BIOGRAPHICAL SKETCH

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NAME: **Drucker, Daniel J**

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

POSITION TITLE: Senior Scientist, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Professor of Medicine University of Toronto

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Toronto, Toronto, ON	M.D.	09/1976	06/1980	Medicine
John Hopkins Hospital, Baltimore, MD		07/1980	06/1981	Internal Medicine
Toronto General Hospital, Toronto, ON		07/1981	06/1984	Int Med/Endocrinology
Massachusetts General Hospital, Boston		07/1984	06/1987	Mol Endocrinology

A. Personal Statement

My laboratory studies the molecular biology, physiology and mechanism(s) of action of peptide hormones, and their G protein coupled receptors. We are particularly interested in the translational relevance of these peptidergic networks for the treatment of human metabolic disorders and the emphasis in our laboratory is on translational science with therapeutic potential. Our contributions to this field are reflected in part by several hundred publications, and 33 issued US patents covering various novel therapeutic aspects of peptide hormone action.

Citation metrics https://scholar.google.co.uk/citations?user=xmFOoRYAAAAJ

B. Positions and Honors

Positions and Employment

1987-	Assistant Professor of Medicine, University of Toronto
1991-6	Associate Professor of Medicine, Clinical Biochemistry, and Genetics, University of Toronto
1992-2000	Director, Division of Endocrinology, Department of Medicine, University of Toronto
1996-	Professor, Departments of Medicine, Molecular and Medical Genetics, Laboratory Medicine
2000-11	Director, Banting and Best Diabetes Centre, University of Toronto
2006-	Senior Scientist, Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital, Toronto

Honors

Societies: Alpha Omega Alpha (1979); ASCI (1995); AAP (2006), Royal Society of Canada (2012), Royal Society of London (UK) 2015, Officer of the Order of Canada 2015

Awards: Richard E. Weitzman Award of the Endocrine Society for Scientific Achievement(1993), Canadian Diabetes Association Outstanding Young Scientist Award (1996), Viktor Mutt Outstanding Research Award from the International Society for Study of Regulatory Peptides (1998), Canadian Society for Clinical Investigation Distinguished Scientist Award(2002), Bristol Myers Squibb Freedom to Discover Award in Metabolic Research (2004), Donald Steiner Award for Diabetes Research, University of Chicago (2007), Prix Galien Canada Award for outstanding scientific research (2008), Endocrine Society Clinical Investigator Laureate Award (2009), CIHR-CMAJ Award for outstanding health research (2012); Claude Bernard Award from the European Association for the Study of Diabetes for Outstanding Diabetes Research (2012); Oon

International Prize & Lectureship, University of Cambridge, UK (2013); Banting Medal for Scientific Achievement, American Diabetes Association (2014). Manpei Suzuki International prize for Diabetes Research (2014), Rachmiel Levine Award for Diabetes Research (2015), Harrington-ASCI Prize for Innovation in Medicine (2017), Rolf Luft Award, Karolinska Institute (2017) The Canadian Organization for Rare Disorders Scientific Leadership Award (2018) EASD Novo Nordisk Prize for Excellence in Diabetes Research (2019) Harold Hamm International Prize for Biomedical Research in Diabetes (2019)

Named Lectures: Annual Peter Laurie Lecture of the Juvenile Diabetes Foundation (1999), University of Utah, Salt Lake City: Tyler Memorial Lecture (2001), The Kroc Lectureship in Diabetes at the University of Alabama, Birmingham (2002), The Williams Lecture in Diabetes, University of Rochester (2005), The Melvin C. Gluck Lectureship, New York University School of Medicine (2005), The John Ensinck Lecture, University of Washington, Seattle (2006), The Rufus Cole Memorial Lecture, Rockefeller University (2006), The Catherine Tuck Memorial Lecture, Columbia University (2007), The Albert and Miriam Weinstein Lectureship, Vanderbilt University (2009), Beth Zaruby Memorial Lecture in Diabetes Research, University of Calgary Faculty of Medicine (2009), Pfizer Visiting Professor Lectureship, University of Pennsylvania (2009), Novo Nordisk Plenary Lecture of the Irish Endocrine Society (2009), Priscilla White Lectureship in Diabetes and Metabolism, Harvard Medical School (2011), AACE Visiting Professor, Beth Israel Hospital, Harvard Medical School (2011), Harold Rifkin Lectureship, Albert Einstein College of Medicine, Yeshiva University New York (2012). Lydia J. Robert lectureship in Molecular Metabolism and Nutrition, University of Chicago (2014) D. Walter Cohen lectureship in Diabetes, Drexel University, Philadelphia (2014), Tisdale Lectureship, University of Vermont (2015), Frank H. Tyler Lectureship, University of Utah (2015), Jacquest Genest Lectureship Award, Canadian Society of Endocrinology & Metabolism (2015) Richard Horton Lecture in Endocrinology, University of Southern California School of Medicine (2016) 3d Annual George Cahill Jr. Lectureship, University of Montreal Diabetes Research Centre (2016) The Oliver Smithies Lecture, University of Toronto (2017) The Piero P. Foa Memorial lectureship Wayne State University, Detroit (2018), The 11th Levi J. Hammond Lecture, University of Pennsylvania Perelman School of Medicine (2018), The 8th Robert D. Utiger Memorial Lecture in Endocrinology, Brigham and Women's Hospital, Harvard University (2018) The Annual Kroc Lectureship, Ohio State University, Wexner Medical Center (2018) Keith Harrison Memorial Lecture of the Australian Endocrine Society (2019)

Selected Editorial Boards and Study Sections: Associate Editor, Endocrinology (2002-2007 and 2012-present); Editorial Board, Nature Reviews Endocrinology and Metabolism (2005-present); Editorial Board, Endocrine Reviews (2006-14); Editorial Board, Gastroenterology(2008-10). Editorial Board, Diabetes (2014-17) Editorial Board, Journal of the Endocrine Society (2016-present), Associate Editor, Molecular Metabolism (2018-); Editor-in-Chief, Endocrine Reviews (3/2-18)

C. Contributions to Science

1. **Delineation of mechanisms controlling glucagon biosynthesis, secretion and action.** We and characterized regulatory regions specifying glucagon gene expression and derived a novel intestinal GLP-1 secreting cell line (GLUTag), subsequently distributed to dozens of scientists worldwide. We identified the importance of Gcgr signaling in liver, islets and cardiovascular function through studies of germline and tissue-specific Gcgr-/- mice

a) **Drucker D. J.,** Philippe J., Jepeal L., and Habener J.F. Glucagon gene 5'-flanking sequences promote islet cell-specific gene transcription J. Biol. Chem. 1987 262:15659-15665
b) **Drucker D. J**., and Brubaker P. Glucagon gene expression in rat intestine is regulated by a cyclic AMP-dependent pathway. Proc. Natl. Acad. Sci (USA) 1989 86:3953-3957
c) **Drucker D. J.**, Jin, T., Asa, S. L., Young, T. A., and Brubaker, P.L. Activation of proglucagon gene transcription by protein kinase A in a novel mouse enteroendocrine cell line. Mol Endo 1994 8:1646-1655
d) Longuet, C., Sinclair, E.M., Maida, A., Baggio, L.L., Maziarz, M., Charron, M.J., and **Drucker, D. J**. Glucagon is essential for control of hepatic lipid metabolism and the adaptive metabolic response to fasting Cell Metabolism 2008:8; 359-371
e) Ali, S., Lamont, B.J., Charron, M., and **Drucker D. J**. Dual elimination of the glucagon and Glp-1 receptors in mice reveals plasticity in the incretin axis J Clinical Investigation 2011 121(5) 1917-29

f) Longuet, C., Robledo, A.M., Dean, E.D., Dai, C., Ali, S., McGuinness, I., de Chavez, V., Vuguin, P.M., Charron, M.J., Powers, A.C., and **Drucker, D.J**. Liver-specific disruption of the murine glucagon receptor produces alpha-cell hyperplasia: evidence for a circulating alpha-cell growth factor Diabetes 2013 (4) 1196-1205
g) Ali, S., Ussher, J. R., Baggio, L. L., Kabir, M. G., Charron, M. J., Ilkayeva, O., Newgard, C. B., **Drucker, D. J.** Cardiomyocyte glucagon receptor signaling modulates outcomes in mice with experimental myocardial infarction Molecular Metabolism 2015(4)132-143.

2. Discovery of multiple novel actions of GLP-1 enabling its therapeutic development We demonstrated that GLP-1(7-37) stimulated insulin secretion, activated islet β cell cAMP-dependent signaling, and increased insulin gene expression in β cells. These findings enabled a whole new field of peptide biology and clinical therapeutics for diabetes and obesity. The Drucker lab cloned exendin-4, a lizard-derived GLP-1R agonist, the first approved for the treatment of diabetes. The biology of GLP-1 action has been elucidated through physiological studies in murine models of metabolic disease.

a) **Drucker D. J**., Philippe J., Mojsov S., Chick W.L., Habener J.F. Insulinotropin: A novel glucagon related peptide stimulates insulin gene expression Proc. Natl. Acad. Sci (USA) 1987 84:3434-3438
b) Chen E., and **Drucker, D. J**. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. J. Biol. Chem. 1997 272:4108-4115
c) Yusta, B., Baggio, L. L., Estall, J. E., Koehler, J. A., Holland, D. P., Li, H., Pipeleers, D., Ling, Z., and **Drucker, D. J**. GLP-1 receptor activation improves β-cell function and survival following induction of endoplasmic reticulum stress Cell Metabolism 2006 Nov;4(5):391-406
d) Noyan-Ashraf M. H., Momen M. A., Ban K., Sadi A. M., Zhou Y. Q., Riazi, A. M., Baggio L. L., Henkelman R.M., Husain M., **Drucker D. J**. The GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes following experimental myocardial infarction in mice. Diabetes 2009 Apr;58(4):975-83.
e) **Drucker, D. J**., Buse, J.B., Taylor, K., Kendall, D., Trautmann, M., Zhuang, D., Porter, L. 2008 Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study Lancet 2008 372:1240-50
f) Kim, M., Platt, M., Shibasaki, T., Quaggin, S., Backx, P. H., Seino, S., Simpson, J., **Drucker, D. J.** GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure Nature Medicine 2013 19: 567-575
g) Varin, EM, Mulvihill E.E., Baggio, L.L., Koehler, J.A., Cao, X., Seeley, R. J., **Drucker D.J**. Distinct Neural Sites of GLP-1R Expression Mediate Physiological versus Pharmacological Control of Incretin Action Cell Reports 2019 Jun 11;27(11):3371-3384.
h) Song, Y., Koehler, J. A., Baggio, L.L., Powers, A. C, Sandoval, D.A., **Drucker D. J.** Gut proglucagon-derived peptides are essential for regulating glucose homeostasis in mice Cell Met 2019 https://doi.org/10.1016/j.cmet.2019.08.009

3. Elucidation of novel mechanisms of gut hormone action in multiple tissues using peptide antagonists and through generation of new lines of mice with inactivating mutations in key hormones and receptors.

a) Scrocchi, L. S., Brown,T. J., MacLusky, N., Brubaker, P. L., Auerbach, A. B., Joyner, A. L. and **Drucker, D. J**. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene Nature Medicine 1996 2:1254-1258
b) Hansotia, T., Maida, A., Flock, G., Yamada, Y., Tsukiyama, K., Seino, S., and **Drucker, D.J.** Extrapancreatic incretin receptors modulate glucose homeostasis and energy expenditure J Clin Invest 2007 117(1): 143–152.
c) Lamont, B., Li, Y., Kwan, E., Brown, T. J., Gaisano, H., and **Drucker D. J**. Pancreatic GLP-1 receptor activation is sufficient for GLP-1R-dependent control of glucose homeostasis in mice J Clin Invest 2012;122(1):388–402
d) Campbell, J. E., Ussher, J. R., Mulvihill, E. E., Baggio, L. L., Kolic, J., Cao, X., Liu, Y., Lamont, B. J., Morii, T., Streutker, C., Tamarina, N., Philipson, L. H., Wrana, J. L., MacDonald, P. E., and **Drucker, D. J**. TCF1 links GIPR signaling to the control of beta cell function and survival Nature Medicine 2016 22:84-90

e) Ussher, J. R., Campbell, J. E., Mulvihill, E. E., . Baggio, L. L., Bates, H. E., McLean, B. A., Gopal, K., Capozzi, M., Yusta, B., Cao, X., Ali, S., Kim, M., Kabir, M. G., Seino, Y., Suzuki, J., **Drucker, D. J.** Inactivation of the Glucose-Dependent Insulinotropic Polypeptide Receptor Improves Outcomes Following Experimental Myocardial Infarction Cell Metabolism 2018 Feb 6;27(2):450-460
f) Beaudry, J. L., Kaur, K. D., Varin, E. M., Baggio, L. L., Cao, X., Mulvihill, E. E., Bates, H. E., Campbell, J. E., **Drucker, D. J**. Physiological roles of the GIP receptor in murine brown adipose tissue Molecular Metabolism 2019 (25) https://www.sciencedirect.com/science/article/pii/S2212877819306179

4. Discovery of the biological actions of GLP-2. In 1996, we reported the first actions of GLP-2, a potent physiological regulator of cell growth and apoptosis in the gastrointestinal mucosa. A GLP-2 analogue (Teduglutide) discovered in the Drucker lab is approved for the treatment of short bowel syndrome in many countries. We cloned, characterized, and knocked out the GLP-2 receptor, elucidated GLP-2-dependent signaling pathways, and identified multiple new actions for GLP-2

a) **Drucker D. J**., Ehrlich, P., Asa, S. L., Brubaker, P. L. Induction of epithelial proliferation by glucagon-like peptide 2. Proc. Natl. Acad. Sci. 1996 93:7911-7916
b) **Drucker D. J**., Shi, Q., Crivici, A., Sumner-Smith, M., Tavares, W., Hill, M. DeForest, L., Cooper, S., and Brubaker, P.L. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV Nature Biotechnology 1997 15:673-677
c) Yusta B., Holland D., Koehler J.A., Maziarz M., Estall J.L., Higgins R., **Drucker D. J**. ErbB signaling is required for the proliferative actions of GLP-2 in the murine gut Gastroenterology 2009 Sep;137(3):986-96
d) Lee, S-J., Lee, J., Li, K. K., Holland, D., Maughan, H., Guttman, D. S., Yusta, B., and **Drucker D. J**. Disruption of the murine Glp2r impairs Paneth cell function and increases susceptibility to small bowel enteritis Endocrinology 2012 153(3):1141-51
e) Lee, K., Koehler, J., Yusta, B., Bahrami, J., Matthews, D., Rafii, M., Pencharz, P. B., **Drucker D. J** Enteroendocrine-derived glucagon-like peptide-2 controls intestinal amino acid transport Molecular Metabolism 6 (2017) 245-255
f) Yusta, B., Matthews, D., Flock, G. B., Ussher, J.R., Lavoie, B., Mawe, G. M., **Drucker, D. J**. Glucagon-like peptide-2 promotes gallbladder refilling via a TGR5-independent, GLP-2R-dependent pathway Molecular Metabolism 2017 6(6):503–511

5. Discovery of mechanisms linking genetic or pharmacological reduction of DPP-4 activity to enhanced glucose homeostasis. We demonstrated that DPP4 was a viable drug target by characterizing *Dpp4*$^{-/-}$ mice, and elucidated how and where DPP-4 inhibitors exert their glucoregulatory, cardiovascular and metabolic actions. DPP-4 inhibitors are now widely used drugs for the treatment of type 2 diabetes

a) Marguet, D., Baggio, L., Kobayashi, T., Bernard, A-M., Pierres, M., Nielsen, P.F., Ribel, U., Watanabe, T., **Drucker, D. J**., and Wagtmann, N. Enhanced insulin secretion and accelerated blood glucose clearance in mice lacking CD26 2000 Proc. Natl. Acad. Sci. USA. 97(12):6874-6879
b) Hansotia, T., Baggio, L. L., Delmeire, D., Hinke, S. A., Preitner, F., Yamada, Y., Tsukiyama, K., Thorens, B., Seino, Y., Holst, J. J., Schuit, F., and **Drucker, D. J**. Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory action of DPP-IV inhibitors Diabetes 2004 May;53(5):1326-1335
c) Sauve, M., Ban, K., Momen, M. A., Zhou, Y-Q., Henkelman, R. M., Husain, M., and **Drucker, D. J**. Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes following myocardial infarction in mice Diabetes 2010 Apr;59(4):1063-73
d) Mulvihill, E. E., Varin, E. M., Gladanac, B., Campbell, J. E., Ussher, J. R., Baggio, L. L., Yusta. B., Ayala, J., Burmeister, M. A., Matthews, D., Bang, K. W. A., Ayala, J. E., **Drucker D. J**. Cellular sites and mechanisms linking reduction of dipeptidyl peptidase-4 activity to control of incretin hormone action and glucose homeostasis Cell Metabolism 2017 Jan 10;25(1):152-165
e) Varin, E. M., Mulvihill, E. E., Beaudry, J. L., Pujadas, G., Fuchs, S., Tanti, J.-F., Fazio, S., Kaur, K., Cao, X., Baggio, L. L., Matthews, D., Campbell, J. E., **Drucker, D. J.,** Circulating levels of soluble dipeptidyl peptidase-4 are dissociated from inflammation and induced by enzymatic DPP4 inhibition Cell Metabolism 2019; 29 (2) 320-334.

D. Ongoing Research Support

CIHR Foundation Grant 154321 Mechanisms of peptide hormone action: metabolic and therapeutic implications PI: Dr. Daniel J. Drucker Date of Approval: July 1 2017-June 30 2024

Research Chair Awards Banting and Best Diabetes Centre-Novo Nordisk Chair in Incretin Biology 2016-2020 $180,000 per annum