

University of California, San Francisco
CURRICULUM VITAE

Name: Stephen L Nishimura, MD

Position: Professor In Residence, Step 3
Pathology
School of Medicine

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EDUCATION

1977 - 1978	Colgate University, Hamilton, NY		
1979 - 1981	Wesleyan University, Middletown, CT	BA	Chemistry
1983 - 1988	University of Vermont College of Medicine	MD	Medicine
1988 - 1991	University of California at San Francisco	Pathology and Laboratory Medicine	
1991 - 1995	University of California at San Francisco	Molecular and Cell Biology	
1997 - 1997	Armed Forces Institute of Pathology, Washington, DC	Pulmonary Pathology	

LICENSES, CERTIFICATION

2010	Medical license (G8337)
1994	Diplomat of the American Board of Pathology, Anatomic and Clinical Pathology

PRINCIPAL POSITIONS HELD

1981 - 1983	Research Assistant in Neuropharmacology	Memorial Sloan-Kettering	Neurology, Cancer Center, NY
1984 - 1984	Research Fellowship in Pharmacology	University of Vermont	Pharmacology
1986 - 1987	Post-Sophomore Fellowship in Pathology	University of Vermont	Pathology

1988 - 1991	Resident in Anatomic Pathology and	University of California	Anatomic pathology and Laboratory Medicine
1990 - 1991	Laboratory Medicine	at San Francisco	Laboratory Medicine
1991 - 1991	Chief Resident in Pathology	San Francisco General Hospital	Pathology
1991 - 1991	Post-Doctoral Research Fellow	University of California	Medicine
1995 - 1995	Clinical Instructor in Pathology	San Francisco General Hospital	Pathology
1995 - 1998	Adjunct Assistant Professor in Pathology	University of California	at San Francisco
1998 - 2003	Assistant Professor in Pathology in Residence	University of California	at San Francisco
2003 - 2009	Associate Professor in Pathology in Residence	University of California	at San Francisco
2009 - present	Professor in residence	University of California	at San Francisco
2009 - 2010	Acting Chief of Pathology	San Francisco General Hospital	Pathology
2014 - 2015	Acting Chief of Pathology	San Francisco General Hospital	Pathology
2016 - present	Interim Chief of Pathology	Zuckerberg San Francisco General	Pathology

OTHER POSITIONS HELD CONCURRENTLY

1997 - 2000	Consultant, Cancer Genomics	Chiron Corporation, Emeryville, CA	
2003 - 2003	Consultant, Pulmonary Pathology	Actelion Pharmaceuticals Ltd.	Build 1 Clinical Trial
2013 - present	Scientific Advisory Board	CSA Medical	

HONORS AND AWARDS

1991	Research Fellowship, Department of Pathology, University of California at San Francisco
1992	College of American Pathologists Foundation Scholar
1993	National Research Service Award (CA09335)
1995	Clinical Investigator Award (KO8 CA63148)
1998	ACS Institutional Award

1998	American Lung Association, Research Grant
1998	Edward Livingston Trudeau Scholar
1998	American Lung Association
1999	American Heart Association, Grant in Aid
2000	UCSF Academic Senate Award
2000	UCSF, REAC Award
2000	Hellman Family Award for Early-Career Faculty
2001	Selected Speaker, Gordon Research Conference on MMPs
2002	Independent Scientist Award (NIH)
2005	Selected Speaker, Gordon Research Conference on Integrins
2006	Invited Speaker, University of Alabama, Cell Biology
2007	Invited Speaker, Gordon Conference, Tissue repair and
2007	injury, Colby-Sawyer College, NH

KEYWORDS/AREAS OF INTEREST

Lung, Airway Remodeling COPD, Pulmonary Fibrosis, Lung Cancer, Airway epithelium, Cell Proliferation, Integrins, TGF- β , Cytokines, Angiogenesis, Vasculogenesis, Surgical Pathology, Lung Pathology

CLINICAL ACTIVITIES SUMMARY

Surgical Pathology Attending: I have attended on the surgical pathology service at SFGH between 8 and 26 weeks/year for the past 20 years. When on service, I supervise 3-4 residents, fellows and medical students.

Currently, I attend on the general pathology service at SFGH for 12-16 weeks a year. During this time I oversee residents, medical students and fellows.

My subspecialty interest is pulmonary pathology and I am responsible for pulmonary pathology at the SFGH all year.

MEMBERSHIPS

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

SERVICE TO PROFESSIONAL PUBLICATIONS

- Journal of Biologic Chemistry (Ad hoc reviewer; 3 papers in 5 years)
- Oncogene (Ad hoc reviewer, 2 papers in 5 years)
- American Journal of Respiratory Cell and Molecular Biology (Ad hoc reviewer 7 papers in 5 years)
- Experimental Cell Research (Ad hoc reviewer, 1 paper in 5 years)
- American Journal of Pathology (Ad hoc reviewer, 9 papers in 5 years)
- Journal of Cell Science (3 papers in five years)
- Journal of Molecular Biology (1 paper in 5 years)
- Journal of Epithelial Biology (1 paper in 5 years)
- Matrix Biology (1 paper in 5 years)
- PLoS Computational Biology (1 paper 5 years)
- American Journal of Physiology (1 paper in 3 years) PLoSone (5 papers in 3 years) Chest, Ad Hoc Reviewer (1 paper in 3 years) Journal of Cell Biology (1 paper in 3 years) Journal of Cell Biology (1 Paper in 5 Years)
- Journal of Cell Biology 1 Paper in 5 years)
- Cell Reports (4 papers in 5 years)

2011 - present Associate Editor, PLoSone

2015 - European Journal of Cell Biology (1 Paper)

2015 - PLoSone, (2 Papers)

2015 - American Journal of Pathology (1 Paper)

INVITED PRESENTATIONS - INTERNATIONAL

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|------|----------------------------------------------------------------------------------------------|---------|
| 2001 | Gordon Conference on Matrix Metalloproteases, Il Ciocco, Italy | |
| 2007 | Gordon Conference on Tissue Repair and Regeneration, Colby-Sawyer College, NH | |
| 2010 | Co-Chair International Blood-Brain-Barrier Consortium, Bend, Oregon | |
| 2012 | American Thoracic Society, San Francisco, CA | |
| 2013 | Keytone Conference, Dendritic Cells, Keystone Colorado | |
| 2016 | American Thoracic Society, San Francisco | Speaker |
| 2017 | FASEB meeting ; TGF-beta super family signaling in development and disease, Lisbon, Portugal | Speaker |

INVITED PRESENTATIONS - NATIONAL

- 2001 Oregon Health Sciences Center, Portland Or.

- 2002 University of New Mexico, Cancer Center
- 2005 Gordon Research Conference on Fibronectin and related molecules, Ventura, CA
- 2006 University of Alabama, Cell Biology program
- 2007 Gordon Conference on Tissue repair and injury, Colby Sawyer College, NH
- 2008 NIH workshop on cerebral vascular malformations, Bethesda, MD
- 2008 University of Vermont Lung Center, Burlington, VT
- 2010 NIH, Epithelial plasticity, Special meeting, Bethesda, MD
- 2011 Genentech, South San Francisco, CA
- 2011 MedImmune, Gaithersburg, MD
- 2012 American Thoracic Society, San Francisco, CA
- 2013 UC Innovation Award presentation , South San Francisco
- 2014 UC Centers for Accelerated Innovation Award, UCLA

INVITED PRESENTATIONS - REGIONAL AND OTHER INVITED PRESENTATIONS

- 2001 UCSF, Pathology and Laboratory Medicine Grand Rounds
- 2002 Stanford University Department of Pathology
- 2003 Neurosurgery Grand Rounds, UCSF
- 2003 Thoracic Oncology Program Retreat
- 2004 Program Project Retreat, UCSF
- 2005 Thoracic Oncology Program Retreat
- 2006 Program Project Retreat, UCSF
- 2006 Thoracic Oncology Program Retreat
- 2007 Deans's research conference, SFGH, UCSF
- 2009 Thoracic Oncology Program Retreat
- 2010 Department of Experimental Medicine
- 2010 Thoracic Oncology Retreat
- 2010 Pulmonary Research Retreat, UCSF
- 2013 UCOP Proof of Concept Technology and Innovation retreat2
- 2013 Pulmonary Research Retreat, UCSF
- 2014 UCSF Liver Center Mini-symposium, Fibrosis
- 2014 Dean's Seminar, UCSF, SFGH

CONTINUING EDUCATION AND PROFESSIONAL DEVELOPMENT ACTIVITIES

2000	Mechanisms of Disease, weekly pathology conference
1997	Pulmonary Clinical Case Conference, SFGH
2006	Amercian Thoracic Society, Moscone Center, San Francisco
2010	Pulmonary Clinical Case Conference, UCSFAmercian Thoracic Society, Moscone Center, San Francisco
2016	Amercian Thoracic Society, Moscone Center, San Francisco

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2006 - 2006	Hellman Family selection committee	
2007 - 2007	Wellcome Trust, Ad Hoc reviewer	
2008 - 2008	Wellcome Trust, Ad Hoc reviewer	
2009 - 2009	NIH, NIDA-Special emphasis panel-Genes and environment initiative	
2010 - 2010	NIH, NHLBI, Ad-Hoc reviewer	
2010 - 2010	Blood Brain Barrier international consortium, Co-chair, Bend, Oregon	
2010 - 2010	NIH, Epithelial plasticity, Special meeting, Bethesda, MD	
2011 - 2011	Grant reviewer, Biotechnology and Biologic Sciences Research Council,	Ad hoc reviewer
2011 - 2011	University of Vermont, School of Medicine, Environmental Lung Health Program	External Advisory Committee
2012 - 2012	NIH, Lung, Cellular, Molecular Immunology study section, Ad Hoc reviewer	
2013 - 2013	NIH, Lung, Cellular, Molecular Immunology study section, Ad Hoc reviewer	
2015 - 2016	Wellcome Trust,	Ad hoc reviewer

SERVICE ACTIVITIES SUMMARY

I attend on the general surgical pathology service providing 24/7 attending coverage approximately 14 weeks/year.

This year, I will assume the role of Acting Chief of Pathology at SFGH, in place of the current Chief, who will be on sabbatical for ~1 yr. This will involve weekly meetings and presentations to the service chiefs regarding the state of the department and the leadership and coordination of all aspects of the clinical service. I current perform the role of assistant chief, and have assumed roles that include covering Dean's meetings and Executive committee meetings when the chief can not attend.

**UNIVERSITY SERVICE
UC SYSTEM AND MULTI-CAMPUS SERVICE**

2012 - 2012	Out-licensing of humanized monoclonal anti-avb8 antibodies	Inventor
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UCSF CAMPUSWIDE

2011 - 2011	Faculty search committee, Pathology	Chair
2012 - 2012	Faculty search committee, Pathology	Member
2005 - 2015	Cancer Committee, SFGH	Member
2015 - present	SFGH research committee	Chair (co-)

SCHOOL OF MEDICINE

1995 - 1998	Attending Autopsy and Surgical Pathologist, SFGH, and UCSF 4 months/year
1998 - 2000	Attending Autopsy and Surgical Pathologist, SFGH, 3 months/year
2000 - 2002	Attending Autopsy and Surgical Pathologist, SFGH, 5 months/year
2002 - 2002	Attending Autopsy and Surgical Pathologist, SFGH, 2 months/year
1998 - 1998	Tumor Board, representing pathology, every other week
1997 - 1997	Multidisciplinary pulmonary teaching Conference, every week
1999 - 1999	Interstitial Lung Disease Multidisciplinary Conference, every week
2000 - 2000	SFGH Cancer Committee
2010 - 2011	Acting Chief of Pathology, SFGH
2014 - 2015	Acting Chief of Pathology, SFGH
2016 -	Interim Chief of Pathology, ZSFG

DEPARTMENTAL SERVICE

2002 - 2002	Department of Pathology Faculty Search Committee
2003 - 2003	Department of Medicine Faculty Search Committee
2008 - 2008	Department of Pathology Faculty Search Committee
2009 - 2009	Department of Pathology Faculty Search Committee
2009 - 2009	Department of Medicine Faculty Search Committee
2010 - 2010	Department of Medicine Faculty Search Committee
2011 - 2012	Department of Pathology Faculty Search Committee, Chair

TEACHING SUMMARY

Over the past 20 years, my teaching interests and efforts have steadily increased and diversified. My efforts can be divided into teaching of house staff/fellows; teaching of medical students; teaching of graduate students and faculty and teaching of post-doctoral fellows and undergraduate students. Some of the most rewarding teaching that I am involved in revolves

around the medical student pathology course. Through the years I have organized a medical student course (Advances in Medical Sciences), given numerous lectures, teaching basic aspects of lung pathology and airway biology. I focus the lectures so that they integrate pathology with immunology, histology, anatomy and with the introduction to clinical medicine course. I am now leading laboratories and small group teaching sessions, both in the old and new curriculum. In lectures, I try to provide a comprehensive base of information that is scientifically and clinically rigorous while at the same time being comprehensible to students with a wide range of scientific and clinical experience. In laboratories, I try to encourage critical thinking and provoke thoughtful discussion and peer-to-peer learning. This, I hope, will improve the transfer of information and will help the students place pathology and pathogenesis into a context relevant to patient care.

I am involved in the teaching of pulmonary fellows. I represent pathology for the weekly pulmonary conference and participate in case discussions. While this is a "working conference" focused mainly on the pulmonary fellows, the audience also includes medical attendings, residents, medical students, undergraduate observers and nurse practitioners. Patients are presented and the differential diagnosis is discussed, the salient pathologic features are pointed out, and therapeutic measures are entertained.

As a surgical pathologist I supervise and provide formal and informal teaching to medical students and pathology residents around the microscope. These sessions included daily "sign-outs" where diagnoses are rendered for current cases. They also include consultations for second opinions of cases and consensus conferences. The audience may vary between one to four residents and medical students. Formal teaching includes monthly teaching sessions for pathology residents designed to hone frozen section technical and diagnostic skills. As interim chief of pathology, I have redesigned and organized the resident teaching curriculum to include formal teaching sessions in cytology, surgical pathology, neuropathology, placental pathology and frozen section diagnosis. I also have started the ZSFG pathology consensus conference which is attended by the surgical pathology attendings, resident, students and fellows. The purpose of this conference is to increase diagnostic accuracy, provoke critical discussion and opinions, standardize wording and grading schemes, and to teach residents and fellows the thought process of rendering diagnoses and communicating those diagnoses accurately and effectively to clinicians.

As a researcher, I am involved in frequent teaching sessions concerning my research interests. These are mostly informal 1-1 sessions with students and fellows where I teach student basic molecular and cellular biology, statistical analysis, critical thinking and hypothesis generation and testing. I have given courses in international meetings, most recently the American Thoracic meeting in 2016. I have supervised undergraduates from UC Berkeley (Ran Chang, Ahmed Ellatma), recent college graduates (Stephanie Gline, Tyren Barker, Kate McNelly, Royce Ma, Michelle Levine, Andrew Bondesson), and post-doctoral fellows Drs. Dez-hi Mu, David O'Connell, Lars Fjellbirkeland, Jun Araya, Jennifer Marcovics., Hideya Kitamura, Sangeeta Somanath, Robert Seed, Oliver Brand, Shunsuke Minagawa, Mitsuo, Hashimoto, Harusuke Yanagisawa, Naoki Takasaka, Catherine Moermans, Saburo Ito, Anthony Cormier). Through didactic teaching and daily discussions, I have acted as a mentor and am closely involved in trainee's career development. I have completed the UCSF Faculty mentoring course. I lead weekly lab meetings, which are informal presentations of information pertinent to our research. I also participate in several multicenter research forums where members of my lab present research findings twice yearly.

FORMAL TEACHING

Not UCSF	Academic Yr	Course No. & Title	Teaching Contribution	School	Class Size
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Not UCSF	Academic Yr	Course No. & Title	Teaching Contribution	School	Class Size
	1997 - 2016	Pulmonary Organ Block	Lecturer	Medicine	All
	1997 - 2016	Organ Blocks	Lab leader	Medicine	60
	2016 - present	Bridges	Lecturer	Medicine	All
	2016 - present	Bridges	Small group leader	Medicine	12-16

INFORMAL TEACHING

1995 - 2014 Over the course of my career at UCSF, I have been continuously involved in the informal training of medical, graduate students and fellows in various departments at UCSF and other Universities. These informal activities center around research methodology, hypothesis testing, preparation of manuscripts and presentation of research findings. These interaction take place through email exchanges, phone conversations and face-to-face meetings at UCSF and at scientific meetings. I spend approximately 2 hrs/day with lab members going over their results, demonstrating techniques and teaching them theory, methodology and statistical analysis.

MENTORING SUMMARY

I consider mentorship to be an integral part of my mission at UCSF. I have recently taken and complete the course in mentoring at UCSF. I have many former students that are in academic positions around the world.

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Program or School	Mentor Type	Role	Current Position
2015 - present	Ahmed Ellatma	UC Berkeley	Research/Scholarly Mentor, Project Mentor, Career Mentor	PI	Junior at UCB

POSTDOCTORAL FELLOWS AND RESIDENTS MENTORED

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2000 - 2000	Karin Chang	Cornell University (So)		Supervised Summer Work	Chicago Medical School-last known
2002 - 2002	Stephanie Gline	Wesleyan University(graduate.)		Supervised post-baccalaureate work	Post-doctoral fellow, University of CaliforniaSan Francisco
1999 - 2000	David O'Connell	Post-doctoral Fellow		Research Supervisor	Head Student Fellowships, Trinity College,Dublin, Ireland
1999 - 2003	Dezhi Mu	Post-doctoral Fellow		Research Supervisor	Associate Professor, Hospital of W. China, Medical University, Chengdu, CHN
2000 - 2003	Lars Fjellbirkeland	Post-doctoral Fellow		Research Supervisor	Dept of Internal Medicine, University of Oslo, Norway
2004 - 2004	Jun Araya	Post-doctoral Fellow		Research Supervisor	Associate Professor, Jikei University, Tokyo < Japan
2005 - 2005	Cedric Govaerts	Post-doctoral Fellow		Co-Mentor	Researcher, University of Brussels, Belgium

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2007 - 2007	Jennifer Markovics	Post-Doctoral Fellow		Research Supervisor	Researcher, Celgene, Mission Bay, San Francisco, UCSF
2008 - 2008	Hideya Kitamura	Post-doctoral Fellow		Research Supervisor	Assistant Professor, Jikei University, Tokyo < Japan
2008 - 2008	Thomas Arnold	Post-doctoral Fellow	Co-Mentor/Clinical Mentor	Co-Mentor	Post-doctoral Fellow, Department of Physiology, UCSF
2010 - 2010	Sangeeta Somanath	Post-doctoral Fellow		Research Supervisor	Instructor, University of Texas,
2010 - 2010	Shunsuke Minagawa	Post-doctoral Fellow		Research Supervisor	Assistant Professor, Jikei University, Tokyo
2012 - 2014	Mitsuo Minagawa	Post-doctoral Fellow		Research Supervisor	Assistant Professor, Jikei University
2012 - 2012	Oliver Brand	Post-doctoral Fellow		Research Supervisor	Fellow, Manchester University, UK
2012 - 2012	Haruhiro Yanagisawa	Post-doctoral Fellow		Research Supervisor	Nishimuura Lab, UCSF
2013 - 2013	Rob Seed	Post-doctoral Fellow		Research Supervisor	Fellow, University of Leeds, UK
2013 - 2013	Anthony Cormier	Post-doctoral Fellow		Research Supervisor	Nishimuura Lab, UCSF

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2014 - 2016	Catherine Moermans	Post-doctoral Fellow		Research Supervisor	Nishimuura Lab, UCSF
2015 - 2016	Naoki Takasaka	Post-doctoral Fellow	Research/Scholarly Mentor	Research Supervisor	Nishimura Lab, UCSF
2014 - 2015	Ran Cheng	Undergraduate Student Volunteer	Research/Scholarly Mentor, Career Mentor	Supervisor	Graduate student, Tokyo University, JP
2013 - 2015	Kate McKnelly	Research Assistant	Research/Scholarly Mentor, Career Mentor	Supervisor	Graduate Student, Chemistry, UC Irvine
2013 - 2015	Royce Ma	Research Assistant	Research/Scholarly Mentor, Career Mentor	Supervisor	Graduate Student Immunology, Baylor University
2014 - 2015	Michelle Levine	Research Assistant	Research/Scholarly Mentor, Career Mentor	Supervisor	Medical Student, Rocky Vista University College of Osteopathic Medicine, CO
2014 - 2015	Han Li	Volunteer	Research/Scholarly Mentor, Career Mentor	Supervisor	Student UC Berkeley
2014 - 2016	Andrew Bondesson	Research Assistant	Research/Scholarly Mentor, Career Mentor	Supervisor	Graduate Student, Immunology, University of WA

FACULTY MENTORING

Dates	Name	Position while Mentored	Mentor Type	Mentoring Role	Current Position
2004 - 2012	Tomoki Hashimoto	Assistant/Associate professor		Career and research advice	Professor

Dates	Name	Position while Mentored	Mentor Type	Mentoring Role	Current Position
2007 - 2012	Jun Araya	Assistant professor		Career and research advice	Associate Professor
2007 - 2012	Roland Bainton	Assistant professor		Political and research advice	Associate Professor
2008 - 2012	Jianlong Lou	Assistant Professor		Career navigation	Assistant Professor
2012 - 2012	Bradley Stohr	Assistant Professor		Career navigation	Assistant Professor
2015 - present	Sarah Umetsu	Clinical Instructor	Career Mentor	Assigned Career Mentor	Clinical Instructor
2016 - present	Rebecca Wolsky	Clinical Instructor	Career Mentor	Career and research advice	Clinical Instructor

RESEARCH AND CREATIVE ACTIVITIES SUMMARY

My research interests focus on the regulation of cell behavior through cell-extracellular matrix interactions. These interactions have been shown to be important in development, cell signaling, tumor growth, metastasis, angiogenesis and wound repair. Major mediators of cell-matrix interactions are the integrin family of cell adhesion molecules. Integrins are integral transmembrane proteins which act to transduce information contained in the extracellular matrix to the cell interior and conversely from the cell interior to the extracellular environment. Bidirectional integrin signaling provides the cell information that leads to cell movement, differentiation, cell death or cell proliferation. As a pathologist, I am most keenly interested in the down stream effects of these molecules pertinent to homeostasis and how perturbation of homeostatic set points lead to fibrosis and cancer progression. As a pulmonary pathologist, I am most keenly interested in these process in the lung.

I have chosen to focus my research primarily on the cell biology of epithelial-mesenchymal interactions in airway development and disease. Our interest in this area began with the identification of the integrin $\alpha v \beta 8$ as a potent inhibitor of airway epithelial proliferation, which led us to identify a novel mechanism of TGF- β activation. In this mechanism, the latent domain of TGF- β binds with high affinity to the integrin $\alpha v \beta 8$ and following the recruitment of the matrix-metalloproteinase MT1-MMP the latent domain of TGF- β is cleaved allowing the paracrine secretion of active TGF- β (this is in contrast to the mechanism utilized by the integrin $\alpha v \beta 6$ where the active TGF- β remains cell associated). We have gone on to show that in cultured fragments of intact bronchial walls from human subjects that this mechanism of TGF- β activation is a major source of regulation of airway epithelial proliferation. We have defined the epithelial and mesenchymal contributions to TGF- β activation and have surprisingly found that $\alpha v \beta 8$ -mediated activation of TGF- β occurs mainly in subepithelial airway fibroblasts where it might play a major role in regulating the reciprocal trophic interactions between airway epithelial and the surrounding fibroblast sheath during human airway development. These spatially restricted reciprocal interactions guide the proper differentiation of airway cell types during development. In chronic obstructive pulmonary disease (COPD), a chronic lung disease where airway remodeling is an important pathologic component, we hypothesized that chronic epithelial injury could lead to aberrant "reactivation" of these normally highly regulated

epithelial-mesenchymal trophic interactions. Indeed, we have recently reported that squamous metaplasia of airway epithelium, a common change in smokers, leads to increased airway epithelial secretion of IL-1 β . Increased IL-1 β acts on adjacent fibroblasts to induce α v β 8 surface expression and α v β 8-mediated activation of TGF- β , which feeds into a self amplifying loop of TGF- β activation. We currently have funding (2RO1- HL63993-01) to study the regulation of β 8 expression and function of α v β 8-mediated activation in COPD using human in vitro and in vivo systems. Our work in COPD has immediate therapeutic implications; selective inhibition of α v β 8 would bypass the undesirable systemic effects of global TGF- β inhibition. We have developed a high affinity Mab (using both human and mouse version) to use in preclinical mouse models to test for efficacy and toxicity in a number of disease models. To test this Mab we have developed a human ITGB8 BAC rescue mouse expressing a single integrated copy of ITGB8 expressed appropriately to rescue the lethal itgb8 null phenotype. This model will be used for both efficacy and toxicity assays.

Another recent focus of research is to understand the cellular interactions required for vessel formation in the central nervous system (CNS). Towards that goal, we will investigate the cell-type specific roles that cell adhesion receptors play in CNS vessel formation. For CNS vessels to become fully competent, interactions of endothelial cells with other cell types are likely required. Genetic evidence has implicated that the recruitment of pericytes/smooth muscle cells is important for proper cerebral vessel development. In vitro studies have pointed toward astrocytes as another putative cell-type required for proper cerebral endothelial development. However, the molecular basis of the reciprocal signaling between CNS endothelial cells and these other cell types is poorly understood. We have previously determined that a cell-adhesion receptor, integrin α v β 8, recently identified as being essential for murine cerebral vascular development, is expressed by astrocytes and not by endothelial cells or smooth muscle cells. That the integrin β 8 subunit knock-out mice die at late gestation of cerebral hemorrhage is the first genetic evidence to support a role for astrocytes in cerebral vascular development and suggests that α v β 8 acts directly through mediating adhesive cell-cell interactions between astrocytes and endothelial cells or indirectly through another pathway. Our data support an indirect mode of action of α v β 8 since our preliminary data suggests that that α v β 8 is the major molecular mediator of TGF- β activation in cultured astrocytes. Furthermore, despite exhaustive efforts, we have no evidence that α v β 8 mediates cell-cell adhesion. TGF- β is likely candidate molecule to provide instructional cues and to orchestrate proliferation and differentiation events between endothelial cells and mesenchymal cell types. TGF- β is essential to normal cerebral vasculogenesis since loss of function of the endothelial receptors for active TGF- β , endoglin and Alk-1, lead to hereditary hemorrhagic telangiectasia (HHT) in humans and a similar cerebral hemorrhagic disorder in mice. Because TGF- β is ubiquitously expressed in tissues almost entirely in an inactive (latent) state, the α v β 8-dependent conversion of latent to active TGF- β could be a major point in the regulation of TGF- β function in CNS vessel development. Future work will include cell biologic work to gain mechanistic insight into TGF- β activation in neural tissues and cell biologic and genetic approaches to understand the role of non-endothelial cells in CNS vasculogenesis. Towards that end we have generated neural-cell specific "knock-in" mice to to rescue the β 8 knock-out lethal phenotype.

In summary, the major theme of our research is to understand how the functions of integrins, cytokines and MMPs are orchestrated to achieve proper development and to achieve homeostatic regulation and how alterations in the orchestration of these molecules influences neoplasia and wound healing.

Most significant recent publications:

I have chosen a spectrum of publications that represent the three different aspects of my experimental work. These are: airway biology, vascular neurobiology and experimental pathology.

Airway Biology: A recently accepted manuscript "Selective Targeting of TGF- β activation in treating fibroinflammatory airway disease" represents 12 years of work in my laboratory. It includes developing a therapeutic monoclonal antibody for treatment of airway disease, efficacy studies in three mouse models of airway disease, and an in-depth structural, biochemical and structural biologic examination of the mechanism of action of the antibody. Other significant recent contributions to epithelial biology that I have made are represented by: Hideya Kitamura, Stephanie Cambier, Sangeeta Somanath, Tyren Barker, Shunsuke Minagawa, Jennifer Markovics, Amanda Goodsell, Jean Publicover, Louis Reichardt, David Jablons, Paul Wolters, Arthur Hill, James D. Marks, Jianlong Lou, Jean Francois Pittet, Jack Gauldie, Jody Baron, Stephen L. Nishimura, Mouse and human lung fibroblasts regulate dendritic cell trafficking, airway inflammation and fibrosis, through integrin $\alpha\beta 8$ -mediated activation of TGF- β , *J Clin Investigation*, 2011 Jul 1;121(7):2863-75.; Jun Araya, Stephanie Cambier, Jennifer A. Markovics, Paul Wolters, David Jablons, Arthur Hill, Walter Finkbeiner, Kirk Jones, V. Courtney Broaddus, Dean Sheppard, Andrea Barzack, Yuanyuan Xiao, David J. Erle, Stephen L. Nishimura, Squamous metaplasia amplifies pathologic epithelial-mesenchymal interactions in COPD, 2007, *J. Clin. Investigation*, Nov 1;117(11):3551-3562 ; Araya, J., Cambier, S., Morris, A., Finkbeiner, W., Nishimura, S.L. Integrin mediated TGF- β activation regulates homeostasis of the pulmonary epithelial-mesenchymal trophic unit, *Am. J. Path.* 2006, In Press; Mu, Dezhi, Cambier, S, Baron, JL, Munger, J, Sheppard, D, Broaddus, VC, Nishimura, SL, The integrin $\alpha\beta 8$ mediates epithelial homeostasis through the MT1-MMP-dependent activation of TGF- β *J. Cell Biol.* 2002, Apr, 157(3),493-507 and Cambier, S, Mu D, O'Connell, D, Liu, W-H, Travis, W, Broaddus, VC, Nishimura, SL, The integrin $\alpha\beta 8$ negatively regulates the growth of airway epithelium, *Cancer Res.* 2000 Dec 15;60(24):7084-93. These publications represent the first papers describing the function of the integrin $\alpha\beta 8$ in the lung and define a novel pathway of integrin-mediated activation of TGF- β . Furthermore, these papers define a novel mechanism of epithelial homeostasis with broad implications to airway remodeling and cancer pathogenesis. In these studies, I functioned as the principal investigator and was responsible for experimental design and interpretation. I performed initial pilot studies and then taught and supervised post-doctoral fellows, students and technical personnel. I forged the collaborative relationships and oversaw the writing of the manuscript. I also played a substantial contributory role in the report, Jarad, G., Wang, B., Khan, S., DeVore, J., Miao, H., Wu, K., Nishimura, S.L., Wible, B.A., Konieczkowski, M., Sedor, J.R., Schelling, J.R., Fas Activation Induces Renal Tubular Epithelial Cell $\beta 8$ Integrin Expression and Function in the Absence of Apoptosis, *J Biol Chem.* 2002 Dec 6;277(49):47826-47833. In this manuscript, I aided in experimental design and contributed a number of crucial molecular and immunologic reagents.

Vascular neurobiology: Two publications in the field of neural vascular biology highlight our interest in cell biology, gene regulation and human genetics (Cambier, S., Gline, S.E., Araya, J, Collins, R., Einheber, S., Dolganov, G., Boudreau, N., Nishimura, S.L., Integrin $\alpha\beta 8$ -mediated activation of TGF- β : an angiogenic control switch, *Am. J. Path.*) which provides the first mechanistic evidence for a CNS-specific mechanism of vessel development involving paracrine interactions between astrocytes and endothelial cells. 28. Su, Hua; Kim, Helen; Pawlikowska, Ludmila; Kitamura, Hideya; Shen, Fanxia; Cambier, Stephanie; Markovics, Jennifer; Lawton, Michael; Sidney, Steve; Bollen, Andrew; Kwok, Pui-Yan; Reichardt, Louis; Yang, GY; Young, William; Nishimura, Stephen. Reduced Expression of Integrin $\alpha\beta 8$ is Associated with Brain Arteriovenous Malformation (BAVM) Pathogenesis, *Am J Pathol.* 2010 Feb;176(2):1018-27

Structural Biology: Our lab has developed an interest in integrin structure. In particular, we are interested in sorting out the structural biology of integrin-TGF- β interaction. Our first contribution to this area was Gline, S.E., Cambier, S., Govaerts, C., Nishimura, S.L., A 50 Å separation of the integrin $\alpha\beta 3$ extracellular domain C- termini reveals an intermediate activation state, *J Biol Chem*, 2004, (e-published, 10/8/04).). We have extended this work to investigate the extracellular domain conformational heterogeneity of $\alpha\beta 8$ to provide initial insight into the structure of the integrin-L-TGF- β complex. This work is in press in *Science Translational Medicine*

SIGNIFICANT PUBLICATIONS

1. Hideya Kitamura, Stephanie Cambier, Sangeeta Somanath, Tyren Barker, Shunsuke Minagawa, Jennifer Markovics, Amanda Goodsell, Jean Publicover, Louis Reichardt, David Jablons, Paul Wolters, Arthur Hill, James D. Marks, Jianlong Lou, Jean Francois Pittet, Jack Gauldie, Jody Baron, Stephen L. Nishimura, Mouse and human lung fibroblasts regulate dendritic cell trafficking, airway inflammation and fibrosis, through integrin $\alpha\beta 8$ -mediated activation of TGF- β , *J Clin Investigation*, 2011 Jul 1;121(7):2863-75.

I served as the PI of this study which is the first to define a role for lung fibroblasts in directing pathologic inflammation. I was the main contributor to the design and conception of all of experiments and supervised the post-docs who performed the studies.

2. Markovics JA, Araya J, Cambier S, Somanath S, Gline S, Jablons D, Hill A, Wolters PJ, Nishimura SL. Interleukin-1 β induces increased transcriptional activation of the transforming growth factor- β activating integrin subunit $\beta 8$ through altering chromatin architecture. *J Biol Chem*. 2011 Aug 30

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4. Shunsuke Minagawa, Jianlong Lou, Robert I. Seed, Anthony Cormier, Shenping Wu, Yifan Cheng, Lynne Murray, Ping Tsui, Jane Connor, Ronald Herbst, Cedric Govaerts, Tyren Barker, Stephanie Cambier, Haruhiko Yanagisawa, Amanda Goodsell, Mitsuo Hashimoto, Oliver J. Brand, Ran Cheng, Royce Ma, Kate J. McNelly, Weihua Wen, Arthur Hill, David Jablons, Paul Wolters, Hideya Kitamura, Jun Araya, Andrea J. Barczak, David J. Erle, Louis Reichardt, James D. Marks, Jody L. Baron, Stephen L. Nishimura, Selective targeting of TGF- β activation to treat fibroinflammatory airway disease, 2014, *Science Translational Medicine*, In Press

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RESEARCH AWARDS - CURRENT

1. 1R01HL113032-01	PI	10 % effort	Nishimura (PI)
NIH/NHLBI		04/01/2012	03/31/2016
Role of genetic variation in TGF-beta overactivation in COPD		\$ 312,973 direct/yr 1	\$ 1,334,063 total

Project goals: AIM1) To discover all common genetic variants in and around ITGB8 associated with increased B8 expression; AIM2) To test common genetic variants in ITGB8 for association with COPD and lung phenotypes; AIM3) To test the hypothesis that genetic variation in ITGB8 leads to increased ITGB8 expression; and AIM4) To test the hypothesis that genetic variation in ITGB8 leads to altered airway disease susceptibility.

Conception, oversight, execution.

2. U54HL119893	PI	5 % effort	Nishimura (PI)
University of California/NIH NHLBI Center for Accelerated Innovation			
Selective targeting of TGF- β activation for airway remodeling with engineered monoclonal antibodies		\$ 100,000 direct/yr 1	\$ 200000 total
AIMs) To optimize glycosylation of anti- $\beta 8$ antibody clone B5 and related antibodies; To create optimized anti- $\beta 8$ antibodies for immunohistochemical detection; To create novel neutralizing anti- $\beta 8$ antibodies			
Overlap: None			

Conception, oversight, execution.

3. 1R01HL134183-01	PI (MPI: Contact PI)	15 % effort	Nishimura (PI)
Structural mechanism of integrin-mediated TGF-b activation		07/04/2016	4/30/2020
Structural mechanism of integrin-mediated TGF-b activation		\$ 338,183 (Total) direct/yr 1	\$ 1,353,622 total

\$536,020 direct/yr1

RESEARCH AWARDS - PAST

1. 01HL090662	PI		Nishimura (PI)
NIH		09/01/2009	08/31/2011
Role of squamous metaplasia in airway wall thickening		\$ 250000 direct/yr 1	\$ 750000 total

Conception, oversight, execution.

2. 2RO1- HL63993-01	PI		Nishimura (PI)
NIH		7/1/2009	6/30/2014
Integrin avb8 Inhibits Airway Epithelial Cell Growth			

Specific Aim 1: To test the hypothesis that the increased $\beta 8$ expression in COPD is mediated by response to inflammatory cytokines and alterations in HDAC activity. Specific Aim 2: To test the hypothesis that increased integrin $\alpha v \beta 8$ expression on airway epithelial cells and lung fibroblasts in COPD leads to increased activation of TGF- β . Specific Aim 3: To test the hypothesis that increased integrin $\alpha v \beta 8$ mediated activation of TGF- β in COPD leads to alterations in airway epithelial and fibroblast functions involved in airway remodeling.

Conception, oversight, execution.

3. NS-44155	Project 4		Young (PI)
NIH		09/1/2009	03/31/2014
Integrative studies of brain vascular malformations (project 4)		\$ 125,000 (Nishimura Project) direct/yr 1	\$ 625000 total

Aim 1: will explore the mechanisms of transcriptional regulation of $\beta 8$. Aim 2: to correlate $\beta 8$ expression, and downstream angiogenic signaling in BAVM and control tissues with allelic variation. Aim 3: to directly test the respective roles of $\alpha v \beta 8$ and TGF- β signaling in CNS vascular integrity

Conception, oversight, execution.

4. The use of a multi-sample bead mill homogenizer to efficiently process biological specimens			
UCSF Academic Sentate		\$12,000 total	\$12,000 total
Mouse smoking machine		\$ 35,000 direct/yr 1	\$ 35,000 total

PEER REVIEWED PUBLICATIONS

1. Nishimura, S., Pasternak, G. W. Opiate and Opioid Peptide Binding in Rat and Goldfish: Further Evidence for Opiate Receptor Heterogeneity. *Br. Res.*, 248:192-195, 1982.
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BOOKS AND CHAPTERS

1. Nishimura, S.L., Broaddus, V.C., Asbestos-related pleural diseases, (Chapter), Chest Clinics of North America 1998;19(2):311-29
2. Nishimura, S.L., Finkbeiner, W., Pulmonary Pathology, (Chapter), in Textbook of Respiratory Medicine, Murray and Nadel, Eds., 4th Ed..

SIGNIFICANT PUBLICATIONS

1. Hideya Kitamura, Stephanie Cambier, Sangeeta Somanath, Tyren Barker, Shunsuke Minagawa, Jennifer Markovics, Amanda Goodsell, Jean Publicover, Louis Reichardt, David Jablons, Paul Wolters, Arthur Hill, James D. Marks, Jianlong Lou, Jean Francois Pittet, Jack Gaudie, Jody Baron, Stephen L. Nishimura, Mouse and human lung fibroblasts regulate dendritic cell trafficking, airway inflammation and fibrosis, through integrin α v β 8-mediated activation of TGF- β , J Clin Investigation, 2011 Jul 1;121(7):2863-75.

I served as the PI of this study which is the first to define a role for lung fibroblasts in directing pathologic inflammation. I was the main contributor to the design and conception of all of experiments and supervised the post-docs who performed the studies.

2. 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-1 β -Mediated Murine Airway Disease. J Immunol. 2015 Apr 15; 194(8):3962-9. PMID: 25786688. PMCID: PMC4390519

I served as PI of the study and oversaw all aspects of the project and wrote the manuscript.

3. 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. PMCID: PMC4506848

I served as PI and oversaw all aspects of the study.

4. 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-1 β Signaling Pathways Converge on the Chemokine CCL20 Promoter. J Biol Chem. 2015 Apr 27. PMID: 25918170. PMCID: PMC4505537

I served as PI and oversaw all aspects of the study.

5. Minagawa S, Lou J, Seed RI, 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 OJ, Cheng R, Ma R, McKnelly KJ, Wen W, Hill A, Jablons D, Wolters P, Kitamura H, Araya J, Barczak AJ, Erle DJ, 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. PMID: 24944194. PMCID: PMC4341974

I served as PI and oversaw all aspects of the study.

PATENTS ISSUED OR PENDING

1. INTEGRIN α V β 8 NEUTRALIZING ANTIBODY (US Provisional Application No. 61/305,749 filed February 18, 2011, and US Provisional Application No. 61/428,814, filed December 30, 2010)
2. ANTIBODIES THAT BIND INTEGRIN α V β 8 (US Provisional Application, filed Aug 17, 2011)
3. IMPROVED ALPHA-V BETA-8 ANTIBODIES (US Provisional Application, filed June 17, 2014)

ACADEMIC LEADERSHIP

Co-chair of the ZSFG research committee. Have played a leadership role in organizing, facilitating planning, dissemination of information and programming the planned new research building at ZSFG.