
Description: Based on results from the past ten years, this ready reference systematically describes how to prepare, carry out, and evaluate animal studies for cancer therapies, addressing the widely recognized lack of reliable and reproducible results.

Following a short historical introduction and a discussion of the ethics surrounding animal experiments, the book describes correct study design as well as the handling and housing of animals. It then goes on to describe the animal models available for different cancer types, from natural cancer models in mice and dogs to humanized animals. An evaluation of previously unpublished long-term data from the Swiss canine and feline cancer registry is also included. The final part of the book reviews the lessons learned over the last decade on how to interpret data from animal studies for improving human therapy and gives recommendations for future drug development.

Contents:

List of Contributors XI

Preface XV

A Personal Foreword XVII

1 Introduction 1
Marianne Isabelle Martic–Kehl, Michael F.W. Festing, Carlos Alvarez, and P. August Schubiger

1.1 Animal Models in Biomedical Research 1

1.2 Animals in the Drug Development Process: Historic Background 2

1.3 Problems with Translation of Animal Data to the Clinic 5

1.4 Animal Studies in Anti–cancer Drug Development 6

1.5 Toward Relevant Animal Data 7

1.6 Aim of the Book 8

References 8

2 Ethical Aspects of the Use of Animals in Translational Research 11
Karin Blumer

2.1 Introduction 11

2.2 Today’s R&D Environment 11

2.2.1 Four Emerging Trends Shaping Today’s Debate 13

2.2.1.1 Growing Lack of Awareness of the Nature of Science and Research 13

2.2.1.2 Increased Pressure on Basic Research 14

2.2.1.3 Pressure to Assign Special Animals a Special Moral and Legal Status 15

2.2.1.4 A Reductionist Approach to the 3Rs 16

2.2.2 Preliminary Conclusions 17
2.3 Do No Harm: the Essential Dilemma of Animal Research

2.4 Man and Animals in Philosophy: an Overview of Key Concepts

2.4.1 Anthropocentrism

2.4.2 Physiocentric Positions

2.4.2.1 Holistic Concepts

2.4.2.2 Radical Biocentrism

2.4.2.3 Pathocentrism

2.4.2.4 Moderate Biocentrism

2.5 Conclusions: Solving the Dilemma

References

3 Study Design

Michael F.W. Festing

3.1 Introduction

3.2 Design Principles

3.3 Experimental Design

3.3.1 The Five Characteristics of a Well-Designed Experiment

3.3.2 The Determination of Sample Size

3.3.2.1 Power Analysis for the Determination of Sample Size

3.3.2.2 The Resource Equation Method of Determining Sample Size

3.3.3 Formal Experimental Designs

3.4 Conclusion

References

4 Improving External Validity of Experimental Animal Data

S. Helene Richter, Chiara Spinello, and Simone Macrì

4.1 Introduction

4.1.1 Individual Phenotype Is the Result of Genetic and Environmental Influences

4.1.2 Why Do Living Organisms Vary?

4.2 Variation in the Laboratory

4.2.1 How Is Inter-individual Variability Generally Dealt With?

4.2.1.1 Genetic Standardization

4.2.1.2 Environmental Standardization

4.2.1.3 Standardization of the Test Situation
4.3 The Fallacies 46

4.3.1 The Standardization Fallacy 46

4.3.2 The Developmental Match Fallacy 47

4.4 Future Perspectives: an Experimental Strategy Integrating Adaptive Plasticity and Fundamental Methodology 48

4.4.1 A Way Out of the Standardization Fallacy? 48

4.4.2 Favoring Adaptive Plasticity through the Provision of Test Strategies Matching Developmental Cues 53

References 55

5 How to End Selective Reporting in Animal Research 61
Gerben ter Riet and Lex M. Bouter

5.1 Introduction 61

5.2 Definition and Different Manifestations of Reporting Bias 63

5.3 Magnitude of Reporting Biases 63

5.4 Consequences 65

5.4.1 Consequences of Reporting Bias in Human Randomized Trials 65

5.4.2 Consequences of Reporting Bias in Experimental Animal Research 66

5.5 Causes of Reporting Bias 66

5.6 Solutions 68

References 73

6 A Comprehensive Overview of Mouse Models in Oncology 79
Divya Vats

6.1 Introduction 79

6.2 Xenograft Mouse Models 81

6.2.1 Cell-Line Xenograft Model 81

6.2.2 Patient-derived Xenografts 82

6.3 Genetically Engineered Mouse Models 83

6.3.1 Limitations 85

6.3.2 Chemical Carcinogenesis: N-ethyl-N-nitrosourea Mutagenesis 86

6.3.2.1 AlkylNitrosamide Compounds 86

6.3.3 Generation of a Transgenic Mouse Using Pronuclear Injections: Direct Insertion of DNA into Fertilized Zygote 87

6.3.4 Gene Targeting via Homologous Recombination in Embryonic Stem Cells: Gene Knockouts and Knock–Ins 87

6.3.5 Conditional Inactivation (or Activation) of Genes 89
6.3.6 Inducible Systems for Gene Targeting 90

6.3.7 RNA Interference for Gene Knockdown 92

6.4 Applications for GEMMs in Compound Development 93

6.4.1 Target Validation and Compound Testing 93

6.4.2 Chemoresistance and Toxicity 94

6.4.3 In vivo Imaging 94

6.5 Humanized Mouse Models: toward a More Predictive Preclinical Mouse Model 95

6.6 Conclusions: Potentials, Limitations, and Future Directions for Mouse Models in Cancer Drug Development 98

6.6.1 Potentials and Limitations 98

6.6.2 Future Directions 100

References 101

7 Mouse Models of Advanced Spontaneous Metastasis for Experimental Therapeutics 109

Karla Parra, Irving Miramontes, Giulio Francia, and Robert S. Kerbel

7.1 Mouse Tumor Models in Cancer Research 109

7.2 The Evolution of Metronomic Chemotherapy 110

7.3 Development of Highly Aggressive and Spontaneously Metastatic Breast Cancer Models 112

7.4 Is There Any Evidence that Models of Advanced Metastatic Disease Have the Potential to Improve Predicting Future Outcomes of a Given Therapy in Patients? 113

7.5 Metronomic Chemotherapy Evaluation in Preclinical Metastasis Models 116

7.6 Experimental Therapeutics Using Metastatic Her-2 Positive Breast Cancer Xenografts Models 116

7.7 Examples of Recently Developed Orthotopic Models of Human Cancers 119

7.8 Factors that Can Affect the Usefulness of Preclinical Models in Evaluating New Therapies 120

7.9 Monitoring Metastatic Disease Progression in Preclinical Models 120

7.10 Alternative Preclinical Models: PDX and GEMMs 121

7.11 Recommendations for the Evaluation of Anti-cancer Drugs Using Preclinical Models 122

7.12 Summary 123

References 124

8 Spontaneous Animal Tumor Models 129

Andreas Pospischil, Katrin Grüntzig, Ramona Graf, and Gianluca Boo

8.1 Introduction 129

8.2 Advantages of Spontaneous Canine/Feline Cancer Registries 130

8.2.1 Effective and Relevant Canine/Feline Cancer Registries Necessary Steps and Existing Registries 131

8.2.1.1 Regional/National/International Population-based Human Cancer Registry with Sufficient Case
Numbers and Patient Data 131

8.2.1.2 Regional/National Population–based Canine/Feline Cancer Registries 132

8.2.1.3 Comparative (Human/Canine/Feline) Geographic and Environmental Risk Assessment of Tumor Incidences 133

8.2.1.4 Tissue/Bio–bank Containing Canine/Feline Tumor Samples (Fresh Frozen, FFPE) for Necessary Re–valuation, and Further Testing 133

8.2.1.5 Comparative Testing of Genetic/Proteomic Tumor Markers on Different Tumor Tissue from Human and Animal Patients 134

8.3 Spontaneous Animal Tumors as Suitable Models for Human Cancers 134

8.3.1 Canine Tumors 134

8.3.2 Feline Tumors 134

8.4 The Swiss Canine/Feline Cancer Registry 1955 2008 135

8.4.1 Swiss Canine Cancer Registry 1955 2008 135

8.4.1.1 Tumor Location 135

8.4.1.2 Malignancy of the Most Common Tumor Diagnoses 136

8.4.1.3 Sex Distribution 136

8.4.1.4 Breed Distribution 138

8.4.1.5 Sample Catchment Area 140

8.4.2 The Swiss Feline Cancer Registry 1964 2008 140

8.4.2.1 Malignancy of the Most Common Tumor Diagnoses 141

8.4.2.2 Breed Distribution 141

8.4.2.3 Sex Distribution 142

8.4.2.4 Most Common Locations of Tumors (1%) 144

8.4.2.5 Catchment Area 144

8.4.3 Comparison of Swiss Canine, Feline, and Human Cancer Registry Data 146

8.4.4 Conclusion 147

References 148

9 Dog Models of Naturally Occurring Cancer 153

9.1 Introduction 153

9.1.1 Animal Models of Human Disease and the Need for Alternatives to the Mouse 153

9.2 Advantages of Spontaneous Cancer Models in Dogs 155

9.2.1 High Level of Evolutionary Conservation with Humans 156
9.2.2 Reduced Heterogeneity within Breeds and Increased Variation across Breeds 157

9.2.3 Potential for Comprehensive Genotyping 163

9.2.4 Understanding Both Somatic and Germline Cancer Genetics 164

9.2.5 Translational Models 169

9.3 Dog Cancer Models 170

9.3.1 Canine Cancer Incidence 170

9.3.2 Genetics of Breed–Specific Cancer Models 177

9.3.2.1 Lymphoma 177

9.3.2.2 Osteosarcoma 181

9.4 Preclinical and Veterinary Translational Investigations in Dogs with Cancer 184

9.4.1 Preclinical Investigations in Dogs with Spontaneous Cancer 184

9.4.2 Conduct of Preclinical and Translational Studies in Pet Dogs with Cancer 186

9.4.3 Examples of Successful Preclinical Investigations in Pet Dogs with Cancer 190

9.5 Necessary Developments for Realizing the Potential of Canine Models 196

9.5.1 Epidemiology, Longitudinal Cohorts, Tissue Repositories, and Integrative Genomics 196

9.5.2 Improved Genome Annotation and Development of Key Research Areas 196

9.5.3 Opportunities for Understanding the Complete Biology of Spontaneous Cancers 197

9.5.4 Development of High–Impact Programs in Preclinical Cancer Studies 198

9.6 Key Challenges and Recommendations for Using Canine Models 200

9.6.1 Challenges of Population Structure in Dog Models 200

9.6.2 Recommendations for Optimal Results in Canine Preclinical Research 201

9.7 Conclusions 202

References 203

10 Improving Preclinical Cancer Models: Lessons from Human and Canine Clinical Trials of Metronomic Chemotherapy 223
Guido Bocci, Esther K. Lee, Anthony J. Mutsaers, and Urban Emmenegger

10.1 Introduction: Low–dose Metronomic Chemotherapy 223

10.2 Clinical Trials of Metronomic Chemotherapy 224

10.2.1 Achievements 224

10.2.2 Challenges 225

10.3 Veterinary Metronomic Trials in Pet Dogs with Cancer 227

10.3.1 Adjuvant Treatment 228

10.3.2 First–Line Therapy for Metastatic Disease 229
10.3.3 Biomarker Studies 229
10.3.4 Other Chemotherapy Drug Choices 230
10.3.5 Combination with Targeted Anti-angiogenic Drugs 230
10.3.6 Combining Metronomic and MTD Protocols 231
10.4 Lessons Learned from Clinical Trials: Improving the Predictability of Preclinical Models 231
10.4.1 Pharmacokinetic and Pharmacodynamic Studies in Preclinical Models 231
10.4.1.1 Pharmacokinetic Preclinical Studies of Metronomic Chemotherapy Regimens 233
10.4.1.2 Pharmacodynamic Analyses in Preclinical Studies 236
10.4.2 Pharmacogenomics in Animal Models 237
10.4.3 Pharmacoeconomics of Metronomic Chemotherapy 238
10.5 Conclusions 240
Acknowledgements 240
References 240
Index 247

Order by Fax - using the form below
Order by Post - print the order form below and send to

Research and Markets,
Guinness Centre,
Taylors Lane,
Dublin 8,
Ireland.
Fax Order Form
To place an order via fax simply print this form, fill in the information below and fax the completed form to 646-607-1907 (from USA) or +353-1-481-1716 (from Rest of World). If you have any questions please visit http://www.researchandmarkets.com/contact/

Order Information
Please verify that the product information is correct.

Web Address: http://www.researchandmarkets.com/reports/3610152/
Office Code: SCH3OFFJ

Product Format
Please select the product format and quantity you require:

<table>
<thead>
<tr>
<th>Quantity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard Copy (Hard Back)</td>
<td>USD 164 + USD 29 Shipping/Handling</td>
</tr>
</tbody>
</table>

* Shipping/Handling is only charged once per order.

Contact Information
Please enter all the information below in BLOCK CAPITALS

Title: Mr  □  Mrs  □  Dr  □  Miss  □  Ms  □  Prof  □
First Name: ____________________________  Last Name: ____________________________
Email Address: * ____________________________
Job Title: ____________________________
Organisation: ____________________________
Address: ____________________________
City: ____________________________
Postal / Zip Code: ____________________________
Country: ____________________________
Phone Number: ____________________________
Fax Number: ____________________________

* Please refrain from using free email accounts when ordering (e.g. Yahoo, Hotmail, AOL)
Payment Information

Please indicate the payment method you would like to use by selecting the appropriate box.

☐ Pay by credit card: You will receive an email with a link to a secure webpage to enter your credit card details.

☐ Pay by check: Please post the check, accompanied by this form, to:
Research and Markets,
Guinness Center,
Taylors Lane,
Dublin 8,
Ireland.

☐ Pay by wire transfer: Please transfer funds to:
Account number 833 130 83
Sort code 98-53-30
Swift code ULSBIE2D
IBAN number IE78ULSB98533083313083
Bank Address Ulster Bank,
27-35 Main Street,
Blackrock,
Co. Dublin,
Ireland.

If you have a Marketing Code please enter it below:

Marketing Code: ____________________________

Please note that by ordering from Research and Markets you are agreeing to our Terms and Conditions at http://www.researchandmarkets.com/info/terms.asp

Please fax this form to:
(646) 607-1907 or (646) 964-6609 - From USA
+353-1-481-1716 or +353-1-653-1571 - From Rest of World