BIOGRAPHICAL SKETCH

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NAME: Wyss-Coray, Tony

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POSITION TITLE: Professor of Neurology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Bern, Switzerland	MS	1989	Microbiology
University of Bern, Switzerland	PhD	1992	Immunology
The Scripps Research Institute, San Diego, CA	Postdoctoral	1995	Neurobiology

A. Personal Statement

Following training in cellular immunology during my graduate studies I have been working in the field of neurobiology and neurodegeneration for more than 20 years. Using cellular and mouse models of aging and disease, my lab is focusing on understanding how immune responses and changes in the systemic environment impact brain health and function. Over the past few years the lab has been particularly intrigued by the observation that brain aging can be altered by changes in the systemic environment and we have shown that blood-derived factors are sufficient to modulate brain physiology at the molecular, cellular, and functional level. We have developed focused proteomic tools to measure thousands of secreted signaling proteins we believe are critical regulators (and indicators) of physiological and pathophysiological processes throughout the body. We are particularly interested in identifying proteins in the systemic circulation which may have a role in neurodegeneration and Alzheimer's disease. In order to pinpoint the possible origin of circulatory proteins we embarked on organism-wide transcriptomic studies in the mouse, analyzing all major tissues and cell types using single cell RNA sequencing. These studies, which were initiated in my lab, led to an effort involving >100 scientists at Stanford University with support from the Chan Zuckerberg Biohub and led to the *Tabula Muris* single cell atlas and the *Tabula Muris Senis* single cell aging atlas.

B. Positions, Scientific Appointments and Honors

Positions and Employment

1996 – 1997 Adjunct Instructor, Department of Neurology, University of California San Francisco
1996 – 1999 Staff Research Scientist, Gladstone Institute of Neurological Disease
1997 – 2002 Assistant Adjunct Professor, Department of Neurology, University of California San Francisco
1999 – 2002 Staff Research Investigator, Gladstone Institute of Neurological Disease
2002 – 2005 Assistant Professor, Research, Department of Neurology and Neurosciences, Stanford University
2002 – 2007 Research Health Science Specialist, GRECC, Veterans Affairs Palo Alto Health Care System
2005 – 2011 Associate Professor, Research, Department of Neurology and Neurosciences, Stanford University
2007 – 2011 Research Career Scientist, Veterans Affairs Palo Alto Health Care System
2011 – 2018 Associate Director, Center for Tissue Regeneration Repair and Restoration, Veterans Affairs Palo Alto Health Care System

2011 – present Professor, University Tenure Line, Department of Neurology and Neurosciences, Stanford University
2011 – 2020 Senior Research Career Scientist, Veterans Affairs Palo Alto Health Care System
2015 – 2020 Co-Director, NIH Alzheimer's Disease Research Center, Stanford University
2018 – present D. H. Chen Distinguished Professorship, Stanford University

Professional Service

2006 – 2014 BrightFocus Foundation, Alzheimer's Disease Research (annual meeting)
2007 – 2012 F03A Fellowship Study Section, NIH-NINDS, regular member
2009 U01 grant review panel, NIH-NIA
2010 P01 ZAG1 grant review panel, NIA special emphasis panel
2010 – 2015 Merit Review Panel, Veterans Administration RR&D grant review panel, ad hoc
2011 Scientific Review Board, Sonderforschungsbund TRR 43, Deutsche Forschungsgesellschaft
2013 – 2019 National Institutes of Health, Regular member CDIN Study Section
2014 – present External reviewer, Division of Aging Biology, NIH-NIA

Honors

1993 – 1996 Fellowship for Junior and Advanced Scientists, Swiss National Science Foundation
2005 – 2007 Zenith Fellow, Alzheimer's Association
2005 – 2009 Distinguished Scholar, John Douglas French Alzheimer's Foundation
2009 Visiting Sabbatical sponsored by the Japan Foundation for Aging and Health
2009 SciCafe Lecture Award, Nature Biotechnology and Nature Medicine
2012 Senior Research Career Scientist, Department of Veterans Affairs
2013 NIH Director's Transformative Research Award
2013 – 2015 Visiting Fellow of NeuroCure, Cluster of Excellence, Berlin, Germany
2015 Speaker and panelist, World Economic Forum, Davos, Switzerland
2015 Speaker at Global TED, Royal Institution, London
2015 Glenn Award for Research in Biological Mechanisms of Aging
2015 NIH Director's Pioneer Award
2017 NOMIS Foundation, Distinguished Scientist Award
2017 Speaker at Tencent WE Summit, Beijing 2017
2018 TIME Magazine "The Health Care 50" most influential people transforming healthcare in 2018
2018 D. H. Chen Distinguished Professorship, Stanford University

C. Contribution to Science

1. Immunity in neurodegeneration. Our lab pioneered the study of immune regulators in mouse models of Alzheimer's disease and we were the first to genetically regulate cytokines, the complement cascade, or innate immune sensors in APP transgenic or aged mice. The transforming growth factor (TGF)-β signaling pathway is one of the key modulators of immunity and we discovered TGF-β1 promotes cerebral amyloid angiopathy while activating microglial phagocytosis and clearance of Aβ in the brain parenchyma of APP transgenic mice. We discovered more recently that VCAM1, a key endothelial cell adhesion molecule necessary for leukocyte binding to inflamed blood vessels and infiltration into tissues is upregulated with aging and promotes neuroinflammation and cognitive dysfunction in mice. In patients with Alzheimer's disease we find accumulation of clonally expanded cytotoxic CD8 T cells in the cerebrospinal fluid and brain parenchyma and some of these cells are specific for viral antigens. These studies support a role for innate and adaptive immune functions in brain aging, neurodegeneration, and Alzheimer's disease.
   a) Wyss-Coray T*, Lin C, Yan F, Yu GQ, Rohde M, McConlogue L, Masliah E and Mucke L. (2001) TGF-β1 promotes microglial amyloid-β clearance and reduces plaque burden in transgenic mice. *Nature Med.* 7:612-18. [PMC11329064] (* corresponding author)
   b) Mathur V, Burai R, Vest RT, Bonanno LN, Lehallier B, Zardeneta ME, Mistry KN, Do D, Marsh SE, Abud EM, Blurton-Jones M, Li L, Lashuel HA, Wyss-Coray T. (2017) Activation of the STING-dependent type I interferon response reduces microglial reactivity and neuroinflammation. *Neuron* 96:1290–1302. [PMC5806703]
   c) Yousef H, Czupallla CJ, Lee D, Chen MB, Burke AN, Zera KA, Zandstra J, Berber E, Lehallier B, Mathur V, Nair RV, Bonanno LN, Yang AC, Peterson T, Hadeiba H, Merkel T, Körbelin J, Schwaninger

M, Buckwalter MS, Quake SR, Butcher EC, Wyss-Coray T. (2019) Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1. *Nature Med.* 25:988-1000 .[PMC6642642]

d) Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, Chen K, Lehallier B, Channappa D, De Los Santos MB, McBride A, Pluvinage J, Elahi F, Tam GK, Kim Y, Greicius M, Wagner AD, Aigner L, Galasko DR, Davis MM Wyss-Coray T. (2020) Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. *Nature* 577: 399-404. [PMC7445078]

2. Adult neurogenesis as a sensor and modulator of the local and systemic environment. Neurons and glial cells are constantly produced in small numbers in the adult hippocampus contributing to plasticity and certain aspects of memory formation. In response to environmental stimuli these numbers can increase or decrease significantly. We are particularly interested in how cell extrinsic, systemic factors regulate neurogenesis and, in turn, how neural stem and progenitor cells regulate their cellular environment through the release of signaling proteins. We discovered that TGF-β1 is a potent inhibitor of neural stem cell proliferation but at the same time promotes the migration, maturation, and survival of newly born neurons in the aging mouse brain. Proteomic profiling of the neural progenitor cell secretome identified these cells as a major source of regulatory proteins including VEGF.
   a) Buckwalter MS, Yamane M, Coleman BS, Ormerod BK, Chin JT, Palmer T, Wyss-Coray T. (2006) Chronically increased TGF-β1 strongly inhibits hippocampal neurogenesis in aged mice. *Am. J. Pathol.* 169:154–164. [PMC1698757]
   b) Mosher KI, Andres RH, Fukuhara T, Bieri G, Hasegawa-Moriyama M, He Y, Guzman R and Wyss-Coray T. (2012). Neural progenitor cells regulate microglia functions and activity. *Nature Neurosci.* 15:1485-1487. [PMC3495979]
   c) He Y, Zhang H, Yung A, Villeda SA, Jaeger PA, Olayiwola O, Fainberg N, Wyss-Coray T. (2014) ALK5-dependent TGF-β signaling is a major determinant of late stage adult neurogenesis. *Nature Neurosci.* 17:943–52. [PMC4096284]
   d) Kirby ED, Kuwahara AA, Messer RL, Wyss-Coray T. (2015) Adult hippocampal neural stem and progenitor cells regulate the neurogenic niche by secreting VEGF. *Proc. Natl. Acad. Sci. USA.* 112:4128–33. [PMC4386397]

3. Proteostasis and neurodegeneration. Because we speculated that autophagy is part of an intracellular "immune response" that helps purge aging cells of unwanted protein aggregates or organelles, we explored the role of this pathway in Alzheimer's disease and published the first genetic manipulation of autophagy in a neurodegenerative disease mouse model. This idea of autophagy being a protective response recently gained traction with the discovery (by others) of a link between innate immune receptors, autophagy and inflammation. As well, efficient phagocytosis is key to maintain brain homeostasis, particularly in microglial cells. We used CRISPR screens to identify a novel regulator of phagocytosis, CD22, only in aged but not young microglia and we re-discovered the presence of lipid droplets in aged microglia and microglia in models of neurodegenerative disease, a finding made originally by Alzheimer and Fisher, but largely forgotten for the past 100 years. We find these lipid droplet-accumulating microglia are highly inflammatory, defective in phagocytosis and possibly involved in neurodegeneration, not only in neurons but, maybe more importantly, in microglia, the main immune cell in the brain.
   a) Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, Wyss-Coray T. (2008) The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice. *J. Clin. Invest.* 118:2190–2199. [PMC2391284]
   b) Lucin KM, O'Brien C, Bieri G, Czirr E, Mosher KI, Mastroeni DF, Rogers J, Spencer B, Masliah E and Wyss-Coray T. (2013). Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. *Neuron*, 79:873–886. [PMC3779465]
   c) Pluvinage JV, Haney MS, Smith BAH, Sun J, Iram T, Bonanno L, Li L, Lee DP, Morgens DW, Yang AC, Shuken SR, Gate D, Scott M, Khatri P, Luo J, Bertozzi CR, Bassik MC, Wyss-Coray T. (2019) CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. *Nature* 568:187–192. [PMC6574119]
   d) Marschallinger J, Iram T, Zardeneta ME, Lee SE, Lehallier B, Haney MS, Pluvinage JV, Mathur V, Hahn O, Morgens DW, Kim J, Tevini J, Felder TK, Wolinski H, Bertozzi CR, Bassik MC, Aigner L,

Wyss-Coray T. (2020) Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat Neurosci* 23:194-208. [PMC7595134]

4. The systemic environment in brain aging and neurodegeneration. To understand brain aging and neurodegeneration at an organismal level and to explore the interactions between the immune system and CNS we employed and developed focused proteomic screens based on the idea that changes in secreted factors that communicate between cells (the "Communicome"), could inform us about the physiological and pathophysiological state of the organism and provide potential new mechanistic information. Using this approach, we described plasma signaling proteins that correlate with brain aging and AD and may have a role in neurodegeneration. Taking this concept further, we discovered that systemic blood-derived factors not only correlate with brain aging but are sufficient to modulate microglial activation, adult neurogenesis, synaptic plasticity, and behavior in mice and that young plasma has beneficial effects in a mouse model of AD. To understand where plasma aging factors are synthesized we have embarked on organism-wide transcriptomic studies in the mouse. To gain better insight into proteomic changes with age in blood we recently characterized age-related changes of ~3,000 plasma proteins in more than 4,000 healthy people and discovered multiple prominent "waves" of changes in relative levels of these proteins. Together, these findings put us closer to discover key proteins and their cellular origins involved in aging and rejuvenation.
   a) Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Després S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA and Wyss-Coray T. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 477:90-4. [PMC3170097]
   b) Schaum N, Karkanias J, Neff NF, May AP, Quake S*, Wyss-Coray T*, Darmanis S*, for the Tabula Muris Consortium (2018) Single-cell transcriptomics of 20 mouse organs creates a *Tabula Muris*. *Nature* 562:367–372. (* corresponding authors) [PMC6598694]
   c) Lehallier B, Gate D, Schaum N, Nanasi T, Lee SE, Yousef H, Moran Losada P, Berdnik D, Keller A, Verghese J, Sathyan S, Franceschi C, Milman S, Barzilai N, Wyss-Coray T. (2019) Undulating changes in human plasma proteome profiles across the lifespan. *Nature Med.* 25: 1843-1850. [PMC7062043]
   d) Schaum N, Lehallier B, Hahn O, Pálovics R, Hosseinzadeh S, Lee SE, Sit R, Lee DP, Losada PM, Zardeneta ME, Fehlmann T, Webber J, McGeever A, Calcuttawala K, Zhang H, Berdnik D, Mathur, V, Tan W, Zee A, Tan, M, The Tabula Muris Consortium, Pisco AO, Karkanias J, Neff NF, Keller A, Darmanis S, Quake SR, Wyss-Coray T. (2020) Aging hallmarks exhibit organ-specific temporal signatures. *Nature* 583:596–602.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=wyss-coray

D. Research Support

Ongoing Research Support

R01 AG059694 MPI (Wyss-Coray/Luo) 08/01/18 – 04/30/23
NIH / NIA
Targeting Cerebrovascular TGF Signaling in Alzheimer's Disease
The research will follow up on studies from our lab showing deficiencies in CNS TGF-beta signaling and aims to understand the role of endothelial cells in abnormal TGF-beta signaling.

RF1AG064897 (Wyss-Coray) 08/01/19 – 03/31/24
NIH / NIA
Targeting CD22 to Restore Brain Homeostasis in Alzheimer's Disease
This project aims to understand the mechanisms of microglial dysfunction in the aging brain and to target these mechanisms to treat or prevent Alzheimer's disease.

RF1AG064928 (Wyss-Coray) 08/015/19 – 04/30/24
NIH / NIA
Microglial Lipid Droplets in Alzheimer's Disease

The major goal of the project is to characterize the mechanisms in which lipid droplets containing microglia are detrimental to aging and the AD brain.

P30AG066515 (Henderson) 06/01/20 – 04/30/25
NIH / NIA
Stanford Alzheimer's Disease Research Center
The major goal of this project is to establish a national center for Alzheimer's disease research.
Role: Admin Core Co-Leader and Project Leader Bioinformatics Core

Simons Foundation (Wyss-Coray) 11/01/20 – 10/31/23
Principles of blood-brain communication in aging and rejuvenation
The purpose of the proposed study is to elucidate the cellular and molecular mechanisms underlying the rejuvenating effects of BBB-permeable and impermeable systemic factors on the aged brain.

Cure Alzheimer's Fund (Wyss-Coray) 02/01/21 – 01/31/22
Principles of blood-brain communication in aging and rejuvenation
The purpose of the study is to elucidate the cellular and molecular mechanisms underlying the rejuvenating effects of BBB-permeable and impermeable systemic factors on the aged brain.

R01AG072255
NIH/NIA (Wyss-Coray) 04/1/21 – 03/31/26
Molecular signal of parabiosis
Here we propose to identify molecular "rejuvenation" signatures across disparate organs and cells with the goal to uncover novel therapeutic targets to slow aging processes and increase healthspan.

Milky Way Foundation (Wyss-Coray) 04/1/21 – 03/31/24
Multi-omic clocks of biological aging and rates of aging
The purpose of this study is to develop tissue, organ, and cell level molecular clocks to record the rate of aging and, ultimately, relate them to functional outcomes.