BIOGRAPHICAL SKETCH

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NAME: Svensson, Katrin Jennifer

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POSITION TITLE: Assistant 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
Lund University, Sweden	M.S.	08/2006	Molecular Biology
Lund University, Sweden	Ph.D.	02/2012	Cell Biology
Harvard Medical School, MA	Postdoctoral fellow	02/2017	Molecular Metabolism

A. Personal Statement

As an Assistant Professor at Stanford University and Affinity Group Leader at the Stanford Diabetes Research Center (SDRC), I lead a lab that is dedicated to uncovering new signal transduction pathways and their therapeutic applications in the fight against metabolic diseases, including obesity, type 2 diabetes, and cardiovascular disease. I assumed the role of director of the Metabolic Core facility within the SDRC in 2022. My laboratory is generously supported by federal and non-federal grants, including R01s, Innovative Medicines Award (IMA), SPARK award, the Merck SEEDs Award, McCormick and Gabilan Award, and Jacob Churg Award. In addition, I hold the position of Associate Editor for Endocrine Reviews and serve on the Advisory Board for STAR protocols. I have published over 40 papers on signaling pathways, secreted macromolecules, and ligand-receptor interactions.

My lab employs a combination of biochemistry, proteomics, gene editing, and physiology techniques to characterize hormones with previously unknown functions. We have made several important discoveries in our pursuit to improve metabolic health, including the identification of Slit2-C, a fragment of a secreted factor that improves diabetes by boosting energy expenditure (Svensson et al., ***Cell Metab, 2016***). Our more recent work has led to the discovery and patenting of Isthmin, a circulating hormone that regulates glucose and lipid homeostasis (Jiang et al., ***Cell Metab, 2021*** and Zhao et al., ***eLife, 2022***).

Highlighted publications and patents

Jiang, Z., Zhao, M., Voilquin L., Jung, Y., Aikio, M.A., Sahai, T., Dou, F., Roche, A., Carcamo-Oribe, I, Knowles, J., Wabitsch, M., Appel, E.A., Maikawa, L.C., Camporez, J.P., Shulman, G.I., Tsai, L., Rosen, E.D., Gardner, C., Spiegelman, B.M., **Svensson, K.J.** Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. ***Cell Metabolism*** (2021) Sep 7;33(9):1836-1852.e11.

Zhao M., Banhos Danneskiold-Samsøe, N., Ulicna, L., Nguyen, Q., Coassolo, L., Lee, D.E., White, J.P., Jiang, Z., Cuthbert, N., Paramasivam, S., Bielczyk-Maczynska, E., Van Rechem, C., **Svensson, K.J.** Phosphoproteomic mapping reveals distinct signaling actions and activation of protein synthesis by Isthmin-1. ***eLife*** 2022 11:e80014 https://doi.org/10.7554/eLife.80014.

Svensson, K.J., Voilquin, L. "BRNP2-Derived Peptide Compositions for Treating Obesity and Weight Management " ***US Patent***. Filing date: 07/01/2022.

Selected ongoing projects in the past three years:

R01DK12526002 (Svensson, Katrin) 07/01/2020 - 05/31/2025
National Institutes of Health
Control of glucose homeostasis through the insulin-independent Isthmin pathway
Major Goals: The major goals are to investigate the role of the hormone Isthmin in glucose homeostasis and diabetes.

Innovative Project Award (Svensson, Katrin) 07/01/2023-06/30/2025
American Heart Association
Novel strategies for improving hepatic lipid metabolism and cardiovascular health
Major Goals: The major goals are to investigate a new mechanism by which fructose is transported into the liver.
Role: PI

Merck SEEDS award (Svensson, Katrin) 12/01/2023 – 04/30/2025
Merck Co., Inc.
A peptide for treating obesity and weight-related disorders
Major Goals: The overall goals are to interrogate the role of an early-stage therapeutic lead — a peptide that controls appetite.
Role: PI

B. Positions, Scientific Appointments, and Honors

Positions

2018	Assistant Professor, Dept of Pathology, School of Medicine, Stanford University
2013-2017	Postdoctoral Fellow, Dana-Farber Cancer Institute and Harvard Medical School Supervisor: Bruce M. Spiegelman
2012-2013	Postdoctoral Fellow, Lund University, Sweden
2006-2012	Ph.D. Student, Lund University, Sweden. Supervisor: Mattias Belting, M.D./Ph.D.

Selected Scientific Appointments

2023-	NIH POMD study section, permanent member
2022-	Associate Editor, Endocrine Reviews (Oxford)
2021-	Advisory Board, STAR Protocols (Cell Press)
2019-	Affinity Group Leader for Stanford Diabetes Research Center (SDRC), Stanford University

Other Experience and Professional Memberships

2020-2022	NIH study section reviewer (POMD, MCE, GRB-J O1, EMNR-K, EMS-K)
2022	Grant reviewer, American Heart Association (AHA)
2022	Keynote speaker, Metabolism Mini-Symposium UCSF Liver Center and UC Berkeley, USA.
2021-	Member, Endocrine Society (Oxford)
2021-	Member, American Society for Biochemistry and Molecular Biology (ASBMB)
2019-	Member, American Diabetes Association (ADA)
2019-	Member, American Heart Association (AHA)
2016-	Ad hoc reviewer: > 30 journals, including Cell Metabolism, Nature Metabolism, Nature Communications, Diabetes Care, Advanced Science, PlosOne

Honors

2019	Jacob Churg Research Award for Junior Faculty, Stanford University
2018	Gabilan Fellow, Stanford University
2016	NIH K99/R00 Pathway to Independence Award
2013	Swedish Research Council Postdoctoral Fellowship
2013	Blanceflor Boncompagni-Ludovisi, née Bildt Postdoctoral Fellowship
2012	Fru Berta Kamprads Society for Cancer Research Award, Sweden
2010	The Royal Physiographic Society Award, Sweden, awarded two consecutive years
2010	Lund University Faculty of Medicine Award for graduate studies, Lund, Sweden

C. Contributions to Science

My research has led to several examples of how secreted factors can advance our understanding of the development of metabolic disorders, including type 2 diabetes, insulin resistance, cancer, and fatty liver disease. Below are some of my major contributions to the field.

1. Physiological regulation of metabolism by adipose-secreted factors

With the growing incidence of type 2 diabetes and fatty liver disease, there is an urgent need to develop therapies that can effectively treat both hyperglycemia and hyperlipidemia. Moreover, there is a need to deepen our understanding of the molecular mechanisms underlying glucose and lipid regulation in normal and pathological conditions. Our research aims to find new regulators of metabolism to help combat metabolic diseases, including insulin resistance and fatty liver disease. Drawing on our extensive knowledge of metabolic control, including the activation of the key transcriptional regulator PRDM16, and our expertise in signal transduction pathways, complex tissue proteomics, genetics, and organismal physiology, we have uncovered novel biological pathways and regulations of cellular functions. Our research has led to the discovery of a new secreted hormone called Isthmin-1, which increases glucose uptake through the PI3K/AKT pathway independent of insulin. This marks the first time a hormone has been described as playing a crucial role in regulating insulin-independent glucose uptake while also suppressing lipid synthesis in the liver. Furthermore, Isthmin-1 promotes protein synthesis in skeletal muscle, showcasing its pleiotropic anabolic effects. As the lead investigator in these studies, I am excited to continue exploring the potential of Isthmin-1 and other regulators of metabolism.

1. Jiang, Z., Zhao, M., Voilquin L., Jung, Y., Aikio, M.A., Sahai, T., Dou, F., Roche, A., Carcamo-Oribe, I, Knowles, J., Wabitsch, M., Appel, E.A., Maikawa, L.C., Camporez, J.P., Shulman, G.I., Tsai, L., Rosen, E.D., Gardner, C., Spiegelman, B.M., **Svensson, K.J.** Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. ***Cell Metabolism*** Sep 7;33(9):1836-1852.e11 (**2021**). PMCID: PMC8429235.

2. Zhao M., Banhos Danneskiold-Samsøe, N., Ulicna, L., Nguyen, Q., Coassolo, L., Lee, D.E., White, J.P., Jiang, Z., Cuthbert, N., Paramasivam, S., Bielczyk-Maczynska, E., Van Rechem, C., **Svensson, K.J.** Phosphoproteomic mapping reveals distinct signaling actions and activation of protein synthesis by Isthmin-1. ***eLife*** 11:e80014 **(2022**) Sep 28;11:e80014. PMID: 36169399; PMCID: PMC9592085.

3. Wei W, Riley NM, Lyu X, Shen X, Guo J, Raun SH, Zhao M, Moya-Garzon MD, Basu H, Sheng-Hwa Tung A, Li VL, Huang W, Wiggenhorn AL, **Svensson KJ**, Snyder MP, Bertozzi CR, Long JZ. Organism-wide, cell-type-specific secretome mapping of exercise training in mice. ***Cell Metab.*** 2023 Apr 28:S1550-4131(23)00138-9. PMID: 37141889.

4. **Svensson, K.J**., Voilquin, L. "Therapeutic uses of Isthmin protein" Provisional patent application No. 63/226,600 Filing date: 07/28/2021. *PCT conversion* 07/28/2022.

2. Methods for prediction and discovery of bioactive peptides and their receptors

The peptide drug discovery field has made significant advancements in medicine, with over 60 peptide drugs approved in the US, including insulin, glucagon, and incretin derivatives. Despite these achievements, the identification of new secreted polypeptide hormones remains a formidable challenge, largely due to their low abundance, small size, and difficulty in predicting their functions. To overcome these challenges, we have developed a combination of computational sequence prediction and functional approaches to understand the mechanisms of metabolic control by small, previously unknown peptides. During my postdoctoral work at Harvard Medical School in the Spiegelman laboratory, I discovered Slit2-C, a proteolytically cleaved fragment of a previously known brain-secreted neurotrophic factor, that activates PKA signaling in adipocytes. This discovery demonstrated the potential for cleavage to generate a product with a distinct function from the parent protein. In my own laboratory, I am continuing this work and systematically mapping secreted peptide hormones based on their tissue of origin to determine their ability to control peripheral and central metabolic functions. Our most recent discovery is a brain-secreted peptide called BRP, which has been shown to effectively reduce appetite and obesity in mice. In our recent work, we demonstrate that secreted protein ligands for single-pass transmembrane receptors can be predicted using AlphaFold. We describe the computational and structural requirements for the prediction screen, performance, and provide proof-of-principle evidence of identification of

high-confidence binders. This work is likely to be relevant to a wide variety of fields and provide a useful resource for future investigations. I am the lead investigator in these studies.

1. **Svensson K.J.**, Long, J.Z., Jedrychowski, M.P., Cohen, P., Lo, J.C., Serag, S., Kir, S., Shinoda, K., Tartaglia, J.A., Rao, R.R., Chédotal, A., Kajimura, S., Gygi, S.P., Spiegelman, B.M. A Secreted Slit2 Fragment Regulates Adipose Tissue Thermogenesis and Metabolic Function.
   Cell Metabolism. 23(3):454-66. (**2016)** PMID: 26876562; PMCID: PMC4785066.

2. Banhos Danneskiold-Samsøe, N., Kavi, D., Jude., K.M., Wat, L.W., Nissen, S.B., Coassolo, L., Zhao, M., Santana-Oikawa G.A., Broido, B.B., K.C. Garcia, **Svensson, K.J.†** Rapid and accurate deorphanization of ligand-receptor pairs using AlphaFold.
   bioRxiv 2023.03.16.531341; https://doi.org/10.1101/2023.03.16.531341

3. **Svensson, K.J**., Coassalo, L. "BRNP2-Derived Peptide Compositions for Treating Obesity and Weight Management " ***US Patent***. Filing date: 07/01/2022.

4. Zhao, M., Jung Y., Jiang, Z., **Svensson, K.J.** Regulation of Energy Metabolism by Receptor Tyrosine Kinase Ligands. ***Frontiers in Physiology***, p. 354. (**2020**) PMCID: PMC7186430.

3. Mechanisms of hepatic glucose and lipid homeostasis

Recently, we employed single-cell RNA sequencing to uncover the hepatocyte-specific transcriptional regulators of lipid synthesis. Our findings showed that the expression of the constitutive androstane receptor (CAR) is elevated in hepatocytes with hepatic steatosis. These findings were supported by experiments using human liver tissues with different levels of fatty liver disease, as well as by computational artificial intelligence network modeling. Furthermore, we have established protocols to isolate, characterize, and phenotype cell populations from metabolic organs in mice with established fatty liver disease. Additionally, we have identified GRP151, a G-protein-coupled receptor, as a potential target for regulating hepatic glucose. These results have significant implications for the development of future drugs aimed at treating fatty liver disease. As the lead or collaborating investigator in these studies, I am excited to continue exploring the impact of these findings.

1. Coassolo L., Liu, T., Jung, Y., Taylor, N.P., Zhao, M., Charville, G., Yki-Jarvinen, H. Altman, R., **Svensson, K.J**. Mapping transcriptional heterogeneity and metabolic networks in fatty livers at single-cell resolution. ***iScience*** 2022;26(1):105802. PMID: 36636354; PMCID: PMC9830221.

2. Bielczyk-Maczynska, E., Zhao, M., Zushin H., P-J., Schnurr, T.M., Kim, H-J., Li, J., Nallagatla, P., Sangwung, P., Park, C., Cornn, C., Stahl, L., **Svensson, K.J**., Knowles, J.W. G protein-coupled receptor 151 regulates glucose metabolism and hepatic gluconeogenesis.
   Nature Commun. 13, 7408 (**2022**) PMCID: PMC9715671.

3. Zhao, M. Wat, L.W., **Svensson, K.J.†** In vivo measurements of tissue-specific glucose uptake.
   ***STAR Protocols*.** 2023 Volume 4, Issue 2, 102179, doi.org/10.1016/j.xpro.2023.102179.

4. Jung, Y., Zhao, M. and **Svensson, K. J.** Isolation, culture, and functional analysis of hepatocytes from mice with fatty liver disease. ***STAR Protocols*** 1(3), p. 100222. (**2020**) PMCID: PMC7757664.

4. New mechanisms for activation of brown fat

Activation of brown or beige fat in humans can increase both basal and insulin-stimulated whole-body glucose disposal, demonstrating a physiologically significant role for these tissues in glucose regulation. There is mounting evidence that thermogenic adipose tissue can mediate some of the beneficial effects through secreted factors, but the molecules and pathways have remained incompletely understood. In collaborative work, I combined my molecular and biochemical skills with studies of mammalian physiology to identify new molecular mechanisms of brown fat activation. Our findings revealed the origins of beige fat and uncovered metabolic functions for the secreted muscle hormone Meteorin-like and the secreted enzyme PM20D1. These results have highlighted the potential for utilizing brown fat activation as a strategy to improve metabolic disorders. I was a co-lead investigator in these studies.

1. Long, J.Z., **Svensson, K.J.,** Bateman, L.A., Lin, H., Kamenecka, T., Lokurkar, I.A., Lou, J., Rao, R.R., Chang, M.R., Jedrychowski, M., Paulo, J.A., Gygi, S.P., Griffin, P.R., Nomura, D.K., Spiegelman, B.M. PM20D1 secretion by thermogenic adipocytes regulates lipidated amino acid uncouplers of mitochondrial respiration.
   Cell. 166(2):424-35. (**2016**) PMCID: PMC4947008.

2. Long, J.Z., **Svensson, K.J**., Tsai, L., Zeng, X., Roh, H.C., Kong, X., Rao, R.R., Lou, J., Lokurkar, I., Baur, W., Castellot, J.J. Jr, Rosen. E.D., Spiegelman, B.M. A smooth muscle-like origin for beige adipocytes.
   Cell Metabolism. May 6;19(5):810-20. (**2014**) PMCID: PMC4052772.

3. Cohen, P., Levy, J.D., Zhang, Y., Frontini, A., Kolodin, D.P., **Svensson, K.J.**, Lo, J.C., Zeng, X., Ye, L., Khandekar, M.J., Wu, J., Gunawardana, S.C., Banks, A.S., Camporez, J.P., Jurczak, M.J., Kajimura, S., Piston, D.W., Mathis, D., Cinti, S., Shulman, G.I., Seale, P., Spiegelman, B.M. Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch.
   Cell. 156(1-2):304-16. (**2014**) PMCID: PMC3922400.

4. Rao, R.R., Long, J.Z., White, J.P., **Svensson, K.J**., Lou, J., Lokurkar, I., Jedrychowski, M.P., Ruas, J.L., Wrann, C.D., Lo, J.C., Camera, D.M., Lachey, J., Gygi, S., Seehra, J., Hawley, J.A., Spiegelman, B.M. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis.
   Cell. 157(6):1279-91. (**2014**) PMCID: PMC4131287.

5. Cellular signal transduction by secreted macromolecules

In a series of studies, I found that cells in the tumor microenvironment crosstalk to non-malignant cells via secreted factors in extracellular vesicles exerting potent pro-tumorigenic effects. These contributions have had important implications for direct inhibition, targeting, and detection of circulating extracellular vesicles in pathophysiological conditions and have provided insights important for the development of diagnostic tools. I served as the lead or co-lead investigator in all these studies.

1. **Svensson, K.J**., Kucharzewska, P., Christianson, H.C., Skold, S., Lofstedt, T., Johansson, M.C., Morgelin, M., Bengzon, J., Ruf, W., and Belting, M. Hypoxia triggers a proangiogenic pathway involving cancer cell microvesicles and PAR-2-mediated heparin-binding EGF signaling in endothelial cells.
   PNAS. 108(32):13147-52. (**2011)** PMCID: PMC3156184.

2. **Svensson, K.J.**, Christianson, H.C., Wittrup, A., Bourseau-Guilmain, E., Lindqvist, E., Svensson, L.M., Morgelin, M., and Belting, M. Exosome uptake depends on ERK1/2-heat shock protein 27 signaling and lipid raft-mediated endocytosis negatively regulated by caveolin-1.
   J Biol Chem. 288(24):17713-24. (**2013)** PMCID: PMC3682571.

3. **Svensson, K.J.**, Welch, J.E., Kucharzewska. P., Bengtson. P., Bjurberg, M., Påhlman, S., Ten Dam, G.B., Persson, L., Belting, M. Hypoxia-mediated induction of the polyamine system provides opportunities for tumor growth inhibition by combined targeting of vascular endothelial growth factor and ornithine decarboxylase.
   Cancer Res. Nov 15;68(22):9291-301. **(2008)** PMID: 19010902

4. Christianson, H.C., **Svensson, K.J.**, van Kuppevelt, T.H., Li, J.P., and Belting, M. Cancer cell exosomes depend on cell-surface heparan sulfate proteoglycans for their internalization and functional activity.
   PNAS. 110(43):17380-5. (**2013)** PMCID: PMC3808637.

Complete List of Published Work in MyBibliography:

Total: 42 publications, H-index: 25. Total citations: > 6200
https://www.ncbi.nlm.nih.gov/myncbi/1zgS-yZ3iSMQK/bibliography/public/