David Borhani, Ph.D.

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Executive Summary

Discipline-bridging biopharmaceutical industry leader with 25 years of experience in small molecule and antibody drug discovery. Strengthened and protected 2 marketed and 2 clinical-stage drugs with strategic input and technical expertise: Humira® (adalimumab); Segard® (afelimomab); ABT-874 (briakinumab); and ABT-325. Led / co-led >10 small molecule, peptide, and monoclonal antibody drug discovery, formulation, and computational technology projects (5 therapeutic areas; immunology and oncology focus) to deliver 6 clinical candidates, 2 deployed computational tools, and 1 negotiated revenue-sharing external collaboration. Inventor, 10 granted patents; author, 50 publications; principal investigator, 5 grants and 2 contracts (NIH, AHA, WHO, BASF; >$1.3 million). Core expertise in structural biology and medicinal chemistry. Apply broad knowledge base and hands-on ability in advanced computer simulations and biology to create, inspire and lead projects, and to identify unseen opportunities. Advise on internal and external collaborative projects. Evaluate licensing opportunities.

Professional Experience

HaNativ, LLC Hartsdale, NY **2018–Present**
Founder

Drug discovery consulting. Strategic planning. Due diligence. Target and technology assessment. Project guidance, planning, and oversight. CRO selection and oversight. Medicinal and computational chemistry. Protein expression and purification. Assay development. Structural biology and biophysics.

D. E. Shaw Research (DESRES) New York, NY **2007–2017**
Chemist (equivalent to Senior Principal Scientist)

First experimental scientist recruited by a supercomputer-based start-up company to guide its entry into drug discovery. Align drug discovery & technology validation efforts with pharmaceutical industry practices. Propose, evaluate, and advise CEO on strategic opportunities and external alliances.

Drug Discovery Advisor	**Advisor on 15 internal and >10 external drug discovery projects.** Guided project teams in target selection, goal setting, experimental plans/design, screening funnel design, CRO selection, Go/No-Go decision making. Learned to be sensitive to client's needs and constraints.
First Pharma Collaboration Leader	**Forged peptide drug discovery project with Zealand Pharma.** Led successful pilot project. Negotiated revenue-sharing (milestones, royalties), multi-year extension. Joint steering committee representative; identified 20 targets, later triaged to 6 high-priority collaboration targets.
Allosteric Drug Designer	**Project Leader, collaboration with Relay Therapeutics.** Defined the allosteric modulation mechanism of an undrugged membrane target. Identified an allosteric, druggable binding site.
Pipeline Builder	Identified 15 targets. Made detailed assessment of medical need; disease/target link; competition; feasibility. **Validated new antibacterial target druggability; progressed to hit-finding.**
Technology Validator	Led 2 projects to validate replication of known drug/target interactions by molecular dynamics (MD) simulations. **Project yielded fast, knowledge-based hydrogen-bond scoring tool.**
Synergistic Collaborator	Enhanced the impact of colleagues' basic research MD simulations by integrating chemical and biological data and mechanistic reasoning. **Co-author on 12 high-profile publications.**

CRO Overseer	Scientific and managerial oversight of synthetic chemistry (4 CROs), crystallography/biophysics (3), cloning/protein production (2), enzymology (2), electrophysiology (3) projects.
Resourceful Leader	**Advanced projects in an FTE-constrained environment** by engaging colleagues, including those in other departments, with a passion for drug discovery. Celebrated their successes.

Abbott (AbbVie) Bioresearch Center Worcester, MA **2000–2007**
Group Leader (Chemistry Dept.) 2005–2007
Group Leader (Biochemistry Dept.) 2001–2005
BASF Bioresearch Corporation Worcester, MA 2000–2001
Group Leader (Biochemistry Dept.)

Provide structural biology support to small molecule & antibody drug discovery. Lead projects.

Founder	**Created Structural Biology group.** Oversaw lab design, construction, equipping, and staffing. Arranged CRO-based synchrotron access to augment Abbott's existing resources. Added computational chemistry and protein NMR to group in 2006. Twelve reports; five direct reports.
Organizational Leader	**Abbott Vice President's Award of Excellence, Dec. 2006, for outstanding contributions.** Co-led Chemistry Department, 12 months. Established senior management diversity training.
Project Creator	**Initiated and led to completion project on novel target.** Assay development, HTS, screening funnel, structural biology, pharmacological and genetic proof-of-concept. Target invalidated.
Collaborative Inventor	**Generated broad intellectual property position in a new research area,** crystalline monoclonal antibody (mAb) formulation (Abbott, Germany). **7 granted patents, 2 pending patents.**
Individual Contributor	25 projects including 3 small-molecule and 3 mAb development candidates. Kinase, mAb/antigen crystal structures; mAb epitope definition; MedChem strategy. 15+ licensing evaluations.

Southern Research Institute Birmingham, AL **1993–2000**

Initiate and lead externally financed, independent drug discovery programs.

Principal Investigator	**Conceived and directed 6 externally funded research projects (>$1.3 MM direct costs).** Set up academic, industrial, and US Govt. collaborations. Mentored 3 fellows and 2 students.
Scientific Pioneer	Determined **broadly influential first crystal structure of human apolipoprotein A-I** (HDL cholesterol). Revealed lipid binding mechanism for entire class of lipoproteins. **345 citations.**
Industrial Collaborator	BASF structural biology support: 4 projects, 2 therapeutic areas, 3 years. Impact example: Enabled scaffold hops by revealing an unknown rearrangement underlying confusing SAR. **1 granted patent.**

BioCryst Pharmaceuticals Birmingham, AL **1990–1993**

Initiate and lead drug discovery programs. Set up company's first independent laboratories.

Principal Investigator	**Earned NIH innovative research grant support (SBIR).** Initiated external collaboration with diabetic eye disease expert on structure-guided design of aldose reductase inhibitors.
Structural Biologist	Brought chemistry skills and insights to a biotech start-up. Solved crystal structures to support drug discovery projects. Led protein purification lab. Selected and maintained all equipment.

Selected Project Leadership

Project	Role	Outcome
Allosteric target (with Relay Therapeutics)	DESRES Leader	Completed. Allosteric mechanism of action defined, and druggable binding site identified.
Bacterial metabolic enzyme	Project Leader	Strategic termination, after allosteric site identification and validation through hit-finding.
Drug/target interactions	Project Leader	Completed. H-bond scoring tool delivered.
Metabolic targets (with Zealand Pharma)	DESRES Leader	Completed. Pilot program succeeded; follow-on contract negotiated; targets triaged, selected.
β-Secretase (with Amgen)	DESRES Leader	Completed. Successful technology evaluation.
Therapeutic antibody crystallization (Humira®, ABT-874, Segard®)	Co-Leader	Completed. Highly successful. Established broad intellectual property position in a new area.
Rip2 (inflammatory kinase)	Project Leader	Terminated. Target pharmacologically invalidated.
Inflammatory kinase	SB Leader	Strategic termination, after candidate selection.
Lck (kinase), cdc25 (phosphatase), and two other kinases (with BASF Bioresearch)	SB Leader	Strategic termination, after candidate selection on two projects.

Education

Harvard University **Postdoctoral Fellow, Structural Biology, 1986–1990**
Project: *Crystallization of the Human Transferrin Receptor* Advisor: Stephen C. Harrison
Howard Hughes Postdoctoral Fellowship 1987–1990

Massachusetts Institute of Technology **Ph.D., Organic Chemistry, 1986**
Thesis: *Reactions of Electron-Deficient Diazenes* Advisor: Frederick D. Greene
N.I.H. Pre-doctoral Trainee, Dept. of Chemistry 1984–1986

Massachusetts Institute of Technology **S.B., Chemistry, 1982**

Awards and Honors

Abbott Vice President's Award of Excellence, **Dec. 2006**
For outstanding contributions in co-leading Chemistry Dept. during prior 12 months

Merck Index Award **1982**
For Scholastic Excellence in Chemistry, M.I.T.

Appendix

David Borhani, Ph.D.

Patents, Publications, and Abstracts

Granted Patents

10. **US 8,940,873** **Crystalline anti-human IL-12 antibodies** **2015-01-27**
David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (AbbVie, Inc.) PCT Int. Appl. WO 2008/121,301 (Filed 2008-03-27, Publ. 2008-10-09). Priority: WO2008US4006A, filed 2008-03-27, U.S. Provisional Appl. No. 2007/920608P, filed 2007-03-29.

9. **US 8,772,458** **Crystalline anti-hTNFalpha antibodies** **2014-07-08**
Anette Koenigsdorfer, Stefan Gottschalk, Hans-Juergen Krause, Gerhard Winter, David W. Borhani, Wolfgang Fraunhofer. (AbbVie Biotechnology Ltd) PCT Int. Appl. WO 2008/057,240 (Filed 2007-10-25, Publ. 2008-05-15). Priority: U.S. Appl. US 2007/977677A, filed 2007-10-25, U.S. Provisional Appl. No. 2006/855104P, filed 2006-10-27.

8. **US 8,753,839** **Compositions and methods for crystallizing antibodies** **2014-06-17**
Wolfgang Fraunhofer, David W.Borhani, Gerhard Winter, Stefan Gottschalk. (AbbVie Inc.) PCT Int. Appl. WO 2009/020,654 (Filed 2008-08-08, Publ. 2009-02-12). Priority: U.S. Provisional Appl. No. 2007/963964P, filed 2007-08-08.

7. **US 8,436,149** **Crystalline anti-hTNFalpha antibodies** **2013-05-07**
David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (AbbVie Biotechnology Ltd) PCT Int. Appl. WO 2008/057,240 (Filed 2007-10-25, Publ. 2008-05-15). Priority: U.S. Appl. US 2007/977677A, filed 2007-10-25, U.S. Provisional Appl. No. 2006/855104P, filed 2006-10-27.

6. **US 8,404,819** **Crystalline anti-human IL-12 antibodies** **2013-03-26**
David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (Abbott Laboratories) PCT Int. Appl. WO 2008/121,301 (Filed 2008-03-27, Publ. 2008-10-09). Priority: WO2008US4006A, filed 2008-03-27, U.S. Provisional Appl. No. 2007/920608P, filed 2007-03-29.

5. **US 8,168,760** **Crystalline anti-human IL-12 antibodies** **2012-05-01**
David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (Abbott Laboratories) PCT Int. Appl. WO 2008/121,301 (Filed 2008-03-27, Publ. 2008-10-09). Priority: WO2008US4006A, filed 2008-03-27, U.S. Provisional Appl. No. 2007/920608P, filed 2007-03-29.

4. **US 8,034,906** **Crystalline anti-hTNFalpha antibodies** **2011-10-11**
David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (Abbott Biotechnology Ltd.) PCT Int. Appl. WO 2008/057,240 (Filed 25-10-2007, Publ. 15-05-2008). Priority: U.S. Appl. US 2007/977677A, filed 25-10-2007, U.S. Provisional Appl. No. 2006/855104P, filed 27-10-2006.

3. **US 8,008,481** **Indazole compounds** **2011-08-30**
Anna M. Ericsson, Andrew Burchat, Kristine E. Frank, David J. Calderwood, Lily K. Abbott, Maria A. Argiriadi, David W. Borhani, Kevin P. Cusack, Richard W. Dixon, Thomas D. Gordon, Kelly D. Mullen, Robert V. Talanian, Xiaoyun Wu, Xiaolei Zhang, Lu Wang, Biqin Li, Claude E. Barberis, Neil Wishart. (Abbott Laboratories, Inc.) PCT Int. Appl. WO 2007/117,465 (Filed 2007-04-02, Publ. 2007-10-18); US Appl. US 2007/0282101A1 (Filed as US2007/731950A, 2007-04-02, Publ. 2007-12-06). Priority: US 2006/788553P, filed 2006-03-31.

2. **US 7,790,741** **Imidazothiazoles and imidazoxazoles** **2010-09-07**
David J. Calderwood, Kristine E. Frank, David W. Borhani, Heather M. Davis, Nathan S. Josephsohn, Barbara S. Skinner. (Abbott Laboratories, Inc.) PCT Int. Appl. WO 2008/063,287 (Filed 2007-10-05, Publ. 2008-05-29); US Appl. US 2008 0161341 A1 (Filed as US2007973147A, 2007-10-05, Publ. 2008-07-03). Priority: US 2007/973147A, 2007-10-05, U.S. Provisional Appl. No. 60/849,873, filed 2006-10-06.

1. **US 7,400,979** **Method of identifying inhibitors of Lck** **2008-07-15**
David W. Borhani, David Calderwood, Richard W. Dixon, Gavin C. Hirst, Peter Hrnciar, Andreas Loew, Adelaine Leung, Kurt Ritter. (Abbott Laboratories, Inc.) PCT Int. Appl. WO 2003/020,880 (Filed 2002-08-02, Publ. 2003-03-13); US Appl. US 2002 10/212,346 A (Filed 2002-08-05, Publ. 2003-09-18). Priority: U.S. Provisional Appl. No. 60/310,051, filed 2001-08-03.

Patent Applications

10. **Methods for screening voltage gated proteins.** Morten Ø. Jensen, David W. Borhani, Vishwanath Jogini. (D. E. Shaw Research, LLC) U.S. Appl. US 2017/0115309 (Filed 2016-10-17, Publ. 2017-04-27). Priority: U.S. Provisional Appl. No. 61/604,897, filed 2012-02-29.

9. **Crystalline anti-hTNFalpha antibodies.** David W. Borhani, Wolfgang Fraunhofer, Hans-Juergen Krause, Anette Koenigsdorfer, Gerhard Winter, Stefan Gottschalk. (AbbVie Biotechnology Ltd) U.S. Appl. US 2015/0183863 (Filed 2014-06-19, Publ. 2015-07-02). Priority: U.S. Provisional Appl. No. 60/855,104, filed 2006-10-27.

8. **Compositions and Methods for Crystallizing Antibodies.** Wolfgang Fraunhofer, David W. Borhani, Gerhard Winter, Stefan Gottschalk. (AbbVie, Inc.) U.S. Appl. US 2015/0166648 (Filed 2014-06-05, Publ. 2015-06-08). Priority: U.S. Provisional Appl. No. 60/963,964, filed 2007-08-08.

7. **Methods and compounds for modulating proteins.** David W. Borhani, *et al.* (D. E. Shaw Research, LLC) US Provisional application, filed 2013-01-08. Abandoned.

6. **Methods for screening voltage gated proteins.** Morten Ø. Jensen, David W. Borhani, Vishwanath Jogini. (D. E. Shaw Research, LLC) PCT Int. Appl. WO 2013/130,808 (Filed 2013-02-28, Publ. 2013-09-06). Priority: U.S. Provisional Appl. No. 61/604,897, filed 2012-02-29.

5. **Anti-IL-12/IL-23 antibodies and uses thereof.** David W. Borhani, Ramkrishnam Sadhukhan, Susan E. Lacy, Holly H. Soutter. (Abbott Laboratories, Inc.) PCT Int. Appl. WO 2012/094,623 (Filed 2012-01-06, Publ. 2012-07-12). Priority: U.S. Provisional Appl. No. 61/460,780, filed 2011-01-07.

4. **Compositions and methods for crystallizing antibody fragments.** Maria A. Argiriadi, David W. Borhani, Tao Xiang, Chengbin Wu, Tariq Ghayur. (Abbott Laboratories, Inc.) PCT Int. Appl. WO 2009/099,545 (Filed 2009-01-29, Publ. 2009-08-13). Priority: U.S. Provisional Appl. No. 62887P, filed 2008-01-30.

3. **Method of identifying inhibitors of Cdc25.** Neil R. Taylor, David Borhani, David Epstein, Johannes Rudolph, Kurt Ritter, Taro Fujimori, Simon Robinson, Jens Eckstein, Andreas Haupt, Nigel Walker, Richard W. Dixon, Deborah Choquette, Jill Blanchard, Arthur Kluge, Kollol Pal, Nicholas Bockovich, Jon Come, Mark Hediger. (BASF Aktiengesellschaft & GPC Biotech, Inc.) PCT Int. Appl. WO 02/070,680 (Filed 2001-03-01, Publ. 2002-09-12); US Appl. US 2002/0183249 A1 (Filed 2001-03-01, Publ. 2002-12-05).

2. **Hydroxysulfonylalkylene-, phosphonoalkylene- or difluoro(phosphononon)methyl- substituted benzene, or benzofuran derivatives as non-peptidic Cdc25 inhibitors.** Neil R. Taylor, David Borhani, David Epstein, Johannes Rudolph, Kurt Ritter, Taro Fujimori, Simon Robinson, Jens Eckstein, Andreas Haupt, Nigel Walker, Richard W. Dixon, Deborah Choquette, Jill Blanchard, Arthur Kluge, Kollol Pal, Nicholas Bockovich, Jon Come, Mark Hediger. (BASF Aktiengesellschaft) PCT Int. Appl. WO 01/027,077 (Filed 2000-10-04, Publ. 2001-04-19).

1. **Method of identifying inhibitors of Cdc25.** Neil R. Taylor, David Borhani, David Epstein, Johannes Rudolph, Kurt Ritter, Taro Fujimori, Simon Robinson, Jens Eckstein, Andreas Haupt, Nigel Walker, Richard W. Dixon, Deborah Choquette, Jill Blanchard, Arthur Kluge, Kollol Pal, Nicholas Bockovich, Jon Come, Mark Hediger. (BASF Aktiengesellschaft) PCT Int. Appl. WO 01/016,300 (Filed 2000-08-25, Publ. 2001-03-08).

Peer-Reviewed Publications

50. **Structural Basis for Nucleotide Exchange in Heterotrimeric G Proteins.** Ron O. Dror, Thomas J. Mildorf, Daniel Hilger, Aashish Manglik, **David W. Borhani**, Daniel H. Arlow, Ansgar Philippsen, Nicolas Villanueva, Zhongyu Yang, Michael T. Lerch, Wayne L. Hubbell, Brian K. Kobilka, Roger K. Sunahara, and David E. Shaw. *Science* (2015) **348**:1361–1365. DOI: 10.1126/science.aaa5264

49. **Structural basis for modulation of a G-protein-coupled receptor by allosteric drugs.** Ron O. Dror*, Hillary F. Green*, Celine Valant*, **David W. Borhani***, James R. Valcourt, Albert C. Pan, Daniel H. Arlow, Meritxell Canals, J. Robert Lane, Raphaël Rahmani, Jonathan B. Baell, Patrick M. Sexton, Arthur Christopoulos, and David E. Shaw. *Nature* (2013) **503**:295–299. (*These authors contributed equally to this work.) DOI: 10.1038/nature12595

48. **Molecular determinants of drug–receptor binding kinetics.** Albert C. Pan, **David W. Borhani**, Ron O. Dror, and David E. Shaw. *Drug Discov. Today* (2013) **18**:667–673. (Invited, peer-reviewed review) DOI: 10.1016/j.drudis.2013.02.007

47. **Enabling structure-based drug design of Tyk2 through co-crystallization with a stabilizing aminoindazole inhibitor.** Maria A. Argiriadi, Eric R. Goedken, David Banach, **David W. Borhani**, Andrew Burchat, Richard W. Dixon, Doug Marcotte, Gary Overmeyer, Valerie Pivorunas, Ramkrishna Sadhukhan, Silvino Sousa, Nigel St. J. Moore, Medha Tomlinson, Jeffrey Voss, Lu Wang, Neil Wishart, Kevin Woller and Robert V. Talanian. *BMC Struct. Biol.* (2012) **12**:22. DOI: 10.1186/1472-6807-12-22

46. **Mechanism of Voltage Gating in K^+ Channels.** Morten Ø. Jensen, Vishwanath Jogini, **David W. Borhani**, Abba Leffler, Ron O. Dror, and David E. Shaw. *Science* (2012) **336**:229–233. DOI: 10.1126/science.1216533

45. **The future of molecular dynamics in drug discovery. David W. Borhani** and David E. Shaw. *J. Comput. Aided Mol. Des.* (2012) **26**:15–26. (Invited, peer-reviewed Perspective) DOI: 10.1007/s10822-011-9517-y

44. **Activation mechanism of the β_2-adrenergic receptor.** Ron O. Dror, Daniel H. Arlow, Paul Maragakis, Albert C. Pan, Thomas J. Mildorf, Xuafeng Xu, **David W. Borhani**, and David E. Shaw. *Proc. Natl. Acad. Sci. USA* (2011) **108**:18684–18689. DOI: 10.1073/pnas.1110499108

43. **Pathway and mechanism of drug binding to G-protein-coupled receptors.** Ron O. Dror, Albert C. Pan, Daniel H. Arlow, **David W. Borhani**, Paul Maragakis, Yibing Shan, Xuafeng Xu, and David E. Shaw. *Proc. Natl. Acad. Sci. USA* (2011) **108**:13118–13123. DOI: 10.1073/pnas.1104614108

42. **Comment on "A bacterium that can grow by using arsenic instead of phosphorus." David Borhani**. *Science* (2011) **332**:1149 (Technical Comment: http://www.sciencemag.org/content/332/6034/1149.5.full). DOI: 10.1126/science.1201255

41. **Rational Mutagenesis to Support Structure-Based Drug Design: MAPKAP Kinase 2 as a Case Study.** Maria A. Argiriadi, Silvino Sousa, David Banach, Douglas Marcotte, Tao Xiang, Medha J. Tomlinson, Megan Demers, Christopher Harris, Silvia Kwak, Jennifer Hardman, Margaret Pietras, Lisa Quinn, Jennifer DiMauro, Baofu Ni, John Mankovich, **David W. Borhani**, Robert V. Talanian, and Ramkrishna Sadhukhan. *Dyes and Drugs: New Uses and Implications* (2011) Ch. 23, pp. 308–331 (Trimm, H.H.; Hunter, W., Jr, Eds.; Apple Academic Press). DOI: 10.1201/b13128-24

40. **Discovery and Characterization of Non-ATP Site Inhibitors of the Mitogen Activated Protein (MAP) Kinases.** Kenneth M. Comess, Chaohong Sun, Cele Abad-Zapatero, Eric R. Goedken, Rebecca J. Gum, **David W. Borhani**, Maria Argiriadi, Duncan R. Groebe, Yong Jia, Jill E. Clampit, Deanna L. Haasch, Harriet T. Smith, Sanyi Wang, Danying Song, Michael L. Coen, Timothy E. Cloutier, Hua Tang, Xueheng Cheng, Christopher Quinn, Bo Liu, Zhili Xin, Gang Liu, Elizabeth H. Fry, Vincent Stoll, Teresa I. Ng, David Banach, Doug Marcotte, David J. Burns, David J. Calderwood, and Philip J. Hajduk. *ACS Chem. Biol.* (2011) **6**:234–244. DOI: 10.1021/cb1002619

39. **Exploring atomic resolution physiology on a femtosecond to millisecond timescale using molecular dynamics simulations.** Ron O. Dror, Morten Ø. Jensen, **David W. Borhani**, and David E. Shaw. *J. Gen. Physiol.* (2010) **135**:555–562. (Invited, peer-reviewed review) DOI: 10.1085/jgp.200910373

38. **Reply to Domene and Furini: Distinguishing knock-on and vacancy diffusion mechanisms.** Morten Ø. Jensen, **David W. Borhani**, Kresten Lindorff-Larsen, Ron O. Dror, and David E. Shaw. *Proc. Natl. Acad. Sci. USA* (2010) **107**:E129 (Online letter: http://www.pnas.org/content/107/33/E129). DOI: 10.1073/pnas.1008197107

37. **Principles of Conduction and Hydrophobic Gating in K^+ Channels.** Morten Ø. Jensen, **David W. Borhani**, Kresten Lindorff-Larsen, Paul Maragakis, Vishwanath Jogini, Michael P. Eastwood, Ron O. Dror, and David E. Shaw. *Proc. Natl. Acad. Sci. USA* (2010) **107**:5833–5838. DOI: 10.1073/pnas.0911691107

36. **2,4-Diaminopyrimidine MK2 Inhibitors. Part II: Structure-Based Inhibitor Optimization.** Christopher M. Harris, Anna M. Ericsson, Maria A. Argiriadi, **David W. Borhani**, Andrew Burchat, David J. Calderwood, George A. Cunha, Richard W. Dixon, Kristine E. Frank, Eric F. Johnson, Joanne Kamens, Silvia Kwak, Biqin Li, Kelly D. Mullen, Denise C. Perron, Lu Wang, Neil Wishart, Xiaoyun Wu, Xiaolei Zhang, Tami R. Zmetra, and Robert V. Talanian. *Bioorg. Med. Chem. Lett.* (2010) **20**:334–337. DOI: 10.1016/j.bmcl.2009.10.103

35. **2,4-Diaminopyrimidine MK2 Inhibitors. Part I: Observation of an Unexpected Inhibitor Binding Mode.** Maria A. Argiriadi, Anna M. Ericsson, Christopher M. Harris, David L. Banach, **David W. Borhani**, David J. Calderwood, Megan D. Demers, Jennifer DiMauro, Richard W. Dixon, Jennifer Hardman, Silvia Kwak, Biqin Li, John A. Mankovich, Douglas Marcotte, Kelly D. Mullen, Baofu Ni, M. Pietras, Ramkrishna Sadhukhan, Silvino Sousa, Medha J. Tomlinson, Lu Wang, Tao Xiang, and Robert V. Talanian. *Bioorg. Med. Chem. Lett.* (2010) **20**:330–333. DOI: 10.1016/j.bmcl.2009.10.102

34. **Unusual Water-Mediated Antigenic Recognition of the Pro-Inflammatory Cytokine Interleukin-18.** Maria A. Argiriadi, Tao Xiang, Chengbin Wu, Tariq Ghayur, and **David W. Borhani**. *J. Biol. Chem.* (2009) **284**:24478–24489. DOI: 10.1074/jbc.M109.023887

33. **Identification of Two Distinct Inactive Conformations of the β_2-Adrenergic Receptor Reconciles Structural and Biochemical Observations.** Ron O. Dror, Daniel H. Arlow, **David W. Borhani**, Morten Ø. Jensen, Stefano Piana, and David E. Shaw. *Proc. Natl. Acad. Sci. USA.* **(**2009) **106**:4689–4694. DOI: 10.1073/pnas.0811065106

32. **Rational Mutagenesis to Support Structure-Based Drug Design: MAPKAP Kinase 2 as a Case Study.** Maria A. Argiriadi, Silvino Sousa, David Banach, Douglas Marcotte, Tao Xiang, Medha J. Tomlinson, Megan Demers, Christopher Harris, Silvia Kwak, Jennifer Hardman, Margaret Pietras, Lisa Quinn, Jennifer DiMauro, Baofu Ni, John Mankovich, **David W. Borhani**, Robert V. Talanian, and Ramkrishna Sadhukhan. *BMC Struct. Biol.* (2009) **9**:16. DOI: 10.1186/1472-6807-9-16

31. **A Scalable Parallel Framework for Analyzing Terascale Molecular Dynamics Trajectories.** Tiankai Tu, Charles A. Rendleman, **David W. Borhani**, Ron O. Dror, Justin Gullingsrud, Morten Ø. Jensen, John L. Klepeis, Paul Maragakis, Patrick Miller, Kate A. Stafford, and David E. Shaw. Accepted for presentation at *SC08, The International Conference for High Performance Computing, Networking, Storage and Analysis*, 15 Nov. 2008, Austin, TX. DOI: 10.1109/SC.2008.5214715

30. **Dynamic Control of Slow Water Transport by Aquaporin 0: Implications for Hydration and Junction Stability in the Eye Lens.** Morten Ø. Jensen, Ron O. Dror, Huafeng Xu, **David W. Borhani**, Isaiah T. Arkin, Michael P. Eastwood, and David E. Shaw. *Proc. Natl. Acad. Sci. USA*. (2008) **105**:14430–14435. DOI: 10.1073/pnas.0802401105

29. **Novel Boron-Containing, Nonclassical Antifolates: Synthesis and Preliminary Biological and Structural Evaluation.** Robert C. Reynolds, Shiela R. Campbell, Ralph G. Fairchild, Roy L. Kisliuk, Peggy L. Micca, Sherry F. Queener, James M. Riordan, W. David Sedwick, William R. Waud, William J. Suling, Adelaine K.W. Leung, Richard W. Dixon, and **David W. Borhani**. *J. Med. Chem.* (2007) **50**:3283–3289. DOI: 10.1021/jm0701977

28. **Discovery of A-770041, a Src-Family Selective Orally Active Lck Inhibitor That Prevents Organ Allograft Rejection.** Andrew Burchat, **David W. Borhani**, David J. Calderwood, Gavin C. Hirst, Biqin Li, and Robert F. Stachlewitz. *Bioorg. Med. Chem. Lett.* (2006) **16**:118–122. *BMCL Most Cited Paper 2006–2009 Award*. DOI: 10.1016/j.bmcl.2005.09.039

27. **Polymerization of *C*-Terminally Truncated *Mycobacterium tuberculosis* FtsZ Is Unlikely to be Physiologically Relevant.** *Microbiology* (2004) **150**:3903–3906. **David W. Borhani** and E. Lucile White. DOI: 10.1099/mic.0.27528-0

26. **Structure of *Mycobacterium tuberculosis* FtsZ Reveals Unexpected, G Protein-Like Conformational Switches.** Adelaine K.W. Leung, E. Lucile White, Larry J. Ross, Robert C. Reynolds, Joseph A. DeVito, and **David W. Borhani**. *J. Mol. Biol.* (2004) **342**:953–970. DOI: 10.1016/j.jmb.2004.07.061

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2. **Application of Molecular Dynamics Simulations to Understanding β-Secretase Dynamics. David W. Borhani**, Alan Cheng, Andrew Kalenkiewicz, Doug Whittington, Morten Ø. Jensen, and David E. Shaw.

1. **Molecular Dynamics Simulations Provide Novel, Potent Activators of a Cardio-Metabolic Receptor. David W. Borhani**, Jesper Mathiesen, Miklos Feher, and David E. Shaw.

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36. Ron O. Dror*, Hillary F. Green*, Celine Valant*, David W. Borhani*, James R. Valcourt, Albert C. Pan, Daniel H. Arlow, Meritxell Canals, J. Robert Lane, Raphaël Rahmani, Jonathan B. Baell, Patrick M. Sexton, Arthur Christopoulos, and David E. Shaw. "Towards the structural basis for allosteric modulation of muscarinic GPCRs." Biophysical Society 58th Annual Meeting, San Francisco, CA, Feb. 2014. *Biophys J.* **2014**, *106*(2), S1, 100a. DOI: 10.1016/j.bpj.2013.11.626

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David Borhani, Ph.D.

Deposited Structural Coordinates and Additional Information

Deposited Structural Coordinates

	PDB ID	Structure
32	4E20	Mouse Tyk-2 • *N*-[4-(3-amino-2*H*-indazol-5-yl)phenyl]-3-methylbenzenesulfonamide
31	4E1Z	Mouse Tyk-2 • *N*-[5-(4-{[(3-methylphenyl)sulfonyl]amino}phenyl)-2*H*-indazol-3-yl]furan-2-carboxamide
30	3O17	Crystal Structure of JNK1-alpha1 isoform
29	3O2M	Crystal Structure of JNK1-alpha1 isoform complex with a biaryl tetrazol, *N*-butyl-4,6-dimethyl-*N*-{[2'-(*2H*-tetrazol-5-yl)biphenyl-4-yl]methyl}pyrimidin-2-amine (A-82118)
28	3NEW	Human p38α • 4-(trifluoromethyl)-3-[3-(trifluoromethyl)phenyl]-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (Compound 10)
27	3KC3	Human MAPKAP kinase 2 • N4-(7-(benzofuran-2-yl)-1*H*-indazol-5-yl)pyrimidine-2,4-diamine
26	3KA0	Human MAPKAP kinase 2 • inhibitor 6-(5-(2-aminopyrimidin-4-ylamino)-2-hydroxyphenyl)-*N*-methylbenzo[*b*]thiophene-2-carboxamide
25	2W3W	*Mycobacterium avium* dihydrofolate reductase • NADPH • 6-((2,5-diethoxyphenyl)aminomethyl)-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine (SRI-8686)
24	2W3V	*Mycobacterium avium* dihydrofolate reductase • NADPH • trimethoprim
23	2W3M	Human dihydrofolate reductase • NADPH • folate
22	2W3B	Human dihydrofolate reductase • NADPH • 6-((2,5-diethoxyphenyl)aminomethyl)-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine (SRI-8686)
21	2W3A	Human dihydrofolate reductase • NADPH • trimethoprim
20	2VXV	Human IgG ABT-325 Fab fragment
19	2VXU	Murine reference antibody 125-2H Fab fragment
18	2VXT	Human IL-18 • murine reference antibody 125-2H Fab fragment
17	2C2T	Human dihydrofolate reductase • NADPH • 2,4-diamino-5-[(7,8-dicarbaundecaboran-7-yl) methyl]-6-methylpyrimidine
16	2C2S	Human dihydrofolate reductase • NADPH • 2,4-diamino-5-(1-*O*-carboranylmethyl)-6-methyl-pyrimidine
15	2C0T	Src family kinase Hck • A-641359, *N*-(4-{4-amino-1-[1-(tetrahydro-*2H*-pyran-4-yl)piperidin-4-yl]-*1H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-*1H*-indole-2-carboxamide
14	2C0O	Src family kinase Hck • A-770041, *N*-(4-{1-[4-(4-acetylpiperazin-1-yl)-*trans*-cyclohexyl]-4-amino-*1H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-*1H*-indole-2-carboxamide
13	2C0I	Src family kinase Hck • A-420983, *N*-(4-{4-amino-1-[4-(4-methylpiperazin-1-yl)-*trans*-cyclo-hexyl]-*1H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-*1H*-indole-2-carboxamide
12	1RQ7	*Mycobacterium tuberculosis* FtsZ • GDP
11	1RQ2	*Mycobacterium tuberculosis* FtsZ • citrate
10	1RLU	*Mycobacterium tuberculosis* FtsZ • GTPγS
9	1QK5	*Toxoplasma gondii* hypoxanthine-guanine phosphoribosyltransferase • XMP • pyrophosphate • $(Mg^{2+})_2$
8	1QK4	*Toxoplasma gondii* hypoxanthine-guanine phosphoribosyltransferase • IMP
7	1QK3	*Toxoplasma gondii* hypoxanthine-guanine phosphoribosyltransferase • GMP
6	1KMV	Human dihydrofolate reductase • NADPH • (*Z*)-6-(2-[2,5-dimethoxyphenyl]ethen-1-yl)-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine (SRI-9662), a lipophilic antifolate

	PDB ID	Structure
5	1KMS	Human dihydrofolate reductase • NADPH • 6-([5-quinolylamino]methyl)-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine (SRI-9439), a lipophilic antifolate
4	1FSG	*Toxoplasma gondii* hypoxanthine-guanine phosphoribosyltransferase • 9-deazaguanine • α-D-5-phosphoribosyl-1-pyrophosphate (PRPP) • $(Mg^{2+})_2$
3	1CX8	Human transferrin receptor ectodomain
2	1AV1	Human apolipoprotein A-I
1	1ABN	Human aldose reductase • NADPH

Invited Lectures

Invited Lecturer	National Institute of Standards & Technology, Center for Advanced Research in Biotechnology, Univ. of Maryland Biotech Institute, Rockville, MD	Nov. 2009
Invited Lecturer	Protein Kinases Targets—Drug Discovery and Design, Boston, MA	Jun. 2009
Discussion Leader	Protein Kinases Targets—Drug Discovery and Design, Boston, MA	Jun. 2009
Speaker	New York Structural Biology Group 4th Winter Meeting, New York, NY	Jan. 2009
Invited Lecturer	Protein Kinases in Drug Discovery, Boston, MA	Jun. 2007
Invited Lecturer	Albert Einstein College of Medicine, Bronx, NY	Mar. 2000
Invited Lecturer	Southeast Regional Lipid Conf., Lake Lanier Islands, GA	Sep. 1998
Invited Lecturer	Deuel Lipoprotein Conference, Monterey, CA	Mar. 1998
Invited Lecturer	Center for Macromolecular Crystallography, Univ. of Alabama Birmingham	Dec. 1997
Invited Lecturer	Dept. of Neurobiology, Univ. of Alabama Birmingham	Nov. 1997

Professional Training

D001x: Medicinal Chemistry	edX/Davidson University	Dec. 2014
2.01x: Elements of Structures	edX/MITx	Jul. 2013
Building a High-Performance Organization	The Lambton Group	Dec. 2005
Supervisory Training Program	Abbott Bioresearch Center	Oct. 2003
Human Interaction Laboratory	NTL Institute	Sep. 2003
Working Through Conflict	Development Dimensions Int'l	Sep. 2003
Facilitating Improved Performance: Interaction Skills for Success	DDI	May 2002
Partnerships: Creating Synergy	DDI	Aug. 2001
Targeted Selection	DDI	Oct. 2000

Reviewer Service

Journals

Acta Crystallographica D
Acta Crystallographica F (Review Panel member)
Archives of Biochemistry & Biophysics
Biochemistry
Biochimica Biophysica Acta
Biophysical Journal
Journal of Biological Chemistry
Journal of Medicinal Chemistry
Journal of Molecular Biology
Medicinal Chemistry Research
Nucleosides and Nucleotides
Science
The Open Diabetes Journal

Graduate Theses

The University of Cape Town, South Africa

Grants

Univ. of Alabama at Birmingham, Comprehensive Cancer Center

Professional Affiliations

American Association for the Advancement of Science • American Chemical Society (Medicinal Chemistry & Organic Chemistry Divisions) • American Crystallographic Association • New York Academy of Sciences • Sigma Xi

David Borhani, Ph.D.

Academic Research Summary

Academic Research Program Summary (1993–2000)

1. Human Apolipoprotein A-I **(American Heart Association Established Investigator Award, 974008N; David W. Borhani, P.I.)**

In a three-way collaboration with Profs. Christie G. Brouillette and Jeffrey A. Engler (Univ. of Alabama at Birmingham), I crystallized a truncation mutant of apo A-I (apo Δ(1–43)A-I) and determined its structure at 4-Å resolution. This novel and unusual structure revealed that apo A-I consists almost entirely of a pseudo-continuous, amphipathic α-helix punctuated by kinks at regularly-spaced proline residues; it adopts a shape similar to a horseshoe of dimensions 125 × 80 × 40 Å. Based on this structure, we proposed a model for the structure of apo A-I bound to high density lipoprotein (HDL) particles. The apo Δ(1–43)A-I crystal structure was broadly influential. It led to a flood of new experimental approaches by laboratories worldwide to test and ultimately provide strong biochemical and biophysical support for our crystal structure-based model.

2. *Toxoplasma gondii* Hypoxanthine-Guanine Phosphoribosyltransferase **(NIH R01 AI-39952; David W. Borhani, P.I.)**

HGPRT is a key enzyme that controls the purine salvage pathway in *T. gondii*, the etiologic agent responsible for toxoplasmic encephalitis in AIDS patients. Inhibition of this pathway is a well-recognized drug design goal for the treatment of protozoal infections such as toxoplasmosis and malaria. In collaboration with Lucile White at Southern Research Institute (SRI), we determined >15 *T. gondii* HGPRT crystal structures, including the enzyme complexed to 9-deazaguanine and PRPP (bi-substrate complex) at 1.05-Å resolution, XMP and pyrophosphate (bi-product complex; D150A active site mutant; 1.6 Å), GMP (1.6 Å), IMP (1.8 Å), XMP (2.2 Å), and a *T. gondii*/human chimera complexed to GMP (2.3 Å). We formulated structural hypotheses on how *T. gondii* HGPRT, unlike human HGPRT, is able to utilize xanthine. We tested these hypotheses by the construction and characterization (enzymology and crystallography) of specific *T. gondii* HGPRT mutants and human–*T. gondii* HGPRT chimeras. Enzymatic assays indicated successful humanization of one chimera.

3. *Pneumocystis carinii* and Human Dihydrofolate Reductases **(NIH R01 AI-38706; James R. Piper, P.I.)**

Lipophilic antifolates widely used to treat pneumocystis pneumonia in AIDS patients are not potent or selective enough for the fungal enzyme. Dr. James R. Piper (SRI) has prepared >150 lipophilic antifolates for use against *P. carinii* and *T. gondii*. While several compounds showed enhanced potency *and* selectivity against *T. gondii* DHFR-TS, success against *P. carinii* DHFR proved difficult. To aid the design of improved inhibitors, we determined the crystal structures of *P. carinii* DHFR•NADPH bound to over twenty different antifolates at 1.6–1.9-Å resolution, as well as the structures of the human DHFR•NADPH•folate ternary complex (1.6 Å) and over ten human DHFR•NADPH•antifolate complexes (1.25–1.8 Å), including two ultra-high (1.09 and 1.05 Å) resolution structures.

4. *Mycobacterium tuberculosis* and *Mycobacterium avium* DHFR **(NIH R01 AI-41348; William W. Barrow, P.I. & Internal SRI Proj. 1039; David W. Borhani, P.I.)**

Several SRI lipophilic antifolates are quite active against both *M. tuberculosis* and *M. avium*. We desired to improve this activity in part by using the crystal structures of the enzymes bound to these inhibitors to guide the design of new inhibitors. We determined the crystal structure of *M. avium* DHFR at 1.9-Å resolution (NADPH•trimethoprim ternary complex), as well as the structure of the ternary complex with an inhibitor very selective toward *M. avium* DHFR, SRI-8686 (1.6 Å). The structures of the corresponding human DHFR ternary complexes were also determined (1.5 and 1.3 Å).

5. *Mycobacterium tuberculosis* FtsZ **(Internal SRI Proj. 1045; David W. Borhani, P.I.)**

Several compounds originally synthesized at SRI as tubulin inhibitors are highly active against *M. tuberculosis.* In collaboration with Lucile White at SRI, we purified the apparent drug target, the critical cell division protein FtsZ. We determined the crystal structures of recombinant *M. tuberculosis* FtsZ at up to 1.9-Å resolution bound to citrate, GDP, and GTPγS, which revealed the existence of unexpected, G protein-like conformational switches. We also collaborated with Prof. Hal Erickson (Duke Univ. Med. Center) on the kinetics of FtsZ polymerization and depolymerization, how inhibitors alter these kinetics, and electron microscopic characterization of FtsZ tubules.

Research Awards

Title: Structural Dissection of the HGPRT Reaction Mechanism
Principal Investigator: Borhani
Funding Organization: NIH/NIAID R21 AI-49443
Funding Period: 9/30/01 – 9/29/03
Total Direct Costs: $175,000
Involvement/%Effort: Principal Investigator; 35%
Major Goals: Crystal structure determination of *T. gondii* HGPRT. Construction of active site mutants and enzyme chimeras. Synthesis of transition-state analogues. Screening and structure-based design of HGPRT inhibitors.

Title: Novel Inhibitors of FGF Signal Transduction in Breast Cancer: Targeting of the FGFR Adapter Protein SNT-1
Principal Investigator: Francis G. Kern
Funding Organization: Breast Cancer Research Program, US Army Medical Research & Materiel Command BC991118
Funding Period: 3/1/00 – 2/28/03 (my involvement ended 8/00)
Total Direct Costs: $225,000
Involvement/%Effort: Co-Investigator; 10% (+25% of one crystallographic technical staff person)
Major Goals: Purification of recombinant human SNT-1 phosphotyrosine binding domain. Crystal structure determination of human SNT-1 PTB domain, alone and complexed to (inhibitory) peptides derived from the FGF receptor.

Title: Crystal Structures of Cell Signaling Proteins
Principal Investigator: Borhani
Funding Organization: BASF Bioresearch Corp.
Funding Period: 7/1/99 - 6/30/00
Total Costs: $200,000
Involvement/%Effort: Principal Investigator; 20%
Major Goals: Crystal structure determination of inhibitor complexes of two human cell signaling proteins which are anti-inflammatory drug targets. Support for structure-based drug design.

Title: Crystal Structure of Human Apolipoprotein A-I
Principal Investigator: Borhani
Funding Organization: American Heart Association Established Investigator Award 974008N
Funding Period: 7/1/98 - 6/30/02
Total Direct Costs: $300,000
Involvement/%Effort: Principal Investigator; 15%
Major Goals: Extension of the crystal structure of human apolipoprotein A-I (apo Δ(1–43)A-I mutant) to higher resolution, and crystallization and structure determination of other forms of apo A-I.

Title: Crystal Structures of the Dual-Specificity Phosphatase Cdc25
Principal Investigator: Borhani
Funding Organization: BASF Bioresearch Corp.
Funding Period: 12/1/97 - 6/30/99
Total Costs: $218,000
Involvement/%Effort: Principal Investigator; 20%
Major Goals: Crystal structure determination of inhibitor complexes of Cdc25. Support for structure-based drug design.

Title: Crystal Structure of *Toxoplasma gondii* HGPRT
Principal Investigator: Borhani
Funding Organization: NIH/NIAID R01 AI-39952
Funding Period: 7/1/96 – 6/30/00
Total Direct Costs: $514,522
Involvement/%Effort: Principal Investigator; 35%
Major Goals: Crystal structure determination of *T. gondii* HGPRT. Construction of active site mutants and enzyme chimeras.

Title: Agents Against Toxoplasma and Pneumocystis
Principal Investigator: James R. Piper
Funding Organization: NIH/NIAID R01 AI-38706
Funding Period: 4/1/96 - 3/31/00
Total Direct Costs: $473,191
Involvement/%Effort: Co-Investigator; 40%
Major Goals: Design and synthesis of lipophilic antifolates active against toxoplasma and pneumocystis. Crystallography of *P. carinii* and human DHFR and the structure-based design of lipophilic antifolates constituted half of this project.

Title: Crystal Structure of *Plasmodium falciparum* HGPRT
Principal Investigator: Borhani
Funding Organization: World Health Organization WHO-950153
Funding Period: 8/1/95 - 7/31/97
Total Direct Costs: $75,663
Involvement/%Effort: Principal Investigator; 6% (No Charge)
Major Goals: Heterologous expression of *P. falciparum* HGPRT in *E. coli*, *Pichia pastoris*, and bacculovirus. Crystallization of *P. falciparum* HGPRT.

Title: Genetic and Biochemical Analysis of Malarial HGPRT
Principal Investigator: Borhani/Vasanthakumar*
Funding Organization: World Health Organization WHO-920170
Funding Period: 6/1/94 - 5/31/95
Total Direct Costs: $60,000
Involvement/%Effort: Principal Investigator; 6% (No Charge)
Major Goals: Heterologous expression of *P. falciparum* HGPRT in *E. coli*.
*Dr. Geetha Vasanthakumar was the original P.I.; leadership of the project was transferred to Borhani when Dr. Vasanthakumar left S.R.I., 8/1/95.

Title: Structure-Based Aldose Reductase Inhibitors
Principal Investigator: Borhani
Funding Organization: NIH/NIDDK R43 DK-44789
Funding Period: 10/1/92 - 3/31/93
Total Direct Costs: $39,200
Involvement/%Effort: Principal Investigator; 75%