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Karen Lackey and Bruce Roth

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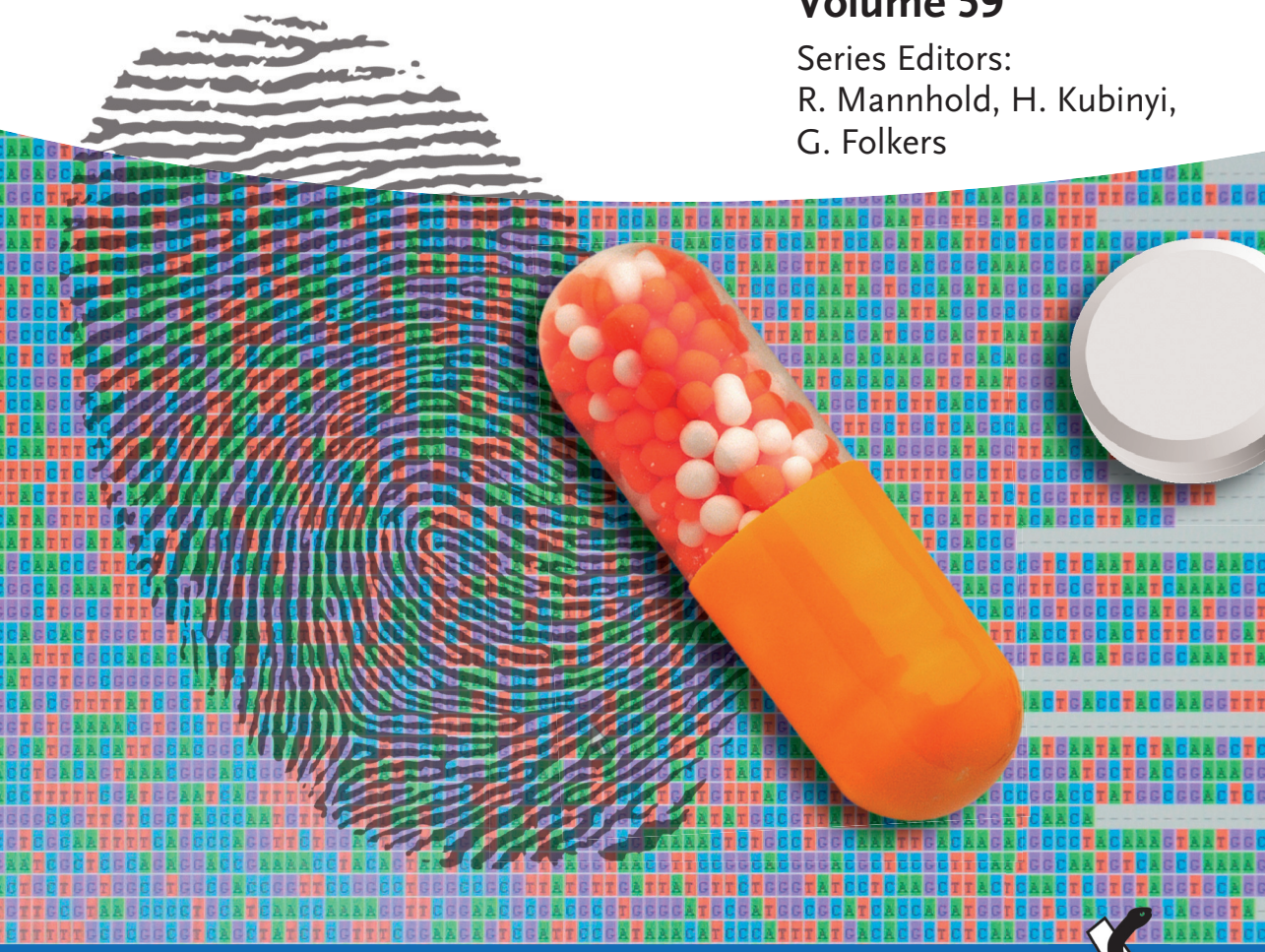

Methods and Principles in Medicinal Chemistry

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Karen Lackey and
Bruce D. Roth

Medicinal Chemistry Approaches to Personalized Medicine

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Previous Volumes of this Series:

Edited by Karen Lackey and Bruce D. Roth

Medicinal Chemistry Approaches to Personalized Medicine

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Foreword

Over the past decade, major advances have been made in elucidating the pathophysiological processes involved in many human diseases, including solid and hematological malignancies, hepatitis C, asthma, Alzheimer's disease, Parkinson's disease, age-related macular edema, and even diabetes. We know more about the biology of human disease than ever before, yet most diseases are still classified by their clinical presentation, associated physical exam, imaging data, and laboratory abnormalities. Only a few diseases are defined by the molecular pathways that cause the disease.

Using a "clinically" oriented approach to medicine results in profound heterogeneity in the molecular underpinnings of a given disease. Compounding this problem is that this heterogeneity has traditionally not been taken into account when studies were designed to evaluate a new molecular entity in a given disease. As an example, in 2005, Peagram *et al.* performed a Medline literature search using the keyword "epidermal growth factor receptor" (EGFR) and found 13 569 citations. Despite this intense level of scientific investigation into the EGFR, it was not until 2004 that important mutations in the kinase domain of the EGFR that identifies patients who are particularly sensitive to the effects of small-molecule tyrosine kinase inhibitors such as gefitinib or erlotinib were first reported. This lack of insight contributed to the numerous failed studies in the frontline non-small cell lung cancer setting when these inhibitors were given to an all-comers population. The authors of this paper also performed simulations to model the impact of including patients in a clinical trial whose disease is not sensitive to a given drug's treatment effect. They simulated administering a highly effective treatment to women with newly diagnosed metastatic breast cancer and found that when a diagnostic was used to select those patients most likely to benefit, the clinical trial was robustly positive. When the percentage of patients who would not benefit was increased, the treatment effect waned. Importantly, if only 25% of patients benefited (as is roughly the case with Herceptin for women with Her2 overexpressing breast cancer), studying an unselected population in a clinical trial (i.e., where 75% are unlikely to benefit) would result in survival curves that are essentially overlapping. In other words,

without appreciating this heterogeneity in disease biology, a clinical trial evaluating a potentially important new therapy would be negative without a diagnostic to identify those most likely to benefit.

The pharmaceutical industry is under intense pressure to improve R&D productivity. This is in large part driven by increasing costs associated with conducting clinical trials compounded by very low success rates once a drug enters clinical testing. One cannot help but wonder how many of the over 90% of drugs that fail during clinical development would have succeeded had more attention been given to identifying the population most likely to benefit.

Fortunately, over the past decade and in particular the last several years, there has been a marked shift in the discovery and development process to incorporate these concepts. Advances in cellular and molecular biology, human genetics, translational medicine (including biomarkers and diagnostics), and innovative clinical trials designs have enabled us to enter the era of so-called personalized health care (PHC). This is leading to some of the most promising new therapies ever developed in the history of medicine. In oncology alone, this new era of medicine has resulted in numerous new drugs for patients. As of 2013, the NCI website has identified over 40 "targeted therapies," although not all of these new medicines would meet the strict definition described above.

For some of these new therapies, we have observed treatment effects of almost unparalleled nature, a shorter time in clinical development, and although it is still in early days, it appears that the success rates are also likely to exceed industry averages.

It should also be pointed out that while the advances in personalized health care have been extremely impressive in oncology drug development, a similar targeted strategy is being embraced in the fields of immunology, neuroscience, and other areas of medicine. It should also be highlighted that while for most areas of medicine PHC is only recently being embraced, the field of infectious disease has adopted this concept for decades. The idea that all cases of "pneumonia" are not the same is today taken for granted. The technology for understanding the pathophysiology of this disease required much less sophisticated tools (i.e., the microscope and Petri dishes). This leads to subclassification of pneumonia by the causal agent with different treatments being prescribed based on the presumed organism responsible for the disease.

With the sequencing of the human genome over a decade ago and an increasingly sophisticated understanding of the pathophysiology of human disease-based metabolomics, proteomics, and other tools, we have clearly ushered in a new era in drug discovery and development. The end result is likely to have a very meaningful and lasting impact on academia, biotechnology and pharmaceutical companies, payers, health care providers, and most importantly patients.

Surprisingly, despite the importance of personalized health care in so many recent advances in drug therapy, there have been few attempts to collect the

success stories across industry and academia that have advanced research toward new, targeted therapies. This book, therefore, fills this gap in the literature and thus should be a useful resource for pharmaceutical and biopharmaceutical researchers for years to come.

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Preface

The notion of personalized medicine, in both the laity and the scientific community, is very often associated with screening, genetic profiling, and risk stratification. While it is unquestioned that genomics is the starting point of future "targeted medicine," personal genomics and individual genetic testing for risk stratification are still under public debate, because of their ethical and legal implications. Therefore, an account of how all this collected genetic information translates into therapeutic practice and how it may do so in near future is of highest importance not only for the public dialogue but also for the experts in drug design and development.

This book provides such an account. Edited by Karen Lackey and Bruce D. Roth, both fundamentally involved in the topic, the book convenes experts from the medicinal chemistry field in the private sector and the academia to provide their perspectives on personalized medicine. Naturally, the scope is broad. The book consisting of 13 chapters covers a more general content on feasibility of medchem approaches, contrasted by those that describe case studies of successful implementations and also others that open up new field to explore. In addition to cancer – the therapeutic area one would expect to have been mainly covered, neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as well as asthma have also been studied in this book. Methodological approaches and targets besides "chemistry" range from molecular profiling, G-quadruplexes, amyloid probes, and PET to histones, plaques in the brain, kinases, ubiquination as a future target superfamily, and DNA repair pathways.

Of course, any book on this broad topic cannot be comprehensive or even encyclopedic. The translational process of personalized medicine is in full swing and many economical questions either for the private sector or for patients and social security systems remain to be solved.

The book parallels success stories – that have been long overdue to be reported – with recent and future developments in the field.

In this respect, it is not only at cutting edge in the field but also fulfills in an excellent way the requirement of this series to serve as a handbook for bench chemists, developers, and the academic realm of research and teaching. Especially teachers may feel encouraged to use the eminent expert information collected, to

challenge their students with this extension in medicinal chemistry to a medicine of the future.

The series editors are indebted to the authors and the editors who made it possible to cover this very essential issue.

We are also very much indebted to Heike Nöthe and Frank Weinreich, both at Wiley-VCH. Their support and ongoing engagement not only for this book but also for the whole series Methods and Principles in Medicinal Chemistry greatly contribute to the success of this excellent collection related to drug research.

Düsseldorf — *Raimund Mannhold*
Weisenheim am Sand — *Hugo Kubinyi*
Zürich — *Gerd Folkers*
October 2013

A Personal Foreword

Personalized medicine and personalized healthcare have become virtual buzzwords used by the lay press and the pharmaceutical and biopharmaceutical industries in describing their current approaches to drug discovery and development aimed at providing patients with individualized therapies. Many established and emerging companies have even suggested that this is the foundation for their business strategy. Fundamentally, creating personalized medicine requires the integration of multiple disciplines, including medicinal chemistry, genetics, diagnostics, biochemistry, cellular biology, pharmacology, formulations, and clinical sciences, in order to ensure that patients have access to and are prescribed medicines with the highest likelihood of effectively treating their specific disease – and that patients unlikely to respond are not given drugs from which they will likely not receive benefit. The ultimate goal of the medical field is to have drugs that treat the underlying causes of the disease pathology. This approach has many benefits: to the companies, lower costs and higher success rates; for the patients, more effective therapies with better risk/benefit ratios. In fact, over the last several decades, many drugs, both small molecules and biologics, have been discovered and developed that would fall under this umbrella, especially in the treatment of cancer, where the emphasis on personalized medicine has led to greatly improved success rates in bringing new medicines to the market. Despite this emphasis on personalized medicine in the last decade, there has been no comprehensive treatment of this subject focusing specifically on the role of the medicinal chemist in this process, despite the fact that virtually all small-molecule drugs originate in the mind of the medicinal chemist.

In this book, we have attempted to bring together the collective experience of the pharmaceutical industry and academia, across multiple therapeutic areas and disciplines, in an attempt to capture the full spectrum of activities in implementing personalized medicine. Thus, we have chapters providing case studies of several recently approved "targeted therapies" in oncology where personalized medicine is most mature, but there are also chapters that cover developments in other therapeutic areas, development of diagnostics, imaging, and several on different aspects of new target discovery. Our hope is that this book will not only be a useful review of past practices in the discovery and development of personalized medicine but will also lay the foundation for future advances in

bringing life-changing, transformative medicines to patients. Ultimately, the goal of all of those who have committed their lives and energies to medicinal sciences is to bring benefit to the patients who are desperately waiting for the drugs that arise from the incredible scientific discoveries emanating from the work of these dedicated researchers.

Finally, we would like to thank all of the more than 40 authors and contributors to this book as well as the support and encouragement of Dr Heike Nöthe and Dr Frank Weinreich of Wiley-VCH. We are also greatly indebted to Ms Christine Cumberton for the finalization and compilation of chapters for submission to the publisher.

Nutley, NJ — *Karen Lackey*
South San Francisco, CA — *Bruce D. Roth*
June 2013

Acronyms

AChE(I)	acetylcholine esterase (inhibitor)
AD	Alzheimer's disease
ADC	antibody drug conjugates
ADME	absorption, distribution, metabolism, and excretion
AE	adverse events
AGC	protein kinase A, G, and C families
AHR	airway hyperresponsiveness
ALCL	anaplastic large-cell lymphoma
ALK	anaplastic lymphoma kinase
AP-1	activating protein 1
APC	adenomatous polyposis coli gene
APP	amyloid precursor protein
ATP	adenosine triphosphate
AUC	area under the curve
BBB	blood–brain barrier
BCC	basal-cell carcinoma
BCRP	breast cancer resistance protein
BER	base excision repair
BID	*bis in die* (Latin) meaning twice a day
BP	binding protein
CAD	coronary artery disease
CBD	corticobasal degeneration
CETP	cholesteryl ester transfer protein
CHMP	Committee for Medicinal Products for Human Use
CIA	collagen-induced arthritis
CI	confidence interval
CLR	clearance rate
CML	chronic myelogenous leukemia
CNS	central nervous system
CNV	copy number variations
COPD	chronic obstructive pulmonary disorder
CR	complete response
CRC	colorectal cancer

CSF	cerebral spinal fluid
CTC	circulating tumor cells
CUP	carcinoma of unknown primary
CDK	cyclin-dependent kinase
COMT	catechol-*O*-methyl transferase
DAG	diacylglycerol
DAT	dopamine transporter
DCR	disease control rate
DDR	DNA damage response
DECP	diethyl cyanophosphonate
DLB	dementia with Lewy bodies
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DR	direct repair
DUPA	(dicarboxypropyl)ureidopentanedioic acid
ER	estrogen receptor
ErbB2	erythroblastic leukemia oncogene homolog 2, also known as HER2/Neu
ERK	extracellular regulating kinase
FAM	6-carboxyfluorescein
FBDD	fragment-based drug discovery
FBLD	fragment-based ligand discovery
FDA	Food and Drug Administration
FDG	fluoro-deoxy-D-glucose
FFPET	formalin fixed paraffin embedded tissue
FISH	fluorescence *in situ* hybridization
FRET	fluorescence resonance energy transfer
FTD	frontotemporal dementia
GEMM	genetically engineered mouse model
GIM	genetic interaction mapping
GIST	gastrointestinal stromal tumors
GLUT	glucose transport proteins
GSK	glycogen synthase kinase
GTPase	guanine triphosphatase
GWAS	genome-wide association studies
HDAC	histone deacetylases
HDM	histone demethylases
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go related gene
HGF(R)	hepatocyte growth factor (receptor)
Hh	hedgehog
HIF	hypoxia inducible factor
HR	homologous recombinations
HSP	heat shock protein

HTS	high-throughput screening
IC_{50}	concentration at 50% inhibition
ICGC	International Cancer Genome Consortium
ICS	inhaled corticosteroids
IGF(R)	insulin growth factor (receptor)
IHC	immunohistochemistry
IL-1	interleukin-1
IMT	inflammatory myofibroblastic tumors
INDEL	insertions or deletions of a short coding region
ITK	interleukin-2-inducible T-cell kinase
IV	intravenous
LABA	long acting beta-2 agonists
LE	ligand efficiency
LipE	lipophilic efficiency
LN	lymph node
MAO	monoamine oxidase
MAPK	mitogen-activated protein kinase
MBC	metastatic breast cancer
MBP	microprecipitated bulk powder
MCI	mild cognitive impairment
MCT	methylcellulose Tween
MGMT	*O*-(6)-methylguanine-DNA methyltransferase
MK	midkine
MLC	myosin light chain
MLK	mixed lineage kinase
MMR	mismatch repair
MMSE	minimental state examination
MOM	methoxymethyl
MP	molecular profiling
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
MTEB	metabotropic glutamate receptor type
mTOR	mammalian target of rapamycin
NA	not applicable
NCI	National Cancer Institute
NER	nucleotide excision repair
NET	norepinephrine transporter
NFT	neurofibrillary tangles
NGS	next-generation sequencers
NHEJ	nonhomologous end joining
NHL	non-Hodgkin lymphoma
NIH	National Institute of Health
NK	natural killer

NME	new molecular entity
NMR	nuclear magnetic resonance
NOAEL	no adverse effect level
NPM	nucleophosmin
NRTK	nonreceptor tyrosine kinase
NSCLC	non-small cell lung cancer
OICR	Ontario Institute for Cancer Research
ORR	overall response rate
OS	overall survival
PARP	poly-ADP-ribose polymerase
PAS	peripheral anionic site
PBCA	poly(butyl-2-cyanoacrylate)
PCR	polymerase chain reaction
PD	pharmacodynamic or progressive disease or Parkinson's disease
PDAC	pancreatic cancer-ductal adenocarcinoma
PDB	Protein Data Bank
PDGF(R)	platelet-derived growth factor (receptor)
PEG	polyethyleneglycol
PET	positron emission tomography
PFS	progression free survival
PI3K	phosphoinositol 3 kinase
PiB	Pittsburgh compound-B
PK	pharmacokinetics
PLGA	poly(DL-lactide-co-glycolide)
PMD	protein misfolding diseases
PSMA	prostate-specific membrane antigen
PSP	progressive supranuclear palsy
PTM	posttranslational modifications
PTN	pleiotrophin
QSAR	quantitative structure-activity relationship
RECISTs	response evaluation criteria in solid tumors
RGD	arginine glycine asparagine
ROC	Ras/GTPase domain in complex proteins
ROCK	Rho-associated coiled coil containing protein kinase
RPLN	retroperitoneal lymph node
RTK	receptor tyrosine kinase
SAR	structure–activity relationship
SBS	sequencing by synthesis
SD	standard deviation
SF	scatter factor
SGA	synthetic genetic array
SGC	Structural Genomics Consortium
SiFA	silicon-based fluoride acceptors
siRNA	small interfering ribonucleic acid
SLAM	synthetic lethal analysis by microarray

SMI	small-molecule inhibitor
SMO	smoothened receptor
SNP	single-nucleotide polymorphism
SPECT	single-photon emission computed tomography
SphK	sphingosine kinase
SPR	surface plasmon resonance
STK	serine threonine kinase
Syk	spleen tyrosine kinase
TAC	time activity curve
TAMRA	6-carboxytetramethylrhodamine
TBAF	tetrabutylammonium fluoride
TBI	traumatic brain injury
TERRA	telomeric repeat-containing RNA
TET	ten-eleven translocation
ThT	thioflavin-T
TKI	tyrosine kinase inhibitor
TKL	tyrosine kinase-like
TNF	tumor necrosis factor
US	United States
UV	ultraviolet
VEGF(R)	vascular endothelial growth factor (receptor)
VMAT	vesicular monoamine transporter
W3C	World Wide Web Consortium
WES	whole-exome sequencing