CURRICULUM VITAE

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PART I: **General Information**

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Place of Birth: Boston, Massachusetts

Education:

1975	A.B.	Harvard University, Cambridge, Massachusetts (Chemistry)
1979	M.D.	Yale University School of Medicine, New Haven, Connecticut
1982	Ph.D.	Yale University (Molecular Biophysics and Biochemistry)

Postdoctoral Training:

Internship and Residencies:

1979-1983	Clinical Fellow in Medicine, Harvard Medical School, Boston, Massachusetts
1979-1980	1st Year Resident Physician (Internal Medicine), Brigham and Women's Hospital, Boston, Massachusetts
1980-1982	2nd Year Resident Physician (Internal Medicine), Brigham and Women's Hospital
1982-1983	3rd Year Resident Physician (Internal Medicine), Brigham and Women's Hospital

Research and Clinical Fellowships:

1975-1981	National Institutes of Health predoctoral trainee, Medical Scientist Training Program, Yale University
1983-1984	Research Fellow in Medicine (Hematology-Oncology), Brigham and Women's Hospital
1984-1985	Research/Clinical Fellow in Medicine (Hematology-Oncology), Brigham and Women's Hospital

Licensure and Certification:

1981	Massachusetts License
1983	Diplomate, American Board of Internal Medicine
1986	Diplomate, Subspecialty of Hematology, American Board of Internal Medicine

Academic Appointments:

1983-1987	Instructor in Medicine, Harvard Medical School
1984-1987	Instructor in Pharmacology, Harvard Medical School
1987-1994	Assistant Professor of Medicine, Harvard Medical School
1987-1994	Assistant Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
1994-2002	Associate Professor of Medicine, Harvard Medical School
1994-2001	Associate Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
2001-	Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
2001-	Scholar and Founding Member, The Academy at Harvard Medical School
2002-	Professor of Medicine, Harvard Medical School

Hospital Appointments:

1985-1992	Associate Physician, Brigham and Women's Hospital
1992-	Physician, Brigham and Women's Hospital
1997-	Clinical Staff in Medical Oncology, Dana-Farber Cancer Institute

Hospital and Health Care Organization Service Responsibilities:

1985-	Attending Physician, Hematology-Oncology Inpatient Service, Brigham and Women's Hospital
1985-	Attending Physician, Hematology-Oncology Consult Service, Brigham and Women's Hospital
1985-1997	Attending Physician, Hematology-Oncology Clinic, Brigham and Women's Hospital
1997-	Attending Physician, Hematology-Oncology Clinic, Dana-Farber Cancer Institute

Major Administrative Responsibilities:

1982-	Director, Scanning Fluorescence Microscope Photometer Facility, Harvard Medical School
1988-1992	Director, Fluorescence Activated Cell Sorter Facility, Bone Marrow Transplantation Program, Brigham and Women's Hospital
1988-1997	Co-Director, Program in Clinical Pharmacology, Harvard Medical School
1997-2004	Executive Director, Confocal Microscopy Facility, Brigham and Women’s Hospital
1997-	Program Leader, Human Pharmacology, Harvard Medical School Scholars in Clinical Science Program
2000-2003	Co-Director, MD-PhD Program, Harvard Medical School
2003	Acting Director, MD-PhD Program, Harvard Medical School
2008-	Director, Research Education Program, Clinical and Translational Science Center (Harvard Catalyst), Harvard Medical School
2008-	Associate Director, Leder Human Biology and Translational Medicine Program, Harvard Medical School

2008- Dean for Graduate Education, Harvard Medical School
2008- Special Advisor to the Dean on Global Programs, Harvard Medical School

Major Committee Assignments:

Harvard Medical School:

1988-2006 Senior Fellow, William Bosworth Castle Society
1989-1993 Committee on Educational Evaluation
1989-1993 Preclinical Promotion Board
1990 Strategic Planning Consulting Group, Francis A. Countway Library of Medicine
1990-2006 Board of Advisors, William Bosworth Castle Society
1990-1995 Curriculum Committee
1990-1991 Committee for Student Health
1991 Policy on Software and Video Committee, Office of Technology Licensing and Industry-Sponsored Research
1991-1992 Committee on Years Three and Four
1992-1997 Educational Task Force, Division on Addictions (Advisory Board; Chair, Subcommittee on Medical Student Education)
1993-1998 Academic Societies Promotion and Review Board (Vice-Chair; Executive Committee; Chair, Subcommittee on Student Conduct and Responsibility)
1993-1996 Technology Subcommittee, Joint Library Committee, Francis A. Countway Library of Medicine
1994-1995 Medical Education Program Self-Study Committee
1994-1995 Curriculum Review Committee, Harvard-MIT Division of Health Sciences and Technology
1994-1996 Faculty Fellowship Committee (Chair, Subcommittee on Pharmacology and Therapeutics)
1994-2003 Subcommittee on Admissions, MD-PhD Program
1995-2001 Council on Student Affairs
1996-2001 Committee on Years One and Two
1996 University Committee on Biological Sciences
1997-1998 Committee on Professional Development (Chair, Subcommittee on Remediation)
1997- Faculty Standing Committee, MD-PhD Program
1998- Executive Committee, Scholars in Clinical Science Program
1998-2001 Committee on Years Three and Four (Chair, Subcommittee on Therapeutics and Evidence-Based Medicine)
1998 Curriculum Planning Committee, MD-PhD Program (Chair)
1998-1999 Committee on Excellence in Tutoring
1998-2001 Academic Societies Promotion and Review Board (Chair; Executive Committee; Chair, Subcommittee on Academic Performance)
1998-1999 *Ad hoc* Committee to Review the MD-PhD Training Program
1999-2001 Main Committee on Admissions
1999- Physician Educator Steering Committee, Harvard Macy Institute Program for Physician Educators
1999- Curriculum Committee, Harvard Initiative for Patient-Associated Science: Training, Education, Understanding, and Research (PASTEUR)
1999- Core Planning Group, International Medical Education Alliances, Harvard Medical International
2000-2003 Committee of Advisors, MD-PhD Program
2001- Executive Committee, The Academy at Harvard Medical School

2001-2005	Council on Educational Policy (Co-Chair, Medical Sciences Education Steering Group)
2001-2002	Selection Committee, The Academy at Harvard Medical School
2001-	Scientific Steering Committee, Division for Research and Education in Complementary and Integrative Medical Therapies
2001-2003	Medical Education Program Self-Study Committee
2001-2004	Committee on Assessment
2001-2002	"Blue Sky" Medical Education Task Force
2002-2006	Steering Committee, The Academy at Harvard Medical School
2002-2004	Coordinating Committee for Curriculum Innovation, The Academy at Harvard Medical School (Chair)
2003-2004	Task Force for a New Curriculum
2003-	International Programs Committee, Office of Enrichment Programs
2003-2004	Medical Education Reform Initiative Blueprint and Themes Committee
2004-2006	Medical Education Reform Initiative Steering Committee (Chair, Working Group on In-Depth Educational Experiences; Chair, Design Group on In-Depth Educational Experiences)
2004-2007	Faculty Council
2004-	Finance Committee, Department of Biological Chemistry and Molecular Pharmacology
2005-2006	Curriculum Committee
2005-	Advisory Committee, The Academy at Harvard Medical School
2005-2008	Subcommittee of Professors
2007-2008	Steering and Curriculum Committee, Program in Human Biology and Translational Medicine (Chair)
2007-2008	Admissions Committee, Program in Biological and Biomedical Sciences
2007-2008	Strategic Advisory Group on Education, Harvard Medical School Strategic Planning Initiative (Chair, Subcommittee on the Continuum of Education)

Brigham and Women's Hospital:

1997-2001	Research Infrastructure Committee
2001-	Faculty Standing Committee on Resident Research, Department of Medicine
2001-	Technology Assessment and Development Committee
2003-	Standing Committee on Innovation, Department of Medicine Education Council

Government Agencies (National):

1997	Special Reviewer, Allergy, Immunology, and Transplantation Research Committee, National Institute of Allergy and Infectious Diseases, National Institutes of Health
1997	Special Reviewer, Biophysical Chemistry Study Section, Division of Research Grants, National Institutes of Health
1998	Source Selection Evaluation Panel, Tissue Based Biosensors Program, Defense Advanced Research Projects Agency
1998-1999	Biophysical and Chemical Sciences Special Reviewer and *ad hoc* Initial Review Group Member, Biophysical Chemistry Study Section, Center for Scientific Review, National Institutes of Health
2000	Special Reviewer, Science Centers Program, United States Civilian Research and Development Foundation for the Independent States of the Former Soviet Union, United States Department of State
2001	Invited Speaker, Workshop on Functional Integration of Cells and Materials, Defense Sciences Research Council, Defense Advanced Research Projects Agency

2001-2004 *ad hoc* Initial Review Group Member, Hematology Study Section, Center for Scientific Review, National Institutes of Health
2006 Invited Participant, Working Group on Biofield Energy Medicine, National Center for Complementary and Alternative Medicine, National Institutes of Health

Industrial Advisory Groups (National):

1994-2000 Member, Medical/Scientific Advisory Board, Alza Corporation, Palo Alto, California
2002-2004 Member, Scientific Advisory Board, Cantata Pharmaceuticals, Cambridge, Massachusetts

Other (National and International):

1995- Member, United States Pharmacopoeia (USP)
1996-1998 Member, Applied Pharmacology Task Force and United States Medical Licensing Examination (USMLE) Step 1 Applied Pharmacology Test Material Development Committee, National Board of Medical Examiners
1996 Consultant on Teaching of the Basic Medical Sciences, Faculty of Medical Sciences, National University of Cuyo, Mendoza, Argentina
1998-2001 Member, Pharmacology Test Committee and USMLE Step 1 Pharmacology Test Material Development Committee, National Board of Medical Examiners
1999 Member, Interdisciplinary Review Committee, USMLE Step 1 Computer-Based Test, National Board of Medical Examiners
1999- Consultant on a New Medical Curriculum, China Medical University, Shenyang, China
2000- Consultant on a New Medical Curriculum, Carl Gustav Carus Medical Faculty of the Technical University of Dresden, Dresden, Germany
2002 Reviewer, Ohio Biomedical Research and Technology Transfer Partnership Awards Program
2002- Consultant on a New Medical Curriculum, Xinjiang Medical University, Ürümqi, China
2002- Consultant on a New Medical Curriculum, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, Ohio
2003- Member, Leukemia, Immunology and Blood Cell Development Committee, American Cancer Society
2005- Consultant on a New Medical Curriculum, Catholic University of Portugal, Lisbon, Portugal

Memberships in Professional Societies:

1980- Biophysical Society
1980- Red Cell Club
1983- Massachusetts Medical Society
1984- American College of Physicians
1986- New York Academy of Sciences
1986- The Protein Society
1987- American Chemical Society
1988- American Society for Cell Biology
1989- American Association for the Advancement of Science
1989- Society for Analytical Cytology
1990- American Medical Association

1992-	American Society of Hematology (2000, National Meeting Abstract Review Committee)
1995-	Fellow, Molecular Medicine Society
1996-	American Society for Clinical Investigation (elected member)

Editorial Boards:

1996-2004	*Ad hoc* reviewer, American Journal of Pathology
1995	*Ad hoc* reviewer, American Journal of Physiology
1991-1992	*Ad hoc* reviewer, Biochimica et Biophysica Acta
1992	*Ad hoc* reviewer, Biochemistry
1990-2008	*Ad hoc* reviewer, Biophysical Journal
1991-2004	*Ad hoc* reviewer, Blood
1991-1993	*Ad hoc* reviewer, Experimental Pathology
1998	*Ad hoc* reviewer, European Biophysical Journal
2000	*Ad hoc* reviewer, European Journal of Biochemistry
1998	*Ad hoc* reviewer, European Journal of Hematology
1993-1995	*Ad hoc* reviewer, FEBS Letters
2000-2002	*Ad hoc* reviewer, Immunity
1989-2001	*Ad hoc* reviewer, Journal of Biological Chemistry
1989-2004	*Ad hoc* reviewer, Journal of Cell Biology
1993	*Ad hoc* reviewer, Journal of Cellular Physiology
1999	*Ad hoc* reviewer, Journal of Clinical Investigation
2004-2005	*Ad hoc* reviewer, Journal of General Physiology
1991	*Ad hoc* reviewer, Journal of Immunology
1991	*Ad hoc* reviewer, Journal of Theoretical Biology
1989-2004	*Ad hoc* reviewer, Nature
2005	*Ad hoc* reviewer, Nature Methods
2000-2008	*Ad hoc* reviewer, New England Journal of Medicine
1995-2006	*Ad hoc* reviewer, Photochemistry and Photobiology

Awards and Honors:

1971	Harvard National Scholar
1971	National Merit Scholar
1975	Detur Prize, Harvard University
1975	Phi Beta Kappa, Harvard University
1975	A.B. *summa cum laude*, Harvard University
1985-1987	Research Fellow, The Medical Foundation, Inc.
1994-1995	Funds for Discovery Award, Harvard Medical School
1996	Elected Member, American Society for Clinical Investigation
1996	Faculty Prize for Excellence in Teaching, Harvard Medical School
1997	Elected Member, Aesculapian Club, Harvard Medical School
1997-2008	Method to Extend Research in Time (MERIT) Award, National Heart, Lung, and Blood Institute, National Institutes of Health
1998-2000	Interdisciplinary Seed Grant Award, Brigham and Women's Hospital Research Organization
1998-2000	Dual-Mentored Fellowship Program Award, Brigham and Women's Hospital Research Organization
1998	Student Award for Excellence in Teaching (Course Director), Harvard Medical School
1998	Student Award for Excellence in Teaching (Tutor), Harvard Medical School

1999	Student Award for Excellence in Teaching (Course Guide, Lecture Notes, Conference Problems, Tutorial Cases, and PharmAid® Manual), Harvard Medical School
2000	Student Award for Excellence in Teaching (Course Guide, Lecture Notes, Conference Problems, Tutorial Cases, and PharmAid® Manual), Harvard Medical School
2001	Scholar and Founding Member, The Academy at Harvard Medical School
2001	Student Award for Excellence in Teaching (Lecturer), Harvard Medical School
2002	Student Award for Excellence in Teaching (Lecturer), Harvard Medical School
2003	Student Award for Excellence in Teaching (Lecturer), Harvard Medical School
2004	Student Award for Excellence in Teaching (Lecturer), Harvard Medical School
2004	Student Award for Excellence in Teaching (Course Guide), Harvard Medical School
2005	Alpha Omega Alpha Robert J. Glaser Distinguished Teacher Award, Association of American Medical Colleges

PART II: Self-Report of Research, Teaching, and Clinical Contributions

A1. Narrative Summary of Major Research Contributions (reference numbers refer to Original Articles as cited in Part III: Bibliography)

My laboratory has studied intensively two scientific areas within the field of cell surface protein and lipid dynamics: (1) the molecular dynamics of membrane proteins and lipids in red cell structure, function, and pathophysiology; and (2) the molecular dynamics of cell surface adhesion receptors in lymphocyte adhesion and activation.

(1) *Our primary research area uses the human red cell membrane as a model system to elucidate, in molecular detail, the mechanisms controlling the lateral and rotational mobility of transmembrane proteins and lipids.* We provided direct evidence that the lateral mobility of band 3 in intact, living red cells is controlled by interactions with membrane skeletal proteins;[2,5] these interactions include steric interactions with the spectrin-based membrane skeleton, and high-affinity (long-lived) and low-affinity (transient) binding interactions with the membrane skeleton-associated proteins ankyrin and band 4.2.[14,20,28,34,38,46,50,53,56,63] We also showed that band 3 lateral and rotational mobility are controlled by different molecular mechanisms in intact red cells,[34] and that the rotational mobility of the various band 3 populations is controlled by band 3 self-association in the plane of the membrane, and by high-affinity and low-affinity binding interactions with ankyrin and band 4.2, but not by steric interactions with the membrane skeleton.[20,28,34,38,46,50,56] These observations have led to a mechanistic model in which (i) steric interactions provided by the spectrin-based membrane skeleton regulate the rate of band 3 lateral diffusion, (ii) low-affinity binding interactions with ankyrin and band 4.2 regulate the rate of band 3 rotational diffusion, (iii) high-affinity binding interactions with ankyrin determine the fraction of rotationally immobile band 3, and (iv) band 3 oligomerization controls the fraction of laterally immobile band 3. We showed that ankyrin is not required for assembly of the normal red cell membrane skeleton, suggesting that a complete and fully developed skeleton can form in the absence of high-affinity nucleation sites at the inner surface of the plasma membrane.[50] We also showed that ankyrin is absolutely required for the association of band 3 dimers to band 3 tetramers in intact red cells, confirming hypotheses, derived primarily from biochemical studies on purified proteins, for the oligomerization state of band 3 in intact cells.[50] We demonstrated that phospholipid and cholesterol mobility in the red cell membrane is controlled primarily by lipid self-diffusion, secondarily by protein-lipid interactions and, under certain pathologic conditions (*e.g.*, excess lysophosphatidylcholine), by lipid domain formation.[3,4,8]

We have used biophysical and other methods to elucidate the biological implications of these protein and lipid mobility control mechanisms for red cell physiology, and for the molecular pathophysiology of hereditary spherocytosis, hereditary elliptocytosis, Southeast Asian ovalocytosis, and sickle cell anemia.[14,20,28,34,38,42,44,46,49,50,56,63] Our observation that ankyrin-deficient mouse spherocytes are mechanically fragile despite the presence of a structurally and functionally normal membrane skeleton demonstrates the critical role of ankyrin-mediated coupling between the membrane skeleton and the red cell lipid bilayer in the mechanical stability and osmotic fragility of the cell.[50] Our findings that red cells from patients with Southeast Asian ovalocytosis manifest decreased band 3 lateral and rotational mobility, increased band 3 tetramer formation, increased band 3 interaction with the membrane skeleton, and formation of linear aggregates of band 3 protein in the membrane provide a structural and functional basis for the important clinical observation that the increased mechanical rigidity of these cells allows the cells to resist invasion by malaria parasites.[14,38] Our use of band 3 lateral and rotational mobility measurements, to show that band 3 is progressively aggregated in the membranes of dense normal (senescent) and sickle red cells, provides support for the hypotheses that (i) band 3 aggregation in the plane of the membrane serves as a signal for removal of senescent and dense sickle red cells from the circulation, and (ii) increased interactions between band 3 and the membrane skeleton underlie the partial resistance of sickle red cells to invasion by malaria parasites.[20,49]

In vivo, human red cells are used as a food source by several clinically important parasites, including *Schistosoma mansoni*. *My group provided evidence for a molecular mechanism by which schistosomula of S. mansoni gain access to host red cell proteins and lipids.* Specifically, we showed that (i) normal human red cells adhere to and are lysed by contact with the schistosomular tegument, (ii) significant amounts of lysophosphatidylcholine (especially monopalmitoyl phosphatidylcholine (MPPC)) are synthesized by schistosomula of *S. mansoni*, and (iii) *S. mansoni*-induced changes in red cell membrane protein and lipid mobility, and in red cell membrane lipid composition, are similar to those caused by MPPC.[5,8,22] Based on these results, we proposed that MPPC generation represents a toxic mechanism by which *S. mansoni* disrupts host blood cell membranes.

(2) *We also have a deep interest in using the human lymphocyte as a model of an adhesive and activatable cell that is capable of fundamental changes in cellular physiology (e.g., cell motility, cell adhesion, cell shape, and molecular secretion) depending on adhesion and activation interactions involving specific cell surface receptors. We study, in molecular detail, mechanisms controlling the lateral mobility, surface distribution, and two-dimensional (membrane) affinity of cell surface receptors in lymphocyte membranes, and biological implications of these control mechanisms for lymphocyte adhesion and activation.* In single cell studies, my colleagues and I found that class I and class II major histocompatibility complex proteins and the lymphocyte adhesion molecule CD2 are laterally mobile in plasma membranes of resting lymphoid cells, and that binding of monoclonal antibodies or ligands to these cell surface receptors induces immobilization of the receptors.[6,9,12] In the case of CD2, we showed that receptor immobilization is regulated by intracellular signaling pathways — involving cytoplasmic calcium ions, calmodulin, calmodulin kinase, calcineurin phosphatase, cyclic AMP, and dynamic linkage to the actin cytoskeleton — that are generated upon cell activation.[36,59,84]

In studies of lymphocytes interacting with model target membranes, we showed that the strength of CD2-CD58 mediated adhesion between T cells and target membranes is regulated by the lateral mobility of this receptor-ligand pair of molecules in the two adhering membranes. We found that laterally mobile CD58 in target membranes supports adhesion at much lower initial surface densities of CD58 than does laterally immobile CD58, and that laterally mobile CD58 allows the development of marked adhesion strengthening over time.[17] Based on these observations, we proposed that the diffusional movement of laterally mobile CD2 and CD58 into areas of cell-bilayer contact promotes increased CD2-CD58 bond formation over time, and that cellular adhesion strength is a direct function of the number of CD2-CD58 bonds formed in the contact area.

To investigate directly and quantitatively the biophysical basis for the influence of receptor and ligand lateral mobility on adhesion strength, my colleagues and I developed a glass-supported planar bilayer system for visualization of the area of contact between a cell membrane and a target membrane, and for analysis of the two-dimensional (membrane) dissociation constant (K_d) of the receptor-ligand pair of adhesion molecules that mediate cell-cell contact. We studied the interaction of CD2 with its ligand CD58 in the contact area between human T leukemia cells and planar phospholipid bilayers containing purified, fluorescently labeled CD58. CD58 was found to accumulate at sites of contact with a half-time that was consistent with the previously determined kinetics of adhesion strengthening for this system, demonstrating that cellular adhesion strength is a function of the number of receptor-ligand bonds formed in the contact area.[45] We developed a quantitative model to describe two-dimensional receptor-ligand binding, and represented the model by a new equation that includes as variables the densities of bound and free CD58 in the contact area, the total number of CD2 molecules per cell, the fraction of laterally mobile CD2, the surface area of the cell, and the contact area at equilibrium.[51,85] Our equation was used to analyze two-dimensional CD2-CD58 binding data and to determine the two-dimensional K_d for the CD2-CD58 interaction. This K_d was found to be considerably lower than the surface densities of CD2 on human T lymphocytes and CD58 on most target or stimulator cells, suggesting that formation of CD2-CD58 complexes should be highly favored in physiological interactions. CD58 molecules in the contact site were capable of lateral diffusion in the plane of the phospholipid bilayer and did not appear to be irreversibly trapped in the contact area,

consistent with a rapid off-rate.[45,51,84,85] Comparison of the two-dimensional (membrane) and three-dimensional (solution) K_ds suggested that the CD2-CD58 interaction cooperates to align apposing T cell and target membranes with nanometer precision, leading to physiologically effective two-dimensional affinity.[51,84,85] These observations represent the first direct demonstration that cell-cell contact formation and bond formation are regulated by the intrinsic two-dimensional affinity of the pair of adhesion molecules mediating the contact.

The αLβ2 integrin (leukocyte function-associated antigen-1 [LFA-1]) is regulated to engage and maintain T cell adhesion. Conformational changes in the receptor are associated with changes in receptor-ligand affinity and are necessary for firm adhesion. Less well understood is the relationship between receptor conformation and the regulation of its lateral mobility. We have recently used fluorescence photobleaching recovery and single-particle tracking to measure the lateral mobility of specific conformations of LFA-1 on model T lymphoblastoid cells as well as peripheral blood lymphocytes. These measurements show that different receptor conformations have distinct diffusion profiles and that these profiles vary according to the activation state of the cell. Cell activation mobilizes the intermediate conformation of LFA-1 in order to maximize receptor-ligand interactions, while cytoskeletal regulators preferentially immobilize the open and ligated conformations of LFA-1 in order to stabilize adhesion. Activation-induced immobilization of the high-affinity LFA-1 conformation is prevented by a calpain inhibitor, likely implicating talin as one of the cytoskeletal regulators. Our results are consistent with a mass-action model of LFA-1 accumulation at sites of adhesion and with the notion that immobilization of ligated LFA-1 through cytoskeletal attachment may be critical in physiological settings. Our results also suggest that the conformational state and lateral mobility of LFA-1 are coupled in order to provide regulation of receptor function on lymphocytes. Coupling between receptor conformation and lateral mobility may be a general mechanism for regulation of cell adhesion.[82]

(3) *In the course of the studies summarized above, my group has made contributions to biophysical theories and methodologies important in the study of cell surface protein and lipid dynamics*. These include:

- Development of a method for accurate and rapid characterization of microscopic laser beams.[11]
- Development of an instrument design for measurement of lateral diffusion in cell membranes by the "spot" fluorescence photobleaching recovery (FPR) technique.[20,27]
- Development of a theory and instrument design for measurement of anisotropic lateral diffusion in cell membranes.[7]
- Development of an instrument design for measurement of rotational diffusion in cell membranes by the polarized fluorescence depletion (PFD) technique.[20]
- Development and testing of a theory for transport of cell surface receptors in a sinusoidal electric field.[21,33]
- Development of a computer-assisted approach to analyze fluctuations in single-cell cytoplasmic calcium ion concentrations.[23,30,35]
- Development of a method and analytic approach for determination of the two-dimensional (membrane) dissociation constant of laterally mobile cell-cell adhesion molecules in a contact area.[45,51,85]
- Development of a quantitative method for determination of the extent of physical interaction between two intracellular proteins by the “donor dequenching after acceptor photobleaching” fluorescence resonance energy transfer (FRET) technique.[73]
- Development of a method, based on laser optical tweezers technology, for determining whether a cell surface receptor is physically linked to the cytoskeleton in a live cell (in preparation).

A2. Narrative Summary of Teaching Contributions:

(1) *Principles of Pharmacology*. From 1989 through 2006, I served as the founding course director of Principles of Pharmacology, the core course in pharmacology taken by all Harvard medical and dental students in the New Pathway curriculum. This course provided an intensive introduction to pharmacology,

emphasizing basic mechanisms of drug action and principles of drug-receptor interactions, pharmacokinetics, and drug metabolism. Drug classes were illustrated using prototypic drugs, focusing on general mechanisms of drug action. Examples were drawn from autonomic nervous system, cardiovascular, and central nervous system pharmacology; autacoids and chemotherapeutic agents were also considered. Principles were developed that allow students to evaluate both drugs currently used in the clinic and those under development in academic, pharmaceutical, and biotechnology laboratories. Relationships between basic mechanisms and clinical uses of therapeutic agents were explored in case-based tutorials, and principles important in the conduct of research in molecular pharmacology were discussed in small-group conferences.

I introduced in the Principles of Pharmacology course a number of teaching methods that were subsequently adopted more widely in the New Pathway curriculum. The course placed the action of drugs in the framework of human biochemistry and physiology, reviewing and building on pathways and mechanisms that the students had recently learned in the Chemistry and Biology of the Cell and Integrated Human Physiology block courses. Principles of Pharmacology laid a strong foundation for learning in pharmacology and therapeutics, allowing students to apply and build on the knowledge and modes of thinking acquired in this course during the many case-based discussions that followed in the remainder of the preclinical New Pathway curriculum and later in clinical clerkships. The course was designed with the recognition that each student had his or her unique style of learning, and that presentation of the same information in multiple different contexts served to reinforce the material and to allow the student to work actively with the key concepts and facts. I worked extensively with each lecturer to insure that the lectures illustrated principles that were key to the understanding of drug action, reviewing the biochemistry and physiology of the relevant system or pathway and illustrating the mechanisms and effects of drug action in the context of that biochemistry and physiology. I recruited lecturers and tutors who also participated in other courses in the New Pathway curriculum to enhance the continuity and complementarity of the overall preclinical curriculum. Course conferences were based on written problem sets; these discussions provided practice in applying the concepts introduced in lectures and tutorial cases to specific problems in pharmacology. Three major case protocols — one on pain medicine and the pharmacology of drug addiction; one on cardiovascular pharmacology; and one on cancer and antimicrobial chemotherapy — formed the core of the tutorial experience. Tutorial discussions, which were guided by the case protocols and facilitated by faculty tutors, illustrated the mechanisms of action and use of drugs from approximately 50 major drug classes in the prevention and pharmacotherapy of disease. I introduced clinics in substance abuse and cancer chemotherapy that consisted of patient interviews by clinicians and students, followed by a general discussion among students, patients, and clinicians. I also introduced an interactive general anesthesia simulator experience that was brought by teleconference technology to the lecture hall. These sessions illustrated the immediate clinical relevance of the material in the course, and demonstrated to the student that therapeutic agents are used in clinical practice in the biopsychosocial context of the whole patient. Finally, I pioneered the use of role-playing in the tutorial process, in which I played the role of the patient in the tutorial case and allowed myself to be interviewed by the students in my tutorial group.

(2) *PharmAid*®. An important adjunct to the Principles of Pharmacology course was PharmAid®, a computer-based pharmacology learning program that I developed in collaboration with Jeffrey Joseph. This program was the first computer-based learning program to be adopted for extensive use in a core New Pathway course; it served as one model for the use of computer technology in other New Pathway courses. PharmAid® contains 573 hypertext cards with extensively linked textual and diagrammatic information about drugs, drug classes, and related agents. Like the Principles of Pharmacology course, the program emphasizes basic principles of pharmacology, enabling the student to understand the action of therapeutic agents in the framework of human biochemistry and physiology. The program also uses a set of six interactive pharmacokinetic models to calculate and display predicted serum drug levels over time given user-defined dosing parameters.

(3) *Pharmacology Paracurriculum.* I worked extensively with course planners in the second-year Human Systems (pathophysiology) modules to develop a pharmacology “paracurriculum” that extended the

concepts introduced in the first-year course to examples of specific therapeutic agents used in the second-year course's tutorial cases. This paracurriculum consisted of a "map" of the various therapeutic agents used in the Human Systems tutorial cases as well as a set of reports from the primary literature on specific drugs that were introduced in the tutorial case protocols.

(4) *Textbook of Pharmacology*. From 2000 to 2004 I led a major effort to write a unique textbook of pharmacology. This project grew out of a series of discussions I had with an extremely thoughtful and motivated group of five Harvard Medical School (HMS) students who had recently completed the first-year New Pathway curriculum. The goal of the project was to produce a new textbook suitable for an intensive course in pharmacology taken by first and second year medical students.

The book, titled *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, departs from standard pharmacology textbooks in three main ways. First, it places pharmacology in the context of the biochemistry and physiology of the various drug targets, and of the pathophysiology of the diseases for which drugs are used clinically. High-quality figures are used to illustrate these relationships among the biochemistry, physiology, pathophysiology, and pharmacology of the various systems considered. This organizational scheme also allows the book to point the way to potential molecular and cellular targets for drug therapies to be developed in the future, and to incorporate such drug classes readily into subsequent editions of the book. Second, the book uses clinical cases or vignettes to illustrate the use of the various drug classes in pharmacotherapy. The cases are presented at the beginning of each chapter, and referred to throughout the chapter at the appropriate points in the discussion of the biochemistry, physiology, pathophysiology, and pharmacology of the system under consideration. Finally, each chapter is written as a collaborative effort between an HMS student(s) and an HMS faculty member(s), incorporating the perspective, enthusiasm, and effort of the student(s) with the knowledge, experience, and expertise of the faculty.

Over the course of the project, we recruited 43 HMS students and 39 HMS faculty to collaborate on the writing of the 52 chapters in the book. Most of the draft chapters were used as primary source material in the 2001, 2002, 2003, and 2004 versions of the Principles of Pharmacology course. We solicited feedback from first-year medical students, advanced medical students, and selected faculty on the strengths and weaknesses of individual chapters and sections of the book, and on the concept of the book as a whole. We incorporated this feedback into final drafts of the book chapters, and Lippincott Williams & Wilkins (LWW) published the 856-page, 400-figure, 200-table textbook in April 2004.

Approximately three years after its publication, *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy* was already in wide use in pharmacology courses and programs at undergraduate, graduate, medical, dental, nursing, and pharmacy schools in the US and abroad. It sold more than 12,000 copies and received more than 30 confirmed adoptions at universities such as Baylor, Brigham Young, Brown, Case Western Reserve, Cornell, Drexel, Harvard, Massachusetts Institute of Technology, Medical College of Virginia, Oregon State, San Juan Bautista, University of Buffalo, University of California at Los Angeles, University of Denver, University of Kansas, University of Miami, University of Puerto Rico, University of Rochester, University of Texas at Galveston, Vanderbilt, and Yale. The first edition of the textbook was translated into Italian and Japanese.

Based on the success of the first edition, LWW asked us to prepare a second edition of the textbook for publication in the spring of 2007. In response to constructive suggestions from students, readers, and reviewers of the first edition, and in light of the many important changes that have taken place across the landscape of pharmacology and therapeutics, we made a number of significant improvements in the second edition. These additions included: (1) Addition of a new chapter on the principles and mechanisms of drug toxicity; (2) Reorganization of the 9-chapter section on principles of chemotherapy — this section was completely reorganized according to therapeutic target, including two chapters on the principles of antimicrobial and antineoplastic pharmacology, two chapters on the pharmacology of bacterial infections,

one chapter each on the pharmacology of fungal, parasitic, and viral infections, and two chapters on the pharmacology of cancer, with the addition of a new chapter on the pharmacology of signal transduction in cancer; (3) Addition of a 3-chapter section on drug discovery, development, and regulation — this new section describes the ‘‘life cycle’’ of a drug from the identification of its potential target through phase IV postmarketing surveillance, with the addition of a new chapter on the systematic detection of adverse events in marketed drugs; (4) Creation of a comprehensive set of 37 drug summary tables that group drugs and drug classes according to their mechanism of action and that list clinical applications, serious and common adverse effects, contraindications, and therapeutic considerations (including important drug interactions) for each drug; (5) Comprehensive updating of all chapters, including new drugs approved through 2006; (6) Comprehensive updating of all figures and tables, including 100 new or substantially modified figures — as in the first edition of the textbook, all the figures were produced by the same artist for uniformity of style and presentation; (7) Comprehensive updating of state-of-the-art chapters at the frontiers of pharmacology, including pharmacogenomics, protein-based therapies, and drug delivery modalities. In addition, we recruited a panel of new chapter authors who added tremendous strength and depth to the existing panel of authors, and the second edition of the textbook was edited even more carefully than the first edition for clarity of content and style and for uniformity of presentation. Finally, the second edition of *Principles of Pharmacology* is accompanied by a case-based *Principles of Pharmacology Workbook* that was written by Susan Farrell, MD and edited by me. The workbook reviews all of the important concepts in pharmacology and the majority of the important drug classes in a question-and-answer format that is conducive to course and board exam review. The second edition of the textbook was published in April 2007 and the workbook was published in June 2007. The textbook sold more than 10,000 copies in its first year of publication. The second edition of the textbook has been translated into Korean; Chinese, Portuguese and Russian translations are in preparation.

(5) *Committee on Therapeutics and Evidence-Based Medicine.* I chaired a committee that was considering mechanisms for extending the concepts and principles of pharmacology introduced in the first and second year curriculum into a systematic treatment of the principles and practice of therapeutics in the third and fourth year curriculum, with close ties to the teaching of evidence-based medicine. Approaches under consideration included developing a required course in clinical pharmacology and therapeutics in the fourth year curriculum; introducing into core and elective clinical clerkships “virtual patient” and “computer cases” that teach and assess skills in therapeutic decision-making; and developing an ongoing program of faculty development to expand the base of clinical faculty who are qualified to teach therapeutics and evidence-based medicine in the clerkships.

(6) *Medical Education Reform Initiative and The Academy at Harvard Medical School.* I have served in a number of roles related to the current medical education reform initiative at Harvard Medical School. Since 2001, I have served on the Medical Education Program Self-Study Committee (2001-2003), the “Blue Sky” Medical Education Task Force (2001-2002) and the Task Force for a New Curriculum (2003-2004). All of these committees reviewed the medical education program at HMS and made recommendations for changes and new program initiatives. From 2004 to 2006 I served on the Medical Education Reform Steering Committee, taking a leadership role by chairing a working group that developed a robust proposal for in-depth educational experiences (also called areas of concentration) as a required component of the curriculum for the MD degree. I also chaired the Design Group on In-Depth Educational Experiences, which developed a detailed proposal for incorporating the areas of concentration into the new medical curriculum at Harvard Medical School. I served as co-chair of the Medical Sciences Education Committee of the Committee on Educational Policy and as a member of the basic science course directors group that was designing the Fundamentals of Medicine component of the new curriculum, which commenced in the fall of 2006.

Part of the medical education reform initiative has involved the creation of The Academy at Harvard Medical School, a service organization whose members include the most creative, innovative and dedicated educators at the School. I am a Scholar and Founding Member of The Academy, and I have served on the Executive Committee and Steering Committee of The Academy since its inception. I also served on the initial Selection Committee for new Academy members and I chaired the Coordinating Committee for Curriculum Innovation that evaluated the appropriateness of Academy members' project proposals for funding.

(7) *Graduate Student Teaching.* My major responsibility in graduate student teaching has been in the course on molecular approaches to drug action and design, directed by Donald Coen. In this course I serve as a lecturer, discussion leader, problem set and examination writer, and student project evaluator. I have also recently taken on a senior role in the design and implementation of the Leder Human Biology and Translational Medicine graduate program at Harvard Medical School. This program will admit its first class of 13 PhD students in September 2008.

(8) *Postgraduate Teaching.* I have assumed leadership roles in the Harvard Medical School Scholars in Clinical Science Program (SCSP) and the Harvard Macy Institute for Physician Educators. In the SCSP, I serve as leader of the Human Pharmacology Program and as one of three directors of the Human Pharmacology and Therapeutics Track. The NIH-funded SCSP is designed to provide, for 10-20 postgraduate fellows per year, a coordinated two-year didactic and practical training program in translational investigation, human pharmacology, and clinical trials. The first group of Scholars entered the Program in July 2000. In the Harvard Macy Institute, I serve on the Physician Educator Steering Committee and co-direct the Information Technology Theme within the Institute, which is designed to provide, for 40 early- to mid-career physician educators, an intensive didactic and practical program to enhance the professional development of physicians as educators.

(9) *International Consultant on Curriculum Design and Development.* I have served as the sole consultant on teaching of the basic medical sciences for the Faculty of Medical Sciences at the National University of Cuyo in Mendoza, Argentina, as the sole consultant on a new medical curriculum for the China Medical University in Shenyang, China, and as a consultant on new medical curricula for the Carl Gustav Carus Medical Faculty of the Technical University in Dresden, Germany and for the Catholic University of Portugal in Lisbon, Portugal. In each of these roles, I have spent one week as a visiting professor, presenting lectures, workshops, computer-based resources, and small-group discussion materials to several hundred faculty members in Argentina, China, Germany, and Portugal, respectively. All of these medical schools are now moving forward with ambitious and comprehensive curriculum reform plans involving active, student-centered, case-based learning methods. I have also been recruited by Harvard Medical International (HMI) to serve as a member of the HMI Core Planning Group for International Medical Education Alliances, and to serve as one of three core consultants from HMI to the new Cleveland Clinic Lerner College of Medicine at Case Western Reserve University in Cleveland, Ohio, which is developing a research-based medical curriculum for a new medical school focused on the education of physician-scientists.

(10) *Medical Student and MD-PhD Student Administration.* I have devoted considerable time, effort, and leadership in designing and developing the policies and processes underlying the evaluation of the academic and professional progress of medical students at Harvard Medical School. I chaired a committee that developed the official Harvard Medical School Policy on Student Conduct and Responsibility, and worked with the Associate Dean for Student Affairs to develop due process guidelines for the academic and professional evaluation of students. I was the first Chair of the Subcommittee on Student Conduct and Responsibility of the Academic Societies Promotion and Review Board, and until recently I chaired the Board and its Subcommittee on Academic Performance. I served for a number of years on the admissions committee of the Harvard-MIT MD-PhD Program, and have served as the liaison between that committee and the main student admissions committee at Harvard Medical School. I have served as an advisor to many Harvard medical students and MD-PhD students interested in academic careers that combine research,

teaching, and clinical work. I recently served as Co-Director of the Harvard-MIT MD-PhD Program, with specific responsibility for design and implementation of the MD-PhD curriculum.

(11) *National Board of Medical Examiners (NBME) Committee Service.* I served from 1996 to 1998 on the Applied Pharmacology Task Force and USMLE Step 1 Applied Pharmacology Test Material Development Committee, and from 1998 to 2001 on the analogous Step 1 Pharmacology Committee and the Step 1 Interdisciplinary Review Committee. I have become known at the NBME for designing a novel item-writing strategy that requires active problem-solving and synthesis of at least two important pieces of information in order to deduce the correct answer in Step 1 multiple-choice questions.

B1. Research Funding Information:

Past:

1984-1993 NIH/R01 HL 32854
PI
Membrane dynamics in normal and abnormal red blood cells

1988-1993 NIH/P60 HL 15157
Section Head (Project PI) and Co-PI of Parent Center Grant
Project: Mobility and distribution of sickle membrane components
Parent Center Grant: Comprehensive sickle cell center

1988-1992 NIH/P01 CA 39542
Co-PI (Core Director)
Core: Fluorescence activated cell sorter facility
Parent grant: Cellular and molecular studies of bone marrow transplantation

1988-1989 NIH Shared Instrumentation Grant/S10 RR 05006
PI
Interactive laser cytometer/cell sorter

1988-1989 Whitaker Health Sciences Fund, Massachusetts Institute of Technology
PI
Significance of transductive electrokinetic processes in cell surface glycoprotein movement

1992-1993 William F. Milton Fund, Harvard University
PI
Mechanism of cellular responses to ac electric fields

1993-1997 NIH/R01 HL 32854
PI
Membrane dynamics in normal and abnormal erythroid cells

1993-1998 NIH/P60 HL 15157
Section Head (Project PI) and Co-PI of Parent Center Grant
Project: Mobility and adhesion of sickle membrane components
Parent Center Grant: Comprehensive sickle cell center

1994-1995 Funds for Discovery, Harvard Medical School
PI
Use of NADH laser fluorimetry for the assessment of oocyte and embryo quality

1996-2000 The Whitaker Foundation/Biomedical Engineering Research Grant
Co-Investigator
Prediction of optimal parameters for electrotherapy of wound healing

1998-2000 Northeastern University Engineering Research Center for Subsurface Sensing and Imaging Systems/Interdisciplinary Seed Grant
PI
Use of computer-enhanced laser and video microscopy techniques to elucidate the physical properties of individual cell surface receptors, channels, and adhesion molecules

1997-2008 NIH/R37 HL 32854
PI
Molecular interactions in erythroid cell membranes

1998-2000 Brigham and Women's Hospital Research Organization/Interdisciplinary Seed Grant
Co-PI
Quantitative analysis of the two-dimensional binding between lipopolysaccharide from *Pseudomonas aeruginosa* and the cystic fibrosis transmembrane conductance regulator (CFTR)

1998-2000 Brigham and Women's Hospital Research Organization/Dual-Mentored Fellowship Grant
Co-Mentor
Cellular imaging of protein-protein interactions: Visualizing the dynamic regulation of eNOS and caveolin in Ca^{2+}-dependent signal transduction

1998-2003 NIH/P60 HL 15157
Section Head (Project PI) and Co-PI of Parent Center Grant
Project: Lymphocyte-erythrocyte adhesion in sickle cell disease
Parent Center Grant: Comprehensive sickle cell center

2000-2002 NSF/EEC-9986821
Section Head (Project PI) and Co-PI of Parent Center Grant
Project: Use of computer-enhanced laser and video microscopy techniques to elucidate the physical properties of individual cell surface receptors, channels, and adhesion molecules
Parent Center Grant: Engineering research center for subsurface sensing and imaging systems

2003-2008 NIH/U54 HL 70819
Section Head (Project PI) and Co-PI of Parent Center Grant
Project: Single molecule analysis of sickle erythrocyte adhesion
Parent Center Grant: Comprehensive sickle cell center

Current:

2008-2012 NIH/R01 HL 32854
PI
Molecular regulation of adhesive integrin interactions in erythroblastic islands

B2. Teaching Funding Information:

Current:

2002- Harvard University Provost's Fund for Innovation in Instructional Technology
PI
Web curriculum in pharmacology

C. Report of Current Research Activities:

Major Projects:

1. Molecular dynamics in erythroid cell membranes, PI
2. Analysis and functional significance of dynamic changes in the biophysical properties of adhesion receptors in cell-cell contact areas, PI

Other Projects:

3. Mechanism of lipopolysaccharide uptake by pulmonary epithelial cells, Co-PI
4. Activation and translocation of endothelial nitric oxide synthase (eNOS), Co-PI

Narrative Summary of Major Current Research Projects:

Our current research program extends and intensifies efforts in our two major areas of investigation: the dynamics of individual transmembrane protein molecules in red cell membranes; and the dynamics of cell surface receptors in lymphocyte membranes.

Having characterized the *average* dynamic properties of populations of band 3 and glycophorin A molecules in normal and pathologic red cells, my laboratory has begun to study the dynamics of *individual* band 3 and glycophorin A molecules labeled with gold-conjugated antibodies or covalent ligands. We have designed and constructed a laser video microscope for imaging and manipulating individual gold-labeled transmembrane proteins using the single particle tracking and laser optical tweezers techniques.[68,82] We are using this apparatus to test specific models, generated by our previous studies of band 3 and glycophorin A populations, for the steric hindrance, low-affinity binding, and high-affinity binding interactions that are expected to control the long-range (μm-scale) and short-range (nm-scale) dynamics of individually labeled transmembrane proteins. These models are being tested in three related erythroid cell systems, including (i) mature red cells from patients with hereditary hemolytic anemias and defects in spectrin, ankyrin, band 3, band 4.1, and band 4.2, (ii) mature red cells from mouse strains with hereditary hemolytic anemias and defects in spectrin and ankyrin, and from transgenic mouse strains with engineered defects in ankyrin, band 3, and band 4.2, and (iii) differentiating human and mouse erythroid cells in culture. Single particle tracking is being used to distinguish among four modes of translational motion of individual protein molecules, including unrestricted diffusion, constrained diffusion, directed movement, and immobilization. Laser optical tweezers are being employed to quantify the strength of high- and low-affinity binding interactions involving individual protein molecules in the native membrane environment. These experiments are expected to provide direct measurements of the forces involved in high- and low-affinity binding interactions among transmembrane and membrane skeletal proteins.

My laboratory is continuing to study molecular interactions among cell surface receptors, cytoskeletal proteins, and intracellular signals in *lymphocyte activation and adhesion interactions*. These studies are currently focused on the signal transduction pathways that couple lymphocyte activation to changes in the lateral mobility, cell surface distribution, cell surface expression, and two-dimensional (membrane) dissociation constant of receptor-ligand pairs of molecules involved in cell adhesion.[84,85] Our working model

for these studies is that (i) CD2 is free to diffuse laterally in the plasma membrane of resting T cells, (ii) the combination of T cell contact with a CD58-expressing target cell, and a T cell stimulatory signal such as antigen receptor engagement, induces accumulation of immobilized CD2 molecules in the area of contact between the T cell and the CD58-bearing membrane, (iii) the immobilization of CD2 molecules in the contact area depends on activation of a CD2 adapter protein(s) that links the cytoplasmic domain of CD2 to the actin cytoskeleton, (iv) the activation of this adapter protein(s) depends on a signaling cascade that involves cytoplasmic calcium, calmodulin, and calmodulin kinase, and (v) the activation of this adapter protein(s) couples cytoskeletal polarization toward the contact area with immobilization of cell surface CD2 in the contact area. We have also initiated collaborations with several groups on the physical forces regulating *cell-cell contact formation and adhesion bond formation* in developing erythroid cells in culture and in pathogen-host cell interactions involving the uptake of *Pseudomonas aeruginosa* lipopolysaccharide (LPS) mediated by the cystic fibrosis transmembrane conductance regulator (CFTR) protein expressed on pulmonary epithelial cells in culture and *in vivo*.[65,70]

D. Report of Teaching:

1. Local Teaching Contributions:

a. Harvard Medical School and Division of Medical Sciences Courses:

1984-1989 **Introduction to Pharmacology (Traditional Pathway)**
Section Leader (years 1-2); Lecturer (years 3-5); Problem Set Writer (years 1-5); Examination Writer (years 1-5)
16 medical students (sections); 160 medical students (lectures)
28 hours/year (as Section Leader); 6 hours/year (as Lecturer)

1986-1987 **Introduction to Clinical Medicine (Traditional Pathway)**
Medical Preceptor
2 medical students
45 hours/year

1989-2006 **Principles of Pharmacology (New Pathway)**
Lecturer; Tutor; Software Author and Computer-Based Learning Resource; Conference Problem Set Writer; Tutorial Case Editor; Examination Writer
160-180 medical and dental students (lectures); 7-9 medical and dental students (tutorials)
20 hours/year (as Lecturer); 20 hours/year (as Tutor); 8 hours/year (as Computer-Based Learning Resource)

1990-1994 **Conduct of Science (Division of Medical Sciences)**
Discussion Group Leader
10 graduate students
18 hours/year

1993-2006 **Human Systems (New Pathway)**
Planning Group Member, Respiratory-Cardiovascular-Hematology (RCH) Module; Planning Group Member, Gastroenterology-Renal-Endocrine/Reproduction-Metabolism (GREM) Module
Principal Author, Human Systems Pharmacology Paracurriculum
160-180 medical and dental students
24 hours/year

1993- **Program for Minority Science Students**
Laboratory Preceptor
1 pre-matriculation medical student
16 hours/year

1994- **Molecular Approaches to Drug Action and Design (Division of Medical Sciences)**
Lecturer; Problem Set and Study Question Author; Discussion Leader
30 graduate and postgraduate students (lectures); 15 graduate and postgraduate students (discussions)
10 hours/year (as Lecturer); 6 hours/year (as Problem Set and Study Question Writer); 10 hours/year (as Discussion Leader)

1994-1998 **Critical Thinking and Research Proposal Writing (Division of Medical Sciences)**
Instructor and Discussion Group Leader
4-8 graduate students
20 hours/year

2002- **Principles of Pharmacology for the Investigator (Scholars in Clinical Science Program and Leder Human Biology and Translational Medicine Program)**
Lecturer; Group Project Facilitator
40 graduate students (lectures); 5 graduate students (project group)
10 hours/year (as Lecturer); 10 hours/year (as Group Project Facilitator)

2004-2005 **Mentored Clinical Casebook Project (New Pathway)**
Project Advisor
3 medical students
12 hours/year

2007- **Cellular Metabolism and Human Disease (Division of Medical Sciences and Faculty of Arts and Sciences)**
Lecturer and Discussion Group Leader
46 graduate and undergraduate students
8 hours/year

2008- **Principles of Human Disease: Physiology and Pharmacology (Division of Medical Sciences and Faculty of Arts and Sciences)**
Lecturer; Case Response Editor; Tutorial Case Editor; Examination Writer
34 graduate and undergraduate students
4 hours/year (as Lecturer); 12 hours/year (as Case Response Editor); 12 hours/year (as Tutorial Case Editor); 6 hours/year (as Examination Writer)

b. Graduate Medical Courses:

1985- **Hematology-Oncology Consult Service and Inpatient Unit Attending, Brigham and Women's Hospital**
Consult Service and Inpatient Unit Attending
1-2 medical students; 1 resident; 1-2 hematology-oncology fellows (Consult Attending);
1-4 medical students; 4 interns; 2 residents; 1 hematology-oncology fellow (Inpatient Unit Attending)
1-2 months/year

1999 **Ambulatory Care Subspecialty Case Discussions, Department of Medicine, Brigham and Women's Hospital**
Case Discussion Leader
4 residents
2 hours

c. Invited Teaching Presentations:

1983- **Introduction to Laboratory Research in Biophysics, Harvard University**
Lecturer
6-8 graduate students
2 hours/year

1988 **Transductive Coupling in Living Cells, Massachusetts Institute of Technology**
Lecturer
20 graduate students and postdoctoral fellows
2 hours

1999- **Principles of Toxicology, Harvard School of Public Health**
Lecturer and Examination Writer
30 graduate students and postdoctoral fellows
8 hours/year

1999- **Biotechnology and Engineering, Massachusetts Institute of Technology**
Case Study Discussant
70 undergraduate students
3 hours/year

d. Continuing Medical Education Courses:

1986-1998 **Intensive Review of Hematology-Oncology, Hematology-Oncology Division, Brigham and Women's Hospital**
Conference Leader and Lecturer
300 postgraduate students
10 hours/every other year

1990-1991 **New Pathways in General Medical Education Continuing Medical Education Course, Harvard Medical School**
Lecturer and Planning Group Member
40 postgraduate students
4 hours/year

1991 **Brigham-Beth Israel Postgraduate Medical Series**
Symposium Organizer and Lecturer on Clinical Pharmacology
150 postgraduate students
6 hours

1997- **Harvard Macy Program for Physician Educators, Harvard Medical School**
Lecturer
40 postgraduate students
2 hours/year

2000- **Harvard Medical International Program in Advanced Medical Education and Harvard Medical International Leadership Program**
Lecturer, Symposium Organizer, Working Group Facilitator
15 postgraduate students
25 hours/year

e. Advisory and Supervisory Responsibilities:

Laboratory Advising and Supervision:

1978- 1-3 research assistants in laboratory/year

1982- 1-3 medical and/or graduate students in laboratory/year

1988- 2-5 postdoctoral fellows in laboratory/year

Clinical Supervision:

1979-1983 Supervision of medical students on Medicine rotation

1984- Supervision of medical students, interns, residents, and hematology-oncology fellows on Hematology-Oncology Clinic, Consult Service and Inpatient Unit rotations

f. Leadership Roles:

Harvard Medical School:

1986-1989 **Introduction to Pharmacology (Traditional Pathway)**
Assistant Course Director (years 1-2); Course Co-Director (year 3)
Organize conference sections and examinations; select and recruit conference leaders; edit problem sets and examinations; supervise examination grading

1989-2006 **Principles of Pharmacology (New Pathway)**
Course Director
Organize course; select and recruit lecturers, clinic preceptors, symposium speakers, conference leaders, and tutors; edit lecture notes, conference problem sets, tutorial cases, and examinations; chair weekly meetings of lecturers, conference leaders, and tutors; supervise review sessions and evaluations of student performance

1997- **Scholars in Clinical Science Program**
Executive Committee Member; Human Pharmacology Program Leader
Member, program organization committee; organize and implement core and elective courses, and mentored clinical research projects, in human pharmacology

1999- **Harvard Macy Program for Physician Educators**
Steering Committee Member; Information Technology Theme Co-Director
Member, course organization committee; organize information technology sessions; select and recruit lecturers; select readings; lead discussions

1999- **International Medical Education Alliances, Harvard Medical International**
Core Planning Group Member
Member, core planning group; organize and implement courses and workshops in curriculum design and development, course design, faculty development, case writing, tutor training, lecturing skills, information technology, critical reading, and student assessment

2000-2003 **Harvard Medical School – Massachusetts Institute of Technology MD-PhD Program**
Co-Director; Subcommittee on Admissions Member; Committee on Advising Member; Faculty Standing Committee Member; Clinical Curriculum Committee Member
Co-direct all aspects of program, including admissions, curriculum, advising, event planning, and integration of medical and graduate education

2001- **The Academy at Harvard Medical School**
Executive Committee Member; Steering Committee Member; Selection Committee Member; Coordinating Committee for Curriculum Innovation Chair
Founding Member of the Academy; member of the executive committee; create the detailed design of the initial structure and function of the Academy, including rules of governance, membership criteria, administrative construct, systems for review and accountability, scope of activities, and relationships with other constituencies of the School; chair committee responsible for evaluating project descriptions from Academy Scholars

2002- **Principles of Pharmacology for the Investigator (Scholars in Clinical Science Program and Leder Human Biology and Translational Medicine Program)**
Course Co-Director
Organize course; co-chair planning meetings; select and recruit lecturers, case study leaders, and teaching fellows; edit examination questions; evaluate student performance

2008- **Principles of Human Disease: Physiology and Pharmacology (Division of Medical Sciences and Faculty of Arts and Sciences)**
Course Co-Director
Organize course; select and recruit lecturers, case discussion leaders, patient presentation leaders, and tutors; edit case response discussions, tutorial cases, and examinations; chair weekly meetings of tutors; supervise evaluations of student performance

Brigham and Women's Hospital:

1995 **Intensive Review of Hematology-Oncology, Hematology-Oncology Division**
Course Co-Director
Member, course organization committee; organize small group conference sessions; select and recruit conference leaders; edit conference materials

g. Advisees and Trainees:

Postdoctoral Trainees and Mentored Visiting Professors:

James D. Corbett, Ph.D. (1988-1992) Research Associate, Department of Laboratory Medicine, University of California, San Francisco, CA
Hemant S. Thatte, Ph.D. (1988-1992, 1993-2000) Assistant Professor, Department of Surgery, Harvard Medical School and West Roxbury Veterans Administration Medical Center, Boston, MA
Laura M. Ferguson, Ph.D. (1989-1990) Senior Manager, Aventis Pasteur, Swiftwater, PA
Michael R. Cho, Ph.D. (1990-2000) Associate Professor, Department of Biomedical Engineering, University of Illinois, Chicago, IL
Margaret R. Kasschau, Ph.D. (1990-1991) Chair, Department of Biological Sciences, University of Sciences in Philadelphia, Philadelphia, PA
Si-qiong J. Liu, M.D., Ph.D. (1990-1994) Assistant Professor, Department of Biology, Pennsylvania State University, University Park, PA
Gilda A. Barabino, Ph.D. (1990-1992) Professor, Department of Chemical Engineering, Vice Provost for Undergraduate Education, Northeastern University, Boston, MA
Katalin Polgar, Ph.D. (1991-1996) Assistant Professor, Departments of Medicine/Nephrology and Obstetrics, Gynecology and Reproductive Biology, Mount Sinai School of Medicine, New York, NY
Kenneth D. Brady, Ph.D. (1993-1994) Consultant, Software Engineering, Staten Island, NY
De-Min Zhu, Ph.D. (1995-1997) Scientist, Department of Vaccine Pharmaceutical Research and Development, Merck & Company, West Point, PA
Prakash Prabhakar, Ph.D. (1997-2000) Investigator, Protein Biochemistry Division, Vertex Pharmaceuticals, Inc., Cambridge, MA
Alev A. Gerçeker, Ph.D. (1998-1999) Assistant Professor of Microbiology, University of Istanbul, Turkey
Torsten H. Schroeder, M.D. (1998-2000) Fellow, Department of Anesthesiology and Critical Care Medicine, Tübingen University Hospital, Tübingen, Germany
Rossen Mirchev, Ph.D. (1998-present) Research Associate in Biological Chemistry and Molecular Pharmacology, Harvard Medical School
Martin M. Lee, Ph.D. (1999-2003) Research Fellow in Medicine, Harvard Medical School
Alison J. Lin, Ph.D. (2001-present) Instructor in Medicine, Harvard Medical School
Aslihan Turhan, Ph.D. (2002-2006) Research Fellow in Medicine, Harvard Medical School

Christopher W. Cairo, Ph.D. (2002-2006) Assistant Professor of Chemistry, University of Alberta, Canada
Marina Marinkovic, Ph.D. (2008-present) Research Fellow, Department of Environmental Health, Harvard School of Public Health

Graduate Student Trainees:

Alan H. Stolpen, M.D., Ph.D. (1982-1988) Associate Professor, Department of Radiology, University of Iowa College of Medicine, Iowa City, IA
Kimberly A. Wagner, Ph.D. (1988-1994) Analyst, Boston Consulting Corporation, New York, NY
Kimberly A. Birch, Ph.D. (1989-1992) Scientist, Department of Diabetes Research, Eli Lilly & Company, Indianapolis, IN
Kerry M. Wong, M.D. (1993) Dermatologist, Needham Heights, MA
Alexandru C. Bageac, M.D. (1995-1997) Chief Resident in Radiology, Beth Israel Deaconess Medical Center, Boston, MA
Mary T. Silvia (1997-1998) Medical Student, Harvard Medical School
Milan Bajmoczi (1999-2007) MD-PhD Student, Harvard Medical School
Joshua M. Galanter, M.D. (2000-2001) Fellow in Pulmonary and Critical Care Medicine, Department of Medicine, University of California at San Francisco, San Francisco, CA
Tanya Korobeinikova (2000-2001) Head of International Operations, Information Technologies Co., Moscow, Russian Federation
Pallop Karnchanaphanurach, Ph.D. (2001-2005) Lecturer, Department of Chemistry, Faculty of Science, Mahidol University, Bangkok, Thailand
Alexander Lam, M.D. (2002-2004) Resident in Emergency Medicine, Boston Medical Center, Boston, MA
Quentin Baca (2005-present) MD-PhD Student, Harvard Medical School

Research Assistants and Undergraduate Students:

Carl D. Brown, Ph.D. (1982-1987) Research Scientist, Applied Precision Incorporated, Issaquah, WA
Adam Abroms, M.D. (1985-1986) Eye Physicians of Olympia, Olympia, WA
John Jin Han, M.D. (1986-1987) GMC Anesthesiology, Danville, PA
Patrick W. Yacono (1987-present) Research Assistant, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
Stephanie K. Sharps, M.D. (1997) Resident, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL
Zelime Ward (1997-1998) Medical Student, University of Texas Medical Branch, Galveston, TX
Joan Marler (1998-1999) Graduate Student, Department of Physics, University of California, San Diego, CA
Vivian Gonzalez, M.D. (1998-1999) Resident in Internal Medicine, Brigham and Women's Hospital, Boston, MA
Timothy Harris (1999) MD-PhD Student, Johns Hopkins University, Baltimore, MD
Charles M. Jobin (2000-2001) Medical Student, University of Colorado, Boulder, CO
Divya Errabelli (2001) Undergraduate, Mount Holyoke College, South Hadley, MA
Shiv Sudhakar (2001) Undergraduate, Duke University, Durham, NC
Yolanda Tseng (2002) Medical Student, Harvard Medical School, Boston, MA
Jordan Amadio (2003) Undergraduate, Princeton University, Princeton, NJ
Theodore Nyame (2004) Undergraduate, Cornell University, Ithaca, NY
Andre Okoreeh (2007) Undergraduate, Morehouse College, Atlanta, GA

2. National and International Teaching Contributions and Visiting Professorships:

1991 Invited speaker; Teaching Institute, American Society of Pharmacology and Experimental Therapeutics Annual Meeting

1991 Invited speaker; Teaching Clinic, American College of Clinical Pharmacology Annual Meeting

1995 Invited speaker; Symposium on EMF Bioeffects, Harvard School of Public Health

1996 Visiting professor; Faculty of Medical Sciences, National University of Cuyo, Mendoza, Argentina

1999 Visiting professor; China Medical University, Shenyang, China

2000 Visiting professor; Carl Gustav Carus Medical Faculty, Technical University, Dresden, Germany

2002 Visiting professor; Xinjiang Medical University, Ürümqi, China

2002 Visiting professor; Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, Ohio

2005 Visiting professor; Catholic University of Portugal, Lisbon, Portugal

2005 Visiting professor; University of Buenos Aires, Buenos Aires, Argentina

2006 Visiting professor; Catholic University of Portugal, Lisbon, Portugal

2008 Visiting professor; University of Lisbon, Lisbon, Portugal

3. Description of Teaching Awards Received:

1996 Faculty Prize for Excellence in Teaching, Harvard Medical School. This annual Prize for excellence in teaching is awarded by the faculty and students to four members of the Faculty of Medicine.

1997 Elected Member, Aesculapian Club, Harvard Medical School. Election to membership in this Club recognizes outstanding service to the students of Harvard Medical School.

1998 Student Award for Excellence in Teaching (Course Director), Harvard Medical School. This Award was presented by the students for the first time in 1998 to several faculty members for their excellence as course directors.

1998 Student Award for Excellence in Teaching (Tutor), Harvard Medical School. This Award was presented by the students for the first time in 1998 to several faculty members for their excellence as tutors.

1999 Student Award for Excellence in Teaching (Course Guide, Lecture Notes, Conference Problems, Tutorial Cases, and PharmAid® Manual), Harvard Medical School. This Award

was presented by the students for the first time in 1999 to the Principles of Pharmacology course for its excellent course guide and accompanying materials.

2000 Student Award for Excellence in Teaching (Course Guide, Lecture Notes, Conference Problems, Tutorial Cases, and PharmAid® Manual), Harvard Medical School. This Award was presented by the students to the Principles of Pharmacology course for its excellent course guide and accompanying materials.

2001 Student Award for Excellence in Teaching (Lecturer), Harvard Medical School. This Award was presented by the students to several faculty members for their excellence as lecturers.

2002 Student Award for Excellence in Teaching (Lecturer), Harvard Medical School. This Award was presented by the students to several faculty members for their excellence as lecturers.

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2004 Student Award for Excellence in Teaching (Lecturer), Harvard Medical School. This Award was presented by the students to several faculty members for their excellence as lecturers.

2004 Student Award for Excellence in Teaching (Course Guide), Harvard Medical School. This Award was presented by the students to the Principles of Pharmacology course for its excellent course guide and accompanying materials.

2005 Alpha Omega Alpha Robert J. Glaser Distinguished Teacher Award, Association of American Medical Colleges. This national award "recognizes the significant contributions to medical education made by gifted teachers." It was accompanied by a $10,000 grant from Alpha Omega Alpha and the Association of American Medical Colleges.

4. Description of Major Curriculum Offerings, Teaching Cases, and Innovative Educational Programs Developed:

My contributions to Principles of Pharmacology, PharmAid®, and the Pharmacology Paracurriculum are described under the Narrative Summary of Teaching Contributions (section IIA2).

E. Report of Clinical Activities:

1. Description of Clinical Practice:

My clinic, inpatient, and consultation practices consist of patients with primary red cell disorders including hereditary and acquired hemolytic anemias; patients with primary disorders of the bone marrow including hematologic malignancies, myeloproliferative syndromes, myelodysplastic syndromes, pure red cell aplasia, and others; patients with iron deficiency and iron overload syndromes; patients with disorders of hemostasis and thrombosis; and other patients with problems in general hematology. All of these patients are seen in the teaching hospital setting. Most of these patients are tertiary care referral patients.

2. Patient Load:

1985- Hematology-Oncology Consult Service and Inpatient Unit Attending, 1-2 months per year; 5-20 inpatients and 1-5 new consults per day

1985- Hematology-Oncology Clinic Attending Physician, 2-8 patients per 1/2 day session per week

PART III: Bibliography

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