BIOGRAPHICAL SKETCH

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NAME: Sarah Spiegel

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

POSITION TITLE: Professor and Chair, Department of Biochemistry and Molecular Biology

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
Hebrew University, Jerusalem, Israel	B.Sc.	09/1974	Chemistry & Biochemistry
Weizmann Institute of Science, Rehovot, Israel	Ph.D.	09/1983	Biochemistry
NINCDS, NIH, Bethesda, MD, USA	Post-doc	1984-86	Cell Biology

Personal statement. My entire scientific career has been focused on lipids, particularly sphingolipids. My lab has been involved in the study of sphingolipids and sphingolipid metabolites as signaling molecules from its origin. Our research is focused on the enigmatic lipid mediator, sphingosine-1-phosphate (S1P), whose role as a signaling lipid was discovered in my lab more than two decades ago. Our lab has discovered that many important physiological and pathophysiological processes important for inflammation and cancer are regulated by S1P. We were the first to clone and characterize sphingosine kinases, SphK1 and SphK2, and S1P phosphatases, the enzymes that regulate S1P levels, providing molecular tools that opened an entire field of research. Our identification of the S1P family of GPCRs set the stage for the elucidation of their important functions. We also showed that S1P is a critical factor that influences cells' decisions to survive, die, proliferate, or differentiate, and we developed the concept of the sphingolipid rheostat, and the paradigm of inside-out signaling by S1P. The puzzle of how such a simple molecule as S1P can have such diverse roles has been resolved by our striking finding that S1P functions not only as a ligand for S1P receptors, but also has important intracellular actions. My current work has primarily focused on the roles of S1P and its precursor ceramide in cancer cell signaling, inflammation and chemotherapy induced pain. I have served as the co-director of the Cancer Cell Signaling Program in the Massey Cancer Center for more than 15 years. I have been very active in the training, having trained 20 predoctoral students and 75 postdoctoral scholars, many of whom have attained independent academic and industrial positions. I also have mentored more than 10 junior scientists towards independence. I am especially proud that 17 of my trainees obtained extramural fellowships, including DoD, AHA, and NIH F30/31/32, K99/R00, K12, K22, and K01 awards. Several were under-represented minorities who are either near graduation or are now independent PIs. Thus, I have the expertise, experience, and qualifications to serve as a PI on this application.

<u>Ongoing and recently completed projects that I would like to highlight include:</u>

1. Project Title: Intracellular Functions of the Bioactive Sphingolipid Metabolites Sphingosine and Sphingosine-1-phosphate
Role: PI Agency: NIH/NIGMS Type: 5R01 GM043880-30 Period: 04-01-1990 to 08-31-2023

2. Project Title: ORMDL3-ceramide axis in allergic asthma
Role: PI Agency: NIH/NIAID Type: 1 R01 AI125433-05 Period: 02-01-2017 - 01-31-2022.

3. Project Title: Targeting sphingosine-1-phosphate axis with FTY720/fingolimod as a novel therapy for triple negative breast cancer and chemotherapy-induced pain.
Role: PI Agency: DoD / CDMRP Type: BCRP-EA-BC191087 Period: 09/30/2020 - 09/29/2023

4. Project Title: Targeting the S1P axis and development of a novel therapy for obesity-related triple negative breast cancer
Role: PI Agency: DoD Type: BCRP (W81XWH-14-1-0086) Period: 09-01-2014 to 08-31-2019

Citations:

1: Spiegel S, Fishman PH, Weber RJ. Direct evidence that endogenous GM1 ganglioside can mediate thymocyte proliferation. Science. 230: 1285-1287, 1985.
2: Zhang H, Desai NN, Olivera A, Seki T, Brooker G, **Spiegel S**. Sphingosine-1-phosphate, a novel lipid, involved in cellular proliferation. J Cell Biol. 114: 155-167, 1991.
3: Olivera A and **Spiegel S.** Sphingosine-1-phosphate as second messenger in cell proliferation induced by PDGF and FCS mitogens. Nature. 365: 557-560, 1993.
4: Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, Luo C, Marmorstein R, Kordula T, Milstien S, **Spiegel S.** Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science. 325:1254, 2009. PMC2850596.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2005-2020	Director, Cancer Cell Biology Program, Massey Cancer Center, Richmond, VA
2005-present	Editorial Board, FASEB Journal
2002-present	Professor and Chair, Department of Biochemistry, Virginia Commonwealth University School of Medicine, Richmond, VA
2000-present	Editorial boards of J. Biol. Chem., Glycoconjugate J., Biochim. Biophys. Acta, Signal Transduction - Receptors, Mediators and Genes, J. Lipid Res., Biological Chem.
1996-2001	Professor, Department of Biochemistry and Molecular Biology, Georgetown University Medical School
1992-1996	Associate Professor, Director, Graduate program in Biochemistry and Molecular Biology Department of Biochemistry and Molecular Biology, Georgetown University Medical School, Washington, DC
1987-1992	Assistant Professor, Department of Biochemistry and Molecular Biology, Georgetown University Medical School, Washington, DC
1984-1986	Visiting Associate, Membrane Biochemistry Section, Developmental and Metabolic Neurology Branch, NINCDS, NIH, Bethesda, MD

Honors

2021	Selected as a Fellow of the American Society of Biochemistry and Molecular Biology
2019	Eicosanoid Research Foundation's Outstanding Achievement Award, St. Petersburg, FL
2018	Distinguished Mentor Award, VCU School of Medicine, Richmond, VA
2017	Keynote Speaker, XII Sphingolipid Club Meeting Sicily, Italy
2017	Organizer Keystone Symposium on Lipidomics and Bioactive Lipids in Metabolism and Disease, Lake Tahoe, CA.
2015	Journal of Lipid Research Special Lectureship and Keynote Speaker, FASEB Summer Conference, Banff, Canada
2014	Sackler Lectureship, Mortimer and Raymond Sackler Institute, Tel Aviv, Israel
2013	Keynote Speaker, 16th GEM 10th GERLI lipidomics meeting, Saint-Jean-Cap-Ferrat, France.
2012	Charles C. Sweeley Endowed Lectureship in Biochemistry, Michigan State
2011	Mann T. and Sara D. Lowry Endowed Chair in Cancer Research
2011	Keynote Speaker, 6th International Ceramide Conference, Villars, Switzerland
2009	ASBMB Avanti Lipids Award, New Orleans, LA
2009	AAAS Fellow, Medical Sciences Section
2008	Virginia Outstanding Scientist of the Year
2008	Ernst and Berta Scharrer Medal, Goethe University, Frankfurt, Germany
2007	University Distinguished Scholarship Award
2007	The Women in Science, Dentistry, and Medicine (WISDM) Professional Achievement Award
2005	Elected as Chair of 2007 FASEB Summer Conference on Lysophospholipids
2005	Elected as Chair of the 2007 Keystone Symposium on Bioactive Lipids in the Lipidomics Era
2003	Keynote Address, FASEB Conference on Lysophospholipids and Related Bioactive Lipids in Biology and Diseases, Snowmass Village, CO
2003	NIH MERIT Award from NIGMS
2002	Chair of the Minisymposium on Signaling and Cell Proliferation at the 42nd Annual Meeting of the American Society for Cell Biology, San Francisco, CA

2001	Co-organizer, FASEB Summer Research Conference on Lysophospholipids and Related Bioactive Lipids in Biology and Diseases, Tucson, AZ
2000	Co-organizer, Keystone Symposium on Lipid Second Messengers IV
1998	Keynote speaker, 33rd Southeastern Regional Lipid Conference, Cashiers, NC
1998	Chair, Gordon Conference on Glycolipid and Sphingolipid Biology
1997	State-of-the-art keynote lecture, National Meeting of the American Pancreas Association
1994, 1995	Nominee for Golden Apple Award for Excellence in Teaching, Georgetown University
1994	ASBMB Travel Grant, 15th International Congress of Biochemistry, Jerusalem, Israel
1994-1998	Member Biological Sciences Study Section, National Institutes of Health
1989	National Science Foundation and Society for Complex Carbohydrates Travel Award
1982-1984	Dr. Chaim Weizmann Post-doctoral Fellowship for Scientific Research

C. Contributions to Science

1. Foundation of the S1P signaling field and the concept of the "sphingolipid rheostat."

Our lab was the first to demonstrate that S1P was more than a mere metabolite: we showed that S1P is a potent bioactive lipid that plays a key role in myriad physiological and pathophysiological conditions. Our lab was the first to demonstrate that agonists induce the production of S1P, and that this S1P is required for various agonists' effects. We purified, characterized, and cloned the two mammalian sphingosine kinases, SphK1 and SphK2, responsible for S1P production as well as S1P phosphatases, enzymes that regulate S1P levels. This provided molecular tools that opened a burgeoning field of research and the discovery that many important physiological and pathophysiological processes are regulated by S1P (nearly 7500 PubMed citations to date). We further showed that S1P generally promotes cell growth while its metabolic precursor, ceramide, generally inhibits cell growth and promotes apoptosis. We termed this the "sphingolipid rheostat," a widely accepted paradigm that puts the enzymes of sphingolipid metabolism, including SphKs and S1P phosphatases that interconvert S1P and ceramide, as central players in cell fate.

1: Cuvillier O, Pirianov G, Kleuser B, Vanek PG, Coso OA, Gutkind JS, **Spiegel S.** Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. Nature. 381: 800-803, 1996.

2: Mandala SM, Thornton R, Tu Z, Kurtz MB, Nickels J, Broach J, Menzeleev R, **Spiegel S**. Sphingoid base 1-phosphate phosphatase: a key regulator of sphingolipid metabolism and stress response. Proc Natl Acad Sci USA. 95: 150-155, 1998. PMC18156.

3: Kohama T, Olivera A, Edsall L, Nagiec MM, Dickson R, **Spiegel S**. Molecular cloning and functional characterization of murine sphingosine kinase. J Biol Chem. 273: 23722-23728, 1998.

4: Le Stunff H, Galve-Roperh I, Peterson C, Milstien S, **Spiegel S**. Sphingosine-1-phosphate phosphohydrolase in regulation of sphingolipid metabolism and apoptosis. J Cell Biol. 158: 1039-1049, 2002.

2. S1P is secreted from cells and acts through a family of G protein-coupled receptors ("inside-out signaling").

One of the keys to understanding the role S1P in cell signaling was our demonstration of the first S1P receptor, EDG-1 (now S1PR1). S1PR1 is a member of a family of 5 cell surface GPCRs, which can account for the diverse array of S1P actions. This was particularly intriguing because the enzymes that make S1P, the SphKs, are intracellular. We demonstrated a novel paradigm, termed "inside-out signaling" in which agonists activate cytosolic SphKs, cells secrete S1P, and this S1P activates S1PRs in an autocrine and/or paracrine fashion. We subsequently characterized several transporters for S1P, including some ABC transporters and Spns2 that play a key role in inflammation and cancer.

1: *Lee MJ, *Van Brocklyn JR, Thangada S, Liu CH, Hand AR, Menzeleev R, ***Spiegel S**, and *Hla T. Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. Science. 279: 1552-1555, 1998. (*these authors contributed equally to this work).

2:Hobson JP, Rosenfeldt HM, Barak LM, Olivera A, Poulton S, Caron MG, Milstien S, **Spiegel S.** Role of the sphingosine-1-phosphate receptor EDG-1 in PDGF-induced cell motility. Science. 291:1800, 2001.

3: Alvarez SE, Harikumar KB, Hait NC, Allegood J, Strub GM, Kim EY, Maceyka M, Jiang H, Luo C, Kordula T, Milstien S, **Spiegel S**. Sphingosine-1-phosphate is a missing cofactor for the E3 ubiquitin ligase TRAF2. Nature. 465: 1084-1088, 2010. PMC2946785.

4: van der Weyden L, Arends MJ, Campbell AD, Bald T, Wardle-Jones H, Griggs N, Velasco-Herrera MD, Tüting T, Sansom OJ, Karp NA, Clare S, Gleeson D, Ryder E, Galli A, Tuck E, Cambridge EL, Voet T, Macaulay IC, Wong K; Sanger Mouse Genetics Project, **Spiegel S,** Speak AO, Adams DJ. Genome-wide in vivo screen identifies novel host regulators of metastatic colonization. Nature. 541:233, 2017. PMC5603286.

3. S1P: a key regulator of motility, growth, and the link between inflammation and cancer

We were the first to show that S1P and S1PR1 are master regulators of cell migration, findings that led to the discovery of the fundamental role of S1PR1 in lymphocyte trafficking and paved the way for the development of the S1PR1 functional antagonist FY720/Fingolimod as a frontline treatment for multiple sclerosis. Our lab was also the first to link the pro-growth effects of S1P and SphK1 to cancer development, developed the first specific SphK1 inhibitor, and showed that the SphK1/S1P axis promotes angiogenesis and lymphangiogenesis, important for tumor growth and metastasis. The relevance of these findings was confirmed by the upregulation of SphK1 in many human cancers that correlates with poor prognosis. We also showed that S1P produced in cancer cells by SphK1 signals through S1PR1 to constitutively activate Stat3 and NF-kB transcription factors that link chronic inflammation to cancer and demonstrated that it was possible to interfere with this malicious feed-forward signaling cycle as a possible therapeutic treatment for inflammation-associated cancers.

1: Olivera A, Kohama T, Edsall L, Nava V, Cuvillier O, Poulton S, and **Spiegel S.** Sphingosine kinase expression increases intracellular sphingosine-1-phosphate and promotes cell growth and survival. J. Cell Biol. 147: 545-558,1999. PMC2151183

2: Paugh SW, Paugh BS, Rahmani M, Kapitonov D, Almenara JA, Kordula T, Milstien S, Adams JK, Zipkin RE, Grant S, and **Spiegel S.** A selective sphingosine kinase 1 inhibitor integrates multiple molecular therapeutic targets in human leukemia. Blood. 112: 1382-1391, 2008. PMC2515133

3: Liang J, Nagahashi N, Kim EY, Harikumar KB, Yamada A, Huang W-C, Hait NC, Allegood JC, Price MM, Avni D, Takabe K, Kordula T, Milstien S, and **Spiegel S.** Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. Cancer Cell. 23: 107-120, 2013. PMC3578577.

4: **Spiegel S**, Milstien S. The outs and the ins of sphingosine-1-phosphate in immunity. Nat Rev Immunol. 11: 403-415, 2011. PMC3368251

4. S1P role in tumor growth, metastasis, and chemotherapy resistance.

Our lab was the first to link the pro-growth effects of S1P and SphK1 to cancer development. We demonstrated that overexpression of SphK1 promoted tumor growth in mouse models of breast cancer, and the importance of this finding was confirmed by the upregulation of SphK1 in many human cancers which correlates with poor prognosis. We developed the first specific SphK1 inhibitor and showed that the SphK1/S1P axis promotes angiogenesis and lymphangiogenesis, important for tumor growth and metastasis. We also showed that S1P produced in cancer cells by SphK1 signals through S1P receptors to constitutively activate Stat3 and NF-kB transcription factors that link chronic inflammation to cancer and demonstrated that it was possible to interfere with this malicious feed-forward signaling cycle as a possible therapeutic treatment for inflammation-associated cancers.

1: Hait NC, Avni D, Yamada A, Nagahashi M, Aoyagi T, Aoki H, Dumur CI, Zelenko Z, Gallagher EJ, Leroith D, Milstien S, Takabe K, **Spiegel S**. The phosphorylated prodrug FTY720 is a histone deacetylase inhibitor that reactivates ERalpha expression and enhances hormonal therapy for breast cancer. Oncogenesis 4**:** e156, 2015. PMC4753524

2: Nagahashi M, Yamada A, Katsuta E, Aoyagi T, Huang WC, Terracina KP, Hait NC, Allegood JC, Tsuchida J, Yuza K, Nakajima M, Abe M, Sakimura K, Milstien S, Wakai T, **Spiegel S**, Takabe K. Targeting the SphK1/S1P/S1PR1 Axis That Links Obesity, Chronic Inflammation, and Breast Cancer Metastasis. Cancer Res. 78:1713, 2018. PMC6945803

3. Maczis MA, Maceyka M, Waters MR, Newton J, Singh M, Rigsby MF, Turner TH, Alzubi MA, Harrell JC, Milstien S**, Spiegel S.** Sphingosine kinase 1 activation by estrogen receptor α36 contributes to tamoxifen resistance in breast cancer. J Lipid Res. 59:2297-2307, 2018. PMC6277156.

4: Lima S, Takabe K, Newton J, Saurabh K, Young MM, Leopoldino AM, Hait NC, Roberts JL, Wang HG, Dent P, Milstien S, Booth L, **Spiegel S**. TP53 is required for BECN1- and ATG5-dependent cell death induced by sphingosine kinase 1 inhibition. Autophagy. 14:942, 2018. PMC6103396.

5. Role of SphK2 in epigenetic regulation and nonalcoholic fatty liver disease

We were the first to clone and characterize the second isoenzyme that phosphorylates sphingosine, SphK2. We found that S1P produced by nuclear SphK2 binds and inhibits HDAC1/2 and regulates histone acetylation and transcription of target genes, linking nuclear sphingolipid metabolism and S1P to epigenetic regulation in response to environmental cues. Further studies demonstrated that the S1P/SphK2 axis has important implications for hepatic gene expression, inflammation, and cancers, including HCC.

1: Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, Luo C, Marmorstein R, Kordula T, Milstien S, **Spiegel S.** Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science. 325:1254, 2009. PMC2850596.

2: Nagahashi M, Takabe K, Liu R, Peng K, Wang X, Wang Y, Hait NC, Wang X, Allegood JC, Yamada A, Aoyagi T, Liang J, Pandak WM, **Spiegel S,** Hylemon PB, Zhou H. Conjugated bile acid-activated S1P receptor 2 is a key regulator of sphingosine kinase 2 and hepatic gene expression. Hepatology. 61:1216, 2015. PMC4376566.

3: Rohrbach TD, Asgharpour A, Maczis MA, Montefusco D, Cowart LA, Bedossa P, Sanyal AJ, **Spiegel S.** FTY720/fingolimod decreases hepatic steatosis and expression of fatty acid synthase in diet-induced nonalcoholic fatty liver disease in mice. J Lipid Res. 60:1311, 2019. PMC6602124.

4: Green CD, Maceyka M, Cowart LA, **Spiegel S.** Sphingolipids in metabolic disease: The good, the bad, and the unknown. Cell Metab, 33:1293, 2021. PMC8269961

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