50 ANNIVERSARY CELEBRATION

Brown & Goldstein Lab

A Scientific Symposium

October 14, 2022

Tom and Lula Gooch Auditorium

UT Southwestern Medical Center, Dallas, Texas

Brown and Goldstein: Celebrating 50 Years of Partnership

This year, Michael S. Brown, M.D., and Joseph L. Goldstein, M.D., celebrate 50 years of their collaborative research. The duo launched their joint laboratory at UT Southwestern Medical Center in 1972, marking the start to one of science's most successful partnerships over the past five decades.

A native of a small town in South Carolina, Dr. Goldstein went to Washington and Lee University in Virginia before attending UT Southwestern Medical School, where he was mentored by Donald Seldin, M.D. Brooklyn-born Dr. Brown grew up in suburban Philadelphia before attending the University of Pennsylvania for his undergraduate and medical school education. They first met in 1966 at the start of their internships and residencies at Massachusetts General Hospital, striking an immediate bond. After long days in the clinic with patients, the two would stay behind and discuss the underlying pathology of the diseases they encountered, trying to gain a deeper understanding of what caused the ailments.

Eventually, they both moved on to research positions at the National Institutes of Health (NIH). Despite working in different labs, the two remained close friends. Dr. Brown was mentored by Earl Stadtman, Ph.D., who went on to receive the National Medal of Science for his research on enzymes and anaerobic bacteria. Meanwhile, Dr. Goldstein worked on protein chain termination under Dr. Marshall Nirenberg, Ph.D., who won a Nobel Prize in 1968. It was at the NIH that Drs. Brown and Goldstein first became interested in familial hypercholesterolemia, an inherited condition in which lipid levels in the blood are extremely high.

Dr. Brown came to UT Southwestern in 1971, and Dr. Goldstein joined him a year later in 1972 after finishing his postdoctoral work in medical genetics at the University of Washington. Soon after, they merged their labs, and together, they focused their research on investigating the cause of familial hypercholesterolemia, the same disorder that caught their attention at the NIH. This work ultimately led to their 1985 Nobel Prize in Physiology or Medicine for discovering the LDL receptor and its role in cholesterol metabolism. Moreover, their findings explained the mechanism of action of statin drugs, which are taken by millions worldwide to lower cholesterol levels and reduce the risk of heart disease.

Together, they have earned some of science's highest honors, including the Lasker Award in Basic Medical Research (1985), the Nobel Prize in Physiology or Medicine (1985), the National Medal of Science (1988), and most recently, the Albany Medical Center Prize in Medicine and Biomedical Research (2003). Both are members of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the Royal Society (foreign members). They continue to be outstanding academic leaders and mentors to graduate students, postdoctoral fellows, and younger colleagues, including many who have gone on to be honored for their own storied achievements.

8:45 a.m.	**Welcome**

Helen Hobbs, M.D., and **Eric Olson, Ph.D.**
Professors and Symposium Chairs | UT Southwestern Medical Center

Daniel K. Podolsky, M.D.
President | UT Southwestern Medical Center

9:00 a.m. **Drifting and Disappearing Sensory Representations in the Cortex**

Richard Axel, M.D.
Professor and Co-Director | Zuckerman Institute, Columbia University

9:30 a.m. **How Do You Feel? The Molecules That Sense Touch**

Ardem Patapoutian, Ph.D.
Professor | Department of Neuroscience, Scripps Research

10:00 a.m. **Neurobiology of the World's Most Dangerous Animal**

Leslie B. Vosshall, Ph.D.
Professor and Head | Laboratory of Neurogenetics and Behavior, The Rockefeller University

10:30 a.m.	**Break**

11:00 a.m. **Small Molecule Mutant-Specific K-Ras Inhibitors**

Kevan M. Shokat, Ph.D.
Professor and Interim Chair | Department of Cellular and Molecular Pharmacology, University of California, San Francisco
Professor | Department of Chemistry, University of California, Berkeley

11:30 a.m. **Exploration of Biological Diversity**

Feng Zhang, Ph.D.
Core Member, Broad Institute
Professor of Neuroscience | Massachusetts Institute of Technology

Noon	**Lunch**

1:30 p.m. **Quorum Sensing Across Domains: From Viruses to Bacteria to Eukaryotes**

Bonnie L. Bassler, Ph.D.
Professor and Chair | Department of Molecular Biology, Princeton University

2:00 p.m. **Organoids to Model Human Disease**

Hans Clevers, M.D., Ph.D.
Head of Pharma Research and Early Development | Roche (Switzerland)
Professor | Molecular Genetics, Utrecht University

2:30 p.m. **Engineering Cell Surface Signaling**

K. Christopher Garcia, Ph.D.
Professor | Department of Molecular and Cellular Physiology and Department of Structural Biology, Stanford University

3:00 p.m. **Break**

3:30 p.m. **Inner Workings of Channelrhodopsins and Brains**

Karl Deisseroth, M.D., Ph.D.
Professor | Department of Bioengineering and Department of Psychiatry and Behavioral Sciences, Stanford University

4:00 p.m. **Rett Syndrome and *MECP2* Disorders: An Enlightening Dialogue Between Bench and Clinic**

Huda Y. Zoghbi, M.D.
Professor | Department of Molecular and Human Genetics and Department of Neuroscience and Neurobiology, Baylor College of Medicine

4:30 p.m. **Closing Remarks**

Michael S. Brown, M.D., and Joseph L. Goldstein, M.D.

4:45 p.m. **Reception**

About the Speakers

Richard Axel, M.D.

Investigator | Howard Hughes Medical Institute
Professor and Co-Director | Zuckerman Institute, Columbia University

Dr. Axel developed gene transfer techniques that permit introduction of virtually any gene into any cell. He introduced molecular biology to problems in neuroscience with the expectation that genetics could inform the relationships between genes, behavior, and perception. His studies on the logic of the sense of smell revealed over 1,000 genes involved in recognition of odors and provided insight into how genes shape our perception of the sensory environment. His current work centers on how recognition of odors is translated into an internal representation of sensory quality in the brain and how this representation leads to meaningful thoughts and behavior. Dr. Axel received the Nobel Prize in Physiology or Medicine in 2004. He is also a member of the National Academy of Sciences, the Royal Society, and the American Academy of Arts and Sciences and has received numerous additional academic awards and honors.

Bonnie L. Bassler, Ph.D.

Investigator | Howard Hughes Medical Institute
Professor and Chair | Department of Molecular Biology, Princeton University

Research from Dr. Bassler's laboratory focuses on the molecular mechanisms that bacteria use for intercellular communication, a process called quorum sensing. Dr. Bassler's research is paving the way toward the development of novel therapies for combating bacteria by disrupting quorum-sensing-mediated communication. Dr. Bassler is a member of the National Academy of Sciences, the National Academy of Medicine, the Royal Society, and the American Academy of Arts and Sciences and has received numerous awards for her work, including a MacArthur Foundation Fellowship, the Shaw Prize in Life Sciences and Medicine, and the Wolf Prize in Chemistry.

Hans Clevers, M.D., Ph.D.

President | Royal Netherlands Academy of Arts and Sciences
Head of Pharma Research and Early Development | Roche (Switzerland)
Professor | Molecular Genetics, Utrecht University

Dr. Clevers works on the role of Wnt signaling in stem cells and in cancer development and discovered that TCF is the nuclear Wnt effector. He found that Lgr5 is a marker of multiple types of adult stem cells and a receptor for the Wnt-amplifying R-spondins. Finally, he has spearheaded the development of a method to grow mini-organs ("organoids") from Lgr5 stem cells derived from a range of healthy and diseased tissues. Dr. Clevers is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the Academie des Sciences and has received numerous awards for his work, including the Breakthrough Prize in Life Sciences.

Karl Deisseroth, M.D., Ph.D.

Investigator | Howard Hughes Medical Institute
Professor | Department of Bioengineering and Department of Psychiatry and Behavioral Sciences, Stanford University

Dr. Deisseroth is a practicing psychiatrist with specialization in major depression and autism-spectrum disease. His laboratory has developed optogenetics, hydrogel-tissue chemistry, and other tools to study single-cell control and investigate intact biological systems. He also discovered the high-resolution structural principles of light-gated ion conduction. Dr. Deisseroth is a member of the National Academy of Sciences and the National Academy of Engineering and has received numerous awards for his work, including the Albert Lasker Award for Basic Medical Research, the Gairdner International Award, and the Breakthrough Prize in Life Sciences.

K. Christopher Garcia, Ph.D.

Investigator | Howard Hughes Medical Institute
Professor | Department of Molecular and Cellular Physiology and Department of Structural Biology, Stanford University

Dr. Garcia's laboratory investigates structural and functional aspects of cell surface receptor recognition and activation. He uses structural information of receptor-ligand complexes to engineer variant proteins and/or surrogates with a goal of altering receptor signaling and cellular function. His focus has been on receptor systems of the immune system (TCR/MHC, cytokines, chemokine GPCR), but he also studies other receptor-ligand complexes that are important in neurobiology and development. He has elucidated the biophysical basis by which different ligands elicit unique intracellular responses and functional outcomes and exploited this information to engineer receptor-specific ligands. Dr. Garcia is a member of the National Academy of Sciences and the National Academy of Medicine.

Ardem Patapoutian, Ph.D.

Investigator | Howard Hughes Medical Institute
Professor | Department of Neuroscience, Scripps Research

Dr. Patapoutian is a molecular biologist specializing in sensory transduction. His research has led to identification of novel ion channels and receptors activated by temperature, mechanical force, and increased cell volume. His laboratory showed that these ion channels play crucial roles in sensing temperature, touch, proprioception, and pain and in regulating vascular tone. Dr. Patapoutian received the Nobel Prize in Physiology or Medicine in 2021. He is also a member of the National Academy of Sciences and the American Academy of Arts and Sciences and has received numerous additional awards, including the Kavli Award in Neuroscience and the Rosenstiel Award for Distinguished Work in Basic Medical Research.

Kevan M. Shokat, Ph.D.

Investigator | Howard Hughes Medical Institute
Professor and Interim Chair | Department of Cellular and Molecular Pharmacology, University of California, San Francisco
Professor | Department of Chemistry, University of California, Berkeley

Dr. Shokat's research focuses on the discovery of new small-molecule tools to target protein/lipid kinases, GTPases, and RNA helicases. Among the tools his laboratory utilizes are synthetic organic chemistry, protein engineering, structural biology, biochemistry, and cell biology. He has co-founded several biotechnology companies to advance the work from his laboratory. Dr. Shokat is a member of the National Academy of Sciences and the American Academy of Arts and Sciences and has received numerous awards for his research.

Leslie B. Vosshall, Ph.D.

Vice President and Chief Scientific Officer | Howard Hughes Medical Institute
Professor and Head | Laboratory of Neurogenetics and Behavior, The Rockefeller University

Dr. Vosshall is a molecular neurobiologist who studies how behaviors emerge from the integration of sensory input with internal physiological states. Her research program is aimed at understanding the molecular neurobiology of host-seeking and blood-feeding in mosquitoes that spread dangerous infectious diseases. Dr. Vosshall is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Philosophical Society and has received numerous awards for her research, including the Alden W. Spencer Award in Neuroscience.

Feng Zhang, Ph.D.

Core Member | Broad Institute
Investigator | McGovern Institute for Brain Research
Professor of Neuroscience | Massachusetts Institute of Technology

Dr. Zhang is a molecular biologist who has developed multiple technologies that are being used around the world to advance the study, diagnosis, and treatment of human diseases. He played an integral role in the development of optogenetics and pioneered the use of CRISPR systems for genome editing. This work is complemented by his work to develop novel delivery modalities for genetic therapeutics. Dr. Zhang is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences. He has received numerous awards for his research, including the Gairdner International Award, the Albany Medical Center Prize, and the Vilcek Prize for Creative Promise in Biomedical Science.

Huda Y. Zoghbi, M.D.

Investigator | Howard Hughes Medical Institute
Professor | Department of Molecular and Human Genetics and Department of Neuroscience and Neurobiology, Baylor College of Medicine
Director | Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital

Dr. Zoghbi's expertise ranges from neurodevelopment to neurodegeneration. She and Dr. Harry Orr discovered that spinocerebellar ataxia type 1 is caused by expansion of a polyglutamine tract. Her subsequent studies demonstrated that such expansion leads to accumulation of the mutant protein in neurons, as occurs in many late-onset neurological disorders. She also discovered that mutations in *MECP2* cause the postnatal neurological disorder Rett syndrome and revealed the importance of this gene for various neuropsychiatric features. Dr. Zoghbi is a member of the National Academy of Sciences and the National Academy of Medicine and has received numerous additional honors, including the Shaw Prize in Life Science and Medicine, the Breakthrough Prize in Life Sciences, and the Gairdner International Award.

About the President and Symposium Chairs

Daniel K. Podolsky, M.D., became President of the University of Texas Southwestern Medical Center in September 2008. Internationally renowned for his contributions to the understanding of intestinal inflammatory diseases, Dr. Podolsky was previously associated with Harvard Medical School and Massachusetts General Hospital, including 20 years of service as Chief of Gastroenterology, and more recently as Chief Academic Officer of Partners HealthCare.

Dr. Podolsky is a member of the National Academy of Medicine and a former President of the American Gastroenterological Association, from which he received the 2009 Julius Friedenwald Medal for Distinguished Service for his lifelong contributions to the field of gastroenterology.

Helen H. Hobbs, M.D., is an Investigator of the Howard Hughes Medical Institute and a Professor of Internal Medicine and Molecular Genetics at UT Southwestern. After completing her clinical training, she worked in the laboratory of Drs. Michael Brown and Joseph Goldstein before joining the UT Southwestern faculty in 1987. She is Director of the McDermott Center for Human Growth and Development.

Together with Jonathan Cohen, Ph.D., she has identified genetic differences that alter levels and distribution of lipids and contribute to cardiovascular disorders and fatty liver disease. She is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences. She was awarded the Breakthrough Prize in 2016.

Eric Olson, Ph.D., was recruited to UT Southwestern in 1995 as the founding Chair of the Department of Molecular Biology. He also directs the Hamon Center for Regenerative Science and Medicine and the Wellstone Center for Muscular Dystrophy Research. He holds The Robert A. Welch Distinguished Chair in Science, the Annie and Willie Nelson Professorship in Stem Cell Research, and the Pogue Distinguished Chair in Research on Cardiac Birth Defects.

Dr. Olson and his trainees discovered many of the genes that control heart and muscle development and disease. His most recent work has provided a new strategy for correction of Duchenne muscular dystrophy using CRISPR gene editing. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences.

UT Southwestern
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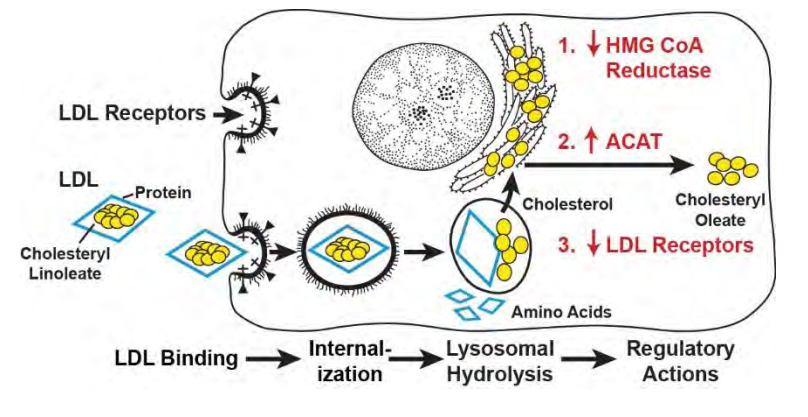
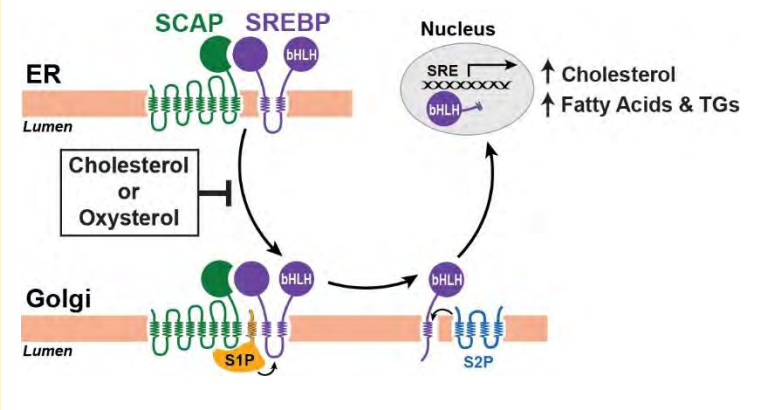
Brown and Goldstein: 50 Years of Discovery

In their 50 years at UT Southwestern, Mike Brown and Joe Goldstein (B & G) have supervised more than 175 students and postdoctoral fellows. Together, they have discovered many proteins and their roles in fundamental biologic mechanisms. They are joint authors on 524 publications that have been cited 197,367 times. Their joint H-Index is 232, indicating that 44% of their papers have been cited more than 232 times *(Google Scholar, Oct. 3, 2022).* B & G opened new avenues in 9 different areas of metabolism. Selected publications are listed on pages 2-4. Shown below are 3 signaling pathways that B & G discovered.

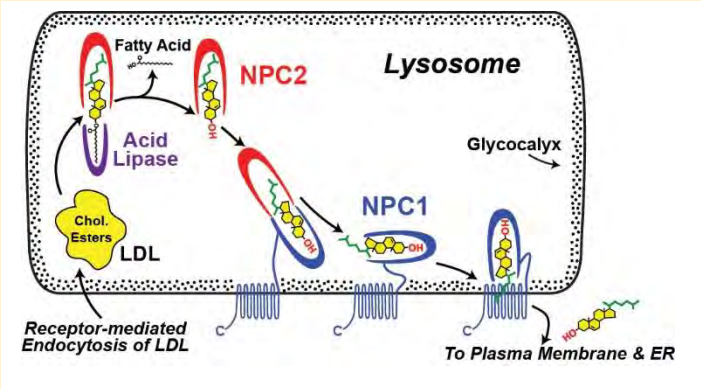
The LDL Receptor Pathway:
Receptor-Mediated Endocytosis of LDL for Cholesterol Homeostasis



The SREBP Pathway:
Transcriptional Control by Sterol-Regulated Intramembrane Proteolysis



The Cholesterol Handoff Pathway:
Lysosomal Transfer of Cholesterol from LDL to NPC2 to NPC1 to Membranes



Selected Publications in 9 Research Areas

LDL Receptor and Receptor-Mediated Endocytosis (1972-1992)

MS Brown and JL Goldstein. Familial hypercholesterolemia: Defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. ***Proc. Natl. Acad. Sci. USA*** 71: 788-792 (1974). **913 citations**

JL Goldstein and MS Brown. Binding and degradation of low density lipoproteins by cultured human fibroblasts: Comparison of cells from a normal subject and from a patient with homozygous familial hypercholesterolemia. ***J. Biol. Chem.*** 249: 5153-5162 (1974). **1775 citations**

JL Goldstein, RGW Anderson, and MS Brown. Coated pits, coated vesicles, and receptor-mediated endocytosis. ***Nature*** 279: 679-685 (1979). **2498 citations**

WJ Schneider, U Beisiegel, JL Goldstein, and MS Brown. Purification of the low density lipoprotein receptor, an acidic glycoprotein of 164,000 molecular weight. ***J. Biol. Chem*.** 257: 2664-2673 (1982). **462 citations**

T Yamamoto, CG Davis, MS Brown, WJ Schneider, ML Casey, JL Goldstein, and DW Russell. The human LDL receptor: A cysteine-rich protein with multiple Alu sequences in its mRNA. ***Cell*** 39: 27-38 (1984). **1694 citations**

TC Südhof, JL Goldstein, MS Brown, and DW Russell. The LDL receptor gene: A mosaic of exons shared with different proteins. ***Science*** 228: 815-822 (1985). **1065 citations**

MS Brown and JL Goldstein. Nobel Lecture: A receptor-mediated pathway for cholesterol homeostasis. ***Science*** 232: 34-47 (1986). **7476 citations**

W-J Chen, JL Goldstein, and MS Brown. NPXY, a sequence often found in cytoplasmic tails, is required for coated pit-mediated internalization of the low density lipoprotein receptor. ***J. Biol. Chem.*** 265: 3116-3123 (1990). **1256 citations**

HH Hobbs, MS Brown, and JL Goldstein. Molecular Genetics of the LDL receptor gene in familial hypercholesterolemia. ***Human Mutation*** 1: 445-466 (1992). **1363 citations**

Macrophage Scavenger Receptors as Mediators of Atherosclerosis (1978-1983)

JL Goldstein, YK Ho, SK Basu, and MS Brown. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. ***Proc. Natl. Acad. Sci. USA*** 76: 333-337 (1979). **3326 citations**

MS Brown and JL Goldstein. Lipoprotein metabolism in the macrophage: Implications for cholesterol deposition in atherosclerosis. ***Ann. Rev. Biochem.*** 52: 223-261 (1983). **3058 citations**

Sterol Regulatory-Element Binding Proteins and Transcriptional Control by Regulated Intramembrane Proteolysis (1986-present)

X Wang, R Sato, MS Brown, X Hua, and JL Goldstein. SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. ***Cell*** 77: 53-62 (1994). **1216 citations**

MS Brown and JL Goldstein. The SREBP pathway: Regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. ***Cell*** 89: 331-340 (1997). **4398 citations**

MS Brown, J Ye, RB Rawson, and JL Goldstein. Regulated intramembrane proteolysis: a control mechanism conserved from bacteria to humans. ***Cell*** 100: 391-398 (2000). **1620 citations**

JD Horton, JL Goldstein, and MS Brown. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. ***J. Clin. Invest.*** 109: 1125-1131 (2002). **5288 citations**

Prenyltransferases Required by Cancer-Causing Ras Proteins and Vesicle-Transporting Rab Proteins (1988-1996)

JL Goldstein and MS Brown. Regulation of the mevalonate pathway. ***Nature*** 343: 425-430 (1990). **6408 citations**

Y Reiss, JL Goldstein, MC Seabra, PJ Casey, and MS Brown. Inhibition of purified $p21^{ras}$ farnesyl:protein transferase by Cys-AAX tetrapeptides. ***Cell*** 62: 81-88 (1990). **1008 citations**

MC Seabra, JL Goldstein, TC Südhof, and MS Brown. Rab geranylgeranyl transferase: A multisubunit enzyme that prenylates GTP-binding proteins terminating in Cys-*X*-Cys or CysCys. ***J. Biol. Chem.*** 267: 14497-14503 (1992). **416 citations**

MCT1: The Monocarboxylate Transporter that Shuttles Lactate and Pyruvate Across Cell Membranes (1990-1996)

CK Garcia, JL Goldstein, RK Pathak, RGW Anderson, and MS Brown. Molecular characterization of a membrane transporter for lactate, pyruvate, and other monocarboxylates: Implications for the Cori cycle. ***Cell*** 76: 865-873 (1994). **606 citations**

Leptin as a Treatment for Lipodystrophy (1997-2001)

I Shimomura, RE Hammer, JA Richardson, S Ikemoto, Y Bashmakov, JL Goldstein, and MS Brown. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. ***Genes Dev.*** 12: 3182-3194 (1998). **958 citations**

I Shimomura, RE Hammer, S Ikemoto, MS Brown, and JL Goldstein. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. ***Nature*** 401: 73-76 (1999). **1252 citations**

Fatty Liver in Diabetes Caused by Insulin Activation of SREBP-1c (1997-present)

I Shimomura, Y Bashmakov, S Ikemoto, JD Horton, MS Brown, and JL Goldstein. Insulin selectively increases SREBP-1c mRNA in livers of rats with streptozotocin-induced diabetes. ***Proc. Natl. Acad. Sci. USA*** 96: 13656-13661 (1999). **903 citations**

MS Brown and JL Goldstein. Selective *vs.* total insulin resistance: a pathogenic paradox. ***Cell Metab.*** 7: 95-96 (2008). **985 citations**

Ghrelin O-Acyltransferase (GOAT) as a Requirement to Withstand Starvation (2006-present)

Yang, J., Brown, M.S., Liang, G., Grishin, N.V., and Goldstein, J.L. Identification of the acyltransferase that octanoylates ghrelin, an appetite-stimulating peptide hormone. ***Cell*** 132: 387-396 (2008). **1318 citations**

T-J Zhao, G Liang, X Xie, MW Sleeman, AJ Murphy, DM Valenzuela, GD Yancopoulos, JL Goldstein, and MS Brown. Ghrelin *O*-acyltransferase (GOAT) is essential for growth hormone-mediated survival of calorie-restricted mice. ***Proc. Natl. Acad. Sci. USA*** 107: 7467-7472 (2010). **455 citations**

Neimann-Pick C1 as a Cholesterol Transporter Defective in a Lethal Genetic Disease (2005-present)

RE Infante, L Abi-Mosleh, A Radhakrishnan, JD Dale, MS Brown, and JL Goldstein. Purified NPC1 protein: I. Binding of cholesterol and oxysterols to a 1278-amino acid membrane protein. ***J. Biol. Chem.*** 283: 1052-1063 (2008). **227 citations**

RE Infante, ML Wang, A Radhakrishnan, HJ Kwon, MS Brown, and JL Goldstein. NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. ***Proc. Natl. Acad. Sci. USA*** 105: 15287-15292 (2008). **488 citations**

HJ Kwon, L Abi-Mosleh, ML Wang, J Deisenhofer, JL Goldstein, MS Brown, and RE Infante. Structure of N-terminal domain of NPC1 reveals distinct subdomains for binding and transfer of cholesterol. ***Cell*** 137: 1213-1224 (2009). **667 citations**

F Lu, Q Liang, L Abi-Mosleh, A Das, JK De Bradbander, JL Goldstein, and MS Brown. Identification of NPC1 as the target of U18666A, an inhibitor of lysosomal cholesterol export and Ebola infection. ***eLife*** 4:e12177, 1-16 (2015). **238 citations**

Reflections on the Surprises and Joys of a Long-Term Partnership

MS Brown and JL Goldstein. *Scientific Side Trips: Six Excursions from the Beaten Path*. ***J. Biol. Chem.*** 287: 22418-22435 (2012).