BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: **Jianchuan Wang**

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

POSITION TITLE: **Research Fellow**

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
Shandong University, China	B.A.	06/2006	Life Science
Shanghai Institute of Biochemical and Cell Biology, Chinese Academy of Sciences	Ph.D.	01/2013	Biochemistry and Molecular Biology

A. Personal Statement

During my Ph.D. training, I accumulated comprehensive knowledge about crystallography and mastered solid experimental skills including gene cloning, protein expression and purification, crystal screening and optimization, data collection and processing, structural model building and refinement, as well as some necessary biochemical and biophysical techniques. After six years training, I think structural biology is the most powerful tool to study the biological phenomenon at atomic level. It provides us with a visual impression of the intrinsic relationship between structure and function. I always had a great passion to understand the structural basis of biomacromolecules regarding their diversified functions in life. In 2013, I joined Dr. Springer's lab in Harvard Medical School/Boston Children's Hospital. By collaboration with my colleagues, I applied X-ray crystallography, negative staining electron microscopy and other methods to investigate the mechanism for the activation of pro-TGF-β by integrin αvβ8. We obtain very promising results to show unique structural features of integrin αvβ8 and will continue to pursue how to connect structural features to physiological functions.

B. Positions and Honors

Positions and Employment

2006-2013 Ph.D. student, Prof. Jianping Ding's lab, Shanghai Institute of Biochemical and Cell Biology, Chinese Academy of Sciences, Shanghai, China

2013-present Research Fellow, Boston Children's Hospital and Harvard Medical School

Honors

2012 Excellent Students Award from the Chinese Academy of Sciences

C. Contribution to Science

1. During the Ph.D. training period, my major research projects including three aspects. The first project was to study the regulation mechanism of S6K1 (a pivotal kinase in mTOR pathway) by critical residue phosphorylation through structural and biochemical analysis. The second project was a collaboration with my colleagues. We studied the recognition mechanism of IL-2Rα (also called CD25) ectodomain by two therapeutic antibodies. The third work was a collaboration with Dr. Jia Li's lab from Shanghai Institute of Materia Medica. We tried to obtain the structure of a protein tyrosine phosphatase with its agonist and antagonist. My current project in Dr. Springer's lab is investigating the mechanism for the activation of pro-TGF-β by integrin αvβ8, which is a key regulatory pathway for TGF-β activation.
   a. **Wang J**, Dong X, Zhao B, Li J, Lu C, Springer TA. (2017) Atypical interactions of integrin αVβ8 with pro-TGF-β1. ***PNAS,*** E4168–E4174, doi: 10.1073/pnas.1705129114. PMC5448207
   b. Xu S❖, **Wang J❖**, Wang H, Springer TA. (2017) Distinct recognition of complement iC3b by integrins αXβ2 and αMβ2. ***PNAS,*** 114(13): 3403-3408 (**❖Co-first author**). PMC5380021
   c. Yang H*, **Wang J***, Du J, Zhong C, Zhang D, Guo H, Guo Y, and Ding J. (2010) Structural basis of

immunosuppression by the therapeutic antibody daclizumab. *Cell Res* 20, 1361-1371 (***Co-first author**). Non-NIH Support. PMCID: In Press

d. Hou L*, **Wang J***, Zhou Y, Li J, and Zang Y. (2011) Structural insights into the homology and differences between mouse protein tyrosine phosphatase-sigma and human protein tyrosine phosphatase-sigma. Acta Biochim Biophys Sin 43, 977-988 (***Co-first author**). Non-NIH Support. PMCID: In Press
e. **Wang J**, Zhong C, Wang F, Qu F, and Ding J. (2013) Crystal structures of S6K1 provide insights into the regulation mechanism of S6K1 by the hydrophobic motif. *Biochemical Journal* 454, 39-47. Non-NIH Support. PMCID: In Press

Full list of publications (copy and paste to a browser):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1PoDv0hoJDIQo/bibliography/45591412/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

NIH 1R01HL134723

Completed Research Support

None.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: **Timothy A. Springer**

POSITION TITLE: **Latham Family Professor of Biological Chemistry and Molecular Pharmacology**

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

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Berkeley	B.A.	1971	Biochemistry
Harvard University, Cambridge	Ph.D.	1976	Molecular Biology and Biochemistry
University of Cambridge, England	Post-doc	1977	Pathology

A. Personal Statement:

I am a biochemist, immunologist, and biophysicist focused on adhesion, the vasculature, how protein allostery responds to force to strengthen and regulate receptor-ligand bonds, disease, and therapy. These themes run through my work on integrins and resonate in new research on the TGF-β family, von Willebrand factor, and malaria.

1. Takagi, J., Petre, B. M., Walz, T., and Springer, T. A. (2002) Global conformational rearrangements in integrin extracellular domains in outside-in and inside-out signaling. *Cell* **110**, 599-611
2. Xiao, T., Takagi, J., Wang, J.-h., Coller, B. S., and Springer, T. A. (2004) Structural basis for allostery in integrins and binding of fibrinogen-mimetic therapeutics. *Nature* **432**, 59-67 PMC4372090
3. Zhu, J., Zhu, J., and Springer, T. A. (2013) Complete integrin headpiece opening in eight steps. *J. Cell Biol.* **201**, 1053-1068 PMC3691460
4. Dong, X., Hudson, N. E., Lu, C., and Springer, T. A. (2014) Structural determinants of integrin β-subunit specificity for latent TGF-β. *Nat. Struct. Mol. Biol.* **21**, 1091-1096. PMC Journal in process.

B. Positions and Honors

Professional Experience:

1977 - 1989 Assistant and Associate Professor of Pathology, Harvard Medical School
1981 - 1988 Chief, Laboratory of Membrane Immunochemistry, Dana Farber Cancer Institute
1988 - 2012 Senior Investigator, Immune Disease Institute (aka CBR Institute for Biomedical Research)
1988 - 1993 Vice President, Immune Disease Institute (Center for Blood Research)
1989 - Latham Family Professor, Harvard Medical School
1989-2011 Professor of Pathology; Harvard Medical School
2011 - Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
2011 - Professor of Medicine, Harvard Medical School
2012 - Senior Investigator, Program in Cellular and Molecular Medicine, Boston Children's Hospital

Honors and Awards:

1966 National Merit Scholarship
1971 Phi Beta Kappa
1971 Biochemistry Departmental citation (awarded to most outstanding graduate)
1971 B.A. with Distinction in Scholarship and Great Distinction in the Major
1984 - 1989 American Cancer Society Faculty Research Award
1986 - 1990 Member, Allergy and Immunology Study Section, National Institutes of Health
1988, 2004 MERIT Grant Award, National Institutes of Health
1989 Councilor, International Leukocyte Workshop
1993 American Heart Association Basic Research Prize
1994 Royal Society of Medicine, Medal, Visiting Professor, United Kingdom
1995 William B. Coley Medal for Distinguished Research in Fundamental Immunology, Cancer Research Institute
1995 Marie T Bonazinga Award for Excellence in Leukocyte Biology Research, Society for Leukocyte Biology
1996 Member, National Academy of Sciences
1997 Wellcome Visiting Professor, Wayne State University
2001 Fellow, American Academy of Arts and Sciences

2004 Crafoord Prize in Polyarthritis 2004, Royal Swedish Academy of Sciences
2004 - Member, Center for Molecular and Cellular Dynamics, Harvard Medical School
2004 - 2007 Chair, Biophysics and Computational Biology (Section 29), Natl. Acad. of Science
2004 - Honorary Chair Professor, Fudan University, Shanghai, China
2006 - Honorary Professor, Nankai University, College of Life Sciences, Tianjin, China
2010 - Board of Trust, Children's Hospital Boston
2011 Doctor Medicinae Honoris Causa, Aarhus University, Denmark
2013 - Fellow, American Association for the Advancement of Science
2014 Meritorious Career Award, American Association of Immunologists
2014 Henry Stratton Medal, American Society of Hematology
2015 Biennial Medal for Contributions in Hemostasis, International Soc. for Thrombosis and Hemostasis

C. Contribution to Science

I discovered the first adhesion molecules of the immune system (3). Previously, immunologists had only thought of "specific" receptors. However, the requirement of Mg^{2+} for antigen-specific lymphocyte conjugation to target cells, and the requirement of divalent cations for adhesion by non-hematopoietic cells, suggested a common recognition principle shared by these cells, which is now known as the integrin family. Pursuing this dream, my lab identified lymphocyte function-associated (LFA) molecules LFA-1, LFA-2 (CD2), and LFA-3 in screens for antibodies that inhibit antigen-specific killing of target cells by T lymphocytes (1). These molecules were present on multiple lymphocyte and leukocyte subsets and were required for antigen-specific T and B cell responses as well as natural killing and antibody-dependent cellular cytotoxicity (4). We discovered the first ligand for LFA-1, intercellular adhesion molecule-1 (ICAM-1), by screening for blockade of LFA-1-dependent adhesion to LFA-1-deficient cells (2). The LFA-1 ligand ICAM-2 was discovered in a search for the constitutively expressed ligand for LFA-1 on endothelium. ICAM-1 became the first adhesion molecule on endothelium inducible by inflammatory mediators (4). Discoveries that LFA-1 was a receptor for ICAMs (4) and CD2 was a receptor for LFA-3 (4) defined the first examples of like-unlike (heterophilic) adhesive recognition pairs in biology. Discoveries of two distinct adhesion pathways each required for antigen recognition led to FDA approval of two drugs for the autoimmune disease psoriasis: an antibody to LFA-1 (efalizumab, Genentech, 2001) and an LFA-3 ectodomain fusion to IgG Fc (alefacept, Biogen, 2001).

1. Sanchez-Madrid, F., Krensky, A. M., Ware, C. F., Robbins, E., Strominger, J. L., Burakoff, S. J., and Springer, T. A. (1982) Three distinct antigens associated with human T lymphocyte-mediated cytolysis: LFA-1, LFA-2, and LFA-3. *Proc. Natl. Acad. Sci. U. S. A.* **79**, 7489-7493. PMC347365
2. Rothlein, R., Dustin, M. L., Marlin, S. D., and Springer, T. A. (1986) A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. *J. Immunol.* **137**, 1270-1274.
3. Marlin, S. D., and Springer, T. A. (1987) Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand or lymphocyte function-associated antigen 1 (LFA-1). *Cell* **51**, 813-819.
4. Springer, T. A. (1990) Adhesion receptors of the immune system. *Nature* **346**, 425-433.

We discovered that LFA-1, Mac-1 (macrophage antigen 1), and p150,95 are $\alpha\beta$ heterodimers with identical β-subunits and distinct but homologous α-subunits (1). These relationships, and the sequences of their α-subunits, provided the first evidence for the integrin family. LFA-1, Mac-1, and 150,95 were absent on the surface of leukocytes from a group of patients with recurring, life-threatening bacterial infections, owing to mutations in their common β-subunit, thus defining leukocyte adhesion deficiency and the importance of integrins in diapedesis. Evidence that integrins could be activated by intracellular signaling to bind ligands outside cells (inside-out signaling) led me to investigate conformational change. Structures of the LFA-1 α-subunit inserted (αI) domain showed three conformational states, and that Mg^{2+} held in the αI domain metal ion-dependent adhesion site (MIDAS) is central in the ligand binding site. Coordination of the Mg^{2+} to a Glu residue in immunoglobulin-like domain 1 of ICAM-1 explained the Mg^{2+} dependence of antigen-dependent cell conjugation. We have since determined crystal and electron microscopy structures of integrins $\alpha_L\beta_2$ (LFA-1), $\alpha_X\beta_2$, (p150,95) $\alpha_V\beta_3$, $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_4\beta_7$, and $\alpha_V\beta_6$ and their complexes with ligands (4). Integrin ectodomains have three overall conformations: bent-closed, extended-closed, and extended open (2,4). The α and β-subunit transmembrane (TM) domains noncovalently associate in the bent-closed conformation, and separation of the TM domains is required for both inside-out and outside-in integrin signaling. Structures that include complexes with ligand and conformation-specific, function-perturbing antibody fragments demonstrate that only the extended-open integrin conformation has high affinity for ligand (2,4). Traction force applied by the actin cytoskeleton to the integrin β-subunit cytoplasmic domain in a direction parallel to the plasma membrane, and resisted by the ligand outside the cell, is aligned with the pathway of conformational change to the extended-open conformation (3). Integrins

thus endow cells with four-wheel drive, enabling them to bind to ligands only in cell surface regions that can gain traction.

1. Kürzinger, K., Ho, M. K., and Springer, T. A. (1982) Structural homology of a macrophage differentiation antigen and an antigen involved in T-cell-mediated killing. *Nature* **296**, 668-670
2. Xiao, T., Takagi, J., Wang, J.-h., Coller, B. S., and Springer, T. A. (2004) Structural basis for allostery in integrins and binding of fibrinogen-mimetic therapeutics. *Nature* **432**, 59-67 PMC4372090
3. Zhu, J., Luo, B. H., Xiao, T., Zhang, C., Nishida, N., and Springer, T. A. (2008) Structure of a complete integrin ectodomain in a physiologic resting state and activation and deactivation by applied forces. *Mol. Cell* **32**, 849-861 PMC2758073
4. Springer, T. A., and Dustin, M. L. (2012) Integrin inside-out signaling and the immunological synapse. *Curr. Opin. Cell Biol.* **24**, 107-115 PMC3294052

Our work on leukocyte adhesion deficiency showed that integrins were required for leukocyte emigration from the bloodstream. In turn, this led us to study leukocyte adhesion to purified molecules on the wall of a flow chamber and to discover the three-step model for leukocyte diapedesis (1-4). When neutrophils were infused to mimic flow in a blood vessel, they bound to P-selectin immobilized on the flow chamber wall and rolled in response to hydrodynamic drag; in contrast, neutrophils could not adhere to or roll on ICAM-1 in flow. If both P-selectin and ICAM-1 were present on the wall, neutrophils rolled on P-selectin; however, when a chemoattractant was added to the flowstream, neutrophils immediately arrested and spread on ICAM-1. Thus, P-selectin was required for rolling and ICAM-1 was required for firm adhesion, which was mediated by the integrins LFA-1 and Mac-1. The three-step paradigm for leukocyte emigration from the bloodstream was generalized to other selectins (rolling), other chemoattractants and receptors (activation), and other integrin-CAM interactions (firm adhesion and emigration out of vessels through endothelium). The steps mirrored what pathologists had seen for over a hundred years by intravital microscopy, and explained how different subsets of lymphocytes and leukocytes could emigrate in a highly tissue or inflammatory stimulus-specific pattern *in vivo.* The three-step model established the molecular logic of tissue and inflammation-specific diapedesis of specific leukocyte subsets. The therapeutic potential of these discoveries led me to found LeukoSite in 1993. LeukoSite went public in 1998, bought ProScript in 1999, and later became 35% of Millennium Pharmaceuticals, which in turn was acquired by Takeda. In 1996 LeukoSite published that an antibody to integrin $\alpha_4\beta_7$, a lymphocyte homing receptor for mucosal tissues, resolved colitis in non-human primates. This antibody, vedolizumab (Entyvio, Takeda) was approved for ulcerative colitis and Crohns disease in 2014. Two further drugs were shepherded to FDA approval through LeukoSite. Alemtuzumab was approved for B chronic lymphocytic leukemia (CAMPATH1H, Millennium, 2001) and for multiple sclerosis (Lemtrada, Genzyme, 2014). Bortezomib was approved for multiple myeloma (Velcade, Millennium, 2003).

1. Lawrence, M. B., and Springer, T. A. (1991) Leukocytes roll on a selectin at physiologic flow rates: distinction from and prerequisite for adhesion through integrins. *Cell* **65**, 859-873
2. Springer, T. A. (1994) Traffic signals for lymphocyte recirculation and leukocyte emigration: the multi-step paradigm. *Cell* **76**, 301-314
3. Bleul, C. C., Farzan, M., Choe, H., Parolin, C., Clark-Lewis, I., Sodroski, J., and Springer, T. A. (1996) The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature* **382**, 829-833
4. Chen, S., and Springer, T. A. (1999) An automatic braking system that stabilizes leukocyte rolling by an increase in selectin bond number with shear. *J. Cell Biol.* **144**, 185-200 PMC2148129

von Willebrand factor (VWF) is an ultra long vascular protein that, like a Jedi knight, uses the bad forces in hemorrhage to do good, and form a platelet plug (3). Mutations in VWF cause von Willebrand disease (VWD), the most common bleeding disorder, and provide deep insights into function. We determined the EM structure of VWF and discovered that its C-terminal 1,300 residues zip up into dimeric bouquets at pH 6.2, enabling compaction of concatemers during biosynthesis (2). We re-annotated the 2,800-residue VWF sequence and correlated its 28 modules with densities seen in EM. We determined structures of its A2 domain and its C-terminal cystine knot domain that dimerizes VWF in the endoplasmic reticulum. With laser tweezers, we measured force-dependent A2 unfolding and refolding kinetics (1). Unfolding is required for cleavage by ADAMTS13, which regulates the length of VWF concatemers after secretion into plasma. ADAMTS13 cleaves in a position that corresponds to a central β-strand in folded A2. VWD type 2A mutations slow the kinetics of A2 refolding and hence enable more cleavage by ADAMTS13. The hydrodynamic force at the center of a VWF concatemer goes up with the square of monomer number, enabling a sharp threshold for length regulation by ADAMTS13. We introduced the concept of elongational flow from polymer physics

into the VWF field, and showed that elongational flow at a site of bleeding may provide the stimulus for VWF activation. Binding of the A1 domain in VWF concatemers to glycoprotein Ib (GPIb) on platelets cross-links platelets to form the plug. Using laser tweezers, we measured force-dependent kinetics for both association and dissociation of A1 and GPIb; for each, we find switching to a second more stable state above a force of 10 pN. Results support a model in which elongational force in hemorrhage converts VWF from an irregularly coiled compact to a threadlike elongated conformation and then force transmitted within the concatemer acts on A1 domains to induce a second state with higher affinity for GPIb. Gain-of-function mutations in A1 and GPIb that cause VWD affect both kinetic constants and mechanical constants that we measure in our single molecule experiments. Force accentuates effects of mutations, and explains VWD pathophysiology (4).

1. Zhang, X., Halvorsen, K., Zhang, C. Z., Wong, W. P., and Springer, T. A. (2009) Mechanoenzymatic cleavage of the ultralarge vascular protein, von Willebrand factor. *Science* **324**, 1330-1334 PMC3209782
2 Zhou, Y., Eng, E., Nishida, N., Lu, C., Walz, T., and Springer, T. A. (2011) A pH-regulated dimeric bouquet in the structure of von Willebrand factor. *EMBO J.* **30**, 4098-4111 PMC3209782
3. Springer, T. (2014) von Willebrand factor, Jedi knight of the bloodstream. *Blood* **124**, 1412-1425 [Review]. PMC4148764
4. Kim, J., Hudson, N. E., and Springer, T. A. (2015) Force-induced on-rate switching and modulation by mutations in gain-of-function von Willebrand diseases. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 4648-4653 PMC4403213

The 33 members of the transforming growth factor-β (TGF-β) family, including bone morphogenetic proteins (BMPs) are secreted as pro-complexes containing a growth factor (GF) dimer associated with two prodomains. My work on pro-TGF-β1 and pro-BMP9 is revealing new paradigms for signaling in the extracellular matrix (1-4). Each prodomain has a β-sandwich arm domain with extensions at the N-terminus (α1-helix, latency lasso and α2-helix) and C-terminus (α5-helix). Despite formation of similar arm domain GF super β-sheets in pro-TGF-β1 and pro-BMP9 pro-complexes, differences in twists give remarkably different arm domain orientations. Pro-BMP9 is open-armed, with the two arm domains pointing away from one another. Pro-TGF-β1 is cross-armed, with the two arm domains pointing towards one another. The cross-armed conformation is fixed in pro-TGF-β1 by disulfide bond linkage of the arm domains in a bowtie. On the opposite side, the α1-helix and latency lasso surround the GF in a straitjacket that keeps TGF-β latent. TGF-β activation requires traction force exerted by integrins. Crystal structures show integrin $\alpha_V\beta_6$ binds to a cryptic RGDLXX(L/I) motif in the TGF-β1 and 3 prodomain. Molecular dynamics shows how force, resisted in the straitjacket α1-helix that is disulfide-linked to the extracellular matrix, unravels the α1-helix and latency lasso and releases TGF-β1; i.e., activates it. Sequences corresponding to the α1-helix and latency lasso are disordered in the open-armed conformation of pro-BMP9, and prodomain-GF interactions are readily reversible. Based on sequence homology and molecular modeling, I propose that pro-BMP9 also possesses a cross-armed, latent conformation that is stabilized by binding to extracellular matrix components, and that interconversion between cross-armed and open-armed conformations is of wide importance in regulating TGF-β family member signaling by the extracellular environment. Structural insights into the TGF-β family stimulated me to found in 2012 Scholar Rock, which is developing biologicals to modulate TGF-β family signaling in niches *in vivo*.

1. Shi, M., Zhu, J., Wang, R., Chen, X., Mi, L. Z., Walz, T., and Springer, T. A. (2011) Latent TGF-β structure and activation. *Nature* **474**, 343-349. PMID 21677751. PMC Journal in process.
2. Wang, R., Zhu, J., Dong, X., Shi, M., Lu, C., and Springer, T. A. (2012) GARP regulates the bioavailability and activation of TGFβ. *Mol. Biol. Cell* **23**, 1129-1139 PMC3302739
3. Dong, X., Hudson, N. E., Lu, C., and Springer, T. A. (2014) Structural determinants of integrin β-subunit specificity for latent TGF-β. *Nat. Struct. Mol. Biol.* **21**, 1091-1096. PMC Journal in process.
4. Mi, L.-Z., Brown, C. T., Gao, Y., Tian, Y., Le, V.Q., Walz, T., and Springer, T. A. (2015) Structure of bone morphogenetic protein 9 procomplex. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 3710-3715 PMC4378411

Full list of publications (copy and paste to a browser):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1D_O97bM_8MAx/bibliography/47920552/public/?sort=date&direction=ascending

D. Research Support (past 3 years)

Ongoing.

NIH 1 R01 CA210920-01A1 (Springer) 07/01/2016-06/30/2021
Structural mechanisms underlying latency and activation of GDF8
The goal of this grant is to obtain greater structural and biochemical understanding of mechanisms underlying latency, storage in the extracellular matrix, and activation by proteolytic cleavage of GDF8.

1 R01 AR067288 (Springer) 7/7/2015 – 6/30/2020
TGF-beta latency and activation
The goal of this grant is to determine the structural mechanisms underlying latency and activation of the transforming growth factor betas (TGF-βs) using X-ray crystallography, SAXS, EM, hydrogen-deuterium exchange, and complimentary biochemical approaches. The grant will also investigate structure-based therapeutics that target TGF-β–activation.

R01 HL131729 (Springer) 04/20/16-03/31/20
Structures and Conformational Equilibria of Integrin alpha5 beta1
This grant investigates the structure of integrin α5β1 and how ligand binding affects its conformation with respect to headpiece opening, and will also measure, for the first time for any integrin, conformational equilibria of α5β1.

NIH 2R01CA031798 (PI: Springer) 07/1/81–07/31/19
Lymphocyte Function Associated Antigens
This award was granted as a competitive renewal for a MERIT award. The goal of this grant is to address the structural mechanism for LFA1 activation. Crystal, SAXS, EM, and multiple fluorescent microscopy experiments will be used to test the hypothesis that activation of LFA1 is coordinated with the cytoskeleton to enable directed migration of leukocytes. This grant will also study how small molecule antagonists work and bind to LFA1, in order to improve drug development to this important therapeutic target.

1R01HL134723 (Springer) 01/01/17-12/31/2020
Atypical integrin alphaV beta8
This grant seeks greater structural and biochemical understanding of how αVβ8 binds and activates the latent form of TGF-β1.

Completed.

NIH 5R01AI072765 (PI: Springer) (NCE) 05/15/88–05/31/18
Leukocyte Adhesion Receptors Mac-1 and P150,95
The goal of this application is to understand at the atomic level 1) how allostery in $\alpha_M\beta_2$ and $\alpha_X\beta_2$ integrins is transmitted from the juxtamembrane regions through the lower legs, upper legs, and βI domain, to the ligand-binding αI domain and 2) how ligands such as iC3b bind.

NIH 1R01AI095686 (PI: Springer) (NCE) 02/01/12–07/31/17
Structural Vaccinology of the Malaria Sporozoite Surface Sheath
The goal is to determine the structures of the TRAP and circumsporozoite proteins, their organization in the sporozoite surface sheath, and their efficacy in vaccines.