BIOGRAPHICAL SKETCH

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NAME: Svensson, Katrin Jennifer

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

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
Harvard Medical School, Boston, MA	Postdoctoral fellow	12/2017	Molecular Metabolism
Lund University, Lund, Sweden	Postdoctoral fellow	03/2013	Cancer Metabolism
Lund University, Lund, Sweden	Ph.D.	02/2012	Cell Biology
Lund University, Lund, Sweden	M.S.	08/2006	Molecular Biology

A. Personal Statement

I am an Assistant Professor at Stanford University and an Affinity Group Leader at the P30-funded Stanford Diabetes Research Center (SDRC). I lead a laboratory dedicated to discovering new signal transduction pathways and their therapeutic applications to metabolic diseases, including obesity, type 2 diabetes, and cardiovascular disease. Since 2022, I am also the director of the Metabolic Core facility within the SDRC. My laboratory is supported by federal and non-federal grants, including R01s, the Merck SEEDs Award, McCormick and Gabilan Award, and Jacob Churg Junior Faculty Award. I am also an Associate Editor for Endocrine Reviews and I serve on the Advisory Board for STAR protocols. I have published >30 papers on signaling pathways, secreted macromolecules, and ligand-receptor interactions.

My laboratory uses a combination of proteomics, gene editing, and physiology approaches to identify protein and peptide hormones with previously uncharacterized functions. We have identified new pathways to increase energy expenditure and improve metabolic health, including the discovery of Slit2-C, a fragment of a secreted factor that improves diabetes by increasing energy expenditure (Svensson *et al*., ***Cell Metab*, 2016**) (US Patent WO/2017/011763.). In my recent work, my laboratory has identified and patented the use of a novel pathway of metabolic regulation, the circulating hormone Isthmin that controls glucose and lipid homeostasis (Jiang *et al.,* ***Cell Metab*, 2021** and Zhao *et al.*, ***eLife* 2022**) and a brain-derived peptide, BRP, that suppresses feeding and obesity.

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 " Provisional patent application. Filing date: 07/01/2022.

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.

Ongoing and recently completed 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.

Merck & Co., Inc. 185164 (Svensson, Katrin) 10/30/2020-12/31/2021
Identification of molecular drivers and biomarkers for NASH
Major Goal: it is to interrogate the roles of novel genes involved in lipid accumulation and hepatic inflammation and fibrosis.

R01DK120565 (Joshua Knowles, Svensson co-I) 09/01/2019 – 05/31/2024
National Institutes of Health
Characterization of novel insulin resistance genes by gene editing, high-throughput phenotyping and in vivo studies
Major Goals: Establish causal genes and mechanisms of action for novel genes involved in development of insulin resistance, by combining a range of innovative methods including highthroughput gene perturbations followed by single-cell transcriptomics, in vitro and in vivo experiments, to characterize loci established using human genetics.

P30DK116074 (Kim, Seung, Svensson - Affinity Group Leader) 07/01/2019-06/30/2021
National Institutes of Health
Stanford Diabetes Research Center
Major Goals: The aims of the Administrative Core include fostering membership of appropriate investigators in the SDRC to stimulate and ensure the growth and maintenance of the vibrant research investigator base, enriching and guiding the career development of junior investigators in diabetes related research, enhancing the environment of training, education and knowledge about opportunities in investigations of diabetes at Stanford, and providing a framework for continuous growth and evolution of resources at Stanford, including links to relevant local, national and international constituencies, that enhance diabetes related research.

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	PhD Student, Lund University, Sweden. Supervisor: Mattias Belting, M.D./Ph.D.

Selected Scientific Appointments

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 increasing prevalence of type 2 diabetes and fatty liver disease, there is still an unmet need to simultaneously treat hyperglycemia and hyperlipidemia. Additionally, there is a need for a greater mechanistic understanding of the molecular basis for glucose and lipid regulation in normal physiology and pathophysiology. Our goals are to identify alternative regulators of metabolism as an approach to combat metabolic diseases, including insulin resistance and fatty liver disease. Building on our knowledge of metabolic control by turning on a key transcriptional regulator, PRDM16, combined with our unique expertise in signal transduction pathways, complex tissue proteomics, genetics, and organismal physiology, we have discovered new biological pathways and regulation of cellular functions. To this end, we have identified a new secreted hormone called Isthmin-1 that increases glucose uptake via the PI3K/AKT pathway independently of insulin. This work represents the first description of a hormone that is important for regulation of insulin-independent glucose uptake while also suppressing lipid synthesis in the liver. Additionally, Ism1 also promote protein synthesis in the skeletal muscle, demonstrating pleiotropic anabolic effects of this circulating polypeptide hormone. I serve as the lead investigator in these studies.

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. Coassolo, L, Danneskiold-Samsøe, N.B., Zhao, M., Allen, H., **Svensson, K.J.†** New players of the adipose secretome: therapeutic opportunities and challenges.
   Curr Opin Pharmacol. Oct 1;67:102302. (**2022**) PMID: 36195010.

2. Mechanisms of hepatic glucose and lipid homeostasis

In recent work, we used single-cell RNA sequencing to identify hepatocyte-specific transcriptional regulators of lipid synthesis. We found that the constitutive androstane receptor (CAR) expression is elevated in hepatocytes with hepatic steatosis. This finding was experimentally validated using human liver tissues with different stages of fatty liver disease and by using computational artificial intelligence network modeling. In addition, we have developed protocols to isolate, characterize and phenotype heterogeneous cell populations from metabolic organs from mice with established fatty liver disease, as well as identified the G-protein coupled receptor

GRP151 as a target for hepatic glucose regulation. These results might be relevant for future drug targeting. I serve as the lead or collaborating investigator in these studies.

1. 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.

2. Coassolo L., Liu, T., Jung, Y., Taylor, N.P., Zhao, M., Charville, G., Yki-Jarvinen, H. Altman, R., **Svensson, K.J.** Single-cell analysis of non-alcoholic fatty livers identifies a role for the constitutive androstane receptor. ***bioRxiv*** 2022.08.15.504026 (**2022**).

3. 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. Methods for prediction, annotation, and discovery of bioactive proteolytic polypeptide fragments

The peptide drug discovery field has revolutionized medicine with the introduction of over 60 peptide drugs approved in the US, including insulin, glucagon, and incretin-derivatives. However, the identification of new secreted bioactive polypeptide hormones presents a daunting challenge owing to their low abundance, small size, and difficulty predicting their functions. We have developed methods combining computational sequence prediction with functional approaches to understand mechanisms of metabolic control by small, previously unknown peptides. In my postdoctoral work in the Spiegelman laboratory at Harvard Medical School, I identified Slit2-C, originally known as a brain-secreted neurotrophic factor, as a proteolytically cleaved adipocyte-secreted fragment that activates PKA-signaling. Slit2-C represents an example of a cleavage that generates a product with a distinct function from the parent protein (Svensson *et al, Cell Metab*. 2016). We have now extended this work in my own laboratory to systematically map secreted peptide hormones by their tissue of origin with the goal to determine their ability to control peripheral and central metabolic functions. Towards this end, we have recently discovered a brain-secreted peptide, BRP, that potently reduces appetite and obesity in mice. I serve as 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. **Svensson, K.J**., Coassalo, L. "BRNP2-Derived Peptide Compositions for Treating Obesity and Weight Management " ***US Patent***. Filing date: 07/01/2022.

3. Spiegelman, B.M, **Svensson, K.J.** Methods for identification, assessment, prevention, and treatment of metabolic disorders using Slit2." ***US Patent***. 15/741, 326. WO/2017/011763.

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.

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. In these studies, we identified the origins of beige fat, and metabolic functions for the secreted muscle-hormone Meteorin-like and the secreted enzyme PM20D1. These studies highlight the potential of using activation of brown fat as a strategy for improving metabolic disorders. I served as the 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. Regulation of cancer cell signaling 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 further 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: 34 publications, H-index: 23. Total citations: > 5500
https://www.ncbi.nlm.nih.gov/myncbi/1zgS-yZ3iSMQK/bibliography/public/