Edited by Karen Lackey and Bruce Roth

Medicinal Chemistry Approaches to Personalized Medicine

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Karen Lackey and
Bruce D. Roth

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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 the 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 this 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 and 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.

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Weisenheim am Sand
Zürich
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Raimund Mannhold
Hugo Kubinyi
Gerd Folkers
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
South San Francisco, CA
June 2013

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