BIOGRAPHICAL SKETCH

NAME: Toren Finkel

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

POSITION TITLE: Director of Aging Institute, G. Nicholas Beckwith III and Dorothy B. Beckwith Endowed Chair of Translational Medicine, University of Pittsburgh/UPMC

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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Maryland, College Park, MD.	B.S.	05/1979	Physics
Harvard University, School of Arts and Sciences, Cambridge, MA.	Ph.D.	06/1986	Biophysics
Harvard Medical School, Boston, MA.	M.D.	06/1986	Medicine

A. Personal Statement

For over twenty years, my research group has focused on a range of issues involved in mitochondrial function, cellular metabolism, oxidative stress, and aging. Due to the wide span of our biological interests, my lab has developed expertise in mitochondrial assays, cell and molecular biology approaches, and the generation of mouse models along with whole animal physiological measurements. Throughout the years, we have worked towards a long-term goal to uncover the molecular basis of mammalian aging and age-related diseases through the study of a variety of different cellular pathways including stem cell self-renewal, reactive oxygen species, sirtuins, autophagy, mTOR signaling and mitochondrial metabolism. A particular focus in the last several years has been the role that a decline in autophagy and mitophagy might phenocopy aging.

B. Positions and Selected Honors

1986 - 1989	Resident, Massachusetts General Hospital
1989 - 1992	Fellow, Cardiology, Johns Hopkins Medical School
1992 - 1998	Investigator, Cardiology Branch, NIH
1998 - 1999	Senior Investigator (tenured), Chief, Cardiology Branch, NIH
1998 - Present	Adjunct Associate Professor of Medicine, Johns Hopkins School of Medicine
1999 - 2001	Chief, Laboratory of Molecular Biology, NHLBI, NIH
2001 - 2007	Chief, Cardiology Branch, NHLBI, NIH
2007 - 2010	Chief, Translational Medicine Branch, NHLBI, NIH
2010 – 2017	Chief, Center for Molecular Medicine, NHLBI, NIH
2017-Present	Professor of Cardiology and Director, Aging Institute, Univ. of Pittsburgh/UPMC

NHLBI Promotions and Tenure Committee	2001 - 2014
Institutional Review Board (IRB) NHLBI	2002 - 2003

American Heart Association Basic Science Leadership Council	2003 - 2005
American Society of Clinical Research - Inducted	2002
Ellison Medical Foundation Senior Scholar in Aging Award	2006 - 2010
Association of American Physicians - Inducted	2009
Fellow, American Association for the Advancement of Science-Inducted	2013
Coordinator, Leducq Transatlantic Network	2014 - 2019
Board of Reviewing Editors, Science Magazine	2015 - present
Harvard Medical School Alumni Council	2017-present

C. Contribution to Science

1. My laboratory has studied the role autophagy plays in cardiovascular biology and the relationship between a decline in autophagy/mitophagy and phenotypic aging. This work involves the first *in vivo* models to disrupt macroautophagy within specific cellular compartments in the vasculature. These studies have elucidated how autophagy contributes to vascular homeostasis, and how a decline in autophagic flux might accelerate vascular aging. We have also generated the first molecular tools to measure mitophagy in an *in vivo* context.

   a. Torisu, T., Torisu, K., lee, I.H., Liu, J., Malide, D., Combs, C.A., Komatsu, M., Cao, L., and Finkel, T. (2013). Autophagy regulates endothelial cell processing, maturation and secretion of von Willebrand factor. ***Nature Medicine**,* 19:1281-1287.

   b. Sun, N., Yun, J., Liu, J., Malide, D., Liu, C., Rovira, I.I., Holmstrom, K.M., Fergusson, M.M., Yoo, Y.H., Combs, C.A., and Finkel, T. (2015). Measuring in vivo mitophagy. ***Molecular Cell*,** 60: 685-696.

   c. Sun N, Malide D, Liu J, Rovira, II, Combs CA and Finkel T. (2017). A fluorescence-based imaging method to measure in vitro and in vivo mitophagy using mt-Keima. ***Nat Protoc***., 12:1576-1587.

   d. Nussenzweig SC, Verma S, Finkel T (2015) The role of autophagy in vascular biology. **Circulation Research** 116: 480-8

2. My laboratory provided the first clear demonstration that reactive oxygen species (ROS) can act as intracellular signaling molecules. Prior to this observation, ROS were viewed solely as being random and damaging intracellular byproducts. Our observations suggested that ROS in certain situations can be purposely produced and have specific cellular (protein) targets. We were able to show, along with our collaborators, that members of the Ras superfamily of small GTPases regulate ROS production. Over the ensuing years, we have made numerous observations that demonstrated a role for the regulated production of ROS in diverse situations including cell death, cellular senescence and aging.

   a. Sundaresan M., Yu Z.-Y., Ferrans V.J., Irani K., and Finkel T. (1995). Requirement for generation of H_2O_2 for platelet-derived growth factor signal transduction. ***Science*** 270:296-299.

   b. Irani K., Xia Y., Zweir J.L., Sollot S., Rosolowski L., Feason E.R., Sundaresan M., Finkel T., and Goldschmidt-Clermont P.J. (1997). Superoxide mediates mitogenic signaling in Ras-transformed fibroblasts. ***Science*** 275:1649-1652.

   c. Johnson T.M., Yu Z.Y., Ferrans V.J., Lowenstein R.A., and Finkel T. (1996). Reactive oxygen species are downstream mediators of p53-dependent apoptosis. ***Proc. Natl. Acad. Sci. U.S.A***. 93:11848-11852

d. Nemoto S. and Finkel T. (2002). Redox regulation of forkhead proteins through a p66shc-dependent signaling pathway. ***Science*** 295:2450-2452.

3. We have also made contributions to understanding the pathways regulating mammalian aging. This includes dissection of the role of the sirtuin family of enzymes. We were able to show how Sirt1 is regulated by nutrient availability. We also demonstrated a role for Sirt1 in autophagy and for Sirt3 in mitochondrial metabolism. In additions to the sirtuins, we have described other pathways that appear to modulate the rate of aging including Wnt signaling and the mTOR pathway.

   a. Nemoto S., Fergusson M., and Finkel T. (2004). Nutritional stress links forkhead proteins to SIRT1. ***Science*** 306:2105-2108.

   b. Lee I.H., Cao L., Mostoslavsky R., Lombard D.B., Liu J., Bruns N., Tsokos M., Alt F.W., and Finkel T. (2008). A role for the NAD dependent deacetylase Sirt1 in the regulation of autophagy. ***Proc. Natl. Acad. Sci. U.S.A.***105:3374-3379.

   c. Liu H., Fergusson M.M., Castilho R.M., Liu J., Cao L., Chen J., Malide D., Rovira I.I., Schimel D., Kuo C.J., Gutkind J.S., Hwang P.M., and Finkel T. (2007). Augmented Wnt signaling in a mammalian model of accelerated aging. ***Science*** 317:803-6.

   d. Wu, J.J., Liu, J., Chen, E.B., Wang, J.J., Cao, L., Narayan, N., Fergusson, M.M., Rovira, I.I., Allen, M., Springer, D.A., Lago, C.U., Zhang, S., Dubosi, W., Ward, T., DeCabo, R., Gavrilova, O., Mock, B., and Finkel, T. (2013). Increased mammalian lifespan and protection against the functional decline of a subset of age-related parameters following genetic reduction of mTOR expression. ***Cell Reports***, 4: 913-920.

4. My lab has also made contributions to understanding mitochondrial function in the context of stem cells, growth, and metabolism. We were among the first to study the role of altered metabolism and redox stress in the context of self-renewing stem cells. We, along with our collaborators, have pursued an understanding of how metabolism is integrated into various aspects of cell cycle regulation. We have also sought to analyze the role of mitochondrial calcium entry in bioenergetics and cell death, including the generation of the first mouse model lacking the mitochondrial calcium uniporter.

   a. Liu J., Cao L., Chen J., Song S., Lee I.H., Quijano C., Liu H., Keyvanfar K., Chen H., Cao L.-Y., Ahn B.-H., Kumar N.G., Rovira I.I., Xu X.-L., van Lohuizen M., Motoyama N., Deng C.-X., and Finkel T. (2009). Bmi1 regulates mitochondrial function and the DNA damage response pathway. ***Nature*** 459:387-392.

   b. Lee I.H., Kawai Y., Fergusson M.M., Rovira I.I., Bishop A.J.R., Motoyama N., Cao L., and Finkel T. (2012). Atg7 modulates p53 activity to regulate cell cycle and survival during metabolic stress. ***Science,*** 336:225-228

   c. Pan, X., Liu J., Nguyen T., Liu C., Sun J., Teng Y., Fergusson M.M., Rovira, I.I., Allen M., Springer D.A., Aponte A.M., Gucek M., Balaban R.S., Murphy E., and Finkel, T. (2013). The physiological role of mitochondrial calcium revealed by mice lacking the mitochondrial calcium uniporter. ***Nat Cell Biol***. 15:1464-72.

   d. Sukumar M, Liu J, Mehta GU, Patel SJ, Roychoudhuri R, Crompton JG, Klebanoff CA, Ji Y, Li P, Yu Z, Whitehill GD, Clever D, Eil RL, Palmer DC, Mitra S, Rao M, Keyvanfar K, Schrump DS, Wang E, Marincola FM et al. (2016) Mitochondrial Membrane Potential Identifies Cells with Enhanced Stemness for Cellular Therapy. **Cell Metabolism** 23: 63-76.

5. My lab has also made contributions to our understanding of diverse topics in the field of vascular biology. This includes one of the first descriptions in human patients on using circulating endothelial progenitor cells (EPCs) to assess vascular risk. We have also studied processes as varied as novel approaches for treating endothelial-derived tumors, assessing the role of endothelial cells in anthrax toxicity, and mechanisms underlying alterations in vascular responses in patients.

   a. Hill J.M., Zalos G.,Halcox J.P.J., Schenke W.H., Walclawiw M.A., Quyyumi A.A., and Finkel T. (2003). Circulating Endothelial Progenitor Cells, Vascular Function, and Cardiovascular Risk. ***New England J. Med***. 348:593-600.

   b. Khakoo A.Y., Pati S., Anderson S.A., Reid W., Elshal M.F., Rovira I.I., Nguyen A.T., Malide D., Combs C.A., Hall G., Zhang J., Raffeld M., Rogers T.B., Stetler-Stevenson W., Frank J.A., Reitz M., and Finkel T. (2006). Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma**. *J. Exp. Med***. 203:1235-1247.

   c. Liu, S., Zhang, Y., Moayeri, M., Liu, J., Crown, D., Fattah, R., Wein, A.N., Finkel, T., and Leppla, S.H. (2013). Cellular targets responsible for anthrax toxin-induced lethality. ***Nature***, 501, 63-68.

   d. Xiong J, Kawagashi H, Yan Y, Liu J, Wells Q, Edmunds LR, Fergusson MM, Yu ZX, Rovira II, Brittain E, Wolfgang MJ, Jurczack MJ, Fessel JP and Finkel T (2018) A metabolic basis for endothelial-to-mesenchymal transition. ***Molecular Cell*** 69: 689-698.

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Finkel+T

D. Research Support

Ongoing

NIH Intramural Funds	1992 – 2017
Ellison Senior Scholar Award in Aging	2006 – 2010
Leducq Foundation Transatlantic Network (PI)	2014 – 2019
R01HL142663 (PI)	2018-2022
R01HL142589 (PI-pending)	2018-2023
Pittsburgh Older Americans Independence Center	2018-2020