BIOGRAPHICAL SKETCH

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NAME: LAWRENCE SHAPIRO

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

POSITION TITLE: Professor, Department of Biochemistry & Molecular Biophysics

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
New York University, New York, NY	B.A.	05/1988	Chemistry & Math/CS
Columbia University, New York, NY	M.S.	06/1993	Biochem. & Biophysics
Columbia University, New York, NY	M.Phil.	05/1994	Biochem. & Biophysics
Columbia University, New York, NY	Ph.D.	06/1996	Biochem. & Biophysics

A. Personal Statement

Studies in our lab focus on characterizing the antibody immune response to viruses such as Influenza A and HIV, and now SARS-CoV2. We are now focused on structural characterization of virus/host interactions and immune complexes using cryo-EM and x-ray crystallography.

References most relevant to this proposal:

1. Gene-Specific Substitution Profiles Describe the Types and Frequencies of Amino Acid Changes during Antibody Somatic Hypermutation. Sheng Z, Schramm CA, Kong R; NISC Comparative Sequencing Program., Mullikin JC, Mascola JR, Kwong PD, Shapiro L. (2017) ***Front Immunol.*** 2017 May 10; 8:537. PMCID: PMC5424261.
2. SONAR: A High-Throughput Pipeline for Inferring Antibody Ontogenies from Longitudinal Sequencing of B Cell Transcripts. Schramm CA, Sheng Z, Zhang Z, Mascola JR, Kwong PD, Shapiro L. (2016) ***Front Immunol.*** Sep 21;7:372. PMCID: PMC5030719.
3. Vaccine-Induced Antibodies that Neutralize Group 1 and Group 2 Influenza A Viruses. Joyce MG, Wheatley AK, Thomas PV, Chuang GY, Soto C, Bailer RT, Druz A, Georgiev IS, Gillespie RA, Kanekiyo M, Kong WP, Leung K, Narpala SN, Prabhakaran MS, Yang ES, Zhang B, Zhang Y, Asokan M, Boyington JC, Bylund T, Darko S, Lees CR, Ransier A, Shen CH, Wang L, Whittle JR, Wu X, Yassine HM, Santos C, Matsuoka Y, Tsybovsky Y, Baxa U; NISC Comparative Sequencing Program., Mullikin JC, Subbarao K, Douek DC, Graham BS, Koup RA, Ledgerwood JE, Roederer M, **Shapiro L**, Kwong PD, Mascola JR, McDermott AB (2016) ***Cell*** 166, 609-23. PMCID: PMC4978566.
4. Maturation and diversity of the VRC01-antibody lineage over 15 years of chronic HIV-1 Infection. Wu X, Zhang Z, Schramm CA, Joyce MG, Do Kwon Y, Zhou T, Sheng Z, Zhang B, O'Dell S, McKee K, Georgiev IS, Chuang GY, Longo NS, Lynch RM, Saunders KO, Soto C, Srivatsan S, Yang Y, Bailer RT, Louder MK; NISC Comparative Sequencing Program, Mullikin JC, Connors M, Kwong PD, Mascola JR, **Shapiro L** (2015) ***Cell*** 161, 470-85. PMCID:PMC4706178.

B. Positions and Honors

Positions and Employment

1996-1997 Associate Research Scientist, Columbia University Department of Biochemistry and Molecular Biophysics (W.A. Hendrickson Lab)

1997-2001 Assistant Professor, Department of Physiology and Biophysics,

Mount Sinai School of Medicine, New York
2001-Present Professor, Columbia University, Department of Biochemistry & Molecular Biophysics; Professor, Department of Systems Biology

Honors

1982-1984 Summer Undergraduate Research Fellowship, California Institute of Technology
1988 University Honors Scholar, New York University
1988 *Magna Cum Laude* Baccalaureate, New York University
1992-1994 National Eye Institute Predoctoral Training Fellowship
1996 Dean's Award for Excellence in Research, Columbia University
1998-2003 Irma T. Hirschl Career Scientist Award
1999-present Member of The Harvey Society of Rockefeller University
2000-2003 American Diabetes Association Career Development Award
2000-2003 Adjunct Professor, The Rockefeller University
2001 Sidhu Award, Pittsburgh Diffraction Society
2002 Jules and Doris Stein Research to Prevent Blindness Professorship,RPB Foundation
2003-2004 Chair and Vice Chair, National Synchrotron Light Source User Executive Committee Brookhaven National Laboratory
2001 Sidhu Award, Pittsburgh Diffraction Society
2002 Jules and Doris Stein Research to Prevent Blindness Professorship,RPB Foundation
2003-2004 Chair and Vice Chair, National Synchrotron Light Source User Executive Committee Brookhaven National Laboratory

C. Contributions to Science

1. Viral immunity, antibody diversity, evolution, and recognition. We have studied the in vivo evolution of broadly neutralizing antibodies by deep sequencing B cell transcripts from influenza A-vaccinated and HIV-1-infected patients. We invented this technology in 2011 (Wu et al, *Science* 333,1593-60, 2011) and it has now become a staple method for vaccinology in many labs and vaccine centers. Coupled with structure (as in Wu et al, 2015 and Doria-Rose et al, 2014, below) this method enables the visualization of antibody evolution from ineffective recombinant to broad neutralizer. In early papers (eg., Zhu et al, 2013a and 2013b), we showed that deep sequencing alone was sufficient to identify and isolate such neutralizing antibodies from a blood sample.

a) Vaccine-Induced Antibodies that Neutralize Group 1 and Group 2 Influenza A Viruses.Joyce MG, Wheatley AK, Thomas PV, Chuang GY, Soto C, Bailer RT, Druz A, Georgiev IS, Gillespie RA, Kanekiyo M, Kong WP, Leung K, Narpala SN, Prabhakaran MS, Yang ES, Zhang B, Zhang Y, Asokan M, Boyington JC, Bylund T, Darko S, Lees CR, Ransier A, Shen CH, Wang L, Whittle JR, Wu X, Yassine HM, Santos C, Matsuoka Y, Tsybovsky Y, Baxa U; NISC Comparative Sequencing Program., Mullikin JC, Subbarao K, Douek DC, Graham BS, Koup RA, Ledgerwood JE, Roederer M, **Shapiro L**, Kwong PD, Mascola JR, McDermott AB (2016) ***Cell*** 166, 609-23. PMCID: PMC4978566.
b) Maturation and diversity of the VRC01-antibody lineage over 15 years of chronic HIV-1 Infection. Wu X, Zhang Z, Schramm CA, Joyce MG, Do Kwon Y, Zhou T, Sheng Z, Zhang B, O'Dell S, McKee K, Georgiev IS, Chuang GY, Longo NS, Lynch RM, Saunders KO, Soto C, Srivatsan S, Yang Y, Bailer RT, Louder MK; NISC Comparative Sequencing Program, Mullikin JC, Connors M, Kwong PD, Mascola JR, **Shapiro L** (2015) ***Cell*** 161, 470-85. PMCID:PMC4706178
c) Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z; NISC Comparative Sequencing Program, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, **Shapiro L**, Mascola JR. (2014) ***Nature*** 509, 55-62. PMCID:PMC4395007
d) Mining the antibodyome for HIV-1-neutralizing antibodies with next-generation sequencing and phylogenetic pairing of heavy/light chains. Zhu J, Ofek G, Yang Y, Zhang B, Louder MK, Lu G, McKee K, Pancera M, Skinner J, Zhang Z, Parks R, Eudailey J, Lloyd KE, Blinn J, Alam SM, Haynes BF, Simek M, Burton DR, Koff WC; NISC Comparative Sequencing Program, Mullikin JC, Mascola JR, **Shapiro L**, Kwong PD. (2013a) ***PNAS*** 110, 6470-5. PMCID:PMC3631616

2. Structure and function of classical cadherins. When we began work on classical cadherins in the early 1990s, they were understood mainly from immunofluorescence patterns in tissue and cell-based aggregation assays. They had not been prepared as purified proteins, and their structures and mechanisms of action were unknown. In early work in 1995, we determined the first structures of an adhesive cadherin EC1 domain. In Boggon et al, 2002, we determined the first structure of a whole functional ectodomain from C-cadherin, which defined the *cis* and *trans* interactions that make up cell junctions. In Harrison et al, 2011, we showed this junctional architecture was general among type I cadherins, with N-, E-, and C-cadherins all forming the same interfaces. In Harrison et al, 2010, we showed that the strand-swap binding interface, which is slow because it requires re-folding of bound domains, requires formation of a fast-forming "X-dimer" as an intermediate in this interaction, and this X-dimer is common to all type I and type II cadherins. Finally, as exemplified by Chen et al., 2006, we have characterized the adhesive binding affinities of cadherins – currently for all type I and type II cadherins – defining their adhesive preferences, and correlating these with features of the tissue structures they help to form.

a) The extracellular architecture of adherens junctions revealed by crystal structures of type I cadherins. Harrison OJ, Jin X, Hong S, Bahna F, Ahlsen G, Brasch J, Wu Y, Vendome J, Felsovalyi K, Hampton CM, Troyanovsky RB, Ben-Shaul A, Frank J, Troyanovsky SM, **Shapiro L**, and Honig B. ***Structure***. 19, 244-256 (2011). PMCID:PMC3070544
b) Two-step adhesive binding by classical cadherins. Harrison OJ, Bahna F, Katsamba PS, Jin X, Brasch J, Vendome J, Ahlsen G, Carroll KJ, Price SR, Honig B, **Shapiro L**. ***Nature Struct Mol Biol****.* 17, 348-357 (2010). PMCID:PMC2872554
c) Type II cadherin ectodomain structures: implications for classical cadherin specificity. Patel SD, Ciatto C, Chen CP, Bahna F, Rajebhosale M, Arkus N, Schieren I, Jessell TM, Honig B, Price SR, and **Shapiro L.** (2006) ***Cell*** 125, 1255-1268.
d) C-cadherin ectodomain structure and implications for cell adhesion mechanisms. Boggon TJ, Murray J, Chapuis-Flament S, Wong E, Gumbiner BM and **Shapiro L**. (2002) ***Science****,* 296, 1308-1313.

3. Diverse biological functions of the larger cadherin superfamily. We have also investigated structure and mechanism for other non-classical cadherin superfamily members. In Brasch et al, 2011, we showed that VE-cadherin, an outlier that is expressed only in the vascular endothelium, has elements of both type I and type II families. We showed in Ciatto, 2010, that T-cadherin, which is truncated and has a GPI anchor, does not bind through strand swapping, but rather has a fast-forming interface specialized to the neural guidance (as opposed to adhesive) function of T-cadherin. Finally, in Jin et al, 2011, we showed that Drosophila cadherins – and many others including desmogleins as demonstrated in this proposal – have incomplete Ca^{2+} binding sites, and these incomplete sites can correspond to large bends in the overall structure.

a) Structural basis of adhesive binding by desmocollins and desmogleins. Harrison OJ, Brasch J, Lasso G, Katsamba PS, Ahlsen G, Honig B, **Shapiro L**. ***PNAS*** (2016) 113, 7160-5. PMCID:PMC4932976
b) Crystal structures of Drosophila N-cadherin ectodomain regions reveal a widely used class of Ca2+-free interdomain linkers. Jin X, Walker MA, Felsövályi K, Vendome J, Bahna F, Mannepalli S, Cosmanescu F, Ahlsen G, Honig B, **Shapiro L.** ***PNAS*** (2011) PMCID:PMC3271863
c) T-cadherin structures reveal a novel adhesive binding mechanism. Ciatto C, Bahna F, Zampieri N, VanSteenhouse HC, Katsamba PS, Ahlsen G, Harrison OJ, Brasch J, Jin X, Posy S, Vendome J, Ranscht B, Jessell TM, Honig B, and **Shapiro L**. (2010) ***Nature Struct Mol Biol****.* 17, 339-347. PMCID:PMC2873897
d) Structure and binding mechanism of vascular endothelial cadherin: a divergent classical cadherin. Brasch J, Harrison OJ, Ahlsen G, Carnally SM, Henderson RM, Honig B, and **Shapiro L**. ***J Mol Biol***. 408, 57-73 (2011). PMCID:PMC3084036

4. Structure and mechanisms of clustered protocadherins. Recognition between multiple Pcdh isoforms presented on opposing membrane surfaces is thought to underlie neuronal self-avoidance in vertebrates. In a collaboration between the Shapiro, Honig, and Maniatis labs we defined the specificity of protocadherins (Thu et al, 2014) and functional molecular architecture of ectodomain regions, identifying both *cis* and *trans* interactions (Rubinstein et al., 2015). Biophysical measurements of soluble Pcdh ectodomains and fragments allowed us to determine the homophilic affinities of these *cis* and *trans* interactions, and demonstrate that the combination of the *cis* and *trans* interactions in complete ectodomains results in the formation of tetramers in solution (Rubinstein et al., 2015; Goodman et al., 2016a). We have so far determined different 16 crystal structures of Pcdh ectodomain fragments, including *trans*-dimer structures of two or more isoforms from each of the Pcdh subfamilies (Goodman et al., 2016a,b), and a *cis*-dimer structure of a gamma isoform (presented in

the preliminary data for Aim 1 of this proposal). The *trans*-dimer structures allowed us, through structure-based sequence analysis and mutagenesis experiments, to determine the basis of the strict homophilic specificity of Pcdh *trans* interactions (Goodman et al., 2016a,b). Together our data led us to propose two potential models for Pcdh-mediated neuronal self-avoidance (Rubinstein et al., 2015).

a) Single-Cell Identity Generated by Combinatorial Homophilic Interactions between alpha, beta, and gamma Protocadherins. Thu CA, Chen WV, Rubinstein R, Chevee M, Wolcott HN, Felsovalyi KO, Tapia JC, **Shapiro L**, Honig B, Maniatis T., ***Cell*** 158, 1045-1059. PMCID: PMC4183217
b) Molecular logic of neuronal self-recognition through protocadherin domain interactions. Rubinstein R, Thu CA, Goodman KM, Wolcott HN, Bahna F, Mannepalli S, Ahlsén G, Cheeve M, Halim A, Clausen H, Maniatis T, **Shapiro L**, Honig B. (2015). ***Cell*** 163(3):629–642. PMCID: PMC4624033
c) Structural basis of diverse homophilic recognition by α- and β-protocadherins. Goodman KM, Rubinstein R, Thu CA, Bahna F, Mannepalli S, Ahlsén G, Rittenhouse C, Maniatis T, Honig B, **Shapiro L.** (2016a). ***Neuron*** 90(4):709–723. PMCID: PMC4873334
d) γ-Protocadherin structural diversity and functional implications.Goodman KM, Rubinstein R, Thu CA, Mannepalli S, Bahna F, Ahlsén G, Rittenhouse C, Maniatis T, Honig B**, Shapiro L**. (2016b). ***eLife*** 5:e20930. PMCID: PMC5106212

5. Methodological contributions to X-ray crystallography. Over the years, we have also made contributions to technical aspects of modern x-ray crystallography. By coincidence, our first paper on cadherins in *Nature* (Shapiro et al., 1995) also performed the first MAD experiment using a third-generation undulator x-ray source. The limited bandwidth of undulators made it unclear whether this approach would work. Nevertheless, now after a decade, such experiments have been standardized to use the undulator-radiation approach we began. Also, in Boggon and Shapiro (2000) we developed a native-gel based method to efficiently screen for phasing-atom derivatives of proteins, another method which is now standard in many labs. We have also – as described in the current proposal – made numerous advances in protein production. The Mancia et al (2004) paper below provides one example of such an advance. Finally, in Liu et al. (2012) we demonstrated that the majority (>95%) of protein structures could in principle be phased by the anomalous scattering of their native sulfur atoms – a method we have now used to solve numerous structures, and for which a new optimized beam line, LAX, is under construction at NSLS-II to perform such low-energy anomalous scattering experiments.

a) Structures from anomalous diffraction of native biological macromolecules. Liu Q, Dahmane T, Zhang Z, Assur Z, Brasch J, **Shapiro L**, Mancia F, Hendrickson WA. (2012) ***Science*** 336, 1033-7. PMCID:PMC3769101
b) Optimization of protein production in mammalian cells with a coexpressed fluorescent marker. Mancia F, Patel SD, Rajala MW, Scherer PE, Nemes A, Schieren I, Hendrickson WA, **Shapiro L**. (2004) ***Structure*** 8, 355-60.
c) Screening for phasing atoms in protein crystallography. Boggon TJ and **Shapiro L**. (2000) ***Structure*** 8, R143-149.
d) Structural basis of cell-cell adhesion by cadherins. **Shapiro L**, Fannon AM, Kwong PD, Thompson A, Lehmann MS, Grübel G, LeGrand J-F, Als-Nielsen J, Colman DR and Hendrickson WA. (1995) ***Nature*** 374, 327-337.

Complete List of Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed?term=Shapiro%20+%20Lawrence

D. Additional Information: Research Support

Ongoing Research Support

R01GM118584-01A1 Shapiro (PI) 3/1/2017 – 2/28/2021
NIH/NIGMS
Structure and Function of Desmosomal Cadherins
The overall goal of this project is to provide an atomic-level understanding of desmosome extracellular architecture.

9R01MH114817-05 Shapiro/Maniatis (MPI) 9/1/2017 – 5/31/2022

NIH/NIMH
The Structural Basis of cis and trans Protocadherin Interactions
The overall objective of the proposed research is to determine the mechanism by which the clustered protocadherins (Pcdhs) mediate neuronal self-avoidance, a critical property of all nervous systems.

P01-AI104722-01A1 R. Wyatt (PI) 4/1/2014 – 3/31/2019
NIH, Subcontract with Scripps
High Resolution Analysis of Env-directed B Cells to Accelerate Vaccine Design
The overall goal of this HIVRAD is to elicit broadly neutralizing antibodies to the human pathogen HIV-1. The successful elicitation of such antibodies would be a large step forward toward the goal of generating a broadly effective HIV-1 vaccine and would have a substantial impact on improving human public health.
Role: Co-PI

Completed Research Support

R01-GM062270-09 Shapiro (PI) 4/1/2012 – 1/31/2016
NIH/NIGMS
Molecular Basis of Cadherin Mediated Cell Adhesion
Goal: To understand the molecular mechanisms of cadherin cell adhesion proteins and their roles in development and tissue patterning.

R01-GM10751-02 Shapiro, Maniatis (MPIs) 9/1/2013 – 5/31/2017
NIH/NIMGS
Structural basis of cis and trans protocadherin interactions.
The Goals of the project are to determine the nature of trans (cell to cell) and cis (same cell surface) interactions of the clustered protocadherin (Pcdh) cell surface proteins.

R01 AI104387 L. Morris (PI) 8/1/2014 – 7/31/2017
NIH/NIAID
Evolution of Glycan-reactive neutralizing anti-V2 antibodies in HIV infection
Subcontract with the National Institute for Communicable Diseases, Sandringham, South Africa
Goal: Bioinformatics-based identification of anti-V2 antibodies from HIV-1 infected human donors.
Role: Co-PI

OPP1110739 R. Friesner (PI) 5/7/2014 – 4/30/2017
Bill and Melinda Gates Foundation
Improvement of HIV-neutralizing Antibodies via High-Resolution Computational Methods
The overall goal of this proposal is to optimize broadly HIV-1-neutralizing antibodies for clinical trials for prevention of mother/child HIV-1 transmission at birth.
Role: Co-investigator

R01 AI104387 L. Morris, (PI) 8/1/2014 – 7/31/2017
NIH/NIAID
Evolution of Glycan-reactive neutralizing anti-V2 antibodies in HIV infection
Subcontract with the National Institute for Communicable Diseases, Sandringham, South Africa
Goal: Bioinformatics-based identification of anti-V2 antibodies from HIV-1 infected human donors.
Role: Co-PI