

CURRICULUM VITAE

Name: B. Michael Silber

Position: Professor of Neurology
Department of Neurology
Institute for Neurodegenerative Diseases
School of Medicine

Professor of Bioengineering and Therapeutic Sciences
Schools of Medicine and Pharmacy

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EDUCATION:

1970 – 72	California State University, Northridge, CA	---	Engineering
1972 – 76	University of Southern California, Los Angeles, CA (Professor Wolfgang Sadee, advisor)	Doctor of Pharmacy	Clinical Pharmacy
1976 – 77	University of California, San Francisco	Postdoctoral Fellow	Clinical Pharmacy
1978 – 81	University of California, San Francisco (Professor Sidney Riegelman, advisor)	Ph.D.	Pharmaceutical Chemistry and Pharmacology

LICENSES, CERTIFICATION:

1976 Pharmacy licensure, California - 30512
1976 Board Certification, Pharmacy

Selected accomplishments:

- Instituted latest research tools to identify and advance NMEs from discovery through non-clinical and early development, including those in pharmacology, toxicology/pathology, DMPK, and lab animal sciences leading to productivity improvements.
- Created the vision, strategies, and implementation plans for clinical pharmacology, pharmacology, toxicology/pathology, DMPK, lab animal sciences, and all non-clinical development to increase product discovery, resulting in a 100% increase in productivity within one year.
- Led biotechnology (e.g., MAb, peptide, protein) R&D projects including pre-clinical safety/efficacy; recognized as industry leader.
- Established a “drug hunting culture” through coaching, mentoring, and teaching scientists, project teams, post doctoral fellows and students.
- Recommended, led, or influenced many pioneering scientific collaborations, investments, licenses, and alliances, including those related to protein chemistry and antibody maturation. Performed due diligence on many in-licensing candidates leading to > \$50M of investment. Responsible for presentations to scientific, business, and analyst communities.
- Influenced R&D, submission and launch strategies and commercial success for Betaseron® and Proleukin®.

**1990 – 2002 Pfizer Global Research Department Head Genomic &
Development, Groton, CT and Director Proteomic Sciences,
Drug Metabolism,
Pharmacokinetics, &
Pharmacodynamics**

Responsible for creating a start-up like environment applying innovative science and technology to significantly increase the discovery to development pipeline in many therapeutic areas. Built start-up organizations, *de novo*, in translational sciences, DMPK, pharmaceuticals, drug delivery, toxicokinetics, toxicogenomics, chemistry, analytical chemistry, biochemistry, pharmacogenomics, biomarkers, proteomics, and pharmacodynamics through recruitment, motivation, and talent management. Directed R & D operations budget of ~ \$50 million and a staff of up to ~130 diversified staff. Routinely presented to the R & D President and CEO.

Selected accomplishments:

- Instituted cutting-edge research tools to identify and advance NCEs from discovery through non-clinical and clinical development, including those in DMPK, pharmaceuticals, toxicology, and genomic and proteomic sciences leading to productivity improvements.
- Created pharmacogenomics, biomarkers and DMPK strategic and business plans *de novo*. Responsible for establishing and supervising laboratory capabilities, and all operational efforts across Pfizer, now recognized as world leaders.
- Led seminal work published in 1995 delineating a novel quantitative method for tracing the biodistribution of radiolabeled drugs using whole body autoradiography and storage imaging detection critical to basic medical research and drug discovery and development.
- Led seminal work published in 1997 demonstrating in-vitro/pre-clinical results predict human DMPK, which led to significantly-reduced attrition of development candidates and many NCEs brought to early development, now recognized as world leaders.
- Established a “drug hunting culture” through coaching, mentoring, and teaching scientists, project teams, post doctoral fellows and students.

process chemistry, Tox/Path, DMPK, toxicogenomics, biopharmaceutical sciences, analytical, M & S, lab animal, and due diligence focused on CNS, inflammatory, and infectious diseases.

Selected accomplishments:

- Created and implemented preclinical R & D vision, strategy, and operational plans addressing capabilities and infrastructure.
- Established a “drug hunting culture” through coaching, mentoring, and teaching scientists, project teams, and post-doctoral fellows and students.
- Championed selection of MAb and small molecule NMEs with up to a 200% increase in Phase 0/I productivity, and for advancing two promising anti-viral medicines for Hepatitis C virus now in Phase II development.
- Responsible for leading Preclinical R & D efforts involving ~ 50 CNS, inflammation, and virology projects.
- Created and led a cross-functional R & D team that developed and implemented “tailor made” research strategies and development plans increasing speed, quality, and efficient use of project resources to Phase II/POC.
- Created and led a global cross-functional R & D team that developed/implemented strategies and plans that significantly reduced the time to bring MAbs to Phase increasing Roche’s competitive Biotech position.
- Responsible overall for Nonclinical Safety (toxicology, safety pharmacology, pathology, investigative toxicology, comparative medicine, laboratory animals, including transgenic and vivarium).
- Responsible overall for Drug Metabolism and Pharmacokinetics (disease oriented projects, ADME, disposition, high throughput screening, analytical, mass spectrometry, NMR, modeling & simulations).
- Responsible overall for Biopharmaceutical Sciences (pre-formulations, formulations, delivery, analytical, CMC, and GLP and GMP clinical supplies, pilot plant).
- Responsible overall for Chemical R & D (process chemistry, GMP API synthesis, pilot plant, analytical, radiochemistry, mass spectrometry and NMR spectroscopy).

2007 – now	University of California San Francisco Francisco, CA	Professor Neurology	Institute for Neurodegenerative San Diseases
		Professor Bioengineering and Therapeutic Sciences	Schools of Medicine and Pharmacy

Responsible for discovering and delivering a pipeline of drug candidates for the treatment of neurodegenerative diseases (e.g., Prion, Alzheimer’s, Parkinson’s, Frontotemporal Dementia) in collaboration with biologists, pharmacologists, chemists, toxicologists, drug metabolism, pharmacokinetic, biopharmaceutical scientists, analytical, M & S, lab animal sciences.

Current Responsibilities and Focus:

- Principal or co-Principal Investigator on several NIH, foundation, and private donor grants.
- Create and implement a drug discovery vision, strategy, and operational plans in neurodegenerative diseases such as CJD, Alzheimer’s, Frontotemporal Dementia, and Parkinson’s disease.

- Establish a “drug hunting culture” that currently does not exist at UCSF through coaching, mentoring, and teaching scientists and project teams.
- Create drug/compound libraries, establish appropriate screening assays, select leads and optimized leads, and select preclinical/clinical candidates for evaluation in Phase 0/I/II.
- Responsible for leading all preclinical R & D efforts and IP strategy.
- Implement “tailor made” research strategies and development plans to Phase II/POC.
- Responsible for high throughput screening (HTS), chemistry, biology, molecular biology, and in vivo pharmacology focused on identification of potential therapeutics.
- Responsible overall for nonclinical toxicology, safety pharmacology, pathology, and investigative toxicology as part of the new chemical entity identification process.
- Responsible overall for drug metabolism and pharmacokinetic activities (ADME, disposition, high throughput screening, analytical, mass spectrometry, NMR, modeling & simulations).
- Responsible overall for biopharmaceutical sciences activities (pre-formulations, formulations, delivery, analytical, CMC, and GLP and GMP clinical supplies).
- Responsible overall for chemical R & D (process chemistry, GMP API synthesis, analytical, radiochemistry, mass spectrometry and NMR spectroscopy).
- Responsible for teaching graduate students, post-docs, and staff scientists in the Schools of Medicine and Pharmacy.

OTHER POSITIONS HELD CONCURRENTLY:

2000 – now	Keystone - Molecular and Cellular Biology	Member, Scientific Advisory Board
2002 – now	University of California Berkeley	Board Member, Engineering School
2004 – 2005	Rational Biotechnology Inc.	Member, Scientific Advisory Board
2004 – 2008	Pertinence	Member, Scientific Advisory Board
2004 – 2008	DecisionView	Member, Scientific Advisory Board
2004 – 2008	Partech Venture Capital Company	Scientific and Strategic Advisor
2006 – 2008	University of Washington	Board Member
2006 – now	Neurokos	Board Member and Senior Advisor
2007 – now	Frazier Healthcare Ventures	Scientific and Strategic Advisor
2007 – 2008	Arête Therapeutics, Inc.	Senior Advisor, R & D
2007 – now	NextBio, Inc.	Member, Scientific Advisory Board
2007 – now	Optivia Biotechnology, Inc.	Member, Scientific Advisory Board
2008 – now	Keelin-Reeds Partners	Scientific and Strategic Advisor

HONORS AND AWARDS:

2000	Invited by President Clinton to the National Medal of Science and Technology Awards
2001	SNP Consortium Excellence Award in Science and Leadership
2009	20 th Most cited paper ever in the Journal of Pharmacology and Experimental Therapeutics

KEYWORDS/AREAS OF INTEREST:

Pharmaceutical and biotechnology industry and academic oriented drug discovery and development, neurodegenerative diseases (e.g., Alzheimer’s, Parkinson’s, Frontotemporal Dementia, and Creutzfeldt-Jakob diseases), cancer, rheumatoid and osteoarthritis, pain, HIV, HCV and bacterial infections, cardiovascular diseases, metabolic, respiratory, and psychotherapeutic diseases,

pharmacology, biomarkers, genetics, pharmacogenomics, proteomics, synthetic chemistry, DM/PK/PD, toxicology, pathology, biochemistry, biology, modeling & simulations, biopharmaceutical sciences, drug targeting and delivery, translational sciences, clinical development, root cause analysis of R & D attrition, registration and regulatory approval, intellectual property, due diligence, and strategic pipeline design, planning, and prioritization.

PROFESSIONAL ACTIVITIES

CLINICAL - none

PROFESSIONAL ORGANIZATIONS

Memberships

American Chemical Society
 American Society of Human Genetics
 American Society for Clinical Pharmacology and Therapeutics
 American Association for the Advancement of Science
 American Association of Pharmaceutical Scientists
 International Society for the Study of Xenobiotics

Service to Professional Organizations

1983-94	Various positions held at Academy of Pharmaceutical Scientists (later American Association of Pharmaceutical Scientists) and International Society for the Study of Xenobiotics; organizations focused on Pharmacokinetics, Pharmacodynamics, and Drug Metabolism areas.	Secretary and Vice Chairman Chairman
1995	ADMET Gordon Conf. on Medicinal Chemistry, New London, NH.	Chairman
1996	Models Predicting Human ADME, ISSX, San Diego, CA.	Chairman
1996	Predicting Human ADME, AAPS, Seattle, WA.	Chairman
1997	Predicting Human Drug Metabolism, ISSX, Hilton Head, SC.	Chairman
1998	Human Genetics and Drug Therapy, ASCPT, New Orleans, LA.	Chairman
1998	Pharmacogenomics, SRI, Princeton, New Jersey.	Chairman
1999	International Society for the Study of Xenobiotics.	Board Member
1999	Biomarkers in Drug Discovery & Development, NIH, Bethesda, MD.	Chairman
1999	Technologies Predicting Drug Safety, PhRMA, Washington, DC.	Chairman
1999	Pharmacogenomics and Proteomics, BIO99, Seattle, WA.	Chairman
1999	Pharmacogenomics and Proteomics, ISSX, Nashville, TN.	Chairman
1999	Single Nucleotide Polymorphism Consortium.	Board Member
2000	Biomarkers in Medicine, BIO2000, Boston, MA.	Chairman
2000	Pharmacogenomics and R&D, Pharma R&D 2000, Barcelona, Spain.	Chairman
2001	Benefits of Genomics, Pharma R&D 2001, Cancun, Mexico.	Chairman
2001	The Structural Genomics Consortium.	Board Member
2001	The FLEXGene Consortium.	Board Member
2001	Benefits of Genomics, Pharma R&D, Cancun, Mexico.	Chairman
2002	AAPS National Biotechnology Conference, San Diego.	Chairman

2003	Biomarkers in R&D and Medicine, BIO2003, Washington, D.C.	Chairman
2004	BIO2004 Steering Committee, representing all of Johnson & Johnson	Board Member
2009	Molecular Medicine Tri-Conference Meeting, San Francisco, CA.	Chairman
2011	Neurodegenerative Diseases Meeting, Keystone Symposia.	Chairman

SERVICE TO PROFESSIONAL PUBLICATIONS

1981 – 88	Ad hoc Referee for J Pharm Sci (~2 papers per year)
1983 – 95	Ad hoc referee for J Pharmacol Exp Ther (~1 paper per year)
1988 – 96	Ad hoc referee for Clin Pharmacol Ther (~1 paper per year)
1998 – now	Ad hoc referee for Amer J of Pharmacogenomics (~1 paper per year)
1998 – now	Ad hoc reviewer for Current Drug Metabolism (~1 paper per year)
2002 – now	Ad hoc referee for Expert Review of Molecular Diagnostics (~ 1 paper per year)
2002 – now	Ad hoc referee for Pharmacogenomics (~1 paper per year)
2008 – now	Annals of Neurology (2-3 papers per year)

INVITED PRESENTATIONS

INTERNATIONAL

- Sixth Annual Phoenix International Symposium on Drug Discovery R & D; Montreal, Canada, 1995 (invited talk).
- The 9th Annual Phoenix International Symposium in Drug Development and Discovery; Montreal, Canada, 1998 (invited talk).
- Wellcome Trust Meeting on Single Nucleotide Polymorphisms; Hinxton, Cambridge, United Kingdom, 1999 (invited talk).
- First International Pharmacogenomics and Pharmacogenetics Forum; Tsukuba, Japan, 1999 (invited talk).
- IBC Drug Discovery Technologies meeting, Pharmacogenomics and Pharmacogenetics Session; Amsterdam, The Netherlands, 1999 (invited talk).
- Pharma R&D Directions 2000 Meeting; Barcelona, Spain, 2000 (invited talk).
- Third Annual Conference of the Genomic Drug Discovery Forum of Japan; Tokyo, Japan, 2000 (invited talk).
- Pharma 2001 R & D Meeting on Embracing the Next Wave of Innovation in Genomics; Cancun, Mexico, 2001 (invited talk).
- BIO2002 Meeting on Novel Drug Delivery Approaches to Delivering Therapeutic Proteins; Toronto, Ontario, June 2002 (invited talk).

NATIONAL

- American Association of Pharmaceutical Scientists 11th Annual Meeting on Predicting Human Pharmacokinetics; Seattle, WA, 1996 (invited talk).
- North American International Society for the Study of Xenobiotics on Drug Metabolism and Predicting Human Kinetics; San Diego, CA, 1996 (invited talk).
- New Methods and Technologies for Functional Genomics meeting; San Diego, CA, 1996 (invited talk).
- Third Annual Conference on Pharmacogenetics: Bridging the Gap between Basic Science and Clinical Application; Washington, D.C., 1997 (invited talk).

North American International Society for the Study of Xenobiotics; Hilton Head Island, SC, 1997 (invited talk).

99th Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics focus on Genetics and Drug Therapy; New Orleans, LA, 1998 (invited talk).

IBC's 4th Annual International Conference on Pharmacogenomics/ Pharmacogenetics; Philadelphia, PA, 1998 (invited talk).

Global Business Research Symposium on Pharmacogenomics: Commercial Developments and Practical Applications; Philadelphia, PA, 1998 (invited talk).

Strategic Research International Symposium on Pharmacogenomics; Princeton, NJ, 1998 (invited talk).

Nature Biotechnology Meeting on Validating Pharmacogenomics: Drug Development Based on Genetic Variation; New York, NY, 1998 (invited talk).

BIO/FDA/PhRMA Educational Conference on Genetics; Gaithersburg, MD, 1998 (invited talk).

Annual Meeting of PhRMA on Drug Safety; Washington, DC, 1999 (invited talk).

BIO99 Meeting, Session on Use of Pharmacogenomics and Proteomics to Understand and Predict Drug Response and Disease Phenotypes; Seattle, WA, 1999 (invited talk).

American Society of Human Genetics Meeting; San Francisco, CA, 1999 (invited talk).

Ninth North American ISSX Meeting on Emerging Tools in Drug Discovery and Development; Nashville, Tennessee, 1999 (invited talk).

Ninth North American ISSX Meeting on Genomics and Proteomics; Nashville, Tennessee, 1999 (invited talk).

CBER/FDA/PhRMA Educational Conference on Pharmacogenetics; Gaithersburg, MD, 2000 (invited talk).

BIO2000 Meeting on Biomarkers in Safety and Efficacy; Boston, Massachusetts, 2000 (invited talk).

Annual Meeting of The Environmental Mutagen Society; New Orleans, Louisiana, 2000 (invited talk).

Drug Information Association, Annual Meeting; Philadelphia, Pennsylvania, 2000 (invited talk).

The Promise of Proteomics, New York Academy of Sciences, New York, 2001 (Keynote speaker).

Keystone Symposia on the Impact of Genomics on Drug Discovery and Development; Santa Fe, New Mexico, 2001 (invited talk).

DIA Innovative Statistical Strategies Workshop on Pharmacogenomics and Opportunities for Innovative Drug Development; Savannah, GA, 2001 (invited talk).

Research!America's Meeting of the Minds: Science, Research and the Media; Harvard Medical School, Boston, MA, 2001 (invited talk).

Roundtable on Global Innovations and their Impact on Drug Discovery; Copenhagen, Denmark, 2001 (invited talk).

Annual Meeting of The Environmental Mutagen Society and the Impact of Biomarkers; Seattle, WA, 2001 (invited talk).

AAPS Meeting on Genomic, Proteomic and Biomarker Data in R & D; Denver, CO, 2001 (invited talk).

IBC's 4th Annual Personalized Medicine Conference; San Francisco, CA, 2002 (invited talk).

Genome Tri-Conference on Genomics and Proteomics; Santa Clara, California, 2002 (invited talk).

AAPS/FDA meeting on Integration of Exposure Response Relationships in Drug Development and Regulatory Assessment – A Revisit with a Decade of Experience; Crystal City, VA, 2002 (invited talk).

AAPS National Biotechnology Conference; San Diego, California, June 2002 (invited talk).

BIO2003 Biomarkers in Medicine Meeting; Washington, D.C., 2003 (invited talk).

Frost & Sullivan Life Sciences Symposium 2003; San Diego, CA, 2003 (invited talk).

2nd Annual Symposium for Chief Scientific Officers, Greensboro, GA, 2004 (Keynote speaker).
Tufts Center for the Study of Drug Development meeting on Build, Sustain, and Protect Blockbuster Therapies; Philadelphia, PA, 2004 (invited talk).
BIOSF Meeting on Drug Targeting; San Francisco, CA, 2004 (invited talk).
rEvolution Symposium for Chief Scientific Officers focused on Drug Discovery in the Product Age; Greensboro, GA, 2004 (invited talk).
Second Annual Strategic Resource Management meeting on Key Approaches to Increasing R&D Productivity; Philadelphia, PA, 2004 (invited talk).
Jumpstart to Products Recognizing R & D Value meeting; San Francisco, CA, 2004 (invited talk).
rEvolution meeting for Chief Scientific Officers focused on discovering and developing new medicines; 2005 (Keynote speaker).
Stanford Research Institute & International Biotechnology Forum 14th Annual Biotech Rebuilding the Pipeline meeting; Menlo Park, CA, 2006 (invited talk).
SRI International Biotechnology Forum, Menlo Park, CA, 2006 (Keynote speaker).
Global Pharma R & D Summit meeting on R & D productivity; Boston, MA, 2007 (Keynote speaker).
Global Pharma R & D Summit, Boston, MA, October 2007 (Keynote speaker).
Health Care Innovation, Stanford University, February 2008 (Keynote address).
Molecular Medicine Tri-Conference Meeting; San Francisco, CA March 2008 (Keynote speaker).
American Association of Pharmaceutical Scientists Meeting, San Francisco, CA, May 2008 (Keynote speaker).
Molecular Medicine Tri-Conference Meeting on translational approaches in drug discovery, San Francisco, CA February 2009 (Chairman and keynote speaker).
Science and Technology Forum on Immunogenicity in Protein Therapeutics, San Francisco, CA, October 2009 (Keynote speaker).

REGIONAL

Gordon Research Conference/Medicinal Chemistry; New London, NH, 1995 (invited talk).
Boston University, Lectures in Medicinal Chemistry; Boston, MA, 1997 (invited talk).
University of California San Francisco Meeting on Genetic Variation in Drug Response; 1999 (invited talk).
NIH meeting on Biomarkers and Surrogate Endpoints: Advancing Clinical Research Applications; Bethesda, MD, 1999 (invited talk).
Wharton School Meeting on Genomics and Proteomics and Drug Discovery; University of Pennsylvania, 2000 (invited talk).
Ohio State University meeting on Drug Discovery; Columbus, Ohio, 2000 (invited talk).
New York Academy of Sciences meeting focused on the Promise of Proteomics; 2001 (invited talk).
Massachusetts Institute of Technology meeting on drug delivery and targeting; Cambridge, MA, 2002 (invited talk).

CME COURSES ATTENDED - none

PROFESSIONAL TRAINING PROGRAMS ATTENDED

1992 Executive Leadership Training Program
1994 Leadership Development Program, Center for Creative Leadership
1999 Harvard Business School Executive Leadership Development Program

1999 Leading Edge and Sharpening the Edge
2002 Johnson & Johnson Executive Leadership Training Program
2006 Stanford University Executive Leadership Training Program

GOVERNMENT and OTHER PROFESSIONAL SERVICE:

2007 – now National Institutes of Health Study Section Grant Reviewer

UNIVERSITY AND PUBLIC SERVICE

UNIVERSITY SERVICE

SYSTEMWIDE:

2002 – now University of California, Berkeley Member, Bioengineering Advisory Board

UCSF CAMPUS-WIDE: none

UNIVERSITY OF WASHINGTON:

2005 – 2008 University of Washington, Seattle Member, Corporate Advisory Board, School of Pharmacy and Graduate Program

DEPARTMENTAL SERVICE:

2007 – now Department of Neurology
Institute for Neurodegenerative Diseases
IND Leadership Strategic Planning Committee
IND Merit and Promotions Committee
Neurosciences Building and Planning Committee

PUBLIC SERVICE:

2007 – 2008 Mediator, Palo Alto Mediation Program, Palo Alto, CA.
2001 – 2003 Science Speaker, Madison Schools, Hopkins School, Branson School.
1993 – 2000 Coach/Manager youth sports (baseball, soccer); science speaker, Madison, CT.

TEACHING AND MENTORING

FORMAL SCHEDULED CLASSES FOR UCSF STUDENTS - none

FORMAL SCHEDULED CLASSES FOR UNIVERSITY OF WASHINGTON STUDENTS

1981 – 1983 Introductory and Advanced Pharmacokinetics and Physical Pharmacy to undergraduate and graduate students in the School of Pharmacy and School of Medicine

POSTGRADUATE AND OTHER COURSES: none

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED AT UNIVERSITY WASHINGTON

Dates	Name	Program or School	Role	Current Position
1981 – 1983	Sylvie Laganiere	Univ. Washington, Dept. Pharmaceutics	Ph.D. Advisor	Director OriGenix
1981 – 1983	Bradley Kerr	Univ. Washington, Dept. Pharmaceutics	Ph.D. Advisor	Vice President Anadys

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED AT UCSF: none

STAFF MENTORING

Dates	Name	Position	Role	Current Position
1983 – 1988	Alfred Tonelli	Ph.D. scientist	Mentor	Vice President, J & J
1983 – 1988	Helen Wu	Ph.D. scientist	Mentor	Retired
1983 – 1988	Wing Cheung	Ph.D. scientist	Mentor	Manager, J & J
1983 – 1988	Andrew Falkowski	Ph.D. scientist	Mentor	Manager
1983 – 1988	Deepak Vechlekar	M.S. scientist	Mentor	Scientist
1990 – 2002	Theodore Liston	Ph.D. scientist	Mentor	Vice President, Pfizer
1990 – 2002	Scott Obach	Ph.D. scientist	Mentor	Distinguished scientist, Pfizer
1990 – 2002	Deepak Dalvie	Ph.D. scientist	Mentor	Group Leader, Pfizer
1990 – 2002	Patrice Milos	Ph.D. scientist	Mentor	CSO, Helicos
1990 – 2002	Michael Potchoiba	M.S. scientist	Mentor	Scientist, Pfizer
1990 – 2002	Sara Jaw	Ph.D. scientist	Mentor	Manager, Theravance
1990 – 2002	Wesley Day	Ph.D. scientist	Mentor	Vice President, Vivus
1990 – 2002	Robert Polzer	Ph.D. scientist	Mentor	Vice President, Pfizer
1990 – 2002	Albert Seymour	Ph.D. scientist	Mentor	Director, Pfizer
1990 – 2002	Michael Lawton	Ph.D. scientist	Mentor	Senior Scientist, Pfizer
1990 – 2002	Renli Teng	Ph.D. scientist	Mentor	Scientist
2002 – 2005	Gary Eichenbaum	Ph.D. scientist	Mentor	Director, J & J
2002 – 2005	Deepti Jaggi	Pharm.D./MBA	Mentor	Business Manager, J & J
2002 – 2005	Lyndon Lien	Ph.D./MBA	Mentor	VP, Elan
2002 – 2005	Andrew Lam	Chemical Engineer	Mentor	Director
2002 – 2005	Atul Ayer	Ph.D./Engineer	Mentor	Retired
2002 – 2005	Jay Audett	Ph.D./Engineer	Mentor	Director, J & J
2002 – 2005	Aravind Mittur	Ph.D. scientist	Mentor	Supervisor, J & J
2005 – 2007	Stefan Platz	VP, Safety	Mentor	VP, Roche
2005 – 2007	Robert Ings	VP, DMPK	Mentor	Consultant
2005 – 2007	Mario Monshouwer	Director	Mentor	Director, Roche
2005 – 2007	Phil Worboys	Senior Director	Mentor	Senior Director, Roche
2005 – 2007	Matthew Cooper	Ph.D.	Mentor	Principal Scientist, Roche

		Toxicologist		
2005 – 2007	Kyle Kolaja	Director, Toxicology	Mentor	Director, Investigative Toxicology
2005 – 2007	Amy Zhou	M.S. scientist	Mentor	Scientist, Roche
2005 – 2007	Cam Greig	Vivarium Head	Mentor	Vivarium Head, Roche
2005 – 2007	Michaela Reddy	Ph.D. scientist	Mentor	Scientist, Roche
2005 – 2007	Michael Brandl	Director	Mentor	Director, Roche
2005 – 2007	Thomas Alfredson	Senior Director	Mentor	Senior Director, Roche
2005 – 2007	Surya Sankuratri	Ph.D. scientist	Mentor	Project Leader, Roche

POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED OR MENTORED AT UCSF

Dates	Name	Fellow	Faculty Role	Current Position
2008 – now	Kim Fife	Post-doc	Mentor	Post-Doc Researcher
2008 – 2009	Silvia Catharino	Post-Doc	Mentor	Post-Doc Researcher
2009 – now	Michal Geva	Post-Doc	Mentor	Post-Doc Researcher

INFORMAL TEACHING

- 2007 – now Weekly Lab Staff Presentations – critical presentation feedback and mentoring (Jan – Dec)
- 2007 – now Weekly Drug Discovery Reviews with 12 staff/Post-Doc/Adj. faculty (Jan – Dec)
- 2007 – now Monthly Drug Discovery reviews (Jan – Dec)

FACULTY MENTORING

FACULTY MENTORED:

- 2009 – now Joel Gever, Professional Researcher, Neurology
- 2009 – 2009 Brigitte Keon, Assistant Adjunct Professor of Neurology
- 2008 – 2009 Henry Lu, Associate Adjunct Professor of Neurology

OTHER VISITING FACULTY SUPERVISED: none

TEACHING AIDS: none

SUMMARY OF TEACHING HOURS:

- 2007 – 2008 Mentoring hours: 20 hours
- 2008 – 2009 Mentoring hours: 60 hours/year
- 2009 – 2010 Mentoring hours: 70 hours/year

ANTICIPATED TEACHING and MENTORING HOURS at UCSF

ANTICIPATED (2008-2009):	HOURS
Invited Lectures	5
Research Discussion	125
Journal Club	20
Research Presentations	30
Research Meetings	40
Mentoring	60
TOTAL:	280

RESEARCH AND CREATIVE ACTIVITIES**RESEARCH AWARDS AND GRANTS**CURRENT

1. P01 AG02132-26 (Prusiner PI; Silber Co-PI Science Core)	02/01/09 – 01/31/14
NIH/NIA	\$137,592 direct/ yr 1
Degenerative and Dementing Diseases of Aging	\$687,960 direct/ yrs 1 – 5

The Science Core exists to provide reagents and services to the various Projects and Cores of the Program Project, specifically it will provide: prion protein (PrP) purified from natural sources; production of anti-PrP antibodies, including human–mouse Fab fragments; development of novel anti-PrP antibodies; wild-type and mutant recombinant PrP; screening of transgenic and knockout mouse lines; quality control of novel transgenic mouse lines.

2. P01 AG021601-04 (Prusiner PI P01; Silber PI – Project 2)	04/01/09 – 3/31/14
NIH/NIA	\$231,447 direct/ yr 1
Novel Therapeutics for Prion Diseases	\$1,157,235 direct/ yrs 1 – 5

The specific aims of this project are to use high-throughput screening (HTS) to screen diverse chemical libraries containing approximately 250,000 compounds including all FDA approved drugs, support and drive SAR studies, in vitro druggability analyses and mouse pharmacokinetic studies, anti-prion bioassay in CJD-infected Tg mice, and iterative assays for anti-prion screening.

3. Alzheimer's Disease (Prusiner PI; Silber Co-PI)	01/01/09 – 01/01/16
Lincy Foundation	\$1,920,000 direct/ yr 1 committed
Novel Therapeutics for Alzheimer's Disease and other Neurodegenerative Disorders	\$13,440,000 over 7 years (projected)

We have developed a research program focused on developing effective medicines for the prevention and treatment of AD. To be successful, we have mounted a highly focused, multidisciplinary and superbly executed campaign. Our studies directed toward developing effective therapeutics for prion diseases will be performed concurrently and will guide development of therapeutics for AD. Our proposal builds upon decades of discovery and highly effective

collaboration among the investigators. We believe that the same principles used in finding a cure for Prion disease and AD will be equally applicable to developing effective treatments for other age dependent neurodegenerative disorders including Parkinson's disease.

4. Alzheimer's Disease (Prusiner PI; Silber Drug Discovery PI) 04/01/09 – 12/31/15
 McCabe Foundation \$960,000/ direct yr 1 committed
 McCabe Alzheimer's Disease Research Program \$6,720,000/ yrs 1 – 7 (projected)

This Research Program is focused on discovering and developing effective medicines for the prevention and treatment of Alzheimer's disease (AD). Fortunately, research over the past 20 years has created an important core of knowledge about the cause of AD, on which we have built a therapeutics research program. The Prion Research Program promises to complement and enhance the AD Program. Some of the initial strategies being used in the Prion Research Program such as developing cell-based assays of brain disease will be adapted to AD.

5. Neurodegenerative Diseases (Prusiner PI; Silber co-PI) 01/05/08 – 12/31/12
 Larry L. Hillblom Foundation Grant \$340,908 direct/ yr 2
 Cure CJD \$1,818,180 direct/yrs 1 - 5

This program will develop a website for physicians with patients suspected of having Creutzfeldt-Jakob disease to learn about the latest diagnostic and therapeutic advances in prion diseases, to develop a section of this website for physicians to report their cases of CJD to the Hillblom Network Program, to screen all FDA-approved drugs for anti-prion activity, and to evaluate FDA-approved drugs that show anti-prion activity in culture, or *in vitro*, for their ability to prolong prion incubation times in mice.

6. Neurodegenerative Diseases (Prusiner PI; Silber co-PI) 01/01/05 – 12/31/09
 Sherman Fairchild Foundation Grant \$608,850 direct/ yr
 Cure CJD and Neurodegenerative Diseases \$3,653,102 direct/ yrs 1 - 5

The goal of this program is to identify small molecule based drugs that can be given orally and that can reduce the formation of PrP^C, block the creation of PrP^{Sc} from PrP^C, safely remove or clear PrP^{Sc}, or achieve a combination of these effects. If a drug or chemical compound is found to be effective in the cell-based test, it is further tested in laboratory mice. Testing must first determine if the drug or chemical compound can penetrate the blood-brain-barrier to achieve and sustain therapeutic drug concentrations after an oral dose. The next step is to treat prion-infected mice with a drug or chemical compound, alone and in combination, to identify a drug or drug combination that cures mice. Ultimately, the goal is to demonstrate effectiveness of drugs in human clinical trials.

7. Discovering Drugs for FTD (Prusiner PI; Silber Co-PI) 10/01/09 – 9/30/10
 Private Family Foundation \$969,013 direct/ yr 1 (committed)
 \$4,845,065 direct/ yrs 1-5

We have a research program to discover drugs for the prevention, treatment, and cure of Frontotemporal Dementia (FTD). We will use three different approaches to discover drugs that will prevent the formation of Frontotemporal Dementia (FTD), slow down or halt FTD progression and severity, reverse or cure the disease in patients with FTD, or some combination of these effects. These approaches rely on critical findings that mutant or normal tau protein is necessary and

sufficient to facilitate the critical cascade that begins with the formation of normal or aberrant tau protein all the way to formation of pathologic fibrils and aggregates of hyperphosphorylated mutant or normal tau proteins. The first approach will search for and discover a drug, alone or in combination, that is already an FDA-approved drug for another (non-FTD) indication. In the second approach, we hypothesize that neuronal cells derived from patients with familial and sporadic FTD will have significantly different molecular signatures when compared with healthy age and sex-matched controls, as measured by gene and protein expression profiling. We expect that FTD patients will have molecular signatures, characteristic of the disease. The third approach will involve the development of animal models of FTD.

PENDING

1. Molecular Pathogenesis of Age-Dependent CNS Degeneration (Prusiner PI; Science Core B Co-PI Silber)	07/01/10 - 6/30/15
NIH/NIA	\$198,350 direct/yr 1 \$1,053,068 direct/ yrs 1-5

The program will continue our studies directed toward elucidating the molecular mechanisms responsible for neurodegeneration caused by prions. Toward achieving this goal, we plan to exploit our ability to generate distinct, synthetic prion strains in mammals and yeast. Bioluminescence imaging promises to accelerate many of our studies; indeed, it may be possible to shorten the incubation times in many of the experiments.

2. High End Instrument Grant (Prusiner PI; Silber Major User)	12/1/09 - 11/30/10
NIH/NIA	\$2,403,693 direct/yr 1

Integrated HTS System for Drug Discovery in Neurodegeneration

Given the current understanding of the mechanisms involved in AD, FTD, PD and in prion replication, several approaches to intervention will be exploited, but the validity of these approaches will need to be confirmed empirically. In order to increase our chances of success in identifying drug therapies, we will need to utilize multiple and diverse in vitro disease models and screen large compound sets across a broad panel of representative assays. Our program will implement the use of a fully integrated high throughput and high content robotic screening platform that contains all crucial experimental stations. It will efficiently perform experiments via state-of-the-art robotics and automation. We plan to perform large-scale assessment of compounds against multiple proposed targets for AD, FTD, PD, and CJD and to perform detailed and rapid characterization of promising compounds, generating large and comprehensive data sets early in the drug discovery program.

3. Shared Instrumentation Grant (Prusiner PI; Silber Major User)	04/01/10 – 03/31/11
NIH	\$370,500 direct/ yr 1

Imaging in Neurodegenerative Diseases Drug Discovery

Our goal is to discover and develop oral therapies to prevent, treat, and cure prion diseases, especially Creutzfeldt-Jakob disease (CJD), and other neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). We recently found that bioluminescence *in vivo* imaging in mice can be used as a surrogate marker for the measurement of prions. Our approach relies on activation of the glial fibrillary acidic protein (GFAP) gene in astrocytes of mice

expressing a firefly luciferase transgene, the expression of which is under control of the GFAP promoter.

4. Shared Instrumentation Grant 04/01/10 – 03/31/11
(Prusiner PI; Silber Major User) \$500,000 direct/ yr 1
 NIH
 AB SCIEX 5500 QTRAP SM System and its Role in Developing Novel Therapeutics
 for Neurodegenerative Diseases

The specific aims for the LC-MS System include (annually): development of high sensitivity bioanalytical assays in brain, plasma, and other tissues for up to 100 compounds; quantitation supporting pharmacokinetic profiling of at least 50 experimental drugs and their metabolites in ~15,000 plasma and brain samples; support of medicinal chemistry-driven lead optimization and clinical candidate selection; enable multiple reaction monitoring for the identification of peptides involved in CJD, AD, FTD, and PD; support pharmacodynamic studies in mouse bioassays; enable quantitative determination of physicochemical properties; development of formulations; evaluation of drug stability; enable drug delivery options; test computational models of PrP^C and PrP^{Sc} and permeability models across the blood-brain-barrier.

PAST

1. Cure CJD Prusiner (Prusiner PI; Silber Co-PI) 06/01/07 – 01/30/09
 Michael Homer Foundation \$3,000,000 direct/ yr 1
 \$4,397,186 direct/ yrs 1 – 2

In the past six months, with assistance from “The Fight for Mike” Foundation, the IND and Memory and Aging Center (MAC) initiated an aggressive multidisciplinary effort to translate what we have learned about prion disease into effective treatments. This was accomplished by screening a large number of small molecules by a cell-based test to identify potent antiprion compounds, optimizing the effectiveness and reducing the toxicity of ‘hits’ by chemically modifying the structure of the compound, analyzing the effectiveness of optimized compounds in infected mice, and assessing effectiveness in human clinical trials.

2. R01 – (co-Investigator) 1981 – 1983
 Wendell Nelson (PI) – University of Washington, Seattle ~\$150,000 direct/yr 1
 NIH ~\$450,000 direct/ yrs 1-3
 Stereoselective metabolism of beta-adrenergic blockers

3. R01 (PI) 1982 – 1983
 American Heart Association ~\$80,000 direct/yr 1
 Relationship between stereoselective disposition ~\$160,000 direct/ yrs 1-2
 and pharmacodynamics

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Method of Monitoring Neuroprotective Treatment, PC 11883, filed September 15, 2001.
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67. Milos, PM, Sachse, C, McElroy, S, Brockmoller, J, Lira, M, Bauer, S, Shah, A, Roots, I, Friedman, DL, Nelms, L, and Silber, BM: Predicting Cytochrome P4502D6 (CYP2D6) Phenotype in Humans from CYP2D6 Genotype: Implications for Drug Therapy, presented at the 99th Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, New Orleans, Louisiana, April 1, 1998.

68. Silber, BM: Emerging Role of Pharmacogenomics in Pharmaceutical R&D, presented at the BIO99 Meeting, Session on Use of Pharmacogenomics and Proteomics to Understand and Predict Drug Response and Disease Phenotypes, Seattle, WA, May 18, 1999.

69. Silber, BM: Biomarkers in Medicine: Safety, Therapeutics, and Outcome Responses, presented at the BIO2000 Meeting, Boston, Massachusetts, March 30, 2000.

RESEARCH PROGRAM

The following 5 publications have had significant impact on medical research and on drug discovery:

1. Potchoiba, MJ, Tensfeldt, TG, Nocerini, MR, and Silber, BM: A Novel Quantitative Method for Tracing the Biodistribution of Radiolabeled Drugs Using Whole Body Autoradiography and Storage Imaging Detection, *J Pharmacol Exp Ther.* 272:1-10, 1995.

I was the principal investigator for this research and I wrote a significant portion of this manuscript. This work became the seminal and definitive work that has become a benchmark for performing quantitative experiments to trace the tissue distribution of labeled drugs using whole body autoradiography and has been used widely in basic and applied medical research. This method links distribution over time to pharmacological and toxicological effects in animals in lieu of human studies. This method replaces x-rays and pinpoints localization of labeled material, determination of the composition of the label, and recovery of such material without its degradation.

2. Obach, RS, Baxter, JG, Liston, TE, Silber, BM, Jones, BC, MacIntyre, F, Rance, DJ, and Wastall, P: The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data, *J Pharmacol Exp Ther.* 283:46-58, 1997.

I was the principal investigator for this research. This research was and still is the definitive work that demonstrates that pharmacokinetic properties in humans can generally be predicted from preclinical experiments and forms the basis for preclinical data leading to lead optimization and candidate selection for entry of potential new medicines into human trials. This work is extensively cited still as the seminal publication.

3. Silber, BM: The Importance of Bio-Markers in Drug Discovery and Development – Focus on Alzheimer’s Disease, in Biomarkers and Surrogate Endpoints: Clinical Research and Applications, edited by G Downing, Elsevier Science, Excerpta Medica, International Congress Series 1205, Amsterdam, 2000.

I was responsible for research efforts at Pfizer focused on finding informative biomarkers of Alzheimer’s disease that were linked to patient status and could provide a signature of disease progression, severity, as well as new targets for drug discovery. I was responsible for establishing and implementing cutting edge proteomic technologies in order to identify protein biomarkers. The proteomic studies that I carried out with colleagues at NIH led to many discoveries and recently led to the development of diagnostics to identify at-risk individuals prior to clinical signs and symptoms. This pioneering work also led to the development of specific biochemical-based assays which are used today to assess the levels of beta amyloid and tau protein in the cerebrospinal fluid and serum.

4. Silber, BM: Pharmacogenomics, Biomarkers and the Promise of Personalized Medicine, in Pharmacogenetics, edited by Werner Kalow, Urs A Meyer, and Rachel Tyndale, Marcel Dekker, Inc., 2001, pp. 11-31.

I have been a pioneer and scientific leader in pharmaceutical R & D encouraging the use of biomarkers for the purpose of early decision-making as a way to make timely GO/NO GO decisions regarding potential new medicines. I have been a leader in the generation and integration of disparate genomic, genetic, proteomic, and metabolomic data and leveraging this data to enhance our understanding of drug effects and in decision-making.

5. McElroy, S, Sachse, C, Brockmoller, J, Richmond, J, Lira, M, Friedman, D, Roots, I, Silber, BM, and Milos, PM: CYP2D6 Genotyping as an Alternative to Phenotyping for Determination of Metabolic Status in a Clinical Trial Setting, AAPS PharmSci, 2(4) Article 33, 2000 (<http://www.pharmsci.org/>).

I led this key work that has culminated in the development of rapid methods to genotype and phenotype patients taking medicines that are substrates for CYP2D6, including development of chip-based diagnostics that have now been commercialized. This is a proven example of leveraging personalized medicine approaches to reduce the likelihood of serious adverse drug reactions.

CURRENT RESEARCH PROGRAM

My current research program is in support of the mission of the UCSF Institute for Neurodegenerative Diseases, focused on discovering new medicines for high unmet medical needs, including Alzheimer’s, Parkinson’s, Frontotemporal Dementia, and Prion diseases. In this regard, I am responsible for developing and implementing a strategy, operational plan, and laboratory experiments for all drug discovery-related activities in each disease. This includes but is not limited to delineating the therapeutic hypothesis underlying the discovery program, selection of druggable targets, development and implementation of biochemical, cell and bioassays assays for screening drugs/compounds, building suitable chemical libraries underlying drug screening efforts, medicinal chemistry and SAR, pharmacokinetics and drug metabolism, toxicology, pharmaceuticals and formulations and drug delivery, and early testing in the clinic in Phase I and II. I am responsible as a principal or co-principal investigator in support of IND program projects for developing strategies

and plans, writing NIH, foundation and donor grant proposals, direct and indirect supervision and leadership of laboratory activities, and fund-raising. Success in this research program depends on me leveraging my knowledge and experience in having participated in the discovery, development, or registration/approval of more than 23 medicines or drug-device products for human use. In this regard, I continue to be a leader in understanding the root cause of attrition in discovering and developing new medicines, in developing more successful approaches to reducing unwanted attrition, and increasing the probability of success in drug discovery R & D. My research plan includes specific efforts not only to develop therapeutics, but also be directly involved in several basic science efforts underlying our therapeutics programs. For example, I have developed and successfully implemented approaches in the pharmaceutical/biotechnology industry and continue to be a leader in this area. For example, I recently completed a major study at Roche developing principles and approaches for alternative drug development strategies dependent on the nature and confidence in the rationale and safety of the target. I developed an approach for small molecule medicines that is being implemented to significantly increase R & D productivity, as measured by the number and quality of drugs that make it to registration and launch. These approaches are directly applicable to what we will be doing at the IND. My results suggest that we could increase productivity (medicines making it to registration and approval) by up to 3-5 times current levels through better scientific and management decisions. Similarly, in biotechnology, I developed and implemented major strategic and operational changes to significantly reduce the time for monoclonal antibodies to go from primary seed/master cell bank to Phase I trials in healthy subjects or patients. In addition to my specific research plans at UCSF, I will continue these general approaches at the IND to safely speed evaluation of potentially important new medicines for the treatment of prion and other neurodegenerative diseases. As such, I am very interested in translational sciences and the importance of developing and using biomarkers of disease progression, severity, and in assessing important Pharmacodynamic responses (efficacy and safety). These biomarkers include genomic, genetic, proteomic, metabonomic, imaging and other improved biomarkers of safety based on preclinical *in vitro* and *in vitro* data that are predictive of human response. This requires significantly improved understanding of interspecies response to drugs at the cellular and molecular level. Inter-related to this area is my interest in applying modeling and simulation science to understanding Pharmacodynamic-pharmacokinetic relationships in the identification of suitable doses that maximize efficacy while minimizing safety issues. I am very interested in maximizing the utility of medicines that can be effective in various neurodegenerative diseases but are limited by their penetration into the brain. As such, I have strong interests in the use of prodrugs as well as targeted prodrugs that bind to transporters on the blood brain barrier and are more effectively transported into the brain and avoid efflux transport related to Pgp. In this regard, I am very interested in selective drug targeting and delivery to the brain, sparing high systemic concentrations, with their attendant potential for dose-limiting adverse effects.