BIOGRAPHICAL SKETCH

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NAME: Melov, Simon L.

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

POSITION TITLE: Professor, Director of Single Cell Core & Co-Director of Phenotyping Core

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 N.S.W., Sydney, Australia	B.S. (2i)	06/1985	Human Genetics
University of London, U.K.	Ph.D.	06/1993	Biochemistry

A. Personal Statement

I have a long-standing interest in the functional decline in aging, coupled with expertise in pre-clinical phenotyping, and exploring gene regulation in multiple model systems of aging. I have investigated physiological decline with regards to different organ systems, species, and cell types, using a battery of tools including; gene expression, 'omics' techniques, cell biology, and functional measures. I have extensively worked with various mouse models of aging and age-related disease for more than 20 years. Included in the techniques routinely used by my lab, are multi-level mixed modeling analysis of phenotypes of aging, as well as a variety of high dimensionality techniques appropriate for analyzing large data sets of diverse origins. Over the last few years, I also founded and have run multiple cores designed to help develop and drive research at the Buck Institute; the Mouse Phenotyping Core, and the Single Cell Core. In March of 2018, Sam Altman from Ycombinator came to the Buck Institute and gave a seminar requesting "best ideas for startups focused on aging". I responded to the call by initiating conversations with my long-standing collaborator Gordon Lithgow, and fellow faculty member Mark Lucanic, about forming a company focused on developing therapeutics for aging. We applied to Ycombinator with our idea for an "aging startup", and were successful in obtaining YC funding ($1M) to found Gerostate Alpha. We were also successful in raising additional VC capital to further our company goals. We have spent the last 18 months developing and fine-tuning workflows to pioneer a platform which can discover new targets of aging biology tractable to pharmaceutical interventions. In GSA, I apply my knowledge of a broad variety of methodologies and appropriate statistical and analytical techniques required for deep phenotyping on aging mice or mouse models of neurological disease. I highlight a few such collaborations illustrating my expertise in geroscience:

H index on publons: 50

Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. (2019) From Discoveries in ageing research to therapeutics for healthy ageing. ***Nature***, Jul; 571(7764):183-192. doi: 10.1038/s41586-019-1365-2. Epub 2019 Jul 10. PMID: 31292558

Zykovich A., Hubbard A., Flynn J. M., Tarnopolsky M., Fraga M. F., Kerksick C., Ogborn D., MacNeil L., Mooney S.D., Melov S. (2014) Genome-wide DNA methylation changes with age in disease-free human skeletal muscle. ***Aging Cell*** 13(2), 360-366. PMCID: PMC3954952

B. Positions and Honors

Positions and Employment

1992-1994 Post-doctoral Associate, Institute for Behavioral Genetics, University of Colorado, Boulder, CO.
1994-1995 Post-doctoral Associate, Dept. Genetics & Molecular Medicine, Emory University, Atlanta, GA.
1995-1997 Associate, Center for Molecular Medicine, Emory University, Atlanta, Georgia, USA
1997-1999 Research Assistant Professor, Center for Molecular Medicine, Emory University, Atlanta, GA.
1999-2003 Assistant Professor, Buck Institute for Research on Aging, Novato, Ca, USA.

2002-2015 Director, Genomics Core, Buck Institute for Research on Aging, Novato, Ca, USA.
2003-2014 Associate Professor, Buck Institute for Age Research, Novato, Ca, USA.
2014-Present Professor, Buck Institute for Research on Aging, Novato, Ca, USA
2011-2017 Director of Phenotyping Core, Buck Institute for Research on Aging, Ca, USA.
2017-Present Co-Director, Phenotyping Core, Buck Institute for Research on Aging, Novato, Ca, USA
2014-Present Adjunct Professor, USC School of Gerontology, Los Angeles, Ca, USA
2017-Present Director, Single Cell Genomics Core

Other Experience and Professional Memberships

1999 Chair & Organizer, First GRC workshop on "Oxidative Stress & Disease"
2002 Founding Chair & Organizer, Inaugural GRC on "Oxidative Stress & Disease"
2002 Co-Founding Editor of the Journal "Aging Cell"
2002-2006 Reviews Editor for the journal "Aging Cell"
2008-2013 Academic Editor, PLoSONE
2009-Present Editorial Board, "Aging"
1999-Present AdHoc member for more than 30 study sections for multiple NIH institutes.
2018 Scientific Director, Buck Institute Symposia "Celebrating 30 years of research in the genetics of aging"

Honors

2001 Senior Scholar Award in Aging, Ellison Medical Foundation
2007 Glenn Award for Research in Biological Mechanisms of Aging
2014 2nd Glenn Award for Research in Biological Mechanisms of Aging

C. Contribution to Science

1. Gene expression and systems biology of aging. I have fostered many collaborations throughout my career, most of which are directly related to functional domains of aging. Amongst this work is combining disparate approaches to better understand degenerative changes with age in diverse model systems. This includes stem cell approaches, the nematode *C. elegans*, *drosophila*, and mouse models of Alzheimer's disease.

1. Puglielli, L., Friedlich, A.L., Setchell, K.D.R., Nagano, S., Opazo, C., Cherny, R.A., Barnham, K.J., Wade, J.D., Melov, S., Kovacs, D.M., et al. (2005). Alzheimer disease beta-amyloid activity mimics cholesterol oxidase. ***J. Clin. Invest.*** *115*, 2556–2563.
2. Bell, R., Hubbard, A., Chettier, R., Chen, D., Miller, J.P., Kapahi, P., Tarnopolsky, M., Sahasrabuhde, S., Melov, S., and Hughes, R.E. (2009). A human protein interaction network shows conservation of aging processes between human and invertebrate species. ***PLoS Genet*** *5*, e1000414. PMCID2657003
3. Rogers, A.N., Chen, D., McColl, G., Czerwieniec, G., Felkey, K., Gibson, B.W., Hubbard, A., Melov, S., Lithgow, G.J., and Kapahi, P. (2011). Life Span Extension via eIF4G Inhibition Is Mediated by Posttranscriptional Remodeling of Stress Response Gene Expression in *C. elegans*. ***Cell Metab***. *14*, 55–66. PMCID: PMC3220185
4. Hernandez-Segura A, de Jong TV, Melov S, Guryev V, Campisi J, Demaria M. Unmasking Transcriptional Heterogeneity in Senescent Cells. ***Curr Biol***. 2017 Sep 11;27 (17):2652-2660.e4. doi: 10.1016/j.cub.2017.07.033. Epub 2017 Aug 30. PMCID: PMC5788810.

2. Oxidative Stress and mitochondrial dysfunction. For 20 years I have been investigating the consequences of endogenous mitochondrial oxidative stress in mouse tissues. The primary focus has been to better understand what molecular targets are vulnerable to mitochondrial dysfunction. Our initial work focused on first characterizing the basic phenotype in mice from genetically inactivating the key mitochondrial antioxidant – superoxide dismutase 2 (*Sod2*). This was work carried out in collaboration with the Epstein laboratory at UCSF, and resulted in a paper in Nature Genetics that has been cited more than 1500 times. We followed up this initial work with the development of a system designed to further uncover targets of endogenous oxidative stress. We did this by treating *Sod2* null mice with synthetic antioxidants, which extended the lifespan by up to 5 fold, and prevented some of the pathologies that arise in untreated mice. What was surprising about this line of research, was how many "garden variety" antioxidants failed to work in the model. This indicated that many antioxidants presumed to work in the context of mitochondrial oxidative stress have limited efficacy in this paradigm. We continued to work on this area, by refining the characterized phenotypes, and discovered that large scale nuclear

genomic instability develops at the single cell level in fibroblasts derived from this model, and isolated heart mitochondria from *Sod2* null mice actually produce less ROS than would be expected from conventional thinking. Other areas we have developed over the years are the characterization of synaptosomes in the context of mitochondrial oxidative stress, where we showed that spare respiratory capacity was markedly diminished from endogenous mitochondrial oxidative insult. This implied that when cellular energy demand was high, the cell would be unable to respond, resulting in cell death.

1. Li Y, Huang T-T, Carlson EJ, Melov S, Ursell P, Olson J, Noble L, Yoshimura MP, Berger C, Chan PH, Wallace DC, Epstein C. (1995) Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. ***Nat Genet***, 11(4):376-381.
2. Melov S, Doctrow R, Schneider A, Harberson J, Patel M, Coskun P, Huffman K, Wallace DC, Malfroy B. (2001) Lifespan extension and rescue of spongiform encephalopathy in superoxide dismutase 2 nullizygous mice treated with superoxide dismutase/catalase mimetics. ***J Neurosci***, 21(21):8348-8353.
3. Flynn JM, Czerwieniec GA, Choi SW, Day NU, Gibson BW, Hubbard A, Melov S (2012) Proteogenomics of synaptosomal mitochondrial oxidative stress. ***Free Radic Biol Med***. 53(5):1048-60. PMCID: PMC3436120
4. Brand MD, Goncalves RL, Orr AL, Vargas L, Gerencser AA, Borch Jensen M, Wang YT, Melov S, Turk CN, Matzen JT, Dardov VJ, Petrassi HM, Meeusen SL, Perevoshchikova IV, Jasper H, Brookes PS, Ainscow EK. Suppressors of Superoxide-H2O2 Production at Site IQ of Mitochondrial Complex I Protect against Stem Cell Hyperplasia and Ischemia-Reperfusion Injury. ***Cell Metab***. 2016 Oct 11;24(4):582-592. doi: 10.1016/j.cmet.2016.08.012. Epub 2016 Sep 22. PMCID: PMC5061631.

3. Biology of Aging. As one of the founding faculty of the Buck Institute (#3 faculty hire), I have helped shape the overall institutes research focus and growth. This includes assisting recruitment of key faculty members, as well as running the institutes Genomics and Animal Phenotyping Cores for many years. I have also had numerous service roles in operating the vivarium, membership on various committees, and giving dozens of talks to the general public about the importance of aging research over the years. However, by far and away the most important contributions of my tenure at the Buck has been in building collaborations between multiple faculty, resulting in the publication of many high impact papers in aging biology. This has been a cornerstone of my philosophy, and we have had some success in this regard. First, was our initial publication in Science in 2000, with my long-standing collaborator Gordon Lithgow on lifespan extension in *C. elegans* using catalytic antioxidants. I have continued to publish with various Buck Faculty, most notably with Dr's Kapahi and Campisi. I have used my skills in animal phenotyping and genomics to augment many ongoing collaborations. My broad skill set has also begun to bear fruit from a translational perspective, which includes evaluating the anti-aging effects of rapamycin on heart function. The 4 publications listed illustrate the breadth, and depth of this approach with regards to both aging biology, and collaborative focus.

1. Flynn, J.M., O'Leary, M.N., Zambataro, C.A., Academia, E.C., Presley, M.P., Garrett, B.J., Zykovich, A., Mooney, S.D., Strong, R., Rosen CJ, Kapahi P, Nelson MD, Kennedy BK, Melov S. (2013). Late life rapamycin treatment reverses age-related heart dysfunction. ***Aging Cell,*** 12, pp 851-862. PMC4098908
2. Velarde MC, Demaria M, Melov S, Campisi J. (2015) Pleiotropic age-dependent effects of mitochondrial dysfunction on epidermal stem cells ***Proc Natl Acad Sci*** *USA* Aug 18;112(33):10407-12. PMCID: PMC4547253.
3. Demaria M, O'Leary MN, Chang J, Shao L, Liu S, Alimirah F, Koenig K, Le C, Mitin N, Deal AM, Alston S, Academia EC, Kilmarx S, Valdovinos A, Wang B, de Bruin A, Kennedy BK, Melov S, Zhou D, Sharpless NE, Muss H, Campisi J. 2016. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. ***Cancer Discov***. 2016 Dec 15. doi: 10.1158/2159-8290.CD-16-0241. PMCID: PMC5296251.
4. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. (2019) From Discoveries in ageing research to therapeutics for healthy ageing. ***Nature***, Jul; 571(7764):183-192. doi: 10.1038/s41586-019-1365-2. Epub 2019 Jul 10. PMID: 31292558

4. Service to the Field of Oxidative stress and Aging. In 1999, I realized the time was right for founding a new forum for discussing and promulgating an exciting new area of research, the intersection between oxidative stress and disease. The forum I ultimately chose was the Gordon Research Conference (GRC). Accordingly, I wrote a justification for establishing a new conference devoted to this topic, which was reviewed and approved

by former chairs of the GRC. This resulted in the GRC for Oxidative stress and disease, which has been running for more than a decade, with over 700 attendees in its history, and dozens of talks helping shape the field of oxidative stress and disease to what it is today. In addition, in the early 2000's, several colleagues and I decided that aging research was sufficiently advanced as to require a specialized premiere journal. I agreed to serve as the founding reviews editor of the journal (one of three founding editors), which would be called "Aging Cell". This journal is now recognized as a premier journal for aging research, and has published hundreds of articles in the field. As one of the founding editorial board, I'm very pleased with the journals role in helping shape aging research to what it is today.

1. First GRC for Oxidative stress and disease http://www.grc.org/programs.aspx?year=2001&program=oxid
2. Founding editorial board for Aging Cell: http://onlinelibrary.wiley.com/doi/10.1046/j.1474-9728.2002.00025.x/full

5. Identification of molecular and pathological hallmarks of aging in multiple systems. Throughout my research career, I've been involved in diverse approaches to better define aging phenotypes, as well as identify potential biomarkers of aging that might be useful in evaluating whether or not one can slow aging-rates in different species by pharmacological or genetic interventions. I have used multiple approaches, encompassing a variety of model systems including mice, *C. elegans*, and *drosophila* as well as human tissues. The following publications illustrate several novel phenotypes associated with aging or age-related disease that we have discovered. These include the discovery of mitochondrial DNA mutations in individual *C. elegans* with age, the discovery of loss of specific cells in the intestine and cuticle of aging *C. elegans* which is relevant to the current R21 application, the discovery of p53 driven dysplasia in the germline of aging *C. elegans,* and the discovery of DNA methylation changes in aging human skeletal muscle associated with R-loop signatures.

1. (1995) Increased frequency of deletions in the mitochondrial genome with age of *Caenorhabditis elegans*. Nucleic Acids Research, 23(8), p1419-1425.
2. McGee M.D., Weber D., Day N., Vitelli C., Crippen D., Herndon L.A., Hall D.H., Melov S. (2011). Loss of intestinal nuclei and intestinal integrity in aging *C. elegans*. ***Aging Cell***, 10(4), p699-710. PMCID: PMC3135675
3. McGee M.D., Day N., Graham J., Melov S. (2012) *Cep-1/p53*-dependent dysplastic pathology of the aging *C. elegans* gonad. ***Aging***, 4(4) p256-259. PMCID: PMC3378273
4. Zykovich A., Hubbard A., Flynn J. M., Tarnopolsky M., Fraga M. F., Kerksick C., Ogborn D., MacNeil L., Mooney S.D., Melov S. (2014) Genome-wide DNA methylation changes with age in disease-free human skeletal muscle. ***Aging Cell*** 13(2), 360-366. PMCID: PMC3954952

Full list of published work as found in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1daJr8K-nlfAu/bibliography/public/

D. Research Support

R01AG055822-01 (MPI, Melov (contact), Campisi, Seals)
Role of cellular senescence in cardiovascular aging 06/01/18-01/31/23
NIH/NIA
Aging is the primary risk factor for cardiovascular disease (CVD), and by 2030, 40% of Americans will have some form of CVD incurring a huge economic and human toll on society. One potential cause of cardiovascular aging is cellular senescence. This complex stress response can be beneficial or detrimental, depending on the physiological context. Senescent cells accumulate with age in the hearts and vasculature of mice and humans, but it is not known if cellular senescence is a cause or consequence of cardiovascular aging. We propose to test the novel hypothesis that *senescent cells, and particularly the senescence associated secretory phenotype (SASP), are an important mechanistic process driving CV aging.* To test this hypothesis, we will develop three specific aims in this multidisciplinary grant bridging mouse models of aging, and human subjects. Aim 1: *In vivo* consequences of senescence in the CV system. Aim 2: Role of senescent cells in modulating cardiac and arterial function. Aim 3: Translational validation of senescent markers identified in Aims 1-2. Overall our program will provide novel insights into the role of senescence as a major mediator of age-related CVD, and potentially provide new targets of opportunity to combat this devastating disorder.
Role: contact PI (multi-PI grant)

U24AG051129-01 (MPI, Cummings, Schork, Melov)
Integrative Resource to Develop Translational Strategies to Promote Longevity 10/01/15 – 04/30/21 (no cost extension)
NIH/NIA
A central theme in this proposal is to develop insights relating molecular and physiologic factors that can be manipulated pharmacologically to healthy aging based on hypothesis rooted in genetic associated studies involving longevity. We will identify candidate genetic variants for in-depth analysis by meta-analyzing results from published genome-wide association studies (GWAS) of longevity and age-related traits and by searching for evidence of genetic variants with pleiotropic effects on aging-related traits. Small scale pilot studies will be initiated using hits from the association studies to investigate potential mechanisms which may modulate healthy aging in human beings.
Role: PI (multi-PI grant)

R01 NS100529 (Ellerby) 09/30/16 − 08/31/21
NIH/NINDS
Identifying Factors Regulating Medium Spiny Neuron Differentiation Or Maintenance As Therapeutic Targets For Huntington's Disease Using Induced Pluripotent Stem Cells
These studies will utilize iPSCs derived from HD patients (HD-iPSCs) as a human model of HD. Using genetic engineering, we generated an isogenic allelic HD-iPSC series for HD modeling (CAG repeat of 21, 45, 72,100). Specific Aims: We will characterize the cellular and functional deficits in normal iPSCs, HD-iPSCs, and genetically corrected HD- iPSCs differentiated into medium spiny neurons using “omics” approaches; Using DARPP-32 genomic elements that direct gene expression specifically in mature MSNs, we will develop a marker of mature MSNs and identify factors that mediate differentiation and maintenance of MSNs for this cellular HD model; Specific Aim 3. We will determine if factors that promote MSN differentiation or maintenance ameliorate HD phenotypes in mouse models of the disease. Therapeutic targets will be identified and new treatments for HD will be explored.
Role: Co-investigator

R01 AG061879 (MPI, Ellerby (contact PI) & Melov) 09/30/18 – 05/31/23
Resilience pathways modeling human longevity-promoting ApoE variants in induced pluripotent stem cells
Isoforms of ApoE modify the risk for developing Alzheimer’s disease (AD) or cardiovascular disease, and are also associated with exceptional longevity. Specifically, the e2/e2 genotype is associated with exceptional longevity while the e4 allele is negatively associated with longevity. The e4 variant of the ApoE gene is also a major risk factor for AD and is associated with higher levels of Ab deposition in the brain. Correspondingly, the ApoE e2 allele is associated with a lower risk of AD-related neurodegeneration. The mechanisms modulating extended lifespan mediated by e2 compared to e3 and e4 genotypes are not clear. Using genetic engineering in preliminary studies, we generated lines carrying e2/e2, e3/e3 and e4/e4 genotypes in control iPSCs and Huntington’s Disease-HD-iPSCs. Recent advances in stem cell research suggest that iPSCs may provide novel models of aging and diseases. We will investigate using stem cell models the role of the exceptional longevity factor ApoE2 in aging and disease.
Role: PI (multi-PI grant).

Industry Research Agreement (Melov PI, Campisi Co-PI)
09/22/17 - 9/22/20
Proprietary