

Contents

<i>Contributors</i>	<i>page xv</i>
<i>Preface</i>	<i>xix</i>
SECTION I: TRANSLATIONAL MEDICINE: HISTORY, PRINCIPLES, AND APPLICATION IN DRUG DEVELOPMENT	I
I. TRANSLATIONAL MEDICINE: DEFINITION, HISTORY, AND STRATEGIES <i>Bruce H. Littman</i>	3
1.1. Biomarkers in Drug Development: A Common Understanding	5
1.2. Pharmacology: Testing the Target (POM)	7
1.3. Study Design Considerations for POM	13
1.3.1. Population	13
1.3.2. Risk	14
1.3.3. Feasibility	14
1.3.4. Endpoints	15
1.3.5. PK–PD and PD–PD Models	16
1.4. Confirming the Hypothesis That a Drug Target (Mechanism of Action) Will Be Efficacious (POC)	17
1.5. Study Design Considerations for POC	17
1.5.1. Population	17
1.5.2. Efficacy Endpoints	19
1.5.3. Dose Selection	20
1.5.4. Cost, Speed, and Risk	20
1.5.5. Multiple Indications (Serial or Parallel)	21

1.6. Human Indications Screening	23
1.6.1. Expl-IND Application	24
1.6.2. Low Cost Attrition and Portfolio Economics	26
1.7. Commercial Profile and Translational Medicine	27
1.7.1. Impact on Survival	27
1.7.2. Impact on Decision Making	29
1.7.3. Translational Medicine and the Personalized Medicine Option	31
1.8. Conclusion	32
1.9. References	32
2. TRANSLATIONAL MEDICINE AND ITS IMPACT ON DIABETES DRUG DEVELOPMENT <i>Roberto A. Calle and Ann E. Taylor</i>	35
2.1. Introduction	35
2.2. Primary Challenges	37
2.2.1. Efficacy	37
2.2.2. Safety	46
2.3. Case Studies	49
2.3.1. Case Study #1: Development of DPP-4i	49
2.3.2. Case Study #2: Development of 11- β -Hydroxysteroid Dehydrogenase Type 1 Inhibitors	50
2.3.3. Case Study #3: Effect of Weight Loss on HbA1c	54
2.4. Conclusions	56
2.5. Acknowledgments	56
2.6. References	56
3. CHALLENGES IN ATHEROSCLEROSIS <i>John S. Millar</i>	62
3.1. Introduction	62
3.2. Prevailing Hypotheses of Atherosclerosis Development	62
3.2.1. The Lipid Hypothesis	62
3.2.2. The Response-to-Injury Hypothesis	63
3.2.3. The Response-to-Inflammation Hypothesis	64
3.2.4. The Response-to-Retention Hypothesis	64
3.3. Clinical Trials Supporting the Lipid Hypothesis	65
3.4. Where We Stand Today	65

Cambridge University Press

978-0-521-88645-1 - Translational Medicine and Drug Discovery

Edited by Bruce H. Littman and Rajesh Krishna

Table of Contents

[More information](#)

3.5. Atherosclerosis and Drug Discovery and Development	67
3.5.1. Lipoprotein Metabolism	67
3.5.2. Antidyslipidemics	69
3.6. The Future Generation of LDL-Lowering Drugs	73
3.6.1. Thyroid Receptor- β Agonism	73
3.6.2. Lipoprotein-Associated-Phospholipase A2 Inhibitors	73
3.6.3. Secretory Phospholipase A2 Inhibitors	74
3.6.4. Microsomal Triglyceride Transfer Protein Inhibitors	74
3.6.5. Antisense/RNA Interference of apoB mRNA	75
3.7. Therapies to Increase HDL Cholesterol Levels and Improve HDL Function	75
3.7.1. CETP Inhibitors	76
3.7.2. PPAR- α Agonists	76
3.7.3. Reconstituted and Recombinant HDL/apoA-I Mimetic Peptides	77
3.8. Biomarkers Linked to Clinical Outcomes	77
3.8.1. Biomarkers	78
3.8.2. Measures of Vascular Function and Atherosclerosis	78
3.9. Case Study: CETP Inhibition with Torcetrapib – Mechanism versus Molecule	80
3.10. Conclusion	82
3.11. References	82
4. OBESITY: NEW MECHANISMS AND TRANSLATIONAL PARADIGMS <i>Gregory Gaich and David E. Moller</i>	89
4.1. Introduction	89
4.1.1. Medical Need and History of Failure	89
4.1.2. Pathophysiology and Principles of Energy Balance	90
4.2. Molecular Pathways and Associated Drug Targets	90
4.2.1. Central Regulation of Satiety–Thermogenesis	92
4.2.2. Modulating the Actions of Gut-Derived Peptide Hormones	96
4.2.3. Targeting Other Peripheral Pathways	98
4.3. Clinical Paradigm and Recent Clinical Experience	100
4.4. Translational Approaches	102
4.4.1. Target Engagement	103
4.4.2. Drug Pharmacology or Mechanism Biomarkers	104

4.4.3. Disease Process or Outcome Biomarkers and Mechanism Biomarkers Linked to Efficacy Outcomes	105
4.4.4. Subject Selection	106
4.4.5. Combination Therapy	107
4.5. Concluding Comments	107
4.6. References	108
5. BONE DISORDERS: TRANSLATIONAL MEDICINE	
CASE STUDIES <i>S. Aubrey Stoch</i>	115
5.1. Introduction	115
5.2. Challenges in Translational Research	116
5.3. Osteoporosis: Biomarker Considerations	116
5.3.1. Biochemical Biomarkers of Bone Turnover	116
5.3.2. Imaging Biomarkers (BMD)	118
5.3.3. Preclinical Models	119
5.4. Antiresorptives	121
5.4.1. Cat K Inhibitors	122
5.4.2. $\alpha_v\beta_3$ Integrin Antagonists	127
5.5. Osteoanabolics	130
5.5.1. Selective Androgen Receptor Modulators	131
5.5.2. Calcium Receptor Antagonists (Calcilytics)	136
5.5.3. Dickkopf-1 (DKK-1) Inhibitors	144
5.5.4. Sclerostin Inhibitors	149
5.6. Conclusions	155
5.7. References	158
6. CASE STUDIES IN NEUROSCIENCE: UNIQUE CHALLENGES AND EXAMPLES <i>Gerard J. Marek</i>	168
6.1. Why Is Neuroscience Not Tractable?	168
6.2. Why Have New Mechanisms Failed?	169
6.3. Can We Predict Efficacy in Short-Term Studies?	173
6.4. What Is the Role for Cognitive Biomarkers?	174
6.5. What Translational Medicine Approaches Will Drive Innovation in Neuroscience Drug Development?	175
6.6. References	177

7. TRANSLATIONAL MEDICINE IN ONCOLOGY <i>Dominic G. Spinella</i>	180
7.1. Pharmacodynamic Biomarkers	180
7.1.1. Traditional Phase 1 Dose Selection versus the Paradigm for Targeted Agents	181
7.2. Outcome Biomarkers	183
7.3. Patient Selection Biomarkers	185
7.4. Putting It All Together: The Translational Approach	188
7.4.1. Preclinical Work	188
7.4.2. The Phase 1 Study	189
7.4.3. The Phase 2 Study	190
7.5. Conclusions	190
7.6. References	191
SECTION II: BIOMARKERS AND PUBLIC–PRIVATE PARTNERSHIPS	193
8. BIOMARKER VALIDATION AND APPLICATION IN EARLY DRUG DEVELOPMENT: IDEA TO PROOF OF CONCEPT <i>Pfizer Global Research and Development 2004</i>	195
8.1. Definitions and Summary of Overarching Principles	195
8.2. Biomarker Validation Terminology	197
8.3. Stages of Biomarker Lifecycle	198
8.4. Why Biomarkers?	200
8.5. Biomarker Validation	202
8.5.1. Define the Specific Purpose(s) of the Biomarker	202
8.5.2. Examine the Business Impact of Making a Wrong Decision	203
8.5.3. Select Appropriate Technical Validation Attributes	205
8.5.4. Create the Biomarker MAC and Appropriate Decision Criteria	209
8.5.5. Summary	214
8.6. When and How to Apply Biomarkers in Drug Development: Biomarker Development Is Described for Each Stage of Drug Development	215
8.6.1. Biomarker Development Must Occur So That Biomarkers Are Validated for Their Purpose Prior to Application for Drug Development Decisions	215

x	Contents	
		<hr style="width: 150px; margin-left: 0;"/>
	8.6.2. Biomarker Selection and Development between “Target Idea” and Decision on Drug Candidate Selection	216
	8.6.3. Biomarker Best Practice between Drug Candidate Selection and First In-Human (FIH) Study	216
	8.6.4. Biomarker Best Practice between FIH and Phase 2 Start	218
	9. IMAGING BIOMARKERS IN DRUG DEVELOPMENT: CASE STUDIES <i>Johannes T. Tauscher and Adam J. Schwarz</i>	222
	9.1. Introduction	222
	9.2. Molecular Imaging: PET “Receptor Occupancy” as a Marker for Target Engagement	224
	9.2.1. A Brief History of Dopamine Receptor Occupancy with Antipsychotics	224
	9.2.2. Serotonin Transporter Occupancy with Antidepressants	226
	9.2.3. Case Study of a Translational PET Imaging Biomarker Strategy	227
	9.3. Functional Imaging: fMRI as a Probe of Drug Effects in the CNS	228
	9.3.1. fMRI Biomarkers and Mechanistic Models in Early Drug Development	230
	9.3.2. Normalization of Brain Function: fMRI Studies in Patient Populations	233
	9.3.3. Validation and Standardization of fMRI for Drug Development Applications	234
	9.4. Imaging as a Biomarker to Enrich Study Populations	235
	9.5. Oncology	236
	9.5.1. Anatomical Imaging in Cancer Drug Development	236
	9.5.2. Functional Imaging in Cancer Drug Development	237
	9.5.3. Imaging the Tumor Vasculature	239
	9.5.4. Imaging of Cellular Proliferation	242
	9.5.5. Tumor Receptor Imaging	244
	9.5.6. Imaging Apoptosis	244
	9.6. Imaging Cardiovascular Disease	245
	9.6.1. Clinical Trials in Atherosclerosis Using Imaging Endpoints	246
	9.6.2. Practicality of Cardiovascular Imaging Trials and Application to Drug Development	247

Cambridge University Press

978-0-521-88645-1 - Translational Medicine and Drug Discovery

Edited by Bruce H. Littman and Rajesh Krishna

Table of Contents

[More information](#)

9.7. Conclusions	247
9.8. Conflict of Interest Statement	249
9.9. References	249
10. EUROPEAN NEW SAFE AND INNOVATIVE MEDICINES INITIATIVES: HISTORY AND PROGRESS (THROUGH DECEMBER 2009) <i>Ole J. Bjerrum and Hans H. Linden</i>	265
10.1. Introduction	265
10.1.1. The EU Research Funding System	265
10.1.2. Stakeholders	266
10.2. Toward the IMI	267
10.2.1. First Round: Establishment of the NSMF Project	267
10.2.2. Second Round: Incorporation of NSMF in FP 6	269
10.2.3. Third Round: The Rise of the IMI	271
10.3. Organizational Structure of the IMI	272
10.4. How Does the SRA of the IMI Address Predictive Markers of Efficacy and Safety?	274
10.4.1. Predictive Markers of Efficacy	274
10.4.2. Predictive Markers of Safety	276
10.5. How Is Off-Target Toxicity Addressed in the SRA?	277
10.6. How Will the IMI Consortium Help in Transforming Current Science?	278
10.7. The Topic Proposals in the First Call of the IMI	280
10.7.1. Predictive Safety	281
10.7.2. Predictive Efficacy	282
10.7.3. Knowledge Management	283
10.7.4. Education and Training	283
10.8. The Call Procedures	285
10.9. Future Perspectives	285
10.10. Acknowledgments	287
10.11. References	287
11. CRITICAL PATH INSTITUTE AND THE PREDICTIVE SAFETY TESTING CONSORTIUM <i>Elizabeth Gribble Walker</i>	289
11.1. Introduction to the Critical Path in Medical Product Development	289

11.2. The Predictive Safety Testing Consortium	290
11.3. Regulatory and Public Health Impact of the PSTC	292
11.4. References	293
12. THE BIOMARKERS CONSORTIUM: FACILITATING THE DEVELOPMENT AND QUALIFICATION OF NOVEL BIOMARKERS THROUGH A PRECOMPETITIVE PUBLIC–PRIVATE PARTNERSHIP	295
<i>David Wholley and David B. Lee</i>	
12.1. References	300
SECTION III: FUTURE DIRECTIONS	301
13. IMPROVING THE QUALITY AND PRODUCTIVITY OF PHARMACOMETRIC MODELING AND SIMULATION ACTIVITIES: THE FOUNDATION FOR MODEL-BASED DRUG DEVELOPMENT	303
<i>Thaddeus H. Grasela, Jill Fiedler-Kelly, and Robert Slusser</i>	
13.1. Introduction	303
13.1.1. Chapter Overview	304
13.2. The Pharmacometric Analysis Process	304
13.2.1. The M&S Process in Pharmacometrics – Current Practice	305
13.2.2. The M&S Process in Pharmacometrics – Future Practice	306
13.2.3. The Central Role of the Franchise Disease–Drug Model	307
13.2.4. Implications of the Future Scenario	310
13.3. Challenges in the Delivery of M&S Results	311
13.3.1. Systematic Needs	311
13.3.2. Informatics Needs	312
13.3.3. Process Needs	313
13.4. Next Steps	314
13.4.1. Strategies for Improving the Quality and Productivity of the Pharmacometrics Process	315
13.4.2. Strategies for Improving the Quality and Robustness of the Informatics Infrastructure for Pharmacometrics	318
13.4.3. A Systematic Process for Assessing Franchise Disease–Drug Model Feasibility	319
13.4.4. Systematizing the Requirements Definition Management Process	322

	Contents	xiii
13.5. Summary	324	
13.6. References	325	
14. EMBRACING CHANGE: A PHARMACEUTICAL INDUSTRY GUIDE TO THE 21ST CENTURY <i>Mervyn Turner</i>	328	
14.1. Introduction	328	
14.1.1. Toward a New Paradigm of Drug Development	330	
14.1.2. Embracing Democratization: Partner or Perish	331	
14.2. Toward a New Paradigm of Drug Development: It's a State of Mind	331	
14.3. Fail Fast, Fail Cheap	332	
14.4. Philosophy in Action: Merck's Clinical Pharmacology and Experimental Medicine Strategies	334	
14.4.1. Embrace Democratization – Partner or Perish	336	
14.4.2. Adapt Culture to Recognize the Benefits and Necessities of Diversifying Pathways to Knowledge	337	
14.4.3. Advance Experimental Medicine through Acquisition and Partnering	339	
14.5. A Blueprint for Change	341	
14.6. References	343	
<i>Index</i>	345	