCSD Medical Center, Clinical Privileges in Endocrinology and Metabolism
2005-2020 VA Medical Center, San Diego, Clinical Privileges in Endocrinology and Metabolism
2005-2020 Member, UCSD/UCLA/Salk Diabetes Research Center
2005-2020 Member, Moores Cancer Center, University of California, San Diego
2005-2020 Member, Biomedical Sciences Graduate Program, University of California, San Diego
2002-2005 Instructor in Medicine, Harvard Medical School
2001-2005 Clinical Assistant in Medicine, Endocrinology & Neuroendocrinology, Mass. General Hospital

Other Experience and Professional Memberships

2022- Vision Advisory Panel/Integration Panel and Programmatic Review, Department of Defense Breast Cancer Research Program
2020-2021 NIH Mechanisms of Cancer Therapeutics-2 (MCT2) Study Section Reviewer
2016-2025 Burroughs Wellcome Fund Advisory Committee, Career Award in Medical Science
2016-2020 Programmatic Review for Dept. of Defense Breast Cancer Research Program
2014- Editorial Board, the Journal of Biological Chemistry
2011- American Society for Clinical Investigation
2008- Faculty of 1000
2006 American Society for Cell Biology National Meeting Local Arrangements Committee
ASCB Women in Cell Biology Roundtable Discussion Leader (2009, 2010, 2012)

Massachusetts Medical Society, American Association for the Advancement of Science, The Endocrine Society, American Society for Cell Biology, American Society for Biochemistry and Molecular Biology

Ad hoc Grant Reviewer: Canada Foundation for Innovation (2007), Diabetes UK (2010), Radcliffe Institute (2010), Hong Kong University of Science and Technology (2011), National Research Agency of France (2015, 2016)

Honors

2018 Chair, 30th Anniversary FASEB Scientific Research Conference on Phospholipid Signaling
2017-2019 Scholar-Innovator Award from the Harrington Discovery Institute
2010-2016 Era of Hope Scholar Award for Breast Cancer Research from the Department of Defense Congressionally Directed Medical Research Program
2014 Editorial Board of the Journal of Biological Chemistry
2008-2013 NIH Director's New Innovator Award
2011 Elected to the American Society for Clinical Investigation
2008 Invited to join the Faculty of 1000
2006-2008 Scholar Award, V Foundation for Cancer Research
2004 Ellison Medical Foundation New Scholars Award in Aging (Declined)
2004-2009 Burroughs Wellcome Fund Career Award in the Biomedical Sciences
2001-2003 Howard Hughes Medical Institute Physician Postdoctoral Fellowship Award
1997-1999 William Osler Society of Fellows in Medicine, Hospital of the University of Pennsylvania
1993-1996 Albert J. Ryan Foundation Fellowship Award
1988-1992 Dennison Biomedical Research Foundation Fellowship Award
1987-1997 Harvard Medical Scientist Training Program Fellow (Fully Funded)
1987 Sigma Xi Honor Society at M.I.T.

C. Contributions to Science

1. Discovery of PtdIns(4)P/GOLPH3/MYO18A/F-actin pathway, role in Golgi trafficking, and cancer

My lab discovered that GOLPH3 is a novel PtdIns(4)P effector, identified the PtdIns(4)P/GOLPH3/MYO18A/F-actin pathway, and demonstrated that the GOLPH3 pathway is fundamental to the process of vesicle budding from the trans-Golgi for trafficking to the plasma membrane. Surprisingly, GOLPH3 and MYO18A are both oncogenes that drive a high proportion of human cancers. We showed that the vast majority of secretory trafficking depends on the GOLPH3 pathway, and that the unique appearance of the Golgi by light and electron microscopy is a consequence of this mechanism of trafficking. Our work has further demonstrated that the GOLPH3 pathway is a convergent hub for regulation of Golgi function, including surprising regulation in response to DNA damage. Our research is making sense of the link between these Golgi proteins and cancer. The GOLPH3 pathway that we discovered is providing important new insight into mechanisms of oncogenic transformation and yielding novel targets for cancer therapeutics. This currently is our major focus. 4 of our 13 publications on the GOLPH3 pathway are listed below.

a. Dippold HC, Ng MM, Farber-Katz SE, Lee SK, Kerr ML, Peterman M, Sim R, Wiharto P, Galbraith KA, Madhavarapu S, Fuchs GJ, Meerloo T, Farquhar MG, Zhou H, **Field SJ**. GOLPH3 Bridges Phosphatidylinositol-4-Phosphate and Actomyosin to Stretch and Shape the Golgi to Promote Budding. Cell 2009; 139:337-351. PMCID: PMC2779841 (Research Highlight of the Week in Nature)

b. Farber-Katz SE, Dippold HC, Buschman MD, Peterman MC, Xing M, Tat J, Noakes CJ, Ng MM, Rahajeng J, Cowan DM, Fuchs GJ, Zhou H, **Field SJ**. DNA Damage Triggers Golgi Dispersal via DNA-PK and GOLPH3. Cell 2014; 156:413-27. PMCID: PMC4018323 (Preview in Cell, Editor's Choice in Science Signaling, News Watch in Cancer Discovery, Research Highlight in Nature Reviews Molecular Cell Biology)

c. Xing M, Peterman MC, Davis RL, Oegema K, Shiau AK, **Field SJ**. GOLPH3 Drives Cell Migration by Promoting Golgi Reorientation and Directional Trafficking to the Leading Edge. Molecular Biology of the Cell 2016; 27:3828-3840. PMCID: PMC5170606

d. Rahajeng J, Makowski SL, Kuna RS, Tran TTT, Buschman MD, Li S, Cheng N, Ng MM, **Field SJ**. Efficient Golgi Forward Trafficking Requires GOLPH3-Driven, PI4P-Dependent Membrane Curvature. Developmental Cell, 2019; 50:573-585. PMID: 31231041

2. Discovery of role of PtdIns(4,5)P2 at the cleavage furrow in cell division

My discovery that PtdIns(4,5)P2 is highly localized to the cleavage furrow and is functionally important for cytokinesis was initially met by skepticism by some of the top scientists in the field. Ultimately, however, this is now well-established to be the case from work by multiple investigators. My work further suggested a role for PtdIns(4,5)P2 to serve to anchor the cytokinetic acto-myosin ring to the plasma membrane. Recent data by several groups provide support for this model.

a. **Field SJ (corresponding author)**, Madson N, Kerr ML, Galbraith KAA, Kennedy CE, Tahiliani M, Wilkins A, Cantley LC. PtdIns(4,5)P2 functions at the cleavage furrow during cytokinesis. Current Biology 2005; 15:1407-1412. (Research Highlight of the Week in Nature)

b. Murray MJ, Ng MM, Fraval H, Tan J, Liu W, Smallhorn M, Brill JA, **Field SJ**, Saint R. Regulation of *Drosophila* mesoderm migration by phosphoinositides and the PH domain of the Rho GTP Exchange Factor Pebble. Developmental Biology 2012; 372:17-27.

3. Discovery of phosphoinositide signaling pathways

Techniques and expertise that I developed to study phosphoinositides provide the ability to make progress on otherwise intractable problems to understand lipid signaling. We have been involved in collaborative studies to enable better understanding of phosphoinositide regulation and function. Included below are 3 of 6 such publications.

a. Bielas SL, Silhavy JL, Brancati F, Kisseleva MV, Al-Gazali L, Sztriha L, Bayoumi RA, Zaki MS, Abdel-Aleem A, Rosti O, Kayserili H, Swistun D, Scott LC, Bertini E, Boltshauser E, Fazzi E, Travaglini L, **Field SJ**, Gayral S, Jacoby M, Schurmans S, Dallapiccola B, Majerus PW, Valente EM, Gleeson JG. Mutations in the inositol polyphosphate-5-phosphatase E gene link phosphatidyl inositol signaling to the ciliopathies. Nature Genetics 2009; 41:1032-6. PMCID: PMC2746682

b. Nhek S, Ngo M, Yang X, Ng MM, **Field SJ**, Asara JM, Ridgway ND, Toker A. Regulation of OSBP Golgi Localization through Protein Kinase D-mediated Phosphorylation. Molecular Biology of the Cell 2010; 21:2327-37. PMCID: PMC2893995

c. Akizu N, Cantagrel V, Zaki MS, Al-Gazali L, Wang X, Rosti RO, Dikoglu E, Gelot AB, Rosti B, Vaux KK, Scott EM, Silhavy JL, Schroth J, Copeland B, Schaffer AE, Gordts P, Esko JD, Buschman MD, **Field**

SJ, Napolitano G, Ozgul RK, Sagiroglu S, Azam M, Ismail S, Aglan M, Selim L, Gamal I, Hadi SA, El Bdawy A, Sadek AA, Mojahedi F, Kayserili H, Masri A, Bastaki L, Temtamy S, Müller U, Desguerre I, Casanova JL, Dursun A, Gunel M, Gabriel SB, de Lonlay P, Gleeson JG. Biallelic mutations in SNX14 cause a syndromic form of cerebellar atrophy and lysosome-autophagosome dysfunction. Nature Genetics 2015; 47:528-34. PMCID: PMC4414867

4. Discovery of PI-3-kinase signaling pathways

Work that I began as a post-doctoral fellow and that continues through recent collaborative research involves developing new techniques to study phosphoinositide lipid signaling in general, and the PI-3-kinase pathway, in particular. In a series of studies I co-discovered that PX domains bind to the lipid products of Class III PI-3-kinase, a new negative feedback loop in insulin signaling involving the O-linked glycosyl transferase with important implications for understanding the clinical phenomenon of glucose toxicity, and an unexpected role for class IB PI-3-kinase in receptor tyrosine kinase signaling that overturned the prevailing dogma that receptor tyrosine kinases signal exclusively through class IA PI-3-kinase. The powerful in vitro and in vivo approaches that I developed to study phosphoinositide signaling enabled progress on scientific problems that were otherwise intractable, resulting in 8 publications involving PI-3-kinases (4 listed here).

a. **Field SJ**[*], Kanai F[*], Liu H[*], Akbary H[*], Matsuo T, Brown GE, Cantley LC, Yaffe MB. The PX domains of p47phox and p40phox bind to lipid products of PI(3)K. Nature Cell Biology 2001; 3:675-8. [*]**these authors contributed equally** (Major focus of review in Cell)
b. Yang X, Ongusaha P, Miles P, Zhang F, So WV, Havstad J, Kudlow JE, Michell RH, Olefsky JM, **Field SJ**, Evans RM. Phosphoinositide Signaling Links Protein O-GlcNAc Modification to Insulin Resistance. Nature 2008; 451:964-9. (Research Article in Nature)
c. Schmid MC, Avraamides CJ, Dippold HC, Franco I, Foubert P, Ellies LG, Acevedo LM, Manglicmot JR, Song X, Wrasidlo W, Blair SL, Ginsberg MH, Cheresh DA, Hirsch E, **Field SJ**, Varner JA. Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3Kγ, a single convergent point promoting tumor inflammation and progression. Cancer Cell 2011; 19:715-27. PMCID: PMC3144144 (Major focus of review in Cancer Cell)
d. Castro-Falcón G, Seiler GS, Demir Ö, Rathinaswamy MK, Hamelin D, Hoffmann RM, Makowski SL, Letzel AC, **Field SJ**, Burke JE, Amaro RE, Hughes CC. Neolymphostin A Is a Covalent Phosphoinositide 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Dual Inhibitor That Employs an Unusual Electrophilic Vinylogous Ester. Journal of Medicinal Chemistry 2018 Nov 28; epub ahead of print. PMID 30380865.

5. Determine the function of E2F family transcription factors and their role in cancer

In work that I began for my doctoral dissertation and continues through recent collaborative work, we revised the previous dogma of Rb-E2F function in the regulation of cell proliferation and cancer. E2Fs were thought to function purely to promote cell proliferation, but were shut-off by Rb. I generated the first knockout mice for E2F1 and for E2F2, and found that, contrary to expectations, that E2F1 is a tumor suppressor. We published 10 papers (4 listed below) showing that E2F1 acts on target genes to silence expression by recruiting Rb. We also found differences between the roles of E2F1 and E2F2. This work moved the field to a more sophisticated understanding of the E2F family of genes and their role in cancer. Recent work finds that E2Fs promote cell cycle regulation of GOLPH3 transcription.

a. **Field SJ**, Tsai F-Y, Kuo F, Zubiaga AM, Kaelin WG, Jr, Livingston DM, Orkin SH, Greenberg ME. E2F-1 Functions in Mice to Promote Apoptosis and Suppress Proliferation. Cell 1996; 85:549-561. (Cover of Cell, Major focus of review in Cell)
a. Wu L, Timmers C, Maiti B, Saavedra HI, Sang L, Chong GT, Nuckolls F, Giangrande P, Wright FA, **Field SJ**, Greenberg ME, Orkin S, Nevins JR, Robinson ML, Leone G. The E2F1-3 transcription factors are essential for cellular proliferation. Nature 2001; 414:457-62.
b. Iglesias-Ara A, Zenarruzabeitia O, Fernandez-Rueda J, Sanchez-Tillo E, **Field SJ**, Celada A, Zubiaga AM. Accelerated DNA Replication in E2F1- and E2F2-deficient Macrophages Leads to Induction of DNA Damage Response and p21CIP1-dependent Senescence. Oncogene 2010; 29:5579-90.
c. Peñalver-González B, Vallejo-Rodríguez J, Mentxaka G, Fullaondo A, Iglesias-Ara A, **Field SJ**, Zubiaga AM. Golgi Oncoprotein GOLPH3 Gene Expression Is Regulated by Functional E2F and CREB/ATF Promoter Elements. Genes 2019; 10:247-261.

Complete List of Published Work in MyBibliography:
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