

**Methods in
ENZYMOLOGY**

Volume 493

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

Edited by

Lawrence C. Kuo



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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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

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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