Despite advancements in the cloning of the total human genome, biomedical innovations at the patient level are becoming rare events. However, translational medicine is a burgeoning science that shows the potential to reverse the trend.

This textbook comprises a state-of-the-art survey of translational medicine, with emphasis on its emerging scientific backbone, its strengths, and its weaknesses. It explores all aspects of preclinical and clinical issues that are relevant to the success of translational pharmaceutical or medical device or diagnostic innovations, including target risk assessment, biomarker evaluation, and predictivity grading for both efficacy and toxicity; early human trial designs that are adequate to guide go-or-no-go decisions on the grounds of biomarker panels; and biostatistical methods for analyzing multiple readout situations and quantifying risk projections. The book provides guidance for designing smart profiling strategies for new approaches aimed at cutting timelines and concentrating on the comparison of quality issues of early developmental processes for pharmaceutical and biotechnology research.

By furthering the substantiation of translational medicine, creating awareness about its potential to promote innovations in clinical practice, and examining the terminology surrounding current biotechnologies, this book hopes to create a dialogue about translational science and what it will mean for patient care in the near future.

Professor Martin Wehling is an internist, cardiologist, and full professor of clinical pharmacology at the University of Heidelberg, Germany. He has authored more than 200 scientific publications and several books and has been a recipient of the Heisenberg Scholarship from Deutsche Forschungsgemeinschaft. He has longstanding experience in basic science (steroid pharmacology and non-genomic steroid actions), clinical trials (translating basic science into human studies), and clinical medicine (invasive cardiology and endocrinology). In 2004, he was appointed by AstraZeneca as director of discovery (i.e., translational) medicine. He returned to his academic position in 2007. In his return to academia, his aim is to further translational medicine by aligning academic and private activities to support biomedical innovation. His main tools are connecting distant players in the translational process; bridging gaps between preclinical and clinical stages; assembling, developing, and profiling biomarkers with particular assessment of their predictive value; and developing smart translational plans to reliably and swiftly promote translatable projects.
Principles of Translational Science in Medicine

From Bench to Bedside

EDITED BY MARTIN WEHLING
University of Heidelberg

Foreword by FRANCESCO M. MARINCOLA
Though this be madness, yet there is method in't.

William Shakespeare

Hamlet, Act 2, scene 2s, 193–206
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Contributors</td>
<td>xi</td>
</tr>
<tr>
<td>Foreword by Francesco M. Marincola</td>
<td>xvii</td>
</tr>
<tr>
<td>Preface</td>
<td>xxi</td>
</tr>
<tr>
<td>1. INTRODUCTION AND DEFINITIONS by M. Wehling</td>
<td>1</td>
</tr>
<tr>
<td>1.1. What Is Translational Medicine?</td>
<td>1</td>
</tr>
<tr>
<td>1.1.1. Primary Translation versus Secondary Translation</td>
<td>3</td>
</tr>
<tr>
<td>1.1.2. The Scope of Translational Medicine, Its Remits, and Why We Need It</td>
<td>4</td>
</tr>
<tr>
<td>1.1.3. What Translational Medicine Can and Cannot Do</td>
<td>8</td>
</tr>
<tr>
<td>1.1.4. The Present Status of Translational Medicine (Initiatives and Deficiencies)</td>
<td>11</td>
</tr>
<tr>
<td>1.1.5. Translational Science in Medicine: The Current Challenge</td>
<td>15</td>
</tr>
<tr>
<td>1.2. References</td>
<td>17</td>
</tr>
<tr>
<td>2. TARGET IDENTIFICATION AND VALIDATION</td>
<td>18</td>
</tr>
<tr>
<td>2.1. Tools</td>
<td>18</td>
</tr>
<tr>
<td>2.1.1. “Omics” Translation: A Challenge for Laboratory Medicine by M. Plebani (corresponding), M. Zaninotto, and G. Lippi</td>
<td>18</td>
</tr>
<tr>
<td>2.1.2. “Omics” Technologies: Promises and Benefits for Molecular Medicine by E. Marrer (corresponding), F. Dieterle, and J. Vonderscher</td>
<td>35</td>
</tr>
<tr>
<td>2.1.3. How to Assess Cellular Products? Potency Analysis of Cellular Therapies: The Role of Molecular Assays by D. Stroncek (corresponding), P. Jin, E. Wang, J. Ren, and F. M. Marincola</td>
<td>59</td>
</tr>
</tbody>
</table>
### 2.1.4. Translational Pharmacogenetics to Support Pharmacogenetically Driven Clinical Decision Making
*by J. Kirchheiner*

2.1.5. Tissue Biobanks
*by W. Peeters, W. J. M. Derksen, D. P. V. de Kleijn, and G. Pasterkamp (corresponding)*

2.1.6. Experimental Surgery and Medical Engineering Groups
*by M. Grasso*

2.1.7. Localization Technologies and Immunoassays: Promises and Benefits for Molecular Medicine
*by E. Marrer, F. Dieterle (corresponding), and J. Vonderscher*

2.1.8. Biomarkers in the Context of Health Authorities and Consortia
*by J. Vonderscher, E. Marrer (corresponding), and F. Dieterle*

2.1.9. Human Studies as a Source of Target Information
*by M. Wehling*

### 2.2. Target Profiling in Terms of Translatability and Early Translation Planning
*by M. Wehling*

#### 2.2.1. Essential Dimensions of Early Translational Assessment

#### 2.2.2. References

### 3. BIOMARKERS

#### 3.1. Defining Biomarkers as the Most Important Contributors to Translational Science
*by M. Wehling*

#### 3.1.1. References

#### 3.2. Classes of Biomarkers
*by M. Wehling*

#### 3.2.1. References

#### 3.3. Development of Biomarkers
*by M. Wehling*

#### 3.3.1. References

#### 3.4. Predictivity Classification of Biomarkers and Scores
*by M. Wehling*

#### 3.4.1. References

#### 3.5. Biomarker Panels and Multiple Readouts
*by D. Bernardi and M. Plebani (corresponding)*

#### 3.5.1. Introduction

#### 3.5.2. Computational Methods in Clinical Proteomics

#### 3.5.3. Multiparameter Approach: Single Results, Score, or Index?

#### 3.5.4. Diagnostic Panels and Algorithms

#### 3.5.5. Conclusions

#### 3.5.6. References
3.6. Typical Examples of Translational Biomarkers 220

3.6.1. Cardiovascular Biomarkers: Translational Aspects of Hypertension, Atherosclerosis, and Heart Failure in Drug Development by L. Lind 220

3.6.2. Biomarkers in Oncology by F. Azam, R. Midgley, and D. J. Kerr (corresponding) 235

3.6.3. Translational Imaging Research by L. Johansson 240

3.6.4. Translational Medicine in Psychiatry: Challenges and Imaging Biomarkers by A. Meyer-Lindenberg (corresponding) and H. Tost 251

4. EARLY CLINICAL TRIAL DESIGN 277

4.1. Methodological Studies by F. Azam, R. Midgley, and D. J. Kerr (corresponding) 277

4.1.1. Conventional Phase I Trial Methodology 277

4.1.2. Measuring Endpoints 283

4.1.3. Mechanism-Oriented Trial Design 284

4.1.4. Can We Make Go-or-No-Go Decisions at the End of Phase I? 286

4.1.5. Phase II Trials 286

4.1.6. Personalized Medicine 287

4.1.7. References 288

4.2. Microdosing and Experimental Investigational New Drug Studies by C. Karlsson 289

4.2.1. Introduction 289

4.2.2. Traditional Drug Development 290

4.2.3. Investigational New Drug Applications 290

4.2.4. Exploratory Investigational New Drug Studies 291

4.2.5. Repeated Dosing 295

4.2.6. Should Exploratory Investigational New Drug Studies Be Performed in All Projects? 296

4.2.7. Practical Applications 296

4.2.8. Conclusions 297

4.2.9. References 298

5. PHARMACEUTICAL TOXICOLOGY by S. Ernst (corresponding), S. Boyer, and S. Platz 299

5.1. Introduction 299

5.2. Basic Principles of Toxicology 300

5.2.1. Elements of Toxicity 300

5.2.2. Viewpoints of Toxicity 307

5.2.3. Risk Assessment 308
5.3. Regulatory Toxicology 309
   5.3.1. Introduction 309
   5.3.2. Regulatory Toxicity Studies 310
   5.3.3. The Importance of Good Laboratory Practice 313
   5.3.4. Animal Models 314
   5.3.5. New Approaches in Regulatory Toxicology: The Exploratory Investigational New Drug Approach 315
5.4. Biomarkers 316
5.5. Links 317
   5.5.1. Regulatory Agencies and Testing Guidelines: Pharmaceuticals 317
   5.5.2. Societies 317
   5.5.3. Related Sites 317
5.6. The Practice of Discovery Safety Assessment 318
   5.6.1. Target-Based Safety Assessment 319
   5.6.2. Safety-Directed Drug Design 322
5.7. Summary 324
5.8. Preclinical Safety from a Translational Perspective 325
5.9. References 326

6. TRANSLATIONAL SCIENCE BIOSTATISTICS 327
   by G. Ferber (corresponding) and E. Glimm
   6.1. Statistical Problems in Translational Science 327
   6.2. Statistical Models and Statistical Inference 329
   6.3. Design and Interpretation of an Experiment 332
   6.4. Multiplicity 337
   6.5. Biomarkers 339
   6.6. Biological Modeling 342
      6.6.1. Example 1: Pharmacodynamics 342
      6.6.2. Example 2: Pharmacokinetics 343
   6.7. Statistical Models 347
   6.8. References 348

7. LEARNING BY EXPERIENCE: EXAMPLES OF TRANSLATIONAL PROCESSES IN THE CARDIOVASCULAR FIELD 350
   by M. Wehling
   7.1. Example of a Smart, Successful Translational Process 350
   7.2. Example of a Failed Translational Process 352
   7.3. References 357

Index 359
List of Contributors

Dr. Faisal Azam  
Department of Medical Oncology  
Churchill Hospital  
Old Road, Oxford  
OX3 7LJ  
UK

Dr. Daniela Bernardi  
Department of Laboratory Medicine  
University-Hospital of Padova  
Via Giustiniani, 2  
35128 Padova  
Italy

Dr. Scott Boyer  
AstraZeneca R&D Mölndal  
Pepparedsleden 1  
431 83 Mölndal  
Sweden

Dr. Dominique P.V. de Kleijn  
Interuniversity Cardiology Institute of the Netherlands and Experimental Cardiology Laboratory  
University Medical Center Utrecht  
Heidelberglaan 100, Room G02–523  
3584 CX Utrecht  
The Netherlands

Dr. Wouter J. M. Derksen  
Experimental Cardiology Laboratory  
University Medical Center Utrecht
Heidelberglaan 100, Room G02–523
3584 CX Utrecht
The Netherlands

Dr. Frank Dieterle
Novartis Pharma AG
Klybeckstrasse 141
WKL-136.2.86
4002 Basel
Switzerland

Dr. Steffen Ernst
AstraZeneca R&D Mölndal
Pepparedsleden 1
431 83 Mölndal
Sweden

Dr. Georg Ferber
Novartis Pharma AG
Biostatistics Neuroscience and IDTI
4056 Basel
Switzerland

Dr. Ekkehard Glimm
Novartis Pharma AG
Biostatistics Neuroscience and IDTI
4056 Basel
Switzerland

Dr. Marco Grasso
Division of Urology
Department of Surgery
Desio Hospital
Via Mazzini 1
20033 Desio (Milan)
Italy

Dr. Ping Jin
Department of Transfusion Medicine
Clinical Center, National Institutes of Health
Building 10, Room 1C711
10 Center Drive-MSC-1184
Bethesda, MD 20892–1184
USA
Dr. Lars Johansson
Institutionen för onkologi, radiologi och klinisk immunologi
Akademiska sjukhuset
751 85 Uppsala
Sweden

Dr. Cecilia Karlsson
AstraZeneca R&D
Pepparedsleden 1
431 83 Mölndal
Sweden

Professor David J. Kerr
Department of Clinical Pharmacology
University of Oxford
Radcliffe Infirmary, Woodstock Road
Oxford, OX2 6HA
UK

Professor Julia Kirchheiner
Universitätsklinikum Ulm
Institut für Naturheilkunde und Klinische Pharmakologie
Helmholtzstraße 20 (Oberer Eselsberg)
89081 Ulm
Germany

Professor Lars Lind
Uppsala universitet
Institutionen för medicinska vetenskaper
Akut- och internmedicin
Akademiska sjukhuset, Ing. 40
751 85 Uppsala
Sweden

Dr. Giuseppe Lippi
Department of Laboratory Medicine
University-Hospital of Padova
Via Giustiniani, 2
35128 Padova
Italy

Dr. Francesco M. Marincola
Department of Transfusion Medicine
Clinical Center, National Institutes of Health
Building 10, Room 1C711
List of Contributors

10 Center Drive-MSC-1184
Bethesda, MD 20892–1184
USA

Dr. Estelle Marrer
Novartis Pharma AG
Klybeckstrasse 141
WK1-136.1.84
4002 Basel
Switzerland

Professor Andreas Meyer-Lindenberg
Central Institute of Mental Health
University of Heidelberg
J 5
68159 Mannheim
Germany

Dr. Rachel Midgley
Department of Clinical Pharmacology
University of Oxford
Old Road Campus Research Building
Churchill Campus, Headington, Oxford
OX3 7DQ
UK

Professor Gerard Pasterkamp
Experimental Cardiology Laboratory
University Medical Center Utrecht
Heidelberglaan 100, Room G02–523
3584 CX Utrecht
The Netherlands

Dr. Wouter Peeters
Interuniversity Cardiology Institute of the Netherlands and Experimental Cardiology Laboratory
University Medical Center Utrecht
Heidelberglaan 100, Room G02–523
3584 CX Utrecht
The Netherlands

Dr. Stefan Platz
Pre-Clinical Safety
Roche
3431 Hillview Avenue
Palo Alto, CA 94304
USA

Professor Mario Plebani
Department of Laboratory Medicine
University-Hospital of Padova
Via Giustiniani, 2
35128 Padova
Italy

Dr. Jiaqiang Ren
Department of Transfusion Medicine
Clinical Center, National Institutes of Health
Building 10, Room 1C711
10 Center Drive-MSC-1184
Bethesda, MD 20892–1184
USA

Dr. David Stroncek
Chief, Cell Processing Section
Department of Transfusion Medicine
Clinical Center, National Institutes of Health
Building 10, Room 1C711
10 Center Drive-MSC-1184
Bethesda, MD 20892–1184
USA

Dr. Heike Tost
Central Institute of Mental Health
University of Heidelberg
J 5
68159 Mannheim
Germany

Dr. Jacky Vonderscher
Molecular Medicine Labs
Roche
4070 Basel
Switzerland

Dr. Ena Wang
Department of Transfusion Medicine
Clinical Center, National Institutes of Health
Building 10, Room 1C711
10 Center Drive-MSC-1184
List of Contributors

Bethesda, MD 20892–1184
USA

Professor Martin Wehling
Clinical Pharmacology Mannheim
University of Heidelberg
Maybachstraße 14
68169 Mannheim
Germany

Dr. Martina Zaninotto
Department of Laboratory Medicine
University-Hospital of Padova
Via Giustiniani, 2
35128 Padova
Italy
The term “translational science” (also “translational medicine” or “translational research”) reflects the pragmatic expectation that resources used to support biomedical research should sustain studies aimed at improvement of public health; this applies particularly to countries whose research spending is predominantly funded through government or public resources. Synonyms suggest that the concept is not novel; terms such as “preclinical research,” “applied research,” and “evidence-based research” similarly have been used in the past to hold the same expectation. Some people suggest that translational medicine is a new term invented to diverge resources from basic sciences, while others feel that the same term is used to derail support from clinical sciences. It should be emphasized that translational science is not in competition with basic research. In fact, little could be achieved without the insights provided by the basic understanding of biology that is sometimes easier to achieve in less-complex organisms. On the contrary, translational research is aimed at reorganizing the preclinical to clinical interface, reassessing the value of preclinical models that cannot be considered part of basic investigations, and at the same time identifying better strategies for more effective and less costly clinical investigations. Thus, the goals of translational medicine are not new and are not different from, for example, those of a scientist studying cell division in frog eggs whose findings may indirectly lead to new treatments for cancer or those of a clinician who is testing a new drug in a clinical protocol. These efforts are ramifications of the first attempts to link clinical observations to improvements for patients in ancient cultures in regions such as Asia, Mesopotamia, Egypt, and Greece.

The contemporary relevance of translational science resides not in its goals but rather in its emphasis on and awareness of the urgent need to achieve them through the identification and solution of the problems that hamper the effective translation of scientific information into useful knowledge. As biomedical research has become increasingly complex, specialized, and fragmented, a need to increase communication between basic and clinical researchers with different skills and expertise has emerged. Furthermore, modern society has seen an increase in social and ethical awareness with the primary goal of protecting all
living creatures, whether human or animal, to the point that experimentation has been progressively restricted and exponentially regulated. Thus, we need to bridge the expanding gap among biomedical disciplines under a unifying concept aimed at identifying ways to better translate basic biomedical achievements into practical benefit. Translational researchers must not only participate in the invention of new technologies or make important discoveries but also facilitate the application of novel ideas through a new kind of clinical research that can incorporate the evolving complexity of high-density information, developing technologies, and socioeconomic considerations. Thus, as aforementioned, the traditional goals of biomedical research function as substrate for the catalytic activity of translational research, which, like an enzyme, enhances rather than modifies the efficiency of a process. The secret to this catalytic reaction rests in the ability to integrate disciplines of increasing complexity by allowing a dialogue among the stakeholders, by identifying the hurdles that hamper this interaction, and by proposing creative solutions.

Is translational research a fad? We do not believe so, for specific reasons. First, the throughput of novel therapeutic entities is increasing exponentially due to the power of present technology; as a result, it is impossible to serially test the thousands of products in the clinics because there are not enough patients and, in any case, the cost would be tremendous. Thus we need to make early judgments about products worth pursuing in the clinical arena. Biopharmaceutical companies are relying increasingly on experimental models to identify therapeutics with significant potential. However, convincing predictive models are often unavailable for many products. Inbred animal models have the advantage of minimizing experimental variance and, therefore, are extremely useful for hypothesis testing. However, they lack the essence of human pathology because they do not encompass its uncontrollable nature – humans are polymorphic and their diseases are heterogeneous. Thus, treatments that successfully apply to preselected experimental systems do not translate into therapeutic benefit when moved to another species and, most importantly, in a genetically and environmentally uncontrollable environment. An alternative to preclinical screening of therapeutics is the identification of biomarkers that could predict at an early stage of clinical experimentation the likelihood of success of a novel therapeutic. This is particularly important for diseases with a long-term natural history such as cancer and cardiovascular, metabolic, and degenerative diseases. Indeed, approximately two-thirds of most nations' health care spending is dedicated to such diseases. The ability to predict survival or other long-term clinical benefits using surrogate biomarkers that could be assessed during treatment or right after would greatly increase the efficiency of clinical research because it would expedite the licensing process and, therefore, relieve the industry of the tremendous costs of long-term product development. However, with a few striking exceptions, such as assessment of viral load as a surrogate biomarker of survival benefit in patients affected with human immunodeficiency virus, most surrogate biomarkers predictive of clinical usefulness are not readily identifiable.

This text represents the first attempt to summarize in a scholarly compendium the state of the science in biomedical research and how it could be
better steered in the direction of relevant clinical practice; the main goal is to make a new generation of individual scientists and/or clinicians sensitive to and prepared for the challenge of incorporating cutting-edge technologies and vast information with clinical practice. Not coincidentally, a large proportion of chapters is dedicated to developing technologies and their application for preclinical and clinical screening of therapeutics. This is truly the heart of translational research; other considerations such as targeted funding, regulatory hurdles, and ethical considerations are also discussed. However, it is only through a clear and unequivocal understanding of the state of the science and the specific goals that those interested in public welfare are trying to achieve through translational science that we will be able to articulate our vision and advocate for the specific needs that challenge this growing field.

Many issues are discussed, and any topics that may have been missed will hopefully be included in future editions thanks to the feedback of readers and the expanding recognition of the challenges. Perhaps, in the future, attention should be given to the design of clinical trials aimed at not only testing the effectiveness of therapeutics but also understanding their mechanisms of actions in humans; more attention should also be given to the process of dissemination of information and to the need for a less competitive and individualistic approach to clinical research that would reward team play and concrete achievements in the clinical arena rather than theoretical success in experimental systems. Several questions and answers are yet to be discovered, but I hope that this book will inspire both basic scientists and clinicians to develop a goal-oriented approach to biomedical research that keeps in mind the needs of the suffering.

Francesco M. Marincola
Infectious Disease and Immunogenetics Section (IDIS), Department of Transfusion Medicine, Clinical Center and Center for Human Immunology (CHI), National Institutes of Health, Bethesda, MD, and editor-in-chief,
Journal of Translational Medicine
Despite tremendous efforts, despite the cloning of the entire human genome, innovations at the patient level are becoming rare events, and insufficiencies in predicting the human efficacy or safety of new drugs from early discovery and development work are blamed for many failures. “Translational medicine” has become a fashionable phrase, but this is just not enough. It is a complex science that is still in its infancy and needs careful development both as a generic science and in concrete projects. As a generic science, the principles of translational activities need to be further explored, standardized, and developed.

A very important milestone in the development of translational science is the classification of biomarkers in regard to their predictive value for cross-species efficacy and safety extrapolations. The institutionalization of translational science and its integration into large networking structures at sites of prime research and clinical facilities seems to be a timely investment. In the United States, an increasing number of universities have undertaken those efforts and built up institutes of translational medicine, partially supported by the National Institutes of Health (NIH). Governmental and regulatory bodies (e.g., the Food and Drug Administration [FDA]) have called for increased activities under those auspices (e.g., the Critical Path Initiative), and the era of using phrases and fashionable titles without true translational content should end as soon as possible. This text aims at addressing the scientific aspects of translational medicine and teaching the essential components of a complex network of activities that should lead to successful and reliable translation of preclinical results into clinical results.

This book deals with major preclinical and clinical issues relevant to the translational success of pharmaceutical or medical device or diagnostic innovations. This includes target risk assessment, biomarker evaluation and predictivity grading for both efficacy and toxicity, early human trial design adequate to guide go-or-no-go decisions on grounds of biomarker panels, and biostatistical methods to analyze multiple readout situations and quantify risk projections. The book provides guidance to design smart profiling strategies for new approaches and aims at showing its readers how to cut timelines and concentrate on quality issues early on in the developmental processes. Translational
efforts are benchmarked against patients’ needs and integrative strategies to optimize yield and cost ratios.

The text comprises state-of-the-art knowledge in translational medicine, with emphasis on its scientific backbone and its strengths, but also on its weaknesses as a young discipline. Under didactic auspices, it is hoped that it will promote the substantiation of this emerging science, create awareness about its potential to promote urgently needed innovations in clinical practice, but also inform about the threat implied by the empty phraseology inherent to the present hype in this area.

Martin Wehling
Mannheim, November 2009