BIOGRAPHICAL SKETCH

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NAME: **Steven E. Artandi, MD PhD**

eRA COMMONS USER NAME: ARTANDI.STEVEN

POSITION TITLE: **Jerome and Daisy Low Gilbert Professor of Medicine and Biochemistry**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	06/1986	Chemistry
Columbia University College Physicians & Surgeons, New York, NY	MD	05/1995	Medicine
Columbia University College Physicians & Surgeons, New York, NY	PhD	05/1995	Microbiology
Massachusetts General Hospital, Boston, MA		06/1997	Internal Medicine Residency
Dana-Farber Cancer Institute, Boston, MA		11/2000	Oncology Fellowship
Post-doctoral Fellowship, Dana-Farber Cancer Institute, Boston, MA		11/2000	Cancer genetics

A. PERSONAL STATEMENT

I have 20 years of experience investigating the origins of cancer and the mechanistic underpinnings governing carcinogenesis. I discovered that dysfunction of telomeres is a potent initiator of chromosomal instability and epithelial tumor formation. Given the fundamental link between telomerase and cancer, we have led the molecular and biochemical dissection of telomerase in human cells. We have identified critical new processes in telomerase regulation in human cancer cells, including steps in assembly, trafficking and recruitment to telomeres. We identified enzymes required for assembly of the telomerase enzyme, and TCAB1, a telomerase required for catalytic activity, telomerase RNA folding, localization in Cajal bodies and recruitment to telomeres. We identified new mutations in dyskeratosis congenita, a premature stem cell failure and cancer-predisposition syndrome, which act in a novel manner by impairing telomerase trafficking. My laboratory uncovered critical new roles for telomerase in stimulating tissue stem cell renewal through a non-canonical pathway, independent of its function in adding telomere repeats. We discovered new hepatocyte stem cells responsible for hepatocyte renewal in homeostasis and injury. My laboratory is pioneering the identification of telomerase-expressing tissue stem cells in adult tissues to explain cellular mechanisms of tissue renewal, to understand potential cancer cells-of-origin and to discover new genetic vulnerabilities of advanced human cancers. I have trained 10 PhD or MD, PhD students and 16 postdoctoral fellows, as well as numerous undergraduates and research assistants.

B. POSITIONS AND HONORS

Positions and Employment

1995-1997 Intern/Resident–Internal Medicine, Massachusetts General Hospital
1997-2000 Clinical Fellowship–Medical Oncology, Harvard Medical School, Dana-Farber Cancer Institute & Brigham's & Women's Hospital, Massachusetts General Hospital
1998-2000 Research Fellowship–Dana-Farber Cancer Institute, Harvard Medical School, Dr. Ron DePinho
2000-2008 Assistant Professor of Medicine, Division of Hematology, Stanford University
2008-2012 Associate Professor of Medicine (Tenure), Division of Hematology, Stanford University
2012-present Professor of Medicine, Stanford University
2012-present Professor of Biochemistry, Stanford University
2015-present Jerome and Daisy Low Gilbert Professor, Stanford University
2018-present Lacob Director, Stanford Cancer Institute, Stanford University

Professional activities, Honors and Awards

1990	Outstanding Medical Student Award, American College of Rheumatology
1993	Dean's Day Award for Medical Student Research, Columbia University
1995	Marion Merrell Dow Prize for Research, Columbia University
1995	Fredrick P. Gay Memorial Award for Research, Columbia University
1999-2000	Howard Hughes Physician Post-doctoral Fellowship
2000-2005	NIH K08 Grant
2001-2004	Rita Allen Scholar Award
2001-2003	V Foundation Scholar Award
2001	Ellison Foundation Scholar Award (declined)
2006-	Editorial board, Journal *Stem Cells*
2006	American Cancer Society Scholar Award (declined)
2007-2012	Senior Editor, *Molecular Cancer Research*
2007	Elected Fellow, American Association for the Advancement of Science (AAAS)
2009	Elected Member, American Society for Clinical Investigation (ASCI)
2011-2015	Associate Director, Paul F. Glenn Laboratories for the Biology of Aging at Stanford
2013	Editorial Board, *Molecular Cancer Research*
2015	Elected Member, Association of American Physicians (AAP)
2015	National Cancer Institute Outstanding Investigator Award

C. CONTRIBUTIONS TO SCIENCE

1. Short telomeres as a cause of chromosomal instability and cancer initiation

Critical telomere shortening in human cells in culture was known to cause replicative senescence, an irreversible cell cycle arrest. Inactivation of the tumor suppressor proteins p53 and Rb in human fibroblasts had been shown to rescue senescence and to allow cells to divide a few more times. This extended proliferative lifespan eventually led to a period of increased apoptosis and the eventual loss of the culture, a state termed crisis. These data were interpreted to mean that telomere shortening evolved as a potent tumor suppressor mechanism, and that either senescence or crisis would block tumor development, helping to stave off cancer in our old age. In this work from my postdoctoral fellowship, we addressed the role of telomere dysfunction in cancer by studying spontaneous tumorigenesis in telomerase-null p53-mutant mice. Surprisingly, we found that telomere dysfunction accelerated the onset of tumors, rather than delayed them. More importantly, we discovered that telomere shortening led to a dramatic change in the tumor spectrum of these mice, promoting the development of epithelial cancers (carcinomas). The mechanism underlying this effect involved unchecked chromosome fusion-bridge-breakage cycles, leading to the generation of non-reciprocal chromosomal translocations and focal gene amplifications and deletions. I recognized that this type of genomic instability closely approximated the genome changes seen in human carcinomas, which led us to propose that progressive telomere shortening in human aging may in part account for why humans become prone to the development of carcinomas with advancing age. These data and conclusions directly contradicted the prevailing paradigm, but now the role of telomere shortening in destabilizing chromosomes and causing cancer has become widely accepted. In fact, patients with dyskeratosis congenita harbor telomerase mutations and have very short telomeres, resulting in a cancer prone condition, consistent with our genetic results in mouse.

A. Artandi SE, Chang S, Lee S-L, Alson S, Gottlieb GJ, Chin L, and DePinho RA (2000) Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. **Nature**, *406*: 641-644.
B. Chin* L, Artandi* SE, Shen Q, Tam A, Lee SL, Gottlieb GJ, Greider CW, and DePinho RA. (1999) p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. **Cell,** 97: 527. [*Co-first author]

2. Identification of a telomerase protein controlling nuclear trafficking and linking this process to human disease

The active telomerase holoenzyme is composed of the catalytic core, formed by TERT and TERC, together with dyskerin, a TERC-binding protein required for telomerase assembly and stability. We reasoned that novel components of the active enzyme could be identified through purification of dyskerin protein complexes from human cancer cells. Using dual affinity purification of dyskerin coupled with mass spectrometry, we identified a new WD40 repeat protein we named TCAB1 (for telomerase Cajal body protein 1). Immunofluorescence

revealed that TCAB1 localizes to the Cajal body, a sub-nuclear structure involved in assembly and modification of RNPs. Although telomerase localizes to Cajal bodies, a process controlled in part the CAB box sequence in TERC, the proteins that recognized the CAB box had remained unknown. The CAB box in TERC is shared by scaRNAs, small non-coding RNAs involved in modification of splicing RNAs. Depletion of TCAB1 using RNA interference crippled the ability of telomerase to localize in Cajal bodies and prevented telomerase from maintaining telomeres. Thus, we identified TCAB1 as a new telomerase holoenzyme component, essential for nuclear trafficking and telomere maintenance. Dyskeratosis congenita (DC) is a genetic multi-systemic stem cell disease causing bone marrow failure, pulmonary fibrosis, liver cirrhosis and cancer. DC is caused by mutations in genes that control telomere homeostasis. I hypothesized that TCAB1 mutations may explain cases of unknown DC. We sequenced the TCAB1 gene in 9 families with unknown DC, and identified two unrelated patients with compound heterozygous point mutations in the TCAB1 gene. Each of the four disease-associated TCAB1 mutant proteins showed a marked defect in accumulation within the Cajal body. Localization of TERC within Cajal bodies was disrupted in patient lymphoblasts and in patient-derived iPS cells, resulting in mislocalization of TERC to nucleoli. These studies also provided the first evidence for a defect in telomerase trafficking as an underlying mechanism in DC patients. We predicted that interrupted telomerase trafficking may represent a general mechanism in disease, an idea now substantiated in pulmonary fibrosis and in DC (see below).

A. Venteicher AS, Abreu EB, Meng Z, McCann KE, Terns RM, Veenstra TD, Terns MP, Artandi SE (2009) A human telomerase holoenzyme protein required for Cajal body localization and telomere synthesis. **Science**, *323*: 644-648. PMCID: PMC2728071.
B. Zhong F, Savage SA, Shkreli M, Giri N, Jessop L, Myers T, Chen R, Alter BA, and Artandi SE (2011). Disruption of telomerase trafficking by TCAB1 mutation causes dyskeratosis congenita. **Genes and Development**, 25:11-16. PMCID: PMC3012932.
C. Batista LFZ, Pech MF, Zhong F, Nguyen HN, Xie KT, Zaug AJ, Crary SM, Choi J, Sebastiano V, Cherry A, Giri N, Wernig M, Alter BP, Cech TR, Savage SA, Reijo Pera RA, and Artandi SE (2011). Telomere shortening and loss of self-renewal in dyskeratosis congenita iPS cells. **Nature**, 474:399-402. PMCID: PMC3155806.
D. Chen L, Roake CM, Freund A, Batista PJ, Tian S, Yin YA, Gajera CR, Lin S, Lee B, Pech MF, Venteicher AS, Das R, Chang HY, Artandi SE (2018) An activity switch in human telomerase based on RNA conformation and shaped by TCAB1. **Cell**, 174:218-230.

3. Non-canonical roles for telomerase in cell proliferation

Telomerase is expressed in certain tissue stem cells and mutations in telomerase in people predispose to severe tissue failure phenotypes. To gain a more complete understanding of telomerase function, we generated transgenic mice in which TERT could be conditionally expressed in adult mouse tissues. Using this system, we made the surprising observation that telomerase overexpression stimulated quiescent epidermal stem cells and induced hair growth through a mechanism that did not require the conventional catalytic function of telomerase. Microarray studies on transgenic mouse skin pointed to an effect on Wnt signaling caused by TERT overexpression. Transgenic overexpression of TERT in vivo also activated quiescent epithelial cells in the kidney – podocytes – cells required for normal filtration. This inappropriate activation induced a specific kidney disease that occurs in humans. We found that in our mice and in human kidney disease samples, Wnt signaling was markedly elevated. These findings highlight the central importance of telomerase in proliferative pathways through a role independent of telomere elongation.

A. Sarin KY, Cheung P, Lee E, Gilison D, Artandi MK, Oro A, Artandi SE (2005) Conditional telomerase induction causes proliferation of hair follicle stem cells. **Nature**, *436*: 1048-1052. PMCID: PMC1361120.
B. Choi J, Southworth L, Sarin K, Venteicher AS, Ma W, Chang W, Cheung P, Jun S, Artandi MK, Shah N, Kim SK, Artandi SE (2008) TERT promotes epidermal proliferation through transcriptional control of a Myc- and Wnt-related developmental program. **PLoS Gen***, 4*: e10. PMCID: PMC2211538.
C. Park J-I, Venteicher AS, Hong JY, Choi J, Jun S, Shkreli M, Chang W, Meng Z, Cheung P, Ji H, McLaughlin M, Veenstra TD, Nusse R, McCrea PD, and Artandi SE (2009) Telomerase modulates Wnt signaling by association with target gene chromatin. **Nature**, *460*: 66-72. PMCID:19571879.
D. Shkreli M, Sarin KY, Pech MF, Papeta N, Chang W, Brockman SA, Cheung P, Lee E, Kuhnert F, Olson JL, Kuo CJ, Gharavi AG, D'Agati VD, Artandi SE (2011) Reversible cell cycle entry in adult kidney podocytes through regulated control of telomerase and Wnt signaling. **Nature Medicine**. Dec 4. doi: 10.1038/nm.2550. PMCID: PMC3272332.

4. Mechanisms controlling telomerase assembly and recruitment to telomeres

Despite progress in understanding telomerase in genetic terms, progress on mechanisms of telomerase regulation and function proved challenging due to the very low abundance of telomerase. Using a dual affinity chromatography strategy coupled with mass spectrometry, we identified the ATPases pontin and reptin as telomerase associated proteins. Pontin and reptin are hexameric AAA+ ATPases (for ATPases associated with a variety of cellular activities) previously linked to diverse cellular complexes but their precise molecular roles remained unclear. We found that pontin/reptin is required for assembly of telomerase and for accumulation of the telomerase RNA component (TERC) and for complex assembly. Based on advances in microscopic detection of telomerase, we deployed the first genome-wide siRNA screen for telomerase regulators in human cells using a high content approach for telomerase localization. We identified the chaperonin TRiC as being required for localization of telomerase in Cajal bodies. We showed that all eight subunits of TRiC were bound to TCAB1, the central regulator of telomerase trafficking. By studying TCAB1 folding in cell-free extracts, we showed that TRiC is essential for folding TCAB1. Furthermore, TCAB1 mutations in patients disrupt TCAB1 function by specifically interfering with the ability of TRiC to fold the TCAB1 protein. These data revealed that the TCAB1-mutant form of dyskeratosis congenita is caused by folding mutations that dramatically impair the ability of correctly folded TCAB1 to be produced, resulting in a severe multi-systemic disease. We sought to understand how telomerase is physically recruited to chromosomes in living cells through the use of a tethering assay, which would allow telomerase associations at an immobilized telomere binding protein to be tested on chromatin away from telomeres. We found that a single module within the telomere binding protein TPP1 – the OB-fold domain – was sufficient to mediate this interaction with telomerase. Importantly, we found that specific TERT mutations derived from patients with familial pulmonary fibrosis, specifically disrupted telomerase recruitment, indicating that in these patients impaired recruitment of telomerase to telomeres is the underlying cause of the disease. These data revealed that the TPP1-TERT association is critical for maintaining telomeres in human cancer cells. Furthermore, these data expanded on our previous findings to reveal that disruption of nuclear trafficking or telomerase recruitment to telomeres are each important mechanisms in telomere disease states such as dyskeratosis congenita and pulmonary fibrosis.

A. Venteicher AS, Meng Z, Mason PJ, Veenstra TD, Artandi SE (2008) Identification of ATPases pontin and reptin as telomerase components essential for holoenzyme assembly. **Cell**, *132*: 945-957. PMCID: PMC2291539.
B. Freund A, Zhong F, Venteicher AS, Meng Z, Veenstra TD, Frydman J, Artandi SE (2014). Proteostatic control of telomerase function through TRiC-mediated folding of TCAB1. **Cell**, 159:1389-403.
C. Zhong F, Batista LZ, Freund A, Pech MF, Venteicher AS, Artandi SE (2012) TPP1 OB-fold domain controls telomere maintenance by recruiting telomerase to chromosome ends. **Cell**, 150:481-94. PMCID: PMC3516183.

5. Identification of new cell populations renewing adult tissues

Based on the importance of telomerase in tissue renewal, we have pursued the idea that many tissues may contain rare subpopulations of telomerase-expressing cells that may serve as key repopulating cells or tissue stem cells. To identify, isolate and study such cells from different tissues, we have created knock-in mice in which fluorescent report proteins, including either CreER or TdTomato are expressed from the endogenous TERT promoter. This approach has enabled the isolation from adult mice of undifferentiated spermatogonia, the population of cells harboring the male germline stem cells. We showed that these cells are the ones depleted by telomere dysfunction in telomerase-deficient mice, revealing that the failure of the male germline in metazoans with telomerase defects is due to a loss of male germline stem cells. Using TERT-CreER knock-in mice, we found that 5% of hepatocytes express high levels of telomerase. These $TERT^{High}$ hepatocytes repopulated the liver during normally homeostasis to replace hepatocytes lost during normal tissue wear and tear. $TERT^{High}$ hepatocytes showed a distribution throughout the lobule and both self-renewed and differentiated while clonally expanding to renew the liver. During injury, clonal expansion of $TERT^{High}$ hepatocytes was markedly accelerated as more severe injury required more rapid cellular repopulation. $TERT^{High}$ hepatocytes differed from bulk hepatocytes in that they showed lower expression of ribosomal proteins genes and electron transport chain genes, indicating that metabolic functions and repopulating activities are compartmentalized within the hepatocyte lineage. Together, these data in the liver provided support for a 'distributed model' in which $TERT^{High}$ hepatocytes clonally expand to maintain liver mass.

A. Pech MF, Garbuzov A, Hasegawa K, Sukhwani M, Zhang RJ, Benayoun BA, Brockman SA, Lin S, Brunet A, Orwig KE, Artandi SE (2015) High telomerase is a hallmark of undifferentiated spermatogonia and is required for maintenance of male germline stem cells. **Genes and Development***,* 29:2420-34.
B. Garbuzov A, Pech MF, Hasegawa K, Sukhwani M, Zhang RJ, Orwig KE, Artandi SE (2018) Purification of GFRα1+ and GFRα1- Spermatogonial Stem Cells Reveals a Niche-Dependent Mechanism for Fate Determination. **Stem Cell Reports**, 10:553-567.
C. Lin S, Nascimento EM, Gajera C, Chen L, Neuhoefer P, Garbuzov A, Wang S, and Artandi SE (2018) Distributed hepatocytes expressing telomerase repopulate the liver in homeostasis and injury. **Nature**, 556:244-248.

Link to NCBI MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/steven.artandi.1/bibliography/43077903/public/?sort=date&direction=ascending.

D. RESEARCH SUPPORT

Active

R35 CA197563 (Artandi, PI) 09/15/15-09/14/22
NCI Outstanding Investigator Award
Reversing Cellular Immortality in Cancer
This proposal strives to understand telomerase regulation in cancers and to develop methods to reverse cellular immortality.

R01 AG056575 (Artandi, PI) 9/15/2017 – 8/31/22
NIH/NIA
Determining the Role of TCAB1 in Shaping Telomerase Function
This proposal studies the function of TCAB1 in telomerase function

Completed Research Support

R01AG033747 (Artandi, PI) 12/1/09-8/31/17
NIH/NIA
Defining the telomerase holoenzyme in progenitor cells with aging
This proposal studied the function of TCAB1 in telomerase during aging.

NIH PO1 AG036695 (Rando, PI) 07/1/11-06/30/16
NIH/NIA
Molecular regulation of stem cell aging
Telomerase in stem cell aging (Artandi, Project Leader)
This project studied how stem cells change with advancing age.

R01 CA111691 (Artandi, PI) 05/01/05-09/14/15
NIH/NCI
Telomeres, telomerase and tumor progression
This proposal studied how TERT is regulated within specific cancer cells in vivo.

R01 CA125453 (Artandi, PI) 09/01/06 – 09/14/15
NIH/NCI
Regulation of the telomerase protein component in cancer
This study analyzed telomerase recruitment to telomeres in human cancer cells.

NIH 1RC1HL100361 (Artandi, PI) 04/07/10-03/31/13
NIH/NHLBI
Studying a human stem cell disease using iPS technology
This study analyzed iPS cells from a human stem cell disease using proteomics.