BIOGRAPHICAL SKETCH

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NAME: An, Steven S.

eRA COMMONS USER NAME (credential, e.g., agency login): san003

POSITION TITLE: Director of Bioengineering and Professor of Pharmacology

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 Virginia, Charlottesville, VA	B.A.	06/1993	Chemistry
Albany Medical College, Albany, NY	M.S.	05/1995	Physiology & Cell Biology
Brown University, Providence, RI	Ph.D.	05/2000	Mol. Pharm. & Physiology
Harvard University, Boston, MA	Postdoctoral	07/2003	Respiratory Physiology & Cellular Biophysics

A. Personal Statement

My current work comprises both basic and translational research focusing on the cellular and molecular basis for obstructive lung disease. I bring to this field, a multi-disciplinary approach that combines a rigorous education in human physiology and cell biology, along with training and research in cell mechanics and bioengineering. My lab has the unique capability to measure, at the single cell level, dynamic changes in stiffness using optical magnetic twisting cytometry (OMTC), contractile force using Fourier transform traction microscopy (FTTM), and discrete molecular-level remodeling of the living cytoskeleton using *spontaneous* nanoscale tracer motions (SNTM). These cutting-edge nanotechnologies are readily applicable to a wide variety of cell types and have broad research applications that are at the interface between engineering, cell biology, and medicine. Over the last 18 years, I have applied these innovative single-cell analyses, in combination with multiple (epi)genome, chemical and mechanical manipulations, to address a range of fundamental questions in biology that have direct bearing on 1) the mechanisms underpinning excitation-contraction coupling in smooth muscle and 2) the discovery of new therapeutic modalities to treat obstructive lung disease. For my earlier contributions to the regulation of airway smooth muscle contraction and airway hyperresponsiveness in asthma, I received 2016 Ann Woolcock Memorial award from the American Thoracic Society. In 2019, I became an elected fellow of the Society. As a principal investigator and/or co-investigator on several NIH-funded grants, I established strong research collaborations and am uniquely positioned to advance these cell-based studies to *ex vivo* and *in vivo* studies using precision-cut lung slices and animal models of asthma. Recently, my lab has developed a new microphysiological engineering platform that reconstitutes 3D co-cultures of human airway smooth muscle cells with clinically-relevant human airway epithelial cells that are fully differentiated in an air-liquid interface (US Provisional Patent application C-13594). This “bronchi-chip” is equipped with OMTC enabling, in real-time, chemical and mechanical interrogations into the heterotypic cell communications driving asthmatic bronchospasm (Nat. Biomed. Eng. 2019: one of the top 25 most-viewed articles in 2019). Of note, these suites of bioengineering methods have been instrumental in elucidating the physiologic functions of previously unidentified chemosensory G protein-coupled receptors on airway smooth muscle, as well as the physical basis of cancer cell migration and metastasis. At Hopkins, I have been an active member of the cross-disciplinary research teams that include faculty from the School of Public Health, the School of Medicine, and the School of Engineering; and have trained or co-mentored 15 pre-doctoral students (5 PhD and 11 MHS/MPH) and 9 postdoctoral fellows, among which 9 are in tenure line positions. Our recent relocation to Rutgers University after 13 years at Hopkins will further strengthen our team science, build new creative tension across scientific disciplines, and empower my trainees in their endeavors to bring groundbreaking measurement technologies to biomedical and health sciences.

Ongoing and recently completed projects that I would like to highlight include:

Intergovernment Personnel Act Mobility Program, NIH / NIA / IRP / Laboratory of Cardiovascular Science
An (PI)
12/30/19-04/19/22
Exploring interactions between age-associated vascular and neurodegenerative processes in cognitive impairment and Alzheimer's disease.

R01 HL058506
Penn (PI)
01/01/17-12/31/22
G protein-coupled receptor regulation in airway myocytes

P01 HL114471
Panettieri (PI/PD)
07/01/19-06/30/24
Novel molecular mechanisms promote GPCR-induced bronchodilation in airway disease

R01 HL155532
Liggett (PI)
01/01/21-12/31/24
Characterization of biased airway smooth muscle TAS2R agonists for treating asthma

R01 HL148112
Santhanam (PI)
04/01/20-03/31/25
Lysyl oxidase-like 2: A novel target in age-associated vascular stiffening

R01 HL153602
Nayak (PI)
07/01/21-06/30/26
Mitochondrial translocator protein: a target for bronchodilation

R01 HL109557
Gerber (PI)
04/15/22-02/28/26
Mechanisms and consequences of gene induction by glucocorticoids in airway smooth muscle

R01 DK129462
Ettickan (PI)
09/15/22-08/31/25
Mechanisms of contractile dysfunction in the obstructed bladder: Role of desmin and vimentin

Citations:

1. Ahn K, Penn RB, Rattan S, Panettieri RA, Voight B & **An SS**. (2023) Mendelian randomization analysis reveals a complex genetic interplay among atopic dermatitis, asthma, and gastroesophageal reflux disease. American Journal of Respiratory and Critical Care Medicine 207, 130-137. PMCID: PMC9893317
2. Cao G, Lam H, Jude JA, Karmacharya N, Kan M, Jester W, Koziol-White C, Himes BE, Chupp GL, **An SS*** & Panettieri RA*. (2022) Inhibition of ABCC1 decreases cAMP egress and promotes human airway smooth muscle cell relaxation. American Journal of Respiratory Cell & Molecular Biology 66, 96-106. PMCID: PMC8803359
3. **An SS**, Kilic O & Levchenko A. Device and method for analysis of tissue constructs. USPTO, Application#62187641 (submitted July 1, 2015)
4. Kim DW, **An SS**, Leahy JW & Liggett SB. Novel bronchodilators for treating obstructive lung disease. USPTO, Application#17464233 (submitted August 9, 2020)

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019-Present	Director of Bioengineering, the Rutgers Institute for Translational Medicine and Science, The State University of New Jersey, New Brunswick, NJ
2019-Present	Professor, Department of Pharmacology, Rutgers-Robert Wood Johnson Medical School, The State University of New Jersey, Piscataway, NJ
2012-2019	Associate Professor, Department of Environmental Health and Engineering, Department of Biochemistry and Molecular Biology, Department of Oncology, and Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD
2006-2012	Assistant Professor, Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2003-2005	Research Associate, Division of Molecular and Integrative Physiological Sciences, Harvard School of Public Health, Boston, MA
2022-Present	Associate Editor, Respiratory Research
2021-Present	Associate Editor, Frontiers in Network Physiology; Frontiers in Physiology (Editorial Board)
2017-Present	Editorial Board, American Journal of Respiratory Cell and Molecular Biology
2017-Present	Member, College of Reviewers, Canadian Institutes of Health Research
2016-Present	Member, Canadian Institutes of Health Research Project Grants
2015	Co-Chair, Respiratory Integrative Biology and Translational Research Study Section, ad hoc
2000-Present	Member, American Thoracic Society (ATS)
2013-2015	Program Chair-Elect & Chair, Respiratory Structure and Function Assembly of the ATS
2011, 2017	Nominating Committee, Respiratory Structure and Function Assembly of the ATS
2009-2016	Program Committee, Respiratory Structure and Function Assembly of the ATS
2007-2011	Planning Committee, Respiratory Structure and Function Assembly of the ATS

Honors

2021	New Jersey Alliance for Clinical and Translational Science (NJ ACTS) Academy of Mentors
2020	Distinguished Scientist Seminars, University of South Alabama
2019	Elected Fellow of the American Thoracic Society
2018	The Frank E. Rath Spang & Company Charitable Trust Scholar
2017	Catalyst Award, Johns Hopkins University
2016	Discovery Award, Johns Hopkins University
2015	Discovery Award, Johns Hopkins University
2014	Semi-Finalists for the President's Frontier Award, Johns Hopkins University
2010	American Asthma Foundation (Sandler) Award
2006	Ann Woolcock Memorial Award for Outstanding Contributions and Future Promise in Asthma Research, American Thoracic Society
2000-2003	Ruth L. Kirschstein National Research Service Award

C. Contributions to Science

1. We have a long-standing interest on understanding the mechanobiology of living cells. In my early work, we developed and validated a suite of quantitative methods to characterize the abilities of living cells to deform, to contract, and to remodel their underlying cytoskeleton, at the single-cell resolution. Most recently, we developed the DNA double-helix based single-molecule tension probe (quenchedTGT) to directly modulate and visualize quantum of forces during excitation-contraction (E-C) coupling in smooth muscle shortening. These single-molecule and single-cell methods are readily applicable to a wide variety of cell types and have broad research applications that are at the interface between engineering, cell biology, and medicine. I served as the primary investigator or co-investigator in all of these studies.
    a. **An SS**, Laudadio RE, Lai J, Rogers RA & Fredberg JJ. (2002) Stiffness changes in cultured airway smooth muscle cells. American Journal of Physiology 283, C792-C801.
    b. Trepat X, Deng L, **An SS**, Navajas D, Tschumperlin DJ, Gerthoffer WT, Butler JP & Fredberg JJ. (2007) Universal physical responses to stretch in the living cell. Nature 447, 592-595. PMCID: PMC2440511

c. Zhu W, Kim BC, Wang M, Huang J, Isak A, Bexiga NM, Monticone R, Ha T, Lakatta EG & **An SS**. (2018) TGFβ1 reinforces arterial aging in the vascular smooth muscle through a long-range regulation of the cytoskeletal stiffness. Scientific Reports 8(1), 2668. PMCID: PMC5805716
d. Jo MH, Kim BC, Sung K, Panettieri RA, **An SS***, Liu J* & Ha T*. (2021) Molecular nanomechanical mapping of histamine-induced smooth muscle cell contraction and shortening. ACS Nano 15, 11585-11596. PMID: 34197709

2. We aim to understand the mechanical endotypes of airflow obstruction in asthma. Patients with asthma have periodic or persistent decreases in airflow, and an exaggerated bronchoconstrictive response to agents such as histamine and methacholine, termed airway hyperresponsiveness (AHR). Using well-established murine models of AHR (e.g. Fisher rats exhibit a greater degree of airway responsiveness than Lewis rats in vivo), we showed that ASM cells isolated from the more responsive Fisher rats manifest increased basal tone and enhaced contractility to the same agonists implicated in inflammatory airway diseases than those isolated from Lewis rats. Further, using cells derived from donor lungs with and without asthma, we identified an inflammation-independent, mechanical endotype of ASM shortening in asthma that is long-lived in culture and sustained across the matrix rigidities mimicking those of healthy and diseased airways. Together these findings support the concept of a non-immunological diathesis of ASM shortening that may be hardwired to the development of AHR.
   a. **An SS**, Fabry B, Trepat X, Wang N & Fredberg JJ. (2006) Do biophysical properties of the airway smooth muscle in culture predict airway hyperresponsiveness? American Journal of Respiratory Cell Molecular Biology 35, 55-64. PMCID: PMC2553364
   b. **An SS**, Bai TR, Bates JHT, Black JL, at al. (2007) Airway smooth muscle dynamics: a final common pathway of airway obstruction in asthma. European Respiratory Journal 29, 834-860. PMCID: PMC2527453
   c. **An SS**, Mitzner W, Tang WY, Ahn K, Yoon AR, Kim J, Kilic O, Yong HM, Fahey JW, Kumar S, Biswal S, Holgate ST, Panettieri RA, Solway J & Liggett SB. (2016) An inflammation-independent contraction mechanophenotype of airway smooth muscle in asthma. Journal of Allergy and Clinical Immunology 138, 294-297. PMCID: PMC4931984
   d. Kilic O, Yoon A, Shah SR, Yong HM, Ruiz-Valls A, Chang Hao, Panettieri RA, Liggett SB, Quinones-Hinojosa A, **An SS*** & Levchenko A*. (2019) A microphysiological model of the bronchial airways reveals the interplay of mechanical and biochemical signals in bronchospasm. Nature Biomedical Engineering 3, 532-544. PMCID: PMC6653686

3. We explore new paradigms in sensory physiology. We discovered 'sensory' GPCRs of the bitter taste receptor (TAS2R) family expressed on the smooth muscle of human bronchi. TAS2Rs effectively reverse bronchoconstriction by a localized calcium flux that activates, in large part, Ca^{2+}-activated K^+ (BK_{Ca}) channels–evoking membrane hyperpolarization and ASM relaxation. In the same vein, we found multiple odorant-sensing GPCRs on ASM cells and showed that activation of the odorant receptor OR51E2 via its cognate ligands acetate and propionate (i.e. endogeneous metabolic byproducts of the gut microbiota) results in marked reductions in cytoskeletal remodeling and ASM proliferation, suggesting previously unidentified "ancient" chemosensors of the gut-lung axis. Most recently, we uncovered a novel chemosensory odorant receptor (OR2W3)-regulated E-C coupling in ASM that evokes bronchodilation via a compartmentalization of calcium flux that is distinct from TAS2Rs. Collectively, our studies elucidated the physiological roles of ectopically expressed sensory GPCRs and advanced the fledgling concept that compartmentalization dictates the multifaceted effect of $[Ca^{2+}]_i$ on ASM contractile state.
   a. Deshpande DA, Wang WCH, McIlmoyle EL, Robinett KS, Schillinger RM, **An SS**, Sham JSK & Liggett SB. (2010) Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. Nature Medicine 16, 1299-1304. PMCID: PMC3066567
   b. **An SS**, Wang WCH, Koziol-White CJ, Ahn K, Lee DY, Kurten RC, Panettieri RA & Liggett SB. (2012) TAS2R activation promotes airway smooth muscle relaxation despite β_2-adrenergic receptor desensitization. American Journal of Physiology 303, L304-L311. PMCID: PMC3423830
   c. Aisenberg WH, Huang J, Zhu W, Rajkumar P, Cruz R, Santhanam L, Natarajan N, Yong HM, De Santiago B, Oh JJ, Yoon A, Panettieri RA, Homann O, Sullivan JK, Liggett SB, Pluznick JL & **An SS**. (2016) Defining an olfactory receptor function in airway smooth muscle cells. Scientific Reports 6, 38231. PMCID: PMC5131280

d. Huang J, Lam H, Koziol-White C, Limjunyawong N, Kim D, Kim N, Karmacharya N, Rajkumar P, Firer D, Dalesio NM, Jude J, Kurten RC, Pluznick JL, Deshpande DA, Penn RB, Liggett SB, Panettieri RA, Dong X & **An SS**. (2020) The odorant receptor OR2W3 on airway smooth muscle evokes bronchodilation via a cooperative chemosensory tradeoff between TMEM16A and CFTR. Proceeding of National Academy of Science U.S.A 117, 28485-28495. PMCID: PMC7668088

4. We seek to understand the physics of cancer cell migration and metastatic spread of primary tumor. In the *classical* metastatic-invasion framework, an individual cancer cell must be able to evade its primitive tumor ecosystem, emigrate through local stroma constituting extracellular matrix, and disseminate to target organ. It is unclear how cancer cells are primed for sensation or avoidance, however, and how external chemical and/or physical cues are received and transduced to cellular signals. It is unclear as well to what extent these signals are integrated to the contractile force driving local cellular motions to cancer metastasis. Our work highlights the physical basis for metastatic-invasion of cancer and identifies unique metabolical and biophysical attributes of epithelilial-mesenchymal and/or mesenchymal-epithelial transitions in the context of the tumor microenvironment.
   a. Hurley PJ, Hughes RM, Simons BW, Huang J, Miller RM, Shinder B, Haffner MC, Esopi D, Kimura Y, Jabbari J, Ross AE, Erho N, Vergara IA, Faraj SF, Davicioni E, Netto GJ, Yegnasubramanian S, **An SS** & Schaeffer EM. (2015) Androgen-regulated SPARCL1 in the tumor microenvironment inhibits metastatic progression. Cancer Research 75, 4322-34. PMCID: PMC4609262
   b. Shiraishi T, Verdone JE, Huang J, Kahlert UD, Hernandez JR, Torga G, Zarif JC, Epstein T, Gatenby R, McCartney A, Elisseeff JH, Mooney SM, **An SS*** & Pienta KJ*. (2015) Glycolysis is the primary bioenergetics pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells. Oncotargets 6, 130-143. PMCID: PMC4381583
   c. Park J, Kim DH, Kim HN, Wang C, Kwak MK, Hur E, Suh KY, **An SS*** & Levchenko A*. (2016) Directed migration of cancer cells guided by the graded texture of the underlying matrix. Nature Materials 15, 792-801. PMCID: PMC5517090
   d. Haffner MC, Esopi DM, Chaux A, Gürel M, Ghosh S, Vaghasia AM, Tsai H, Kim K, Castagna N, Lam H, Hicks J, Whys N, Biswal Shinohara D, Hurley PJ, Simons BW, Schaeffer EM, Lotan TL, Isaacs WB, Netto GJ, De Marzo AM, Nelson WG, **An SS** & Yegnasubramanian S. (2017) AIM1 is an actin binding protein that suppresses cell migration and micrometastatic dissemination. Nature Communications 8, 142. PMCID: PMC5529512

5. We seek to identify and characterize new targets and agents in the treatment of obstructive lung and cardiovascular diseases, and regenerative medicine. Toward this end, we are collaborating with investigators across the scientific discipline to explore new therapeutic approaches to treat airflow obstruction in asthma, age-associated vascular stiffening, and cancer.
   a. Kim D, Tokmakova A, Lujan LK, Strzelinski HR, Kim N, Beidokhti MN, Giulianotti MA, Mafi A, Woo JAA, **An SS**, Goddard WA & Liggett SB. (2021) Identification and characterization of an atypical Gαs-biased β2AR agonist that fails to evoke airway smooth muscle cell tachyphylaxis. Proceeding of National Academy of Science U.S.A 118(49), e2026668118. PMCID: PMC8670521
   b. Zhen G, Guo Q, Li Y, Wu C, Zhu S, Wang R, Guo XE, Kim BC, Huang J, Hu Y, Dan Y, Wan M, Ha T, **An SS** & Cao X. (2021) Mechanical stress determines the configuration of TGFβ1 activation in articular cartilage. Nature Communications 12(1), 1706. PMCID: PMC7969741.
   c. Murphy S, Miyamoto M, Kervadec A, Kannan S, Tampakakis E, Kambhampati S, Lin BL, Paek S, Anderson P, Lee D, Zhu R, **An SS**, Kass DA, Uosaki H, Colas AR & Kwon C. (2021) PGC1/PPAR drive cardiomyocyte maturation at single cell level via Yap1 and SF3B2. Nature Communications 12(1), 1648. PMCID: PMC7955035.
   d. De Pascali F, Ippolito M, Wolfe E, Komolov KE, Hopfinger N, Lemenze D, Kim N, Armen RS, **An SS**, Scott CP & Benovic JL. (2022) β_2-adrenoceptor agonist profiling reveals biased signalling phenotypes for the β_2-adrenoceptor with possible implications for the treatment of asthma. British Journal of Pharmacology 179(19), 4692-4708. PMCID: PMC9474705.

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