METHODS IN MOLECULAR BIOLOGY

Series Editor
John M. Walker
School of Life and Medical Sciences
University of Hertfordshire
Hatfield Hertfordshire, UK

For further volumes:
http://www.springer.com/series/7651

High Throughput Screening

Methods and Protocols

Third Edition

Edited by

William P. Janzen

Epizyme, Inc.
Cambridge, MA, USA

Humana Press

Editor
William P. Janzen
Epizyme, Inc.
Cambridge, MA, USA

ISSN 1064-3745 ISSN 1940-6029 (electronic)
Methods in Molecular Biology
ISBN 978-1-4939-3671-7 ISBN 978-1-4939-3673-1 (eBook)
DOI 10.1007/978-1-4939-3673-1

Library of Congress Control Number: 2016941460

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer Science+Business Media LLC New York

Preface

Everything changes and nothing stands still—Heraclitus of Ephesus

This quote from Heraclitus was written almost 2500 years ago but could not fit the modern world more clearly. It has definitely proven true of the field of High Throughput Screening (HTS). When I began to work in HTS in 1989 it was virtually unheard of outside of a few industrial research laboratories. As an illustration, there are nine citations in PubMed from that year that contain "HTS" or "High Throughput Screening" in the title or key words. In 2013 there were over 2000. HTS has become integrated with large segments of research and across many fields. It has evolved from a highly specialized and secretive activity to a function that is made available to researchers through academic core labs.

But, "the more things change the more they stay the same" (Jean-Baptiste Alphonse Karr). This quote is also true of HTS. The basic processes underlying HTS have not changed in the last 25 years. Test a large number of potential effectors of a biological system as rapidly as possible while maintaining sufficient rigor to allow conclusions to be drawn from the data that is generated. The size, quality, and complexity of the chemical libraries used in HTS have changed, growing into the millions of compounds with rapid QC of compound composition. HTS assays have expanded to include complex cellular systems, mass spectrometer techniques, microfluidics and, in the most telling change of all, many of these have become widely available as kits. Systems that are capable of capturing, calculating, and visualizing millions of data points have become competitive sets of commercial software rather than custom-built systems that often relied on spreadsheet calculators. And last, but certainly not least, the recognition that quality is paramount in all of these factors has become an accepted tenet of not only HTS, but drug discovery in general.

So, in short, HTS has become mainstream. It is an important part of the drug discovery process, but is integrated with many other tools and techniques. The road that HTS has traveled in this period is paralleled by the three editions of this book. The first edition was designed to introduce the reader to basic HTS techniques and the chapters were designed to cover broad applications while the second added more detail and included key chapters providing detailed protocols. In recognition of this evolution, I have tried to move this edition more towards the traditional format of Method in Molecular Biology and have asked the authors to present detailed protocols for the techniques that they describe. The introductory chapter (Chapter 1) still provides an overview of important assay development techniques, but the following chapters provide what is needed in HTS today: details on how to develop and execute screens at whatever throughput the user needs.

I hope you enjoy this volume and find it useful.

Cambridge, MA, USA *William P. Janzen*

Contents

Contributors

Ann Aulabaugh • *Immunology, Inflammation and Infectious Diseases Discovery and Translational Area Roche Pharma Research & Early Development, Roche Innovation Center Shanghai Roche R&D Center (China) Ltd, Pudong, Shanghai, P. R. China*

Alexandre Chigaev • *University of New Mexico Cancer Center, Center for Molecular Discovery, University of Mexico, Albuquerque, NM, USA*

Robert A. Copeland • *Epizyme, Inc., Cambridge, MA, USA*

Nathan P. Coussens • *Division of Pre-Clinical Innovation, National Center for Advancing Translational Sciences (NCATS), National Institute of Health (NIH), Rockville, MD, USA*

Alberto Di Silvio • *Screening Technologies Unit, AXXAM SpA, Bresso-Milan, Italy*

Peter Drueckes • *CPC Screening Sciences, Novartis Pharma AG, Novartis Institutes for Biomedical Research, Inc., Basel, Switzerland*

Adam I. Fogel • *Biogen, Cambridge, MA, USA*

Haian Fu • *Department of Pharmacology and Emory Chemical Biology Discovery Center, Emory University School of Medicine, Atlanta, GA, USA; Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA*

Kathleen Gallagher • *Department of Target & Pathway Validation, Target Sciences, GlaxoSmithKline, Collegeville, PA, USA*

Samuel A. Hasson • *National Center for Advancing Translational Sciences, National Institute of Health, Rockville, MD, USA; Pfizer, Inc., Cambridge, MA, USA*

Bianca Heedmann • *Center for Proteomic Chemistry, Novartis Institute for Biomedical Research Basel, Inc., Basel, Switzerland*

Robert P. Hertzberg • *GSK Pharmaceuticals R&D, retired, Philadelphia, PA, USA*

Xinyi Huang • *Immunology, Inflammation and Infectious Diseases Discovery and Translational Area Roche Pharma Research & Early Development, Roche Innovation Center Shanghai Roche R&D Center (China) Ltd, Pudong, Shanghai, P. R. China*

Emily A. Hull-Ryde • *Center for Integrative Chemical Biology and Drug Discovery, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Ajit Jadhav • *National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA*

William P. Janzen • *Epizyme, Inc., Cambridge, MA, USA*

Chatura Jayakody • *Warp Drive Bio LLC, Cambridge, MA, USA*

Kathy Johnson • *Department of Target & Pathway Validation, Target Sciences, GlaxoSmithKline, Collegeville, PA, USA*

Dmitri Kireev • *Center for Integrative Chemical Biology and Drug Discovery, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Martin Klumpp • *Center for Proteomic Chemistry, Novartis Institute for Biomedical Research Basel, Basel, Switzerland*

Hu Li • *Department of Biological Sciences, Platform Technology and Science, GlaxoSmithKline, Collegeville, PA, USA*

Quinn Lu • *Department of Target & Pathway Validation, Target Sciences, GlaxoSmithKline, Collegeville, PA, USA*

Chen-Ting Ma • *Conrad Prebys Center for Chemical Genomics, Sanford-Burnham-Prebys Medical Discovery Institute, La Jolla, CA, USA*
Ricardo Macarrón • *Alternative Drug Discovery, GSK Pharmaceuticals, Upper Providence, PA, USA*
Scott E. Martin • *Department of Discovery Oncology, Genentech Inc., South San Francisco, CA, USA*
Lisa McWilliams • *Discovery Sciences, Innovative Medicine, AstraZeneca, Macclesfield, UK*
Xiu-Lei Mo • *Department of Pharmacology and Emory Chemical Biology Discovery Center, Emory University School of Medicine, Atlanta, GA, USA*
Monica Montoute • *Department of Biological Sciences, Platform Technology and Sciences, GlaxoSmithKline, Collegeville, PA, USA*
David Murray • *Discovery Sciences, Innovative Medicines, AstraZeneca, Macclesfield, UK*
Michael Ouellette • *Department of Biological Sciences, Platform Technology and Science, GlaxoSmithKline, Collegeville, PA, USA*
Dominique Perez • *University of New Mexico Cancer Center, Center for Molecular Discovery, University of New Mexico, Albuquerque, NM, USA*
David J. Powell • *Alternative Drug Discovery, GSK Pharmaceuticals, Stevenage, Herts, UK*
Lynn Rasmussen • *High Throughput Screening Center, Southern Research Institute, Birmingham, AL, USA*
Daryl L. Richie • *Department of Infectious Diseases, Novartis Institutes for Biomedical Research, Inc., Emeryville, CA, USA*
Thomas V. Riera • *Epizyme, Inc., Cambridge, MA, USA*
Mattias Rohman • *Reagent and Assay Development, AstraZeneca R&D, Mölndal, Sweden*
Jean Francois Rolland • *Electrophysiology Unit, AXXAM SpA, Bresso-Milan, Italy*
Eduard A. Sergienko • *Conrad Prebys Center for Chemical Genomics, Sanford-Burnham-Prebys Medical Discovery Institute, La Jolla, CA, USA*
Robert Silvers • *Department of Biological Sciences, Platform Technology and Sciences, GlaxoSmithKline, Collegeville, PA, USA*
Anton Simeonov • *National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, Rockville, MD, USA*
Peter C. Simons • *University of New Mexico Cancer Center, Center for Molecular Discovery, University of New Mexico, Albuquerque, NM, USA*
Larry A. Sklar • *University of New Mexico Cancer Center, Center for Molecular Discovery, University of New Mexico, Albuquerque, NM, USA*
Yelena Smagley • *University of New Mexico Cancer Center, Center for Molecular Discovery, University of New Mexico, Albuquerque, NM, USA*
Thomas M. Smith • *Center for Proteomic Chemistry, Novartis Institutes for Biomedical Research, Inc., Cambridge, MA, USA*
Michela Stucchi • *Screening Technologies Unit, AXXAM SpA, Bresso-Milan, Italy*
Jianshi Tao • *Genomics Institute of the Novartis Research Foundation, San Diego, CA, USA*
Nichole A. Tower • *High Throughput Screening Center, Southern Research Institute, Birmingham, AL, USA*
E. Lucile White • *High Throughput Screening Center, Southern Research Institute, Birmingham, AL, USA*
Mark Wigglesworth • *Discovery Sciences, Innovative Medicine, AstraZeneca, Macclesfield, UK*
Tim J. Wigle • *Ribon Therapeutics, Cambridge, MA, USA*

Jonathan Wingfield • *Screening Sciences, AstraZeneca, Cambridge, UK*
Zining Wu • *Department of Biological Sciences, Platform Technology and Science, GlaxoSmithKline, Collegeville, PA, USA*
Wensheng Xie • *Department of Target & Pathway Validation, Target Sciences, GlaxoSmithKline, Collegeville, PA, USA*
Adam Yasgar • *National Center for Advancing Translational Sciences (NCATS), National Institute of Health, Rockville, MD, USA*