BIOGRAPHICAL SKETCH

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NAME: Stephen L. Nishimura

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

POSITION TITLE: Professor and Chief of Pathology

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
Wesleyan University, Middletown, CT	BA	06/1981	Chemistry
University of Vermont College of Medicine	MD	06/1988	Medicine
University of California San Francisco		06/1991	Pathology and Laboratory Medicine
University of California San Francisco		06/1995	Molecular and Cell Biology
Armed Forces Institute of Pathology, Washington, DC		06/1997	Pulmonary Pathology

A. Personal Statement

Stephen L. Nishimura, MD, is a molecular and cell biologist and a practicing lung and anatomic pathologist with expertise in integrin biology, structural biology, TGF-β, fibrosis, chronic inflammatory diseases and cancer immunology. Dr. Nishimura is a member of Thoracic Oncology Research Group, and the UCSF ImmunoX program and closely affiliated with the Lung Biology, Liver and Helen Diller Cancer Centers at UCSF. Dr. Nishimura's research focuses on basic structural and cell biology with additional translational and clinical research themes. The major scientific focus is on the regulation of cell-extracellular matrix interactions by integrins, and the structural mechanisms of activation and function of TGF-β in fibrosis and cancer. Additionally, the laboratory studies the role of TGF-β on cancer resistance to immunotherapy, the role of host-pathogen interactions in innate and adaptive immunity in the evolution of lung fibroinflammatory disease. Clinical/translational projects focus on the use of human lung lung resection biospecimens and correlation of morphometry, gene expression and genetic variation in disease susceptibility and role of adaptive and innate immunity in disease. We have extensive experience with use of human and mouse primary and transformed cell lines as well as complex in vitro models, genetic manipulation of mice including transgenesis, knock-out, knock-in, cell-type conditional gene deletion, immune cell reporter mice, and immune cell analysis. Our program leverages a collaborative basic science group including the Cheng (electron cryomicroscopy), Marks (antibody engineering) and Baron (pathologic immunity) laboratories. Together we study the function of integrins in fibrosis and cancer using a structure-guided approach to manipulate the immune response for therapeutic purposes.
Ongoing and recently completed projects that I would like to highlight include:

<u>On-going Research</u>
R01HL134183-05
Nishimura (PI) ; Role: PI (MPI: Contact PI)
6/1/20- 5/31/25 (NCE for 6/01/24-5/31/25)
NIH/NHLBI
Structural mechanism of integrin-mediated TGF-β activation

R01 HL165175-01PI contact (MPI)
Nishimura (PI); Role: PI (MPI: Contact PI)
NIH
7/1/23-6/30/27
Conformational regulation of TGF-β activation by integrin αvβ6

Completed Research

24RT-0020
Nishimura (PI)
08/31/15-07/30/18
UCOP, Tobacco-Related Disease Research Program
Airway inflammation in the evolution of airway fibrosis

1R01HL113032-01
Nishimura (PI)
04/01/12-03/31/17
NIH/NHLBI
Role of genetic variation in TGF-β overactivation in COPD

U54HL119893
Nishimura (PI)
09/01/14-08/31/16
University of California/NIH NHLBI Center for Accelerated Innovation
Selective targeting of TGF-β activation for airway remodeling with engineered monoclonal antibodies

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2021-Present	Corbus Pharmaceuticals, Scientific Advisory Board Member
2019-Present	Venn Therapeutics, LLC, Scientific Advisory Board Member
2016-present	Zuckerberg San Francisco General, Pathology, Chief of Pathology
2014-2015	San Francisco General Hospital, Pathology, Acting Chief of Pathology
2013-2014	CSA Medical, Scientific Advisory Board
2009-2010	San Francisco General Hospital, Pathology, Acting Chief of Pathology
2009-present	University of California San Francisco, Professor in Residence
2003-2009	University of California San Francisco, Associate Professor in Pathology in Residence
2003-2003	Actelion Pharmaceuticals Ltd., Build 1 Clinical Trial, Consultant, Pulmonary Pathology
1998-2003	University of California San Francisco, Assistant Professor in Pathology in Residence
1997-2000	Chiron Corporation, Emeryville, CA, Consultant, Cancer Genomics
1995-1998	University of California San Francisco, Adjunct Assistant Professor in Pathology
1995-1995	San Francisco General Hospital, Pathology, Clinical Instructor in Pathology

Other Experience and Professional Memberships

1995-	American Society of Investigative Pathology
1998-	Cancer and Leukemia Group B
1998-	UCSF/Mt Zion Cancer Center
1998-	Thoracic Oncology Research Group, UCSF
1998-	American Thoracic Society
2015-	College of American Pathologists
2014-	American Society for Biochemistry and Molecular Biology

Honors

2023 Invited Speaker: Gordon Conference, Fibronectin, Integrins and Related Molecules,Ventura, CA
2017 University of California Catalyst Award
2017 Invited Speaker, The TGF-β Superfamily: Signaling in Development and Disease, FASEB, Lisbon, PT
2016 University of California Center for Accelerated Innovation Award
2007 Invited Speaker, Gordon Conference, Tissue repair and injury, Colby-Sawyer College, NH

2006 Invited Speaker, University of Alabama, Cell Biology
2005 Selected Speaker, Gordon Research Conference on Integrins
2002 Independent Scientist Award (NIH)
2001 Selected Speaker, Gordon Research Conference on MMPs
2000 UCSF Academic Senate Award
2000 UCSF, REAC Award
2000 Hellman Family Award for Early-Career Faculty
1999 American Heart Association, Grant in Aid
1998 ACS Institutional Award
1998 American Lung Association, Research Grant
1998 Edward Livingston Trudeau Scholar
1998 American Lung Association
1995 Clinical Investigator Award (KO8 CA63148)
1993 National Research Service Award (CA09335)

C. Contributions to Science

1. Integrin biology: I have had a long-standing interest in the biology and function of integrins in development and disease. Integrins are highly conserved heterodimers consisting of a single α and single β subunit. Through promiscuous pairing 24 unique integrins are formed. The five integrins sharing the αv-subunit play important roles in vasculogenesis, organ morphogenesis and immune cell. In adult tissues, the αv-integrins play important roles in vascular, epithelial, mesenchymal and immune cell homeostasis. Since my post-doctoral fellowship in the laboratory of the integrin biologist Robert Pytela, I have studied the αv-integrins in development and disease focusing mainly on the integrin αvβ8. I made the key initial observations that the αvβ8 integrin was functionally divergent and was the first to uncover a role for αvβ8 in the regulation of cell growth, the subcellular and tissue distribution of the β8 integrin subunit. I discovered the first blocking antibody to the αv-integrin and β8 integrin subunit. Antibodies to the αv-integrin subunit are now in phase II clinical trials (Intetumumab). Using electron cryomicroscopy (cryoEM), we found that the integrin αvβ8 adopts a stable extended "closed" conformation, and we have defined a general mechanism of integrin extension that provides an essential step in integrin function. Recently, we have used cryoEM to address fundamental mechanisms of TGF-β action in cell-cell communication. We have provided structural evidence that TGF-β does not need to diffuse in order to function, but rather remains cell-associated. These data change basic concepts of TGF-β function in the immune system and explain the equisite cell-type specificity of TGF-β.

1) Gline SE, Cambier S, Govaerts C, **Nishimura SL**. A 50 Å separation of the integrin αvβ3 extracellular domain C-termini reveals an intermediate activation state. J Biol Chem. 2004 Dec 24; 279(52):54567-72. PMID: 15475365

2) Cormier A, Campbell MG, Ito S, Wu S, Lou J, Marks JD, Baron JL, **Nishimura SL***, Cheng Y. Cryo-EM structure of the αvβ8 integrin reveals a mechanism for stabilizing integrin extension, Nature Struct Mol Biol, 2018, Aug;25(8):698-704, PMID: 30061598 PMCID: PMC6214843 ***Co-corresponding author

3) Campbell, MG, Cormier, A, Ito, S, Seed, RI, Bondesson, AJ, Lou, J, Marks, JD, Baron, JL, Cheng, Y, **Nishimura, SL**, Cryo-EM reveals integrin-mediated TGF-β activation without release from latent TGF-β, Cell, 2020 Feb 6;180(3):490-501.e16. doi: 10.1016/j.cell.2019.12.030. PMID: 31955848 PMCID: PMC7238552, Epub 2020 Jan 16.

4) Jin, M.J.· Seed, R.I., Cai, G.,· Shing, T. Wang, Li, Ito, S., Cormier, A., Wankowicz, S.A., Jespersen, J.M., Baron, J.L., Carey, N.D., Campbell, M.G., Yu, Z., Tang, P.K., Cossio, P., Wen. W.,·Lou, J., Marks, J., ***Nishimura, S.L.,** *Cheng, Y., Dynamic allostery drives autocrine and paracrine TGF-β signaling, Cell (2024) ISSN 0092-8674 (https://doi.org/10.1016/j.cell.2024.08.036.) *co-senior authors

2. Identification of the integrin αvβ8 as a central mediator of TGF-β activation and discovery of unique roles for integrin αvβ8-mediated TGF-β activation in vascular development and epithelial homeostasis. In the search for ligands for the αvβ8 integrin, I discovered that the only biologically relevant ligands were TGF-β1 and TGF-β3. Both TGF-β1 and TGF-β3 are ubiquitously expressed in a latent form that must be activated in order to function. Latency is conferred by the association of the latency-associated peptide (LAP) of TGF-β. LAP is a homodimer and each subunit contains an RGD integrin-binding motif that binds to the integrin αvβ8 with high affinity (low pM range). Binding of latent-TGF-β to cell-surface expressed integrin αvβ8 efficiently liberates active TGF-β. We developed and utilized a number of in vitro models using human cells and tissues to define the role of αvβ8-mediated TGF-β activation in vascular and tissue homeostasis. We predicted that the integrin αvβ8 expressed by select populations of astrocytes, epithelial cells and mesenchymal cells and would liberate TGF-β to act as a paracrine modulator of vascular development, and epithelial homestatsis. This basic

mechanism has been confirmed by a number of different laboratories in mice using a variety of conditional deletion models.

1) Mu D, Cambier S, Baron JL, Munger J, Sheppard D, Broaddus VC, **Nishimura SL.** The integrin αvβ8 mediates epithelial homeostasis through the MT1-MMP-dependent activation of TGF-β. J Cell Biol, 2002, Apr 29;157(3):493-507. PMID: 11970960; PMC2173277

2) Cambier S, Gline S, Araya J, Collins R, Einheber S, Dolganov G, Boudreau N, **Nishimura SL.** Integrin αvβ8-mediated activation of TGF-β: an angiogenic control switch Am J Pathol. 2005 Jun;166(6):1883-94. PMCID: PMC160240

3) Cambier S, Mu D, O' Connell D, Boylen K, Travis W, Liu W, Broaddus VC, **Nishimura SL.** A role for the divergent integrin αvβ8 in negative regulation of epithelial cell growth Cancer Res, 2000 Dec 15;60(24):7084-93. PMID: 11156415

4) Araya J, Cambier S, Morris A, Finkbeiner W, **Nishimura SL**. Integrin mediated TGF-β activation regulates homeostasis of the pulmonary epithelial-mesenchymal trophic unit, Am. J. Path. 2006, 169:405-415; PMID: 16877343. PMC1698780

3. Role of integrin-mediated TGF-β activation in airway pathology: The cell type distribution of integrin αvβ8 suggested that αvβ8-mediated TGF-β activation played a role in lung fibrogenic reactions. The expression of αvβ8 in airway epithelial cells and subepithelial fibroblasts suggested that αvβ8 might be a therapeutic target. We have made seminal observations linking αvβ8-mediated TGF-β activation to establishing a proinflammatory and profibrogenic environment that plays a role in chronic obstructive pulmonary disease (COPD) pathogenesis.

1) **Nishimura SL.** Integrin-mediated transforming growth factor-β activation, a potential therapeutic target in fibrogenic disorders. Am J Pathol. 2009 Oct;175(4):1362-70. PMCID: PMC2751532

2) Araya J, Cambier S, Markovics JA, Wolters P, Jablons D, Hill A, Finkbeiner W, Jones K, Broaddus, VC, Sheppard D, Barzcak A, Xiao Y, Erle DJ, **Nishimura SL.** Squamous metaplasia amplifies pathologic epithelial-mesenchymal interactions in COPD, 2007, J Clin Investigation, Nov 1;117(11):3551-3562. PMID: 17965775; PMC2040320

3) Markovics JA, Araya J, Cambier S, Jablons D, Hill A, Wolters PJ, **Nishimura SL**. Transcription of the transforming growth factor-β activating integrin β8 subunit is regulated by SP3, AP-1 and the P38 pathway. J Biol Chem. 2010 Aug 6;285(32):24695-70. PMID: 20519498; PMC2915706

4) Minagawa S, Araya J, Numata T, Nojiri S, Hara H, Yumino Y, Kawaishi M, Odaka M, Morikawa T, Kawabata Y, **Nishimura SL**, Nakayama K, Kuwano K. Accelerated Epithelial Cell Senescence in IPF and the Inhibitory Role of SIRT6 in TGF-β-induced Senescence of Human Bronchial Epithelial Cells, Am J Physiol Lung Cell Mol Physiol 300, L391-401 (2011). PMID: 21224216; PMC3284316

4. Mechanism of integrin-mediated TGF-β activation in chronic inflammation and lung fibrosis: To understand how αvβ8-mediated TGF-β activation increased inflammation and fibrosis, we deleted αvβ8 from lung fibroblasts in mice. Conditional deletion of itgb8 protected mice from IL-1β-induced airway fibrosis and also markedly decreased lung and airway inflammation. We used a proteomic approach to reveal that one of the major chemokines that was regulated by αvβ8-mediated TGF-β activation was CCL20, the ligand for the chemokine receptor CCR6. We have now linked αvβ8-mediated TGF-β activation to a direct interaction on the CCL20 promoter, the first evidence that the TGF-β and IL-1β signaling pathways directly and positively converge to mediate inflammation. Dendritic cells are sentinel antigen presenting cells and we have determined that they are a major downstream effector cell involved in mediating the effects of αvβ8-mediated TGF-β activation. These findings to implicate CCR6 as an additional therapeutic target in airway disease.

1) Kitamura H, Cambier S, Somanath S, Barker T, Minagawa S, Markovics J, Goodsell A, Publicover J, Reichardt L, Jablons D, Wolters P, Hill A, Marks JD, Lou J, Pittet JF, Gauldie J, Baron JL, **Nishimura SL**, Mouse and human lung fibroblasts regulate dendritic cell trafficking, airway inflammation and fibrosis, through integrin αvβ8-mediated activation of TGF-β, 2011, J Clin Investigation, Jul 1;121(7):2863-75. PMID: 21646718; PMC3223836

2) Brand OJ, Somanath S, Moermans C, Yanagisawa H, Hashimoto M, Cambier S, Markovics J, Bondesson AJ, Hill A, Jablons D, Wolters P, Lou J, Marks JD, Baron JL, **Nishimura SL**. Transforming Growth Factor-β and Interleukin-1β Signaling Pathways Converge on the Chemokine CCL20 Promoter. J Biol Chem. 2015 Apr 27. pii: jbc.M114.630368. PMC4505537

3) Hashimoto M, Yanagisawa H, Minagawa S, Sen D, Goodsell A, Ma R, Moermans C, McKnelly KJ, Baron JL, Krummel MF, **Nishimura SL**. A critical role for dendritic cells in the evolution of IL-1β-mediated murine airway disease, J Immunology, 2015, Apr 15;194(8):3962-9. doi: 10.4049/jimmunol.1403043. Epub 2015 Mar 18. PMID: 25786688 PMC43905119

4) Hashimoto M, Yanagisawa H, Minagawa S, Sen D, Ma R, Murray LA, Tsui P, Lou J, Marks JD, Baron JL, Krummel MF, **Nishimura SL**. TGF-β-Dependent Dendritic Cell Chemokinesis in Murine Models of Airway Disease. J Immunol. 2015 Aug 1; 195(3):1182-90. PMID: 26109638. PMC4506848

5. Role of αvβ8-mediated TGF-β activation in fibrosis and cancer pathogenesis: To understand how to target αvβ8-mediated TGF-β activation and its downstream targets, we have developed an array of function blocking antibodies to either the αv-subunit or the β8 subunit that both potently inhibit αvβ8-mediated TGF-β activation. We have used this approach to successfully block both airway inflammation, fibrosis and cancer in mouse models that recapitulate key features of their human disease counterparts.

1) Minagawa S, Lou J, Seed R, Cormier A, Wu S, Cheng Y, Murray L, Tsui P, Connor J, Herbst R, Govaerts C, Barker T, Cambier S, Yanagisawa H, Goodsell A, Hashimoto M, Brand O, Cheng R, Ma R, McKnelly KJ, Wen W, Hill A, Jablons D, Wolters P, Kitamura H, Araya J, Barczak A, Erle D, Reichardt LF, Marks JD, Baron JL, **Nishimura SL**. Selective targeting of TGF-β activation to treat fibroinflammatory airway disease. Sci Transl Med. 2014 Jun 18;6(241):241ra79. doi: 10.1126/scitranslmed.3008074. PMID: 24944194 PMCID4341974

2) Takasaka N, Seed RI, Cormier A, Bondesson AJ, Lou J, Elattma A, Ito S, Yanagisawa H, Hashimoto M, Ma R, Levine MD, Publicover J, Potts R, Jespersen JM, Campbell M, Conrad F, Marks JD, Cheng Y, Baron JL, and **Nishimura SL**. Integrin αvβ8 expressing tumor cells evade host immunity by regulating TGF-β activation in immune cells, *JCI Insight.* 2018; 3(20):e122591. https://doi.org/10.1172/jci.insight.122591. PMID: 30333313 PMC6237456

3) Seed RI, Kobayashi K, Ito S, Takasaka N, Cormier A, Jespersen JM, Publicover J, Trilok S, Combes AJ, Chew NW, Chapman J, Krummel MF, Lou J, Marks J, Cheng Y, Baron JL, **Nishimura SL**. A tumor-specific mechanism of Treg enrichment mediated by the integrin αvβ8. Sci Immunol. 2021 Mar 26; 6(57). PMID: 33771888 PMC8425767

Complete List of Published Work in MyBibliography:

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