



Steven Artandi

Jerome and Daisy Low Gilbert Professor and Professor of Biochemistry
Medicine - Hematology

 NIH Biosketch available Online

CONTACT INFORMATION

• Administrative Contact

Christine Yi - Executive Assistant

Email cyi1@stanford.edu

Tel (650)725-4216

Bio

BIO

Steven Artandi, MD, PhD is the Laurie Kraus Lacob Director of the Stanford Cancer Institute and the Jerome and Daisy Low Gilbert Professor of Medicine and Biochemistry at Stanford University. He also serves as the inaugural Senior Associate Dean for Cancer Programs for Stanford School of Medicine and the Chief Cancer Officer for Stanford Health Care. He received his undergraduate degree from Princeton University, and MD and PhD degrees from Columbia University. He trained in Internal Medicine at Massachusetts General Hospital and in Oncology at Dana-Farber Cancer Institute before joining the Stanford faculty in 2000. Dr. Artandi is an oncologist and cancer biologist whose research work has focused on the role played by the enzyme telomerase in cancer, aging and stem cell function. His work has produced new insights into the origins of cancer, revealing how telomerase endows cells with immortal growth properties and how aspiring cancers circumvent critical bottlenecks encountered during carcinogenesis. He has received a number of awards including an Outstanding Investigator Award from the National Cancer Institute and is an elected member of the American Association for the Advancement of Science, the American Society for Clinical Investigation and the Association of American Physicians. He serves on the Editorial Boards of the journals Molecular Cancer Research and Stem Cells.

ACADEMIC APPOINTMENTS

- Professor, Medicine - Hematology
- Professor, Biochemistry
- Member, Bio-X
- Member, Maternal & Child Health Research Institute (MCHRI)
- Member, Stanford Cancer Institute

ADMINISTRATIVE APPOINTMENTS

- Director, Stanford Cancer Institute, (2018- present)
- Senior Associate Dean for Cancer Programs, Stanford School of Medicine, (2021- present)
- Chief Cancer Officer, Stanford Health Care, (2021- present)

HONORS AND AWARDS

- Fellow, American Association for the Advancement of Science (AAAS) (2008)

- Elected Member, American Society for Clinical Investigation (2008)
- Elected Member, Association of American Physicians (2015)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Member, American Association for Cancer Research (2002 - present)
- Editorial Board, Stem Cells (2006 - present)
- Member, American Society of Hematology (2008 - present)
- Member, American Society for Clinical Investigation (2009 - present)
- Editorial Board, Molecular Cancer Research (2013 - present)
- Member, Association of American Physicians (2015 - present)
- Member, American Association for the Advancement of Science (2019 - present)

PROFESSIONAL EDUCATION

- Fellowship: Dana Farber Cancer Institute Hematology Oncology Fellowship (2000) MA
- Residency: Massachusetts General Hospital (1997) MA
- Medical Education: Columbia University (1995) NY
- A.B., Princeton University , Chemistry (1986)
- M.D., Columbia University (1995)
- Ph.D., Columbia University , Microbiology (1995)
- Internship, Massachusetts General Hospital (1996)
- Residency, Massachusetts General Hospital (1997)
- Board Certification, Internal Medicine, American Board of Internal Medicine (1998)
- Oncology Fellowship, Dana-Farber Cancer Institute (2000)
- Board Certification, Oncology, American Board of Internal Medicine (2001)

LINKS

- Artandi Lab home page: <http://www.artandilab.stanford.edu>
- Stanford Cancer Institute: <http://med.stanford.edu/cancer.html>
- Uniquely Stanford Cancer: <https://www.youtube.com/channel/UC7VM8K6EwEf32lpwDajtx6Q>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Telomeres are nucleoprotein complexes that protect chromosome ends and shorten with cell division and aging. We are interested in how telomere shortening influences cancer, stem cell function, aging and human disease. Telomerase is a reverse transcriptase that synthesizes telomere repeats and is expressed in stem cells and in cancer. We have found that telomerase also regulates stem cells and we are pursuing the function of telomerase through diverse genetic and biochemical approaches.

Teaching

STANFORD ADVISEES

Med Scholar Project Advisor

Santiago Sanchez

Doctoral Dissertation Reader (AC)

Tara Murty

Postdoctoral Faculty Sponsor

Mennatallah Albarqi, Aya Awad, Seung Kuk Park, Yan Wang, Jun Wu

Doctoral Dissertation Advisor (AC)

Santiago Sanchez

Postdoctoral Research Mentor

Yan Wang

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biochemistry (Phd Program)
- Cancer Biology (Phd Program)
- Hematology (Fellowship Program)
- Oncology (Fellowship Program)

Publications

PUBLICATIONS

- **TRF2 rescues telomere attrition and prolongs cell survival in Duchenne muscular dystrophy cardiomyocytes derived from human iPSCs** *Proceedings of the National Academy of Sciences of the United States of America*
Eguchi, A., Gonzalez, A. G., Torres-Bigio, S. I., Koleckar, K., Birnbaum, F., Zhang, J. Z., Wang, V. Y., Wu, J. C., Artandi, S. E., Blau, H. M.
2023; 120 (6): e2209967120
- **Acinar cell clonal expansion in pancreas homeostasis and carcinogenesis.** *Nature*
Neuhofer, P., Roake, C. M., Kim, S. J., Lu, R. J., West, R. B., Charville, G. W., Artandi, S. E.
2021
- **Tissue-specific telomere shortening and degenerative changes in a patient with TINF2 mutation and dyskeratosis congenita.** *Human pathology (New York)*
Roake, C. M., Juntilla, M., Agarwal-Hashmi, R., Artandi, S., Kuo, C. S.
2021; 25
- **Targeted replacement of full-length CFTR in human airway stem cells by CRISPR/Cas9 for pan-mutation correction in the endogenous locus.** *Molecular therapy : the journal of the American Society of Gene Therapy*
Vaidyanathan, S. n., Baik, R. n., Chen, L. n., Bravo, D. T., Suarez, C. J., Abazari, S. M., Salahudeen, A. A., Dudek, A. M., Teran, C. A., Davis, T. H., Lee, C. M., Bao, G. n., Randell, et al
2021
- **Analysis of RNA conformation in endogenously assembled RNPs by icSHAPE** *STAR protocols*
Chen, L., Chang, H. Y., Artandi, S. E.
2021; 2 (2)
- **A novel DDB2 mutation causes defective recognition of UV-induced DNA damages and prevalent equine squamous cell carcinoma.** *DNA repair*
Chen, L., Bellone, R. R., Wang, Y., Singer-Berk, M., Sugasawa, K., Ford, J. M., Artandi, S. E.
2020; 97: 103022
- **Loss of human TGS1 hypermethylase promotes increased telomerase RNA and telomere elongation** *Cell Reports*
Chen, L., Roake, C. M., Galati, A., Bavasso, F., Micheli, E., Saggio, I., Schoeftner, S., Cacchione, S., Gatti, M., Artandi, S. E., Raffa, G. D.
2020: 1358-1372
- **Regulation of human telomerase in homeostasis and disease.** *Nature reviews. Molecular cell biology*
Roake, C. M., Artandi, S. E.
2020

- **A novel DDB2 mutation causes defective recognition of UV-induced DNA damages and prevalent equine squamous cell carcinoma** *DNA Repair*
Chen, L., Bellone, R. R., Wang, Y., Singer-Berk, M., Sugasawa, K., Ford, J. M., Artandi, S. E.
2020
- **HiChIRP reveals RNA-associated chromosome conformation.** *Nature methods*
Mumbach, M. R., Granja, J. M., Flynn, R. A., Roake, C. M., Satpathy, A. T., Rubin, A. J., Qi, Y., Jiang, Z., Shams, S., Louie, B. H., Guo, J. K., Gennert, D. G., Corces, et al
2019
- **Disruption of Telomerase RNA Maturation Kinetics Precipitates Disease.** *Molecular cell*
Roake, C. M., Chen, L., Chakravarthy, A. L., Ferrell, J. E., Raffa, G. D., Artandi, S. E.
2019
- **An Activity Switch in Human Telomerase Based on RNA Conformation and Shaped by TCAB1** *CELL*
Chen, L., Roake, C. M., Freund, A., Batista, P. J., Tian, S., Yin, Y. A., Gajera, C. R., Lin, S., Lee, B., Pech, M. F., Venteicher, A. S., Das, R., Chang, et al
2018; 174 (1): 218+
- **Distributed hepatocytes expressing telomerase repopulate the liver in homeostasis and injury** *NATURE*
Lin, S., Nascimento, E. M., Gajera, C. R., Chen, L., Neuhofer, P., Garbuzov, A., Wang, S., Artandi, S. E.
2018; 556 (7700): 244+
- **Approaching TERRA Firma: Genomic Functions of Telomeric Noncoding RNA** *CELL*
Roake, C. M., Artandi, S. E.
2017; 170 (1): 8–9
- **Control of Cellular Aging, Tissue Function, and Cancer by p53 Downstream of Telomeres.** *Cold Spring Harbor perspectives in medicine*
Roake, C. M., Artandi, S. E.
2017; 7 (5)
- **Pulmonary arteriovenous malformations: an uncharacterised phenotype of dyskeratosis congenita and related telomere biology disorders** *EUROPEAN RESPIRATORY JOURNAL*
Khincha, P. P., Bertuch, A. A., Agarwal, S., Townsley, D. M., Young, N. S., Keel, S., Shimamura, A., Boulad, F., Simoneau, T., Justino, H., Kuo, C., Artandi, S., McCaslin, et al
2017; 49 (1)
- **DNA repair: Telomere-lengthening mechanism revealed.** *Nature*
Roake, C. M., Artandi, S. E.
2016; 539 (7627): 35-36
- **Dual SMAD Signaling Inhibition Enables Long-Term Expansion of Diverse Epithelial Basal Cells.** *Cell stem cell*
Mou, H., Vinarsky, V., Tata, P. R., Brazauskas, K., Choi, S. H., Crooke, A. K., Zhang, B., Solomon, G. M., Turner, B., Bihler, H., Harrington, J., Lapey, A., Channick, et al
2016; 19 (2): 217-231
- **Mechanisms Governing Disruption of Telomere Maintenance in Dyskeratosis Congenita**
Artandi, S.
AMER SOC HEMATOLOGY.2015
- **High telomerase is a hallmark of undifferentiated spermatogonia and is required for maintenance of male germline stem cells.** *Genes & development*
Pech, M. F., Garbuzov, A., Hasegawa, K., Sukhwani, M., Zhang, R. J., Benayoun, B. A., Brockman, S. A., Lin, S., Brunet, A., Orwig, K. E., Artandi, S. E.
2015; 29 (23): 2420-2434
- **Keeping It in the Family: ATRX Loss Promotes Persistent Sister Telomere Cohesion in ALT Cancer Cells.** *Cancer cell*
Roake, C. M., Artandi, S. E.
2015; 28 (3): 277-279
- **Reversibility of Defective Hematopoiesis Caused by Telomere Shortening in Telomerase Knockout Mice** *PLOS ONE*
Raval, A., Behbehani, G. K., Le Xuan Truong Nguyen, L. X., Thomas, D., Kusler, B., Garbuzov, A., Ramunas, J., Holbrook, C., Park, C. Y., Blau, H., Nolan, G. P., Artandi, S. E., Mitchell, et al
2015; 10 (7)

- **Stem Cells and Aging: What's Next?** *CELL STEM CELL*
Artandi, S. E., Blau, H. M., de Haan, G., Geiger, H., Goodell, M. A., Jones, L., Levine, R. L., Munoz-Canoves, P., Rodewald, H., Wagers, A., Wang, Z., Yamashita, Y.
2015; 16 (6): 578–81
- **A platform for rapid exploration of aging and diseases in a naturally short-lived vertebrate.** *Cell*
Harel, I., Benayoun, B. A., Machado, B., Singh, P. P., Hu, C., Pech, M. F., Valenzano, D. R., Zhang, E., Sharp, S. C., Artandi, S. E., Brunet, A.
2015; 160 (5): 1013-1026
- **A platform for rapid exploration of aging and diseases in a naturally short-lived vertebrate.** *Cell*
Harel, I., Benayoun, B. A., Machado, B., Singh, P. P., Hu, C., Pech, M. F., Valenzano, D. R., Zhang, E., Sharp, S. C., Artandi, S. E., Brunet, A.
2015; 160 (5): 1013-1026
- **Inhibition of pluripotency networks by the rb tumor suppressor restricts reprogramming and tumorigenesis.** *Cell stem cell*
Kareta, M. S., Gorges, L. L., Hafeez, S., Benayoun, B. A., Marro, S., Zmoos, A., Cecchini, M. J., Spacek, D., Batista, L. F., O'Brien, M., Ng, Y., Ang, C. E., Vaka, et al
2015; 16 (1): 39-50
- **Reversibility of Defective Hematopoiesis Caused by Telomere Shortening in Telomerase Knockout Mice.** *PloS one*
Raval, A., Behbehani, G. K., Nguyen, L. X., Thomas, D., Kusler, B., Garbuzov, A., Ramunas, J., Holbrook, C., Park, C. Y., Blau, H., Nolan, G. P., Artandi, S. E., Mitchell, et al
2015; 10 (7)
- **Proteostatic Control of Telomerase Function through TRiC-Mediated Folding of TCAB1** *CELL*
Freund, A., Zhong, F. L., Venteicher, A. S., Meng, Z., Veenstra, T. D., Frydman, J., Artandi, S. E.
2014; 159 (6): 1389-1403
- **Understanding telomere diseases through analysis of patient-derived iPSCs.** *Current opinion in genetics & development*
Batista, L. F., Artandi, S. E.
2013; 23 (5): 526-533
- **Reactivation of Telomerase in Late Generation Tert^{-/-} Mice Results in Reversal of Anemia** *54th Annual Meeting and Exposition of the American-Society-of-Hematology (ASH)*
Raval, A., Kusler, B., Garbuzov, A., Artandi, S., Mitchell, B. S.
AMER SOC HEMATOLOGY.2012
- **TPP1 OB-Fold Domain Controls Telomere Maintenance by Recruiting Telomerase to Chromosome Ends** *CELL*
Zhong, F. L., Batista, L. F., Freund, A., Pech, M. F., Venteicher, A. S., Artandi, S. E.
2012; 150 (3): 481-494
- **Reversible cell-cycle entry in adult kidney podocytes through regulated control of telomerase and Wnt signaling.** *Nature medicine*
Shkreli, M., Sarin, K. Y., Pech, M. F., Papeta, N., Chang, W., Brockman, S. A., Cheung, P., Lee, E., Kuhnert, F., Olson, J. L., Kuo, C. J., Gharavi, A. G., D'Agati, et al
2012; 18 (1): 111-119
- **Reversible cell-cycle entry in adult kidney podocytes through regulated control of telomerase and Wnt signaling** *NATURE MEDICINE*
Shkreli, M., Sarin, K. Y., Pech, M. F., Papeta, N., Chang, W., Brockman, S. A., Cheung, P., Lee, E., Kuhnert, F., Olson, J. L., Kuo, C. J., Gharavi, A. G., D'Agati, et al
2012; 18 (1): 111-119
- **Genomic Maps of Long Noncoding RNA Occupancy Reveal Principles of RNA-Chromatin Interactions** *MOLECULAR CELL*
Chu, C., Qu, K., Zhong, F. L., Artandi, S. E., Chang, H. Y.
2011; 44 (4): 667-678
- **Defective Hematopoiesis and Erythroid Differentiation Resulting From Telomerase Deficiency**
Raval, A., Kusler, B., Artandi, S., Mitchell, B. S.
AMER SOC HEMATOLOGY.2011: 1036–37
- **In Situ Genetic Correction of the Sick Cell Anemia Mutation in Human Induced Pluripotent Stem Cells Using Engineered Zinc Finger Nucleases** *STEM CELLS*

- Sebastiano, V., Maeder, M. L., Angstman, J. F., Haddad, B., Khayter, C., Yeo, D. T., Goodwin, M. J., Hawkins, J. S., Ramirez, C. L., Batista, L. F., Artandi, S. E., Wernig, M., Joung, et al
2011; 29 (11): 1717-1726
- **Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells** *NATURE*
Batista, L. F., Pech, M., Zhong, F. L., Nguyen, H. N., Xie, K. T., Zaug, A. J., Crary, S. M., Choi, J., Sebastiano, V., Cherry, A., Giri, N., Wernig, M., Alter, et al
2011; 474 (7351): 399-?
 - **TRAPping telomerase within the intestinal stem cell niche** *EMBO JOURNAL*
Pech, M. F., Artandi, S. E.
2011; 30 (6): 986-987
 - **Disruption of telomerase trafficking by TCAB1 mutation causes dyskeratosis congenita** *GENES & DEVELOPMENT*
Zhong, F., Savage, S. A., Shkreli, M., Giri, N., Jessop, L., Myers, T., Chen, R., Alter, B. P., Artandi, S. E.
2011; 25 (1): 11-16
 - **Short Telomeres and Stem Cell Exhaustion Model Duchenne Muscular Dystrophy in mdx/mTR Mice** *CELL*
Sacco, A., Mourkioti, F., Tran, R., Choi, J., Llewellyn, M., Kraft, P., Shkreli, M., Delp, S., Pomerantz, J. H., Artandi, S. E., Blau, H. M.
2010; 143 (7): 1059-1071
 - **Shared molecular mechanisms regulate multiple catenin proteins: canonical Wnt signals and components modulate p120-catenin isoform-1 and additional p120 subfamily members** *JOURNAL OF CELL SCIENCE*
Hong, J. Y., Park, J., Cho, K., Gu, D., Ji, H., Artandi, S. E., McCrea, P. D.
2010; 123 (24): 4351-4365
 - **Mutations In TCAB1 Cause Dyskeratosis Congenita** *52nd Annual Meeting and Exposition of the American-Society-of-Hematology (ASH)*
Savage, S. A., Zhong, F., Giri, N., Jessop, L., Myers, T., Chen, R., Alter, B. P., Artandi, S.
AMER SOC HEMATOLOGY.2010: 90-91
 - **Telomeres and telomerase in cancer** *CARCINOGENESIS*
Artandi, S. E., DePinho, R. A.
2010; 31 (1): 9-18
 - **Reverse Transcribing the Code for Chromosome Stability** *MOLECULAR CELL*
Artandi, S. E., Cooper, J. P.
2009; 36 (5): 715-719
 - **Telomerase modulates Wnt signalling by association with target gene chromatin** *NATURE*
Park, J., Venteicher, A. S., Hong, J. Y., Choi, J., Jun, S., Shkreli, M., Chang, W., Meng, Z., Cheung, P., Ji, H., McLaughlin, M., Veenstra, T. D., Nusse, et al
2009; 460 (7251): 66-U77
 - **Stem Cell Aging and Aberrant Differentiation within the Niche** *CELL STEM CELL*
Choi, J., Artandi, S.
2009; 5 (1): 6-8
 - **Telomere Uncapping, Chromosomes, and Carcinomas** *CANCER CELL*
Batista, L. F., Artandi, S. E.
2009; 15 (6): 455-457
 - **TCAB1 Driving telomerase to Cajal bodies** *CELL CYCLE*
Venteicher, A. S., Artandi, S. E.
2009; 8 (9): 1329-1331
 - **Telomerase in stem cell regulation and cancer**
Artandi, S., Venteicher, A., Choi, J., Park, J., Shkreli, M., Chang, W., Jun, S.
AMER ASSOC CANCER RESEARCH.2009
 - **A Human Telomerase Holoenzyme Protein Required for Cajal Body Localization and Telomere Synthesis** *SCIENCE*
Venteicher, A. S., Abreu, E. B., Meng, Z., McCann, K. E., Terns, R. M., Veenstra, T. D., Terns, M. P., Artandi, S. E.
2009; 323 (5914): 644-648

- **Telomerase-dependent and -independent chromosome healing in mouse embryonic stem cells** *DNA REPAIR*
Gao, Q., Reynolds, G. E., Wilcox, A., Miller, D., Cheung, P., Artandi, S. E., Murnane, J. P.
2008; 7 (8): 1233-1249
- **Identification of ATPases pontin and reptin as telomerase components essential for holoenzyme assembly** *CELL*
Venteicher, A. S., Meng, Z., Mason, P. J., Veenstra, T. D., Artandi, S. E.
2008; 132 (6): 945-957
- **Telomere uncapping in progenitor cells with critical telomere shortening is coupled to S-phase progression in vivo** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Rajaraman, S., Choi, J., Cheung, P., Beaudry, V., Moore, H., Artandi, S. E.
2007; 104 (45): 17747-17752
- **DNA-dependent protein kinase catalytic subunit is not required for dysfunctional telomere fusion and checkpoint response in the telomerase-deficient mouse** *MOLECULAR AND CELLULAR BIOLOGY*
Maser, R. S., Wong, K., Sahin, E., Xia, H., Naylor, M., Hedberg, H. M., Artandi, S. E., DePinho, R. A.
2007; 27 (6): 2253-2265
- **Aging, graying and loss of melanocyte stem cells** *STEM CELL REVIEWS*
Sarin, K. Y., Artandi, S. E.
2007; 3 (3): 212-217
- **Telomeres, telomerase, and human disease.** *New England journal of medicine*
Artandi, S. E.
2006; 355 (12): 1195-1197
- **Telomerase flies the coop: the telomerase RNA component as a viral-encoded oncogene** *JOURNAL OF EXPERIMENTAL MEDICINE*
Artandi, S. E.
2006; 203 (5): 1143-1145
- **Regulation of cellular immortalization and steady-state levels of the telomerase reverse transcriptase through its carboxy-terminal domain** *MOLECULAR AND CELLULAR BIOLOGY*
Middleman, E. J., Choi, J. K., Venteicher, A. S., Cheung, P., Artandi, S. E.
2006; 26 (6): 2146-2159
- **Conditional telomerase induction causes proliferation of hair follicle stem cells** *NATURE*
Sarin, K. Y., Cheung, P., Gilson, D., Lee, E., Tennen, R. I., Wang, E., Artandi, M. K., Oro, A. E., Artandi, S. E.
2005; 436 (7053): 1048-1052
- **Pathways connecting telomeres and p53 in senescence, apoptosis, and cancer** *BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS*
Artandi, S. E., Attardi, L. D.
2005; 331 (3): 881-890
- **Complex roles for telomeres and telomerase in breast carcinogenesis** *BREAST CANCER RESEARCH*
Artandi, S. E.
2003; 5 (1): 37-41
- **Constitutive telomerase expression promotes mammary carcinomas in aging mice** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Artandi, S. E., Alson, S., Tietze, M. K., Sharpless, N. E., Ye, S., Greenberg, R. A., Castrillon, D. H., Horner, J. W., Weiler, S. R., Carrasco, R. D., DePinho, R. A.
2002; 99 (12): 8191-8196
- **Telomere shortening and cell fates in mouse models of neoplasia** *TRENDS IN MOLECULAR MEDICINE*
Artandi, S. E.
2002; 8 (1): 44-47
- **Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice.**
Artandi, S. E., Chang, S., Alson, S., Lee, S. L., Gottlieb, G., Chin, L., DePinho, R. A.
AMER SOC HEMATOLOGY.2000: 705A

- **Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice** *NATURE*
Artandi, S. E., Chang, S., Lee, S. L., Alson, S., Gottlieb, G. J., Chin, L., DePinho, R. A.
2000; 406 (6796): 641-645
- **Mice without telomerase: what can they teach us about human cancer?** *NATURE MEDICINE*
Artandi, S. E., DePinho, R. A.
2000; 6 (8): 852-855
- **A critical role for telomeres in suppressing and facilitating carcinogenesis** *CURRENT OPINION IN GENETICS & DEVELOPMENT*
Artandi, S. E., DePinho, R. A.
2000; 10 (1): 39-46
- **p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis** *CELL*
Chin, L., Artandi, S. E., Shen, Q., Tam, A., Lee, S. L., Gottlieb, G. J., Greider, C. W., DePinho, R. A.
1999; 97 (4): 527-538