BIOGRAPHICAL SKETCH

NAME: Glass, Christopher K.

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

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

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 in health and disease. A major direction over the past five years has been to define the genome-wide locations and functions of these proteins through the use of 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 gene expression and function that are relevant to a broad range of devastating human disorders for which treatments are not available or are ineffective. One of most important recent efforts has been to define the transcriptomes and regulatory landscapes of human microglia in order to better understand pathogenic mechanisms underlying Alzheimer's Disease.

Selected publications indicating active areas of investigation involving transcriptional control of macrophage gene expression:

1. Ogawa S, Lozach J, Benner C, Pascual G, Tangirala RK, Westin S, Hoffmann A, Subramaniam S, David M, Rosenfeld M, **Glass, CK**. (2005). Molecular determinants of crosstalk between nuclear receptors and toll-like receptors. Cell 122(5):707-721.
2. 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.
3. 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): eaal3222.
4. Nott A*, Holtman IR*, Coufal NG*, Schlachetzki JCM, Yu M, Hu R, Han CZ, Pena M, Xiaoi 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. 2019 Nov 14. pii: eaay0793. doi: 10.1126/science.aay0793.

Ongoing and recently completed projects that I would like to highlight include:

R01 AG056511-04 (MPI: Glass CK, Rosenfeld) 08/01/18 – 03/31/23
NIH The Enhancer Code of AD-A Genetic Approach
In this application, we propose to define the `Enhancer codes of Alzheimer's Disease' to qualitatively advance our understanding of cell autonomous and non-cell autonomous factors that drive pathogenic programs of gene expression. In Specific Aim 1, we will define transcriptomes and enhancer landscapes of nuclei isolated from neurons and microglia derived from sporadic and genetic AD brains and brains from age and sex-matched controls. In Specific Aim 2, we will validate and explain AD-specific enhancer codes of neurons by direct reprogramming of fibroblasts from sporadic and genetic AD patients and age/sex-matched control subjects. In Specific aim 3, we will define cell autonomous AD-specific enhancer codes of microglia obtained by reprograming of iPSCs and monocytes from control and AD subjects. In Specific Aim 4, we will define consequences of neuron-microglia interactions on the transcriptomes and epigenomes of each cell type.
Role: PI

5R01 AG057706-04 (MPI: Rosenfeld, Gage, Suh, Glass CK) 09/30/17 – 05/31/22
NIH/NIA - Combinatorial Actions of Genetic Variants and Gender Bias of Alzheimer's Disease
The collaborative studies performed under the support of this grant will exploit the power of contemporary genomics assays to define alterations in regulatory elements in neurons associated with sex specific differences in gene expression and Alzheimer's disease. Follow-up gene editing approaches in control or patient-derived iPS cells differentiated to specific neuronal cell types will be used to assess the transcriptional phenotypes and functional behaviors of neurons harboring different combinations of risk alleles. The Glass laboratory will primarily contribute to genomic studies of neuronally-derived nuclei from AD patients and corresponding genomic studies of reprogrammed neurons.
Role: PI

R01 DK091183-31 (PI: Glass, CK) 04/01/91 – 01/31/25
NIH/NIDDK - Transcriptional Co-Regulators and Macrophage Gene Expression
Specific Aim 1 is to define liver environmental factors and downstream transcription factors required to establish Kupffer cell identity. Specific Aim 2 is to define the network of collaborative transcription factors required for establishing the Kupffer cell enhancer landscape and quantify cell autonomous and non-cell autonomous effects of natural genetic variation. Specific Aim 3 is to define gene by environment interactions that regulate myeloid cell phenotypes in NASH. Specific Aim 4 is to define the transcriptomes and epigenetic landscapes of myeloid populations in the human liver.
Role: PI

P01 HL147835-01A1 (PI: Glass CK) 09/01/20 – 07/31/25
NIH/HL - A Cardiovascular-NASH disease nexus: Common Mechanisms and Treatments?
The overall goal of this PPG is to determine the relationship of liver fat and fibrosis to cardiovascular disease (CVD) risk in human subjects and to identify actionable molecular mechanisms connecting non-alcoholic steatohepatitis (NASH) to increased risk of CVD. The overall hypothesis of our PPG is that interventions targeting Liver X receptors (LXRs) in macrophages, the farnesyl X receptor (FXR) in the gut, and oxidation specific epitopes (OSEs) in the liver and artery wall will reveal common mechanisms that contribute to the clinical association between NASH and CVD.
Role: PI

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2018-present 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
1986-1989 Fellowship in Endocrinology, Department of Medicine, University of California, San Diego
1985-1986 Residency in Internal Medicine, Brigham and Women's Hospital, Harvard Medical School
1984-1985 Internship in Internal Medicine, Brigham and Women's Hospital, Harvard Medical School

Other Experience and Professional Membership

2015- NIDDK RC2 Editorial Board Member
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- Associate Director, UC San Diego Medical Scientist Training Program

Selected Honors

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
2009 Adjunct Professor, Salk Institute for Biological Studies
2008 Honorary Doctorate of Medicine, University of Linköping, Sweden
2006 Association of American Physicians
2002 Stanford Reynolds Scholar
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. Transcriptional control of macrophage development and function

A major focus of the lab is to define transcriptional mechanisms that control macrophage development and function. 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. This model 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 used natural genetic variation as an '*in vivo* mutagenesis screen' to directly validate this model with respect to both collaborative binding of lineage determining transcription factors and their requirement for subsequent binding of NF-kB. We extended these studies to demonstrate how different tissue environments drive the selection and function of enhancers in different tissue environments.

1. 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.
2. 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. PMC3994126.
3. 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.
4. Link VM, Duttke SH, Chun HB, Holtman IR, Westin E, Hoeksema MA, Abe Y, Skola D, Romanoski CE, Tao J, Fonseca GJ, Troutman TD, Spann NJ, 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. PMC6003872.

2. Macrophage activation and chronic inflammatory diseases

Our demonstration that PPARγ is a negative regulator of macrophage activation led to a broad range of studies of roles of members of the nuclear receptor family of ligand dependent transcription factors in the control of inflammatory responses. These studies led to the demonstration of anti-inflammatory and homeostatic roles of PPARγ and liver X receptors (LXRs) in atherosclerosis and diabetes, and anti- inflammatory roles of Nurr1 and estrogen receptor β in microglia in animal models of Parkinson's disease and multiple sclerosis. These studies have evolved to a broad analysis of mechanisms that control cell-autonomous responses of macrophages and microglia to pathogenic environments, exemplified by our discovery that mutant Huntingtin protein potentiates microglia activation by increasing the expression of PU.1.

1. Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, Gage FH, **Glass CK**. (2009). A Nurr1/CoREST transrepression pathway attenuates neurotoxic inflammation in activated microglia and astrocytes. Cell 137(1):47-59. PMC2754279.
2. Saijo K, Collier JG, Li AC, Katzenellenbogen JA, **Glass CK.** (2011). An ERβ-CtBP transrepression pathway negatively regulates microglia-mediated inflammation. Cell 145(4):584-95. PMC3433492
3. Crotti A, Benner C, Kerman BE, Gosselin D, Lagier-Tourenne C, Zuccato C, Cattaneo E, Gage FH, Cleveland DW, **Glass CK**. (2014). Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat Neurosci 17(4):513-521. PMC4113004.
4. Oishi Y, Spann NJ, Link VM, Muse ED, Strid T, Edillor C, Kolar MJ, Matsuzaka T, Hayakawa S, Tao J, Kaikkonen MU, Carlin AF, Lam MT, Manabe I, Shimano H, Saghatelian A, **Glass CK**. (2017). SREBP1 contributes to resolution of pro-inflammatory TLR4 signaling by reprogramming fatty acid metabolism. Cell Metab 25(2):412-427. PMC5568699.

Complete List of Published Work in MyBibliography (>300 publications):
https://www.ncbi.nlm.nih.gov/pubmed/?term=glass+ck