OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

NAME: **Simon, Scott I.**

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

POSITION TITLE: **Professor**

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 | Completion Date | FIELD OF STUDY |
| --- | --- | --- | --- |
| UC San Diego, La Jolla, CA | BS | 1983 | Engineering Sciences |
| UC San Diego, La Jolla, CA | MS | 1984 | Engineering Sciences |
| UC San Diego, La Jolla, CA | PhD | 1988 | Biomedical Engineering |
| Scripps Clinic & Research Foundation, La Jolla, CA | Post-Doc | 1988-90 | Inflammation Biology |

# A. Personal Statement

My laboratory studies the innate immune mechanisms governing inflammation and infection. Our laboratorydevelops technologies to delve the force and molecular dynamics by which neutrophils and monocytes recruit to inflamed endothelium and respond to tissue insult. Imaging technologies are developed to delve the multistep sequence by which leukocytes roll-arrest and transmigrate to a site of acute inflammatory tissue insult. Our strategy is to mimic the hydrodynamic shear, chemokine gradients, and adhesion molecule presentation using recombinant protein substrates and endothelial monolayers in microfluidic based lab-on-a-chip devices that enable experiments to be performed in reduced systems accessible to real-time observation. We are currently funded by two R01 awards to study the neutrophil response to acute inflammatory stimuli and also Staphylococcus aureus bacterial infection that governs the innate immune response. Primary goals is to not only develop translatable strategies to overcome the intractable problem of antibiotic resistant *S. aureus* skin infections in immunodeficient subjects, but also train bioengineer and immunological scientists in requisite skills. The Simon laboratory has trained dozens of Ph.D. graduates over the past two decades. This is a diverse group in terms of gender and race. We foster an inclusive and supportive environment for acquiring skills to pursue either academic or industry careers. Through weekly lab meetings and one on one training at the bench, we provide rigorous biomedical training. A hierarchical approach in which postdocs and senior graduate students take on responsibilities of working with newer graduate and undergraduate trainees facilitates a robust learning and working experience.

Innate immune response to S. aureus infection in skin

1. Anderson LS, Yu S, Rivara KR, Reynolds MB, Hernandez AA, WuX, YangH, IsseroffRR, MillerLS, HwangST, **Simon SI**. 2019. CCR6+ γδ T cells home to skin wounds and restore normal wound healing in CCR6-deficient mice. ***J. Invest. Derm.*** *Sep;139(9):2061-2064.*
2. Falahee PC, Anderson LS, Reynolds MB, Pirir M, McLaughlin BE, Dillen CA, Cheung AL, Miller LS, **Simon SI.** 2017. [α-Toxin Regulates Local Granulocyte Expansion from Hematopoietic Stem and Progenitor Cells in *Staphylococcus aureus-*Infected Wounds.](https://www.ncbi.nlm.nih.gov/pubmed/28733486) ***J Immun.*** 199(5) 1772-1782. Cited 5 times.
3. Granick, JL, Falahee, P, Dahmubed, D, Borjesson, Miller, LS, **Simon, SI.** 2013. *Staphylococcus aureus* recognition by hematopoietic stem and progenitor cells via TLR2/MyD88/PGE2 stimulates granulopoiesis in wounds. ***Blood*** 122(10): 1770-1778. Cited 38 times.
4. Kim, M-H, Granick, JL, Kwok, C, Walker, N, Borjesson, DL, Curry, FE, Miller, LS, **Simon, SI.** 2011. Neutrophil survival and c-kit+ progenitor proliferation in *Staphylococcus aureus* infected skin wounds promote resolution. ***Blood*** 117(12):3343-52. Cited 86 times.

# B. Positions and Honors

Positions and Employment

1988-90 **Post-Doctoral Fellow**, Research Institute of Scripps Clinic, La Jolla, CA

1990-93 **Assistant Professor**, Dept of Pathology University of New Mexico School of Medicine, NM

1993-99 **Assistant Professor**, Dept of Pediatrics, Baylor College of Medicine, Houston TX

1994-99 Adjunct Assistant Professor, Dept of Biomedical Engineering, Rice University, Houston TX

1999-2001 **Associate Professor**, Dept of Biomedical Engineering, UC Davis

2001-present **Professor**, Biomedical Engineering, College of Engineering, UC Davis

Scientific Activities and Professional Memberships

2016-2017 Vice President, Science Policy, FASEB

2009-2018 Deputy Editor in Chief, *Annals of Biomedical Engineering*

2003-2009 Associate Editor, *Annals of Biomedical Engineering*

2015-2019 NIH permanent member of MTE integrated review group.

2006-2015 NIH study section membership; ICI-Intercellular interactions; BTSS-Bioengineering; MOSS-NIBIB

Honors

2019 Director, Bioengineering Institute of California (10 UC campuses)

2015 Member, U.S. National Committee on Biomechanics

2013 Board of Directors and Program Advisory Committee, FASEB

2010 College of Reviewers; CSR, NIH

2010 Fellow, Biomedical Engineering Society

2005 Fellow, American Institute for Medical and Biological Engineering

2004 Board of Directors, Biomedical Engineering Society

1996 Established Investigator Award of the American Heart Association

1995 Whitaker Foundation Investigator Award

1992 Recipient, National Institute of Health F.I.R.S.T. Award

1988 American Heart Association Post-Doctoral Fellowship

# C. Contribution to Science

# 1. Discovered the respective adhesive roles of L-selectin and 2-integrins in neutrophil tethering and arrest under hydrodynamic shear flow. The multistep process of leukocyte recruitment is characterized by capture to inflamed endothelium where leukocytes integrate multiple signals. Our group was the first to define the mechanical role of selectins as tethering molecules and integrins as firmly adherent receptors requiring the initial durable contact duration afforded by selectins.

# a) Simon, S.I., Chambers, D.C., Butcher, E., Sklar, L.A. (1992) Neutrophil aggregation is2 Integrin and L-selectin dependent in blood and isolated cells as measured by flow cytometry. *J.Immun*. 149:2765-2771.

b) **Simon, S.I.**, Rochon, Y.P., Smith, C.W., Anderson, D.C.,and L.A. Sklar. (1993) 2-Integrin and L-Selectin are Obligatory Receptors in Neutrophil Aggregation*. Blood.* 82:1097-1106.

c) Taylor, A., Neelamegham, S., Smith, C.W., Hellums, D., **Simon, S.I.**  (1996) Molecular dynamics of the transition from L-selectin to ß2-integrin dependent neutrophil adhesion. *Biophys. J.* 71: 3488-3500.

d) Neelamegham, S., Taylor, A.D., Hellums, J.D., Dembo, M., Smith, C.W. **Simon, S.I.** (1997) Modeling the reversible kinetics of neutrophil adhesion under hydrodynamic shear. *Biophys J.* 72:1527-1540.

2. Ours was the first group to report that L-selectin ligation and clustering signaled from the outside-in activation of 2-integrins. This observation also led the way to defining mechanical cooperativity between selectins and integrins during neutrophil recruitment and transmigration. It also provided first assays to describe the mechanisms by which selectin antagonists can function as effective anti-inflammatories.

a) Hwang, S.T., Singer, M.S., Giblin, P.A. Yednock, T., Bacon, K.B., **Simon, S.I.**, Rosen, S.D. (1996) GlyCAM-1, a physiologic ligand for L-selectin activates ß2-integrins on naive peripheral lymphocytes. *J. Exp. Med.* 184:1343-1348

b) Tsang, Y., Neelamegham, S., Burns, A.R., Berg, E., Smith, C.W., **Simon, S.I.** (1997). Synergy between L-selectin signaling and chemotactic activation during neutrophil adhesion and transmigration. J*. Immunol.* 159: 4566-4577.

c) Evans E., Leung A., Hammer D., and **S.I. Simon**. Chemically-distinct transition states govern rapid rupture of single L-selectin bonds under force. (2001) *Proc Natl Acad Sci* U S A. 2001 Mar 27;98(7):3784-3789.

d) Green, C.E., Pearson, D.N., Christensen, N.B., and **S.I. Simon**. (2003) Topographic requirements and dynamics of signaling via L-selectin on neutrophils. *Am J Physiol* (Cell Physiol). 284:1-13.

**3.** Our group discovered that neutrophil rolling on E-selectin activates integrin-dependent arrest. This observation was the first to show that outside-in signaling through rolling on E-selectin activates 2-integrin dependent arrest, which has been the subject of hundreds of subsequent reports indicating crosstalk between selectins and integrins during leukocyte recruitment. We subsequently worked out the signaling pathway involved.

a) **Simon, S.I.,** Hu, Y, Vestwebber, D., Smith, C.W. (2000)Neutrophil tethering on E-selectin activates ß2–integrin binding to ICAM-1 through a MAP kinase signal transduction pathway. *J. Immun.* 164: 4348-4358.

b) Hentzen, E., McDonough, D., McIntire, L., Smith, C.W., Goldsmith, H.L., and **S.I. Simon**. (2002) Hydrodynamic Shear and tethering through E-selectin signals phosphorylation of p38 MAP Kinase and Adhesion of Human Neutrophils. *Annals of Biomed. Eng*. 30:1-16.

c) Green C. E., Pearson D.N., Camphausen R.T., Staunton D.E. and **S.I. Simon** (2004) Shear dependent capping of L-selectin and PSGL-1 by E-selectin signals activation of high avidity β2-integrin on neutrophils. *J. Immun.* 172(12):7780-90.

d) Morikis VA, Chase S, Wun T, Chaikof EL, Magnani JL, **S.I. Simon** (2017)Selectin catch-bonds mechanotransduce integrin activation and neutrophil arrest on inflamed endothelium under shear flow.*Blood.* 130(19):2101-2110.

**4.** 2-Integrins function as mechano-sensors in guidance of neutrophil transmigration was first reported by our group. We developed vascular mimetic microfluidic systems to study the process in real-time using fluorescence techniques. Subsequently, we introduced a novel outside-in signaling pathway involving the CRAC channel Orai1, LFA-1, and Kindlin-3.

a) Sarantos MR, Zhang H, Schaff UY, Dixit N, Hayenga HN, Lowell CA, and **SI Simon** Transmigration of Neutrophils across Inflamed Endothelium is Signaled Through LFA-1 and Src-family kinase *J Immunol.* 181:8660-9.

b) Schaff UY, Dixit N, Procyk E, Yamayoshi I, and **SI Simon** (2010) Orai1 regulates intracellular calcium, arrest, and shape polarization during neutrophil recruitment in shear flow. *Blood* 115:657-66

c) Dixit N, Yamayoshi I, Nazarian A, **Simon SI.** (2011) Migrational guidance of neutrophils is mechanotransduced via high-affinity LFA-1 and calcium flux*. J Immunol.* 187(1):472-81.

d) Dixit N, Kim MH, Rossaint J, Yamayoshi I, Zarbock A, **S I. Simon**. (2012) Leukocyte Function Antigen-1, Kindlin-3, and Calcium Flux Orchestrate Neutrophil Recruitment during Inflammation. *J. Immunol.* 189(12):5954-64.

**5.** Monocyte interaction with inflamed aortic endothelium is an early event in atherogenesis. Our laboratory produced the first artery-on-a-chip to examine cooperativity between CD11c/CD18 and VLA-4 and that triglyceride rich lipoprotein amplifies cytokine mediated expression of VCAM-1. The mechanism was found to involve IRF-1 and post transcriptional amplification via miRNA126. More recently, we reported that VCAM-1 is highly expressed on circulating endothelial cells and micoparticles obtained during following percutaneous angioplasty.

a) Foster GA, Gower RM, Stanhope KL, Havel PJ, **Simon SI**, and Armstrong EJ. On-chip phenotypic analysis of inflammatory monocytes in atherogenesis and myocardial infarction (2013) *Proc Natl Acad Sci*; Aug 20;110(34):13944-9

b) Foster GA, Xu L, Chidambaram AC, Soderberg SR, Armstrong EJ, Wu H, and **SI Simon**. CD11c/CD18 Signals Very Late Antigen-4 Activation To Initiate Foamy Monocyte Recruitment during the Onset of Hypercholesterolemia. (2015) *J. Immuno.*, 195: 95(11):5380-92

c) Xu L, Dai Perrard X, Perrard JL, Yang D, Xiao X, Teng BB, Simon SI, Ballantyne CM, Wu H. Foamy monocytes form early and contribute to nascent atherosclerosis in mice with hypercholesterolemia. Arterioscler Thromb Vasc Biol 2015; 35: 1787-1797. PMID: 26112011. PMC4514542.

d) Sun C, Simon SI, Foster GA, Radecke CE, Hwang HV, Zhang X, Hammock BD, Chiamvimonvat N, Knowlton AA. 11,12-Epoxyecosatrienoic acids mitigate endothelial dysfunction associated with estrogen loss and aging: Role of membrane depolarization. J Mol Cell Cardiol. 2016 May;94:180-8.

**H-index of 56 and >9600 citations.**

**URL to a list of published work as found in NCBI:** <http://www.ncbi.nlm.nih.gov/sites/myncbi/scott.simon.1/bibliography/41156051/public/?sort=date&direction=ascending>

**D. Research Support**

ACTIVE:

R01 AI047294 (PI: Scott Simon) 07/01/17 – 06/30/22

National Institutes of Health (NIH)

*Outside-in Mechanotransduced Inflammatory Targets*

This study focuses on the regulation of adhesion receptors and signaling pathways in neutrophil adhesion to venous endothelium under defined fluid shear and force fields.

R01 AI129302 (mPI: Scott Simon & J. Kent Leach) 07/01/17 – 6/30/22

National Institutes of Health (NIH)

*Engineering the innate immune response to Staphaureus infection*

This study is begins where the previous R56 left off in terms of mechanisms by which innate immune cells control Staphaureus infection in cutaneous wounds. The focus here is on how the wound niche stimulates local emergency granulopoiesis and develops a human mouse model to evaluate translational therapy aimed at stimulating this novel mechanism of bacterial clearance and wound healing.

**Overlap- the current U01 application compliments the aims of this grant by using in-vitro Immune-chip technology to test mechanism of human innate immunity to S. aureus infection in a simulated environment.**

R01 HL098839 (PI: HuaiZhu Wu) 01/01/15 – 12/31/19

National Institutes of Health (NIH)

*Monocyte Activation and the Role of CD11c in Obesity-linked Metabolic Syndrome*

To determine if obesity related up-regulation of CD11c on peripheral monocytes contributes to adhesion and migration on endothelial cells in shear flow.

**Completed**

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| R01 AI108713-01 (PI: Jay Solnick) | 08/01/14 – 07/31/18 | .60 cal mos |
| National Institutes of Health (NIH) | $315,238 annual direct |  |

 *Functional Plasticity in the Helicobacter plyolri Type IV Secretion System*

 The goal of this project is to understand the mechanism and host immunity that underlie functional plasticity in the type IV secretion system in Helicobacter plyori.

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| R01 HL082689 (PI: Scott Simon) | 01/01/13 – 02/28/18 | 3.0 cal mos |
| National Institutes of Health (NIH) | $278,921 annual direct |  |

 *Vascular Mimetics to Study Inflammation and Atherosclerosis*

The focus of this grant is to study post prandial hyperlipemia and its effect on inflammation, specifically how triglycerides rich lipoproteins (TGRLs) prime aortic endothelium for enhanced expression of adhesion molecules and monocyte recruitment.

Overlap: This is the competitive renewal for this grant.

 R56 AI103687 (PI: Simon (PI) 08/01/13-07/31/14 3.0 cal mos

 National Institutes of Health (NIH) $250,000 annual direct

 *Engineering the Immune Response for Improved Resolution of Staphylococcus Infectio*