BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Campisi, Judith

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

POSITION TITLE: Professor/Senior Scientist

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
State University New York, Stony Brook	B.A.	05/74	Chemistry
State University New York, Stony Brook	Ph.D.	10/79	Biochemistry

A. Personal Statement

My laboratory has studied the molecular and cellular links between cancer and aging for more than two decades, and recently explored the links between cancer, tissue degeneration/regeneration, aging phenotypes and both degenerative and hyperplastic pathologies of aging. We mainly focus on the tumor suppressive response termed cellular senescence, and its relationships to DNA and epigenomic damage, proliferation signals, nuclear/chromatin organization, mitochondrial function, chronic inflammation and more recently cellular reprogramming. Our work has challenged existing paradigms, and created a number of new paradigms for understanding the molecular and cellular bases for how aging drives a plethora of apparently disparate age-related phenotypes and pathologies.

We use simple and complex human and mouse cell cultures, mouse models and human tissues to understand how senescent cells and other cell fates influence tissue structure and function, aging phenotypes and age-related disease. We have numerous national and international collaborations, and mentor many students and postdoctoral fellows both locally and from other national and international institutions. Our most recent studies bring our basic and preclinical studies toward more translational relevance and utility.

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. 2017. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. **Cancer Discov** 7:165-176. PMC5296251

Jeon OK, Kim, C Laberge RM, Demaria M Rathod S, Vasserot A, Chung JW, Kim DH, Poon Y, David N, Baker D, van Deursen JM, Campisi J, Elisseeff JH. Clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. **Nature Med**. In press. PMCID in progress.

B. Positions and Honors

Professional Positions:

1980-1984 Postdoctoral Fellow/Instructor, Dana-Farber Cancer Inst/Harvard University Medical School
1984-1989 Assistant Professor, Department of Biochemistry, Boston University Medical School
1989-1991 Associate Professor, Department of Biochemistry, Boston University Medical School
1991-present Senior Scientist, Life Sciences Division, Lawrence Berkeley National Laboratory
1994-1999 Head, Department of Cell and Molecular Biology, Lawrence Berkeley National Laboratory
1999-2009 Co-Head, Center for Research and Education on Aging, Lawrence Berkeley National Lab
2002-present Professor, Buck Institute for Research on Aging

Major Research Awards (not including numerous named and endowed lectures):

1985 Evangeline Athanas Cancer Research Scholar Award, American Cancer Society
1988 Established Investigator of the American Heart Association
1997 AlliedSignal Award for Research on Aging
1998 Ellison Medical Foundation, Senior Scholar Award

1999 Glenn Foundation Award, Gerontological Society of America
2002 Irving Wright Award of Distinction, American Federation for Aging Research
1995, 2005 MERIT Awards, National Institute on Aging
2010 Longevity Prize, IPSEN Foundation
2011 Bennett Cohen Award, University of Michigan
2012 Elected fellow of the American Association for the Advancement of Science
2013 Schober Award, Halle University Hospital, Germany
2015 First International Prize in Natural Sciences and Medicine, Olav Thon Foundation
2015 ICCNS-Springer Award for research excellence, International CCN Society

Selected Professional Service:

1988-1992 Biological & Clinical Aging Review Committee, National Institute on Aging
1993-present Scientific Advisory Board, Alliance for Aging Research
1994-1998 Board of Scientific Counselors, National Institute on Aging
1999-2002 National Advisory Council on Aging, National Institutes of Health
2001-2013 Ellison Medical Foundation, Review Group
2003-2012 Co-Chair, Task force on Cancer and Aging, American Association for Cancer Research
2003-2012 Scientific Advisory Board, Keystone Symposia
2004-present Medical Research Committee, Progeria Research Foundation
2008 National Academies, Grand Challenges of an Aging Society Planning Committee
2011-2017 Steering Committee, National Institute on Aging Intervention Testing Program

Current Editorial Board memberships: Aging, Aging & Dis, Aging Cell, Cancer Convergence, Cell Cycle, EBioMed, Exp Cell Res, FASEB J, J Cell Bioch, J Cell Physiol, Mech Ageing Dev, Molec Cell Oncol, Molec Biol Rep, Oncoscience, Oncotarget, PLoS Biology, Rejuven Res

C. Contributions to Science

Major contribution: Causes, consequences and health implications of cellular senescence.

Senescence biomarker discovery.

Since the 1960s, cellular senescence – the process that limits the proliferation of normal cells – was thought to suppress cancer and promote aging, based mostly on cell culture models. My laboratory first showed that senescent cells have a strikingly altered gene expression program. We also discovered the first biomarker of senescent cells (senescence-associated β-galactosidase) and used it to demonstrate for the first time that senescent cells accumulate with age in human tissue. We subsequently discovered additional markers of senescent cells, which we used to further demonstrate the existence of senescent cells in vivo, and better understand how senescent phenotypes develop. These markers include distinct persistent DNA damage foci with properties that differ from those of transient DNA damage foci, a sharp decline in the expression of a major nuclear lamina protein (lamin B1) and loss of the nuclear protein HMGB1 and its subsequent secretion and activity as a pro-inflammatory alarmin. These markers now are important tools for charting the appearance and disappearance of senescent cells during aging and tumorigenesis, and assessing the efficacy of interventions that promote, suppress or reverse senescent phenotypes.

Dimri G, Lee, X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, Peacocke M, Campisi J. 1995. A novel biomarker identifies senescent human cells in culture and aging skin in vivo. **Proc Natl Acad Sci USA** 92:9363-9367. PMC40985

Rodier F, Munoz DP, Teachenor R, Chu V, Le O, Bhaumik D, Coppe JP, Campeau E, Beausejour C, Kim SH, Davalos AR, Campisi J. 2011. DNA-SCARS: Distinct nuclear structures that sustain the damage-induced senescence growth arrest and inflammatory cytokine secretion. **J Cell Sci** 124:68-81. PMC3001408

Freund A, Laberge RM, Demaria M, Campisi. 2012. Lamin B1 loss is a senescence-associated biomarker. **Molec Biol Cell** 23:2066-2075. PMC3364172

Davalos AR, Kawahara M, Malhotra GK, Schaum N, Huang J, Ved U, Beausejour C, Coppe JP, Rodier F, Campisi J. 2013. p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. **J Cell Biol** 201:613-629. PMC3653366

Senescent cells, aging and cancer.

For years, the role of cellular senescence in tumor suppression and aging focused on the growth arrest. We questioned this focus. In a prophetic review (Cell, 1996), we speculated that senescent cells might drive

aging, including late life cancer, cell non-autonomously. Subsequently, we showed that senescent cells secrete numerous molecules that can stimulate nearby cells to adopt aberrant phenotypes in culture and *in vivo*. We provided the first high content description of the senescence-associated secretory phenotype (SASP) and documented a role for the SASP in disrupting normal tissue morphogenesis and differentiation, fueling tumor cell growth, vascularization and chemo-resistance, and altering the ability of tissue stem cells to participate in tissue repair *in vivo*. We showed that the SASP includes pro-inflammatory cytokines, which evolve slowly once cells received a senescence stimulus, and is conserved between human and mouse cells, opening the way for using mouse models to explore this phenotype *in vivo*. Recently, using a novel mouse model we developed that allows us to inducibly eliminate senescent cells, we identified an early SASP component (PDGF-A) that was important for optimal wound healing. Our findings solidify the idea that the senescence response and SASP are the result of an evolutionary trade-off, balancing tumor suppression against tissue repair. They also pave the way to developing interventions that mitigate the maladaptive consequences of this trade-off (aging), while preserving its benefits (tumor suppression and tissue repair).

Krtolica A, Parrinello S, Lockett S, Desprez P, Campisi J. 2001. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging. **Proc Natl Acad Sci USA** 98:12072-12077. PMC59769

Parrinello S, Coppe JP. Krtolica A, Campisi J. 2005. Stromal-epithelial interactions in aging and cancer: Senescent fibroblasts alter epithelial cell differentiation. **J Cell Sci** 118:485-496. PMC4939801

Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J. 2008. Senescence-associated secretory phenotypes reveal cell non-autonomous functions of oncogenic RAS and the p53 tumor suppressor. **PLoS Biol** 6:2853-2868. PMC2592359

Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, Laberge RM, Vijg J, van Steeg H, Dolle ME, Hoeijmakers JH, de Bruin A, Hara E, Campisi J. 2014. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. **Dev Cell** 31:722-733. PMC4349629

Molecular control of senescent phenotypes.

Several laboratories established the importance of the senescence growth arrest as a barrier to replicative immortality and cancer, identifying the p53/p21 and $p16^{INK4a}$/pRb tumor suppressor pathways as critical regulators. We showed that the p53/p21 pathway initiates the senescence growth arrest, while the $p16^{INK4a}$/pRb pathway, over time, locks the arrest, making it irreversible and impervious to subsequent loss of $p16^{INK4a}$ or pRb. We also showed that the replicative senescence of mouse and human cells in culture were fundamentally distinct; the former is driven by the severe oxidative stress of standard culture conditions and is devoid of a SASP, whereas the latter is driven by telomere attrition and an unknown component of culture stress and is accompanied by a robust SASP. However, moderate (more physiological) oxidative stress induces a senescence growth arrest and SASP in cells of both species, in culture and *in vivo*. Recently, we uncovered an unexpected role for mitochondrial dysfunction and subsequent senescent phenotypes: dysfunctional mitochondria results in an altered SASP, which promotes wound healing in young organisms, but delays wound healing in aged mice, due primarily to senescence-driven exhaustion of stem cells.

Beausejour CM, Krtolica A, Galimi F, Narita M, Lowe S, Yaswen Y, Campisi J. 2003. Reversal of human cellular senescence: Roles of the p53 and p16 pathways. **EMBO J** 22:4212-4222. PMC175806

Parrinello S, Samper E, Krtolica A, Goldstein J, Melov S, Campisi J. 2003. Oxygen sensitivity severely limits the replicative senescence of murine cells. **Nature Cell Biol** 5:741-747. PMC4940195

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** 112:10407-10412. PMC4547253

Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Shirakawa K, Lim H, Davis S, Ramanathan A, Gerencser AA, Verdin E, Campisi J. 2016. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. **Cell Metab** 23:303-314. PMC4749409

Molecular control of the SASP.

Because the SASP is important for driving aging and cancer phenotypes, we identified pathways that regulate this phenotype and interventions that can blunt its deleterious effects. We found that the p53/p21 pathway is essential for activation of the SASP. We discovered a hierarchy in which senescence signals first induce expression of the membrane-associated cytokine IL-1α, which establishes a positive feedback loop that slowly increases NF-κB activity, which drives expression of downstream inflammatory cytokines such as IL-6 and IL-8, and is eventually dampened by two micro-RNAs. We identified 3 pathways, each amenable to intervention, that positively regulate the SASP: 1) DNA damage response (DDR) signals that act upstream of p53, with crucial roles played by the DDR kinases ATM and CHK2; inhibitors of these kinases suppress the

SASP; 2) the p38MAPK-NF-kB axis; inhibitors of each protein suppress the SASP; 3) the mTOR pathway; the mTORC1 inhibitor rapamycin suppresses IL-1α, thereby breaking the IL-1α/NF-κB feedback loop. This body of work establishes a mechanistic understanding of the SASP, and a framework for interventions.

Orjalo A, Bhaumik D, Gengler B, Scott GK, Campisi J. 2009. Cell surface IL-1 is an upstream regulator of the senescence-associated IL6/IL-8 cytokine network. **Proc Natl Acad Sci USA** 106:17030-17035. PMC2761322

Rodier F, Coppe JP. Patil CK, Hoeijmakers WAM, Munoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J. 2009. Persistent DNA damage signaling triggers senescence-associated inflammatory cytokine secretion. **Nature Cell Biol** 11:973-979. PMC2743561

Freund A, Patil CK, Campisi J. 2011. p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. **EMBO J** 30:1536-1548. PMC3102277

Laberge RM, Sun Y, Orjalo AV, Patil PK, Freund A, Zhou L, Curran SC, Davalos AR, Wilson-Edell KA, Liu S, Limbad C, Demaria M, Li P, Hubbard GB, Ikeno Y, Javors M, Desprez PY, Benz CC, Kapahi P, Nelson PS, Campisi J. 2015. mTOR regulates the tumour-promoting senescence-associated secretory phenotype by promoting IL-1 translation. **Nature Cell Biol** 17:1049-1061. PMC4691706

Other contributions: Telomeres, RECQ proteins and DNA damage responses.

Telomere attrition is a prime cause of replicative senescence, which led us in the late 1990s to identify mediators of this senescence response. We consequently discovered the major shelterin protein TIN2, and its role in determining cell fates resulting from dysfunctional telomeres. We also developed an interest in premature aging syndromes, particularly those caused by defects in RECQ helicases, which participate in a variety of DNA transactions. We discovered the exonuclease function of the WRN protein, which causes the adult onset progeria Werner syndrome, and determined its interactions with critical DNA repair proteins, including XPG and BRCA1. We also studied the regulation of senescence-associated phenotypes by micro-RNAs (Bhaumik et al, 2009), which led to the discovery of GATA4 as a master transcriptional regulator of the SASP. These studies enrich our molecular understanding of how cell fate decisions that lead to aging, cancer and degenerative disease are determined in mammalian cells.

Huang S, Li B, Gray MD, Oshima J, Mian S, Campisi J. 1998. The premature aging syndrome protein WRN is a 3' to 5' exonuclease. **Nature Genet** 20:114-116. PMC4940158

Kim SH, Kaminker P, Campisi J. 1999. Tin2, a new regulator of telomere length in human cells. **Nature Genet** 23:405-412. PMC4940194

Kang C, Xu Q, Martin TD, Li MZ, Demaria M, Aron L, Lu T, Yankner BA, Campisi J, Elledge SJ. 2015. The DNA damage response activates inflammation and senescence by protecting GATA4 from selective autophagy. **Science** 349:aaa5612. PMC4942138

Trego KS, Groesser T, Davalos AR, Parplys AC, Zhao W, Nelson MR, Hlaing A, Shih B, Rydberg B, Pluth JM, Tsai MS, Hoeijmakers JH, Sung P, Wiese C, Campisi J, Cooper PK. 2016. Non-catalytic roles for XPG with BRCA1 and BRCA2 in homologous recombination and genome stability. **Molec Cell** 61:535-546. PMC4761302

Full list of published work as found in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1VSa_Rnfwi5k2/bibliography/43735851/public/?sort=date&direction=ascending

D. Research Support

Current

1. **NIH/NIA, R37 AG009909** **Cellular senescence and control of gene expression**
   3/01/06 – 6/30/16 Role: PI
   This project, the recipient of two consecutive MERIT awards, is the major grant that funds the fundamental biology of cellular senescence and aging in my laboratory. It continues to explore the molecular and cellular causes of cellular senescence, and the effects of senescent cells on aging phenotypes and age-related pathologies using both mouse models and human cells and tissues. *On no-cost extension*.
2. **NIH/NIA, P01 AG017242** **DNA repair, mutations and cell aging**
   4/01/14 – 3/31/19 Role: Subproject PI; Program PI: J Vijg, Albert Einstein College of Medicine
   This subproject explores the role of somatic mutations and defects in DNA repair in causing cellular senescence and aging phenotypes using human and mouse cell cultures and mouse models.
3. **NIH/NIA, T32-AG00266** **Training in basic aging research and age-related disease**

5/01/12 – 4/30/17 Role: PI; Co-PI: Lisa Ellerby, Buck Institute (no salary as per NIH policy)
This grant provides stipends for 10 postdoctoral fellows per year in >30 laboratories at the Buck Institute for Research on Aging, the Lawrence Berkeley National Laboratory, Stanford University and the University of California Berkeley.

4. **NIH/NIEHS, R01 ES019935 Novel interactions of DNA repair processes in replication fork maintenance**
12/01/11-11/30/16 Role: Co-PI; Project PI: Priscilla Cooper, Lawrence Berkeley Natl Laboratory
This project explores the role of DNA repair proteins XPG and WRN in maintaining replication fork integrity and preventing deleterious DNA damage responses in the face of endogenous and exogenous damage. *Currently on no-cost extension.*
5. **NIH/NIA, P01 AG041122 Cellular senescence and aging**
5/01/12 – 4/30/17 Role: Subproject PI; Program PI: James Kirkland, Mayo Clinic
This subproject determines the mechanisms by which the mTOR longevity pathway drives senescence-associated inflammation, and tests interventions for ability to delay aging and age-related disease.
6. **NIH/NCI, R01 CA166347 The role of senescent cells in late-life tumorigenesis**
4/1/12 – 3/31/17 Role: Co-PI; Project PI: Jan van Deursen, Mayo Clinic
This project will test the hypothesis that senescent cells fuel cancer progression. The Campisi lab will characterize senescent phenotypes of cells from lung and mammary tumors in INK-ATTAC mouse tissues.
7. **NIH/NIA, R56 AG052988 Senescent cells as a source of pro-geronic factors**
04/01/16 – 3/31/17 Role: PI; Irina Conboy, co-PI
This 1 year bridge grant provides funds to acquire additional preliminary data exploring the role of senescent cells in creating a pro-aging systemic milieu in mice in anticipation of resubmission. Resubmission is planned for early 2017.
8. **NIH/NIA, R01 AG051729 Cellular senescence as a mediator of mitochondrial dysfunction-induced aging**
10/01/16—09/30/21 Role: PI; Martin Brand, co-PI
This proposal will explore how mitochondrial dysfunction induces cellular senescence, a characteristic secretory phenotype and age-related phenotypes and pathologies in human cells and mouse models.

Recently Completed (past 5 years)

1. **NIH/NIA, P01 AG025901 Mitochondrial functions and phenotypes that impact aging**
3/01/07-2/28/12 Role: Subproject PI (Program PI, J Andersen, Buck Institute)
This subproject determined the dynamic and reciprocal interactions between the p53 tumor suppressor protein and mitochondria in modulating aging and cancer phenotypes.
2. **NIH/NIA, R01 AG034421 Single cell functional genomics (EUREKA)**
7/15/09 – 6/30/13 Role: co-PI; Project PI: J Vijg, Albert Einstein College of Medicine
This project determined the extent of cell-to-cell variation in genomic damage and epigenomic drift in somatic and human embryonic stem cells.
3. **NIH/NCI, R21 CA170610 Cellular senescence, aging and cancer development (PQ7)**
9/12/12-8/31/14 Role: PI; Simon Melov, co-PI
This project used a hybrid mouse model of SOD2 deficiency and senescent cell elimination to determine whether senescent cells, which accumulate as a consequence of oncogenic stress, initiate or promote skin carcinogenesis.
4. **NIH/NIEHS, R21 ES024357 Environmental exposure and astrocytic senescence: novel link to PD?**
8/1/14 – 7/31/16 Role: Co-PI; Project PI: Julie Andersen, Buck Institute
This project screened small molecule toxicant libraries to identify environmental agents capable of inducing senescence in astrocytes, thus compromising neural stem cell and dopaminergic neuron functions.