BIOGRAPHICAL SKETCH

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NAME: Glass, Christopher K.

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POSITION TITLE: Professor of Cellular and Molecular Medicine, UCSD

Professor of Medicine, UCSD

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Berkeley	B.A.	06/1977	Biophysics
University of California, San Diego	M.D.	06/1984	Medicine
University of California, San Diego	Ph.D.	06/1984	Biology
Brigham and Women's Hospital, Harvard Medical School	Internship	06/1985	Internal Medicine
Brigham and Women's Hospital, Harvard Medical School	Residency	06/1986	Internal Medicine
University of California, San Diego	Fellowship	06/1989	Endocrinology

A. Personal Statement

The primary goal of my laboratory is to understand the mechanisms by which sequence-specific transcription factors, co-activators and co-repressors regulate the development and function of macrophages and microglia in health and disease. A major direction over the past ten years has been to define molecular mechanisms that control macrophage and microglia phenotypes using assays that are based on massively parallel DNA sequencing. The combination of these technologies with molecular, genetic, lipidomic and cell-based approaches is providing new insights into mechanisms that regulate macrophage and microglia gene expression and function that are relevant to their pathogenic roles in cancer, atherosclerosis, and neurodegeneration. A corresponding activity has been mentoring graduate students, MSTP students and postdoctoral fellows, the majority of whom have pursued productive careers in academia or industry.

B. Positions and Honors

Positions and Employment

2024- Assistant Vice Chancellor for Integrated Research, UC San Diego Health Sciences
2018- Distinguished Professor of Cellular and Molecular Medicine and Medicine, Division of Endocrinology and Metabolism, University of California, San Diego
1999-2018 Professor of Cellular and Molecular Medicine and Professor of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego
1995-1999 Associate Professor of Medicine, Divisions of Endocrinology and Metabolism and Cellular and Molecular Medicine, University of California, San Diego
1992-1995 Assistant Professor of Medicine, Divisions of Endocrinology and Metabolism and Cellular and Molecular Medicine, University of California, San Diego
1989-1992 Assistant Professor of Medicine in Residence, Divisions of Endocrinology and Metabolism and Cellular and Molecular Medicine, Dept of Medicine, University of California, San Diego

Other Experience and Professional Membership

2019-2022 Member and Chair (2022) Endocrine Society Laureate Award Committee
2017-2023 Editorial Board, Proceedings of the National Academy of Sciences
2015-2022 NIDDK RC2 Editorial Board Member
2012-2017 Editorial Board, eLife
2009-2012 Council Member, National Institute of Diabetes, Digestive and Kidney Disease
2001-2003 Program Director, Minority Summer Graduate Research Fellowships (SURF)
2000-2002 Council Member, American Society for Clinical Investigation
1999-2004 Member, Endocrinology Study Section, NIH (Chair 2002-2004)
1993- Fellow, American Heart Association,
1989-present Member, Endocrine Society
1989-2024 Associate Director, UC San Diego Medical Scientist Training Program

Selected Honors

2024 Grand Prix Scientifique, Fondation Lefoulon-Delalande, Institut de France
2017 Election to National Academy of Sciences
2016 Ben and Wanda Hildyard Chair for Hereditary Diseases
2015 Election to National Academy of Medicine (formerly Institute of Medicine)
2014 Election to American Academy of Arts and Sciences
2013 University Lecture, UT Southwestern Medical Center
2013 Russell Ross Memorial Lecture – University of Washington
2013 NIH Director's Transformative R01 'Enhancer Therapy'
2012 Page Lecture, Cleveland Clinic
2008 Honorary Doctorate of Medicine, University of Linköping, Sweden
2006 Association of American Physicians
2000 Ernst Oppenheimer Award of the Endocrine Society
1995 American Society for Clinical Investigation
1995 Established Investigator, American Heart Association
1989 Wilson S. Stone Award for the M.D. Andersen Cancer Center
1987 Lucille P. Markey Scholarship for Biomedical Sciences
1977 Departmental honors in Biophysics, UC Berkeley

C. Contributions to Science

1. Microglia and neurodegenerative diseases

2. Based on our studies of pathogenic roles of macrophages in cardiovascular and metabolic disease, we hypothesized analogous roles of microglia in neurodegenerative diseases more than 15 years ago. This view was shared by a small number of investigators, but the prevailing view in the neuroscience community at that time was that the presence of activated microglia in neurodegenerative disease was a secondary response to neuronal injury and death and not linked to pathogenesis. Nevertheless, we were able to provide experimental evidence that microglia activation could in turn activate astrocytes, resulting in the production of neurotoxic mediators (a). We also showed that mutant forms of the Huntington protein associated with Huntington's disease could activate microglia in a cell autonomous manner. The emergence of GWAS studies identifying numerous risk alleles associated with genes predominantly or exclusively expressed in microglia had a major impact on the further consideration of microglia in both protective and pathogenic mechanisms. Working with Dr. Nicole Coufal, we were able to generate transcriptomic and epigenetic atlases of human microglia for the first time. These studies confirmed that a large fraction of the genes implicated in AD risk by GWAS studies were indeed primarily expressed in microglia. Further, alignment of the epigenetic landscape of human microglia with genomic locations indicated that many non-coding risk loci overlapped microglia regulatory elements (b). To investigate the specificity of this observation, we developed nuclear sorting protocols to sort nuclei from microglia, astrocytes, oligodendrocytes and neurons of human brain tissue. This technology enabled us to generate enhancer landscapes for each cell type and assess enrichment for AD risk alleles. We observed the highest enrichment of non-coding risk alleles in microglia specific enhancers, exemplified by a putative causal SNP associated with *BIN1*. Dr. Coufal deleted the region containing this microglia-specific enhancer from iPSC and ES cell lines, which were then differentiated into microglia,

astrocytes and neurons in vitro. The enhancer deletion nearly abolished *BIN1* expression in microglia but had no effects on *BIN1* expression in astrocytes or neurons. These studies thereby provided a powerful confirmation of the usefulness of epigenetic data combined with iPSC technology in interpretation of GWAS risk alleles (c). In a recent collaborative study with Dr. Holtzman we performed snRNA-seq and ATAC seq analysis of microglia in the PS19 tauopathy x APOE4 (TE4) mouse model of neurodegeneration. These studies led to our identification of a previously unrecognized microglia phenotype resulting from the interaction of Tau and APOE4 that we call TERMs (c). Most recently, we defined super enhancer that transduces brain environmental signals to regulate the expression of the microglia lineage determining factor Sall1 (d). Knockout of this enhancer in the germ line resulted in selective loss of Sall1 expression in microglia and a molecular signature highly related to that observed in aged microglia.

a. Gosselin D, Skola, D, **Coufal NG**, Holtman, IR, Schlachetzki JCM, Sajti E, Jaeger BN, O'Connor C, Fitzpatrick C, Pasillas MP, Pena M, Adair A, Gonda DG, Levy ML, Ransohoff RM, Gage FH, **Glass CK**. (2017) An environment-dependent transcriptional network specifies human microglia identity. Science. Jun 23;356(6344). PMID: 28585919.
b. Nott A, Holtman IR, **Coufal NG**, Schlachetzki JCM, Yu M, Hu R, Han CZ, Pena M, Xiao J, Wu Y, Keulen Z, Pasillas MP, O'Connor C, Nickl CK, Schafer ST, Shen Z, Rissman RA, Brewer JB, Gosselin D, Gonda DD, Levy ML, Rosenfeld MG, McVicker G, Gage FH, Ren B, **Glass CK**. (2019) Brain cell type-specific enhancer-promoter interactome maps and disease-risk association. Science. 366(6469):1134-1139. PMID: 31727856.
c. Gratuze, M., Schlachetzki, J.C.M., D'Oliviera Albanus, R., Jain, N., Novotny, B., Brase, L., Rodriquez, L., Mansel, C., Kipnis, M., O'"Brien, Pasillas, M., Lee, C, Mannis, M., Colonna, M., Harari, O., **Glass, CK.**, Ulrich, JD., and **Holtzman, DM**. (2023). TREM2-independent microgliosis promotes tau-mediated neurodegeneraton in the presence of ApoE4. Neuron 111:202-219 PMID: 36368315
d. Fixsen BR, Han CZ, Zhou Y, Spann NJ, Saisan P, Shen Z, Balak C, Sakai M, Cobo I, Holtman IR, Warden AS, Ramirez G, Collier JG, Pasillas MP, Yu M, Hu R, Li B, Belhocine S, Gosselin D, Coufal NG, Ren B, Glass CK. (2023) SALL1 enforces microglia- specific DNA binding and function of SMADs to establish microglia identity. Nat Immunol. 24(7):1188-1199. PMID: 37322178

3. Transcriptional mechanisms underlying the development and function of macrophages and microglia We were among the first laboratories to clone cDNAs encoding the macrophage lineage-determining factor PU.1 and demonstrated combinatorial roles with AP-1 factors in regulating macrophage-specific gene expression. In 2010 we determined the genome-wide binding patterns of PU.1 in macrophages and B cells and proposed a general, hierarchical model for the selection and function of cell-specific enhancers. In this model, relatively simple combinations of lineage determining transcription factors are proposed to select the majority of cell- specific enhancers by binding to closely spaced recognition motifs in a collaborative manner. These initial binding events result in chromatin remodeling and enable the subsequent binding of signal-dependent transcription factors (a). This paper, now cited more than 10,000 times, provides a molecular explanation for how small numbers of transcription factors can reprogram cell fates as well has for how broadly expressed signal dependent transcription factors regulate gene expression in a cell-specific manner. We went on to explore how distinct tissue environments drive the selection and function of enhancers that are required for the specification of mouse peritoneal macrophages and microglia in vivo (b). We extended this concept to human microglia by profiling microglia gene expression and epigenetic landscapes immediately after isolation from the brain and following transfer to a tissue culture environment. These studies established an essential role of the brain environment in maintaining the transcriptional regulatory elements necessary for microglia specific gene expression (c). We provided proof of principle for the concept that quantitative analysis of changes in enhancer landscapes can be used to infer the transcription factors responsible for cell fate or cell state changes. A representative paper investigated changes in the phenotypes of Kupffer cells in the liver in response to a diet that causes the development of Nonalcoholic steatohepatitis. In this model, there are more than 800 significant changes in Kupffer cell gene expression that are associated with more than 4000 significant changes in enhancer activity. Motif analysis and subsequent validation studies demonstrated that these changes were in part due to alterations in the activities and expression of ATF3, Egr2 and LXR transcription factors (d).

a. Heinz S, Benner C, Spann N, Bertolino E, Lin YC, Laslo P, Cheng JX, Murre C, Singh H, **Glass CK**. (2010). Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. Mol Cell 38(4):576-589. PMC2898526.
b. Gosselin D, Link VM, Romanoski CE, Fonseca GJ, Eichenfield DZ, Spann NJ, Stender JD, Chun HB, Garner H, Geissmann F, **Glass CK.** (2014). Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. Cell 159(6):1327-1340. PMC4364385.
c. Gosselin D, Skola, D, **Coufal NG**, Holtman, IR, Schlachetzki JCM, Sajti E, Jaeger BN, O'Connor C, Fitzpatrick C, Pasillas MP, Pena M, Adair A, Gonda DG, Levy ML, Ransohoff RM, Gage FH, **Glass CK**. (2017) An environment-dependent transcriptional network specifies human microglia identity. Science. 356(6344). PMID: 28585919.
d. Seidman JS, Troutman TD, Sakai M, Gola A, Spann NJ, Bennett H, Bruni CM, Ouyang Z, Li RZ, Sun X, Vu BT, Pasillas MP, Ego KM, Gosselin D, Link VM, Chong L, Evans RM, Thompson BM, McDonald JG, Hosseini M, Witztum JL, Germain RN, **Glass CK**. (2020) Niche-Specific Reprogramming of Epigenetic Landscapes Drives Myeloid Cell Diversity in Nonalcoholic Steatohepatitis. Immunity. May 1;S1074- 7613(20)30159-X. doi: 10.1016/j.immuni.2020.04.001.

4. Regulation of macrophage lipid metabolism by LXRs and SREBPs

My work as a graduate student under the direction of Dr. Daniel Steinberg focused on the metabolism of high-density lipoproteins (HDL). Using a dual label approach to simultaneously trace the ApoAI and cholesterol ester components of HDL in vivo in the rat, I discovered that HDL could deliver cholesterol esters to the liver without being taken up as a particle, as is the case for LDL. This established the concept of a pathway for selective uptake of cholesterol esters as the major mechanism for HDL mediated reverse cholesterol transport. Through these studies I established a strong connection to the lipoprotein community that persists to this day. As an independent investigator, I became interested in a subset of nuclear hormone receptors that play key roles in regulation of macrophage lipid metabolism and inflammation that included Peroxisome Proliferator Activated Receptor gamma (PPARγ) and the Liver X Receptors (LXRs). A key finding in this area was our discovery that PPARγ is a negative regulator of macrophage activation (a). This paper propelled substantial subsequent work by many investigators and has been cited more than 4000 times. Prior work that is most highly relevant to this application is based on our discovery that the major endogenous ligand of LXRs in macrophage foam cells is the sterol intermediate desmosterol (b). Unlike selective synthetic LXR agonists, such as GW3965, desmosterol not only activates LXR, but simultaneously represses the SREBP pathway by interacting with SCAP. As a consequence, this single molecule integrates the functions of the LXR and SREBP pathways with respect to cholesterol and fatty acid homeostasis. These findings suggested a concept that is a foundational aspect of the current proposal, i.e., that desmosterol mimetics might overcome the major toxicity of conventional LXR agonists of driving marked hypertriglyceridemia due to activation of SREBP1c. To test this hypothesis, we showed that the sterol-based LXR agonist DMHCA is a desmosterol mimetic and worked with medicinal chemists at CALIBR to develop novel desmosterol-like compounds. We showed that these molecules activated LXR and suppressed SREBP function in macrophages but not in hepatocytes (c), thereby supporting the concept that desmosterol mimetics might provide a pathway to safely target LXRs for therapeutic purposes.

a. Ricote M., Li A.C., Willson T.M., Kelly C.J. and **Glass, C.K.** (1998) The peroxisome proliferator-activated receptor gamma is a negative regulator of macrophage activation. Nature 391:79-82.
b. Spann NJ, Garmire LX, McDonald JG, Myers DS, Milne SB, Shibata N, Reichart D, Fox JN, Shaked I, Heudobler D, Raetz CRH, Wang EW, Kelly SL, Sullards MC, Murphy RC, Merrill AH, Brown HA, Dennis EA, Li AC, Ley K, Tsimikas S, Fahy E, Subramaniam S, Quehenberger O, Russell DW, **Glass CK**. (2012). Regulated accumulation of desmosterol integrates macrophage lipid metabolism and inflammatory responses. Cell 151(1):138-52. PMCID: PMC346491
c. Muse ED, Yu S, Edillor CR, Tao J, Spann NJ, Troutman TD, Seidman JS, Henke A, Roland JT, Ozeki KA, Thompson BM, McDonald JG, Bahadorani J, Tsimikas S, Grossman TR, Tremblay MS, **Glass CK**. (2018) Cell-specific discrimination of desmosterol and desmosterol mimetics confers selective regulation of LXR and SREBP in macrophages. Proc Natl Acad Sci U S A. E4680-E4689 PMCID: PMC5960280.

5. Impact of natural genetic variation on macrophage gene expression

Most of the natural genetic variation that is associated with differences in traits and risk of disease resides in

non-coding regions of the genome. We have been very interested in studying how this variation impacts transcriptional regulatory elements and in parallel have been interested in using natural genetic variation as a perturbation to test mechanistic hypotheses. Collectively, our goal is to use knowledge gained from these studies to better understand the relationship between common forms of genetic variation and disease. We were among the first to directly assess the impact of natural genetic variation on enhancer selection and function (a). Using two genetically diverse inbred strains of mice, we leveraged single nucleotide polymorphisms in binding sites for lineage-determining and signal dependent transcription factors to test the collaborative and hierarchical model for enhancer selection and function described in Section 2, above. We then went on to systematically study the impact of a much greater degree of genetic variation using 5 strains of inbred mice. This enabled us to provide genetic evidence for dozens of transcription factors that interact with lineage determining factors to set up macrophage-specific enhancers. In addition, we discovered a high degree of genetically determined correlation between adjacent enhancers that led to the discovery of what we termed cis-regulatory domains (CRDs) (b). Most recently, we exploited these same 5 inbred lines of mice to define genetic mechanisms that determine the degree of responsiveness of macrophages to the cytokine IL-4 (c). Collectively, this work is highly relevant to our interests in understanding the relationship between natural genetic variation and risk of Alzheimer's disease.

a. Heinz S, Romanoski CE, Benner C, Allison KA, Kaikkonen MU, Orozco LD, **Glass CK.** (2013). Impact of natural genetic variation on enhancer selection and function. Nature 503(7477):487-492. PMC399412.
b. Link VM, Duttke SH, Chun HB, Holtman IR, Westin E, Hoeksema MA, Abe Y, Skola D, Romanoski CE, Tao J, Fonseca G, Troutman TD, Spann N, Strid T, Sakai M, Yu M, Hu R, Fang R, Metzler D, Ren B, **Glass CK**. (2018) Analysis of genetically diverse macrophages reveals local and domain-wide mechanisms that control transcription factor binding and function. Cell. 173(7):1796-1809. PMID: 29779944.
c. Bennett H, Troutman TD, Zhou E, Spann NJ, Link VM, Seidman JS, Nickl CK, Abe Y, Sakai M, Pasillas MP, Marlman JM, Guzman C, Hosseini M, Schnabl B, Glass CK. Discrimination of cell-intrinsic and environment-dependent effects of natural genetic variation on Kupffer cell epigenomes and transcriptomes. Nat Immunol. 2023 24(11):1825-1838. PMID: 37735593; PMCID: PMC10602851.

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