

**Methods in  
ENZYMOLOGY**

**Volume 493**

**Fragment-Based Drug Design:  
Tools, Practical Approaches,  
and Examples**

*Edited by*

**Lawrence C. Kuo**



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# METHODS IN ENZYMOLOGY

*Editors-in-Chief*

JOHN N. ABELSON AND MELVIN I. SIMON

*Division of Biology  
California Institute of Technology  
Pasadena, California*

*Founding Editors*

SIDNEY P. COLOWICK AND NATHAN O. KAPLAN

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Academic Press is an imprint of Elsevier  
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA  
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA  
32 Jamestown Road, London NW1 7BY, UK

First edition 2011

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ISBN: 978-0-12-381274-2

ISSN: 0076-6879

Printed and bound in United States of America

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## CONTRIBUTORS

### **Marta C. Abad**

Structural Biology and Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

### **Thomas B. Acton**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

### **Yasushi Amano**

Advanced Genomics, Molecular Medicine Research Labs, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan

### **Stephen Anderson**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

### **James Aramini**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

### **Jark Böttcher**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

### **Darren W. Begley**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

### **William A. Buchwald**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

### **Colleen Ciccianti**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Miles Congreve**

Heptares Therapeutics, Biopark, Welwyn Garden City, Hertfordshire, United Kingdom

**Ken Conover**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Douglas R. Davies**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**Renee L. Desjarlais**

Structural Biology, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Hugh L. Eaton**

Global Structural Chemistry, Merck Research Laboratories, Kenilworth, New Jersey, USA

**Thomas E. Edwards**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**John Everett**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Francis Figaroa**

Leiden Institute of Chemistry, ZoBio and Leiden University, Einsteinweg 55, Leiden, The Netherlands

**Anthony M. Giannetti**

Genentech Inc., 1 DNA Way, South San Francisco, California, USA

**Alan C. Gibbs**

Structural Biology and Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Keith Hamilton**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Robert C. Hartley**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**Yuanpeng Janet Huang**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Roderick E. Hubbard**

Vernalis (R&D) Ltd., Granta Park, Cambridge, and YSBL & HYMS, University of York, Heslington, York, United Kingdom

**Haleema Janjua**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Anja Jestel**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Reiner Kiefersauer**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Anthony E. Klon**

Department of Design, Ansaris, Four Valley Square, Blue Bell, Pennsylvania, USA

**Zenon D. Konteatis**

Department of Design, Ansaris, Four Valley Square, Blue Bell, Pennsylvania, USA

**Gregory Kornhaber**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**James K. Kranz**

Biopharmaceutical Technologies, GlaxoSmithKline Biopharmaceutical Research and Development, Upper Merion, Pennsylvania, USA

**Stephan Krapp**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Lawrence C. Kuo**

Structural Biology, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**James Lanter**

Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Jessica Lau**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Dong Yup Lee**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Christopher A. Lepre**

Structural Biology, Vertex Pharmaceuticals, Incorporated, Cambridge, Massachusetts, USA

**Gaohua Liu**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Betsy L. Lytle**

Department of Biochemistry, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

**Lichung Ma**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Melissa Maglaqui**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Lei Mao**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Fiona H. Marshall**

Heptares Therapeutics, Biopark, Welwyn Garden City, Hertfordshire, United Kingdom

**Till Maurer**

Department of Structural Biology, Genentech Inc., South San Francisco, California, USA

**Siavash Meshkat**

Discovery Technologies Department, Ansaris, Four Valley Square, Blue Bell, Pennsylvania, USA

**Gaetano T. Montelione**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, and Department of Biochemistry, Robert Wood Johnson

---

Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey, USA

**James B. Murray**

Vernalis (R&D) Ltd., Granta Park, Cambridge, United Kingdom

**Peter J. Myler**

Seattle Biomedical Research Institute, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**David G. Myszka**

Department of Biochemistry, University of Utah, Salt Lake City, Utah, USA

**Susanna Nagel**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Lars Neumann**

Proteros Biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Tatsuya Niimi**

Chemistry for Leads, Chemistry Research Labs, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan

**Kazuki Ohno**

Chemistry for Leads, Chemistry Research Labs, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan

**Masaya Orita**

Chemistry for Leads, Chemistry Research Labs, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan

**Michael H. Parker**

Structural Biology and Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Dayaban Patel**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Francis C. Peterson**

Department of Biochemistry, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

**Rebecca L. Rich**

Department of Biochemistry, University of Utah, Salt Lake City, Utah, USA



**Paolo Rossi**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Seema Sahdev**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Celine Schalk-Hihi**

Structural Biology, Johnson & Johnson Pharmaceuticals Research and Development, LLC, Spring House, Pennsylvania, USA

**Ritu Shastry**

Department of Biochemistry, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey, USA

**Gregg Siegal**

Leiden Institute of Chemistry, ZoBio and Leiden University, Einsteinweg 55, Leiden, The Netherlands

**John C. Spurlino**

Structural Biology, Johnson & Johnson Pharmaceutical Research and Development, LLC, Pennsylvania, USA

**Bart L. Staker**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**Stefan Steinbacher**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Holger Steuber**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Lance J. Stewart**

Emerald BioStructures, Bainbridge Island, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**Zhihua Sui**

Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**G. V. T. Swapna**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Yeufeng Tang**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Saichiu Tong**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Brett A. Tounge**

Structural Biology and Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Dirk Ullmann**

Proteros Biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Wesley C. Van Voorhis**

Department of Medicine, University of Washington, and Seattle Structural Genomics Center for Infectious Disease, Seattle, Washington, USA

**Brian F. Volkman**

Department of Biochemistry, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

**Konstanze von König**

Proteros biostructures GmbH, Am Klopferspitz 19, Martinsried, Germany

**Dongyan Wang**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Huang Wang**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Masaichi Warizaya**

Advanced Genomics, Molecular Medicine Research Labs, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan

**Daniel F. Wyss**

Global Structural Chemistry, Merck Research Laboratories, Kenilworth, New Jersey, USA

**Rong Xiao**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Xuqing Zhang**

Structural Biology and Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Spring House, Pennsylvania, USA

**Li Zhao**

Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, and Northeast Structural Genomics Consortium, Rutgers University, Piscataway, New Jersey, USA

**Joshua J. Ziarek**

Department of Biochemistry, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

**Jinming Zou**

Department of Design, Ansaris, Four Valley Square, Blue Bell, Pennsylvania, USA

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## PREFACE

There has been a plethora of technological innovations since the late 1980s that have influenced the way research is pursued in the biotechnology and pharmaceutical arena. Investigators are now applying ever more elaborate methods to elucidate the molecular basis underlying the biology of human diseases and to tackle discovery of new medicine. A few of these new technologies have fundamentally altered the means by which we look for hits as well as the routes we use to evolve hits to leads. Notably, protein crystallography was applied in the early 1990s to provide a structure-based approach to optimize drug leads and at about the same time high-throughput automated screening was introduced to evaluate at an unprecedented speed the effect of compounds on protein targets. Both were adopted swiftly as standard operating procedures by the pharmaceutical industry. In contrast, the use of very low molecular weight compounds, known as fragments and introduced by Abbott Laboratories in the mid-1990s, has only gained widespread acceptance in recent years.

A typical screening exercise searches a compound library with the aim of finding inhibitors against a protein target. Traditional high-throughput screening does not always offer hits of sufficient quality to be progressed into a lead compound. Fragment-based approaches utilize low molecular weight compounds that are associated with favorable physicochemical and pharmacokinetic properties. Hits derived from low molecular weight compounds offer a viable and an orthogonal entry point to finding lead compounds that in principle and by design shun unappealing pharmacophores. The use of fragments is now accepted as a “legitimate” starting point in the discovery of new medical entities as therapeutics. There are numerous, excellent reviews on Fragment-Based Drug Design (FBDD). For those new to the field, there is a need for comprehensive walk-through protocols with which one can embark readily on this creative approach to complement traditional screening methodologies. This *Methods in Enzymology* volume offers tools, practical approaches, and hit-to-lead examples on how to conduct FBDD screens. The chapters in this volume are written by experts in the field to cover methods that have proven to be successful with a focus on how to mount a successful FBDD campaign. The chapters include computational techniques, nuclear magnetic resonance, surface plasma resonance, thermal shift and enzyme kinetic assays, protein crystallography, and medicinal chemistry. Emphasis is placed on practical aspects and effective progression of lead generation to include sample preparations

of fragments, proteins, protein crystals, and G-protein coupled receptors. Explicit examples are given on how to generate leads from low-affinity fragment hits.

I want to thank all the authors; it is solely their contributions that render this volume possible. I want to thank Paul Prasad Chandramohan and Zoe Kruze of Elsevier Publishing Company for their guidance and patience throughout all stages of putting this volume together. Thanks are also due to Drs. John Abelson and Melvin Simon for their support in selecting the timely topic. I am grateful to my wife and my children for their patience during my time spent on this volume.

LAWRENCE C. KUO

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