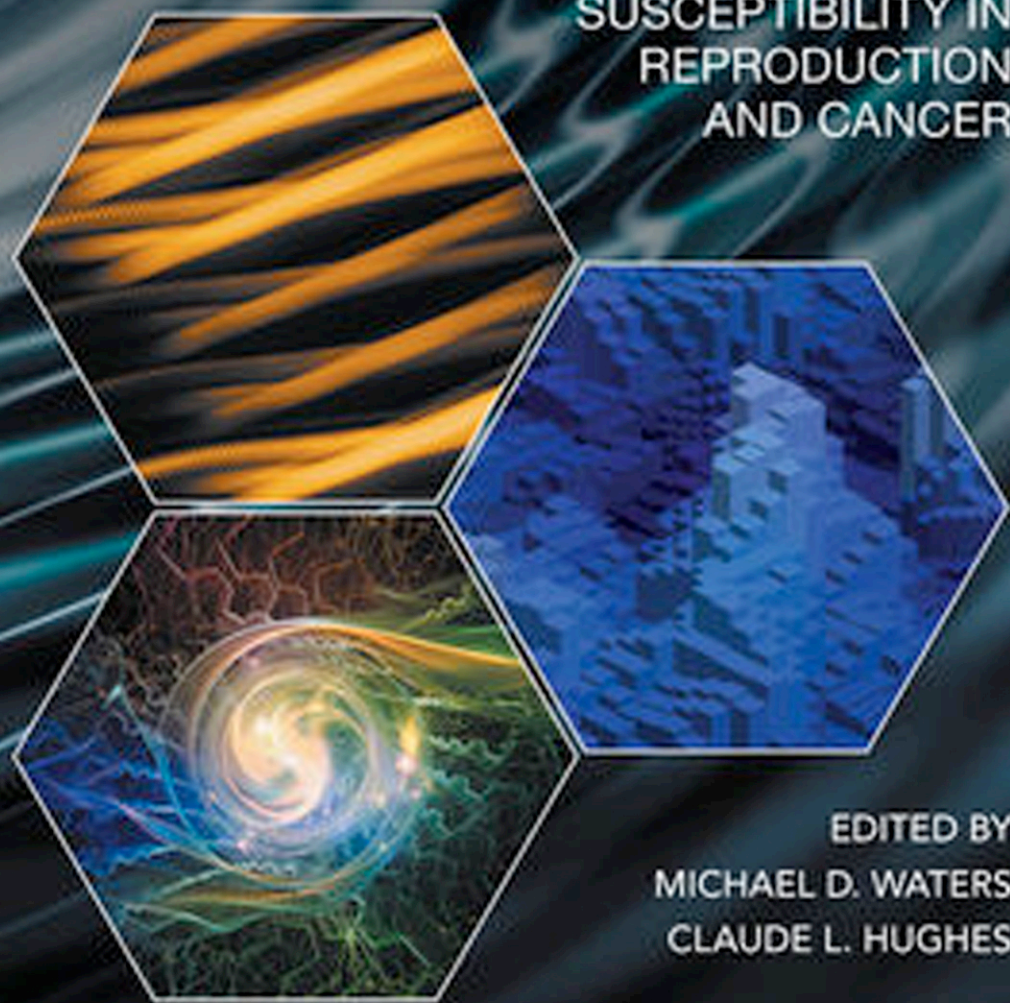


# TRANSLATIONAL TOXICOLOGY AND THERAPEUTICS

WINDOWS OF DEVELOPMENTAL  
SUSCEPTIBILITY IN  
REPRODUCTION  
AND CANCER



EDITED BY  
MICHAEL D. WATERS  
CLAUDE L. HUGHES

WILEY

**Translational Toxicology  
and Therapeutics**



# Translational Toxicology and Therapeutics

Windows of Developmental  
Susceptibility in Reproduction  
and Cancer

*Edited by*

*Michael D. Waters*

Michael Waters Consulting USA  
Hillsborough, NC, USA

*Claude L. Hughes*

Therapeutic Science and Strategy Unit QuintilesIMS Inc.  
Morrisville, NC, USA

Department of Obstetrics and Gynecology  
Duke University Medical Center  
Durham, NC, USA

Department of Mathematics North Carolina State University  
Raleigh, NC, USA

**WILEY**

This edition first published 2018

© 2018 John Wiley & Sons, Inc

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at <http://www.wiley.com/go/permissions>.

The right of Michael D. Waters and Claude L. Hughes to be identified as the editors of this work has been asserted in accordance with law.

#### *Registered Offices*

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

#### *Editorial Office*

111 River Street, Hoboken, NJ 07030, USA

For details of our global editorial offices, customer services, and more information about Wiley products visit us at [www.wiley.com](http://www.wiley.com).

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

#### *Limit of Liability/Disclaimer of Warranty*

The publisher and the authors make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or website is referred to in this work as a citation and/or potential source of further information does not mean that the author or the publisher endorses the information the organization or website may provide or recommendations it may make. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

#### *Library of Congress Cataloging-in-Publication Data applied for.*

Hardback ISBN: 9781119023609

Cover image: (Background) © portishead1/Gettyimages; (Top left, lower left and right side hexagon) © John Rensten/Gettyimages; © agsandrew/Gettyimages; © tashechka/Gettyimages  
Cover design by Wiley

Set in 10/12pt WarnockPro-Regular by Thomson Digital, Noida, India

10 9 8 7 6 5 4 3 2 1

## Contents

List of Contributors *xix*

**Part One Introduction: The Case for Concern about Mutation and Cancer Susceptibility during Critical Windows of Development and the Opportunity to Translate Toxicology into a Therapeutic Discipline 1**

<b>1</b>	<b>What Stressors Cause Cancer and When?</b>	<b>3</b>
	<i>Claude L. Hughes and Michael D. Waters</i>	
1.1	Introduction	3
1.1.1	General Information about Cancer	5
1.1.2	Stressors and Adaptive Responses	8
1.2	What Stressors Cause Cancer and When?	8
1.2.1	Mutagenic MOAs	13
1.2.1.1	DNA Repair	14
1.2.2	Epigenetic MOAs	16
1.2.3	Nongenotoxic Carcinogens, ROS, Obesity, Metabolic, Diet, Environment, Immune, Endocrine MOAs	20
1.2.4	Tumor Microenvironment MOAs	25
1.3	Relevance of Circulating Cancer Markers	26
1.4	Potential Cancer Translational Toxicology Therapies	29
1.4.1	Well-Established/Repurposed Pharmaceuticals	31
1.4.2	GRAS/GRASE, Diet, and Nutraceuticals	34
1.4.2.1	Suppression of Cell Proliferation and Induction of Cell Death	35
1.4.2.2	Anti-Inflammatory Effects: Insights from Various Diseases	36
1.4.2.3	Upregulation of Tumor Suppressor MicroRNAs	38
1.4.2.4	Regulation of Oxidative Stress	38
1.4.2.5	Activation of Signal Transduction Pathways	39
1.4.2.6	Mitigating Inherited Deleterious Mutations	40
1.4.2.7	Mitigating Adverse Epigenetic States	42

1.4.2.8	Paradigm for Study of Cancer Chemoprevention	43
1.5	Modeling and the Future	47
	References	51
<b>2</b>	<b>What Mutagenic Events Contribute to Human Cancer and Genetic Disease?</b>	<b>61</b>
	<i>Michael D. Waters</i>	
2.1	Introduction	61
2.1.1	Childhood Cancer, Developmental Defects, and Adverse Reproductive Outcomes	62
2.1.2	Newborn Screening for Genetic Disease	62
2.1.3	Diagnosis of Genetic Disease	63
2.1.4	Familial and Sporadic Cancer	65
2.2	Genetic Damage from Environmental Agents	67
2.3	Testing for Mutagenicity and Carcinogenicity	71
2.4	Predictive Toxicogenomics for Carcinogenicity	73
2.5	Germ Line Mutagenicity and Screening Tests	76
2.6	Reproductive Toxicology Assays in the Assessment of Heritable Effects	80
2.6.1	Segmented Reproductive Toxicity Study Designs	80
2.6.2	Continuous Cycle Designs	81
2.6.2.1	One-Generation Toxicity Study	81
2.6.2.2	Repeat Dose Toxicity Studies	82
2.7	Assays in Need of Further Development or Validation	82
2.7.1	Transgenic Rodent Gene Mutation Reporter Assay	82
2.7.2	Expanded Simple Tandem Repeat Assay	84
2.7.3	Spermatid Micronucleus (MN) Assay	85
2.7.4	Sperm Comet Assay	86
2.7.5	Standardization of Sperm Chromatin Quality Assays	86
2.8	New Technologies	87
2.8.1	Copy Number Variants and Human Genetic Disease	87
2.8.2	Next-Generation Whole Genome Sequencing	88
2.8.3	High-Throughput Analysis of Egg Aneuploidy in <i>C. elegans</i> , and Other Alternative Assay Systems	90
2.9	Endpoints Most Relevant to Human Genetic Risk	91
2.10	Worldwide Regulatory Requirements for Germ Cell Testing	94
2.11	Conclusion	95
	Acknowledgments	96
	References	96
<b>3</b>	<b>Developmental Origins of Cancer</b>	<b>111</b>
	<i>Suryanarayana V. Vulimiri and John M. Rogers</i>	
3.1	Introduction	111

3.2	Current Trends in Childhood Cancer	112
3.3	Potential Mechanisms of Prenatal Cancer Induction	113
3.4	Ontogeny of Xenobiotic Metabolizing Enzymes and DNA Repair Systems	113
3.5	The Developmental Origins of Health and Disease (DOHaD) Theory	115
3.6	Epigenetic Regulation during Development	115
3.6.1	Critical Periods for Epigenetic Regulation	116
3.7	Mechanisms of Cancer in Offspring from Paternal Exposures	117
3.8	Parental Exposures Associated with Cancer in Offspring	118
3.8.1	Radiation	118
3.8.2	Diethylstilbestrol	119
3.8.3	Tobacco Smoke	120
3.8.4	Pesticides	122
3.8.5	Arsenic	123
3.9	Models for the Developmental Origins of Selected Cancers	124
3.9.1	Breast Cancer	124
3.9.2	Leukemia	127
3.10	Public Health Agencies' Views on Prenatal Exposures and Cancer Risk	129
3.10.1	The United States Environmental Protection Agency (US EPA)	129
3.10.2	The California Environmental Protection Agency (CalEPA)	131
3.10.3	Washington State Department of Ecology (WA DoE)	133
3.11	Conclusions	134
	Acknowledgment	135
	References	135
<b>4</b>	<b>The Mechanistic Basis of Cancer Prevention</b>	<b>147</b>
	<i>Bernard W. Stewart</i>	
4.1	Introduction	147
4.2	A Mechanistic Approach	147
4.2.1	Specifying Carcinogens	148
4.2.2	Cancer Risk Factors Without Carcinogen Specification	148
4.3	Preventing Cancer Attributable to Known Carcinogens	149
4.3.1	Involuntary Exposure	149
4.3.1.1	Infectious Agents	149
4.3.1.2	Occupation	150
4.3.1.3	Drugs	151
4.3.1.4	Pollution	152
4.3.1.5	Dietary Carcinogens	152
4.3.2	Tobacco Smoking	153
4.3.2.1	Measures to Limit Availability and Promotion	154
4.3.2.2	Product Labeling, Health Warnings, and Usage Restrictions	154



- 4.3.2.3 Smoking Cessation 155
- 4.3.3 Alcohol Drinking 155
- 4.3.4 Solar and Ultraviolet Radiation 156
- 4.4 Prevention Involving Complex Risk Factors 157
- 4.4.1 Workplace Exposures 157
- 4.4.2 Diet and Overweight/Obesity 157
- 4.5 Prevention Independent of Causative Agents or Risk Factors 158
- 4.5.1 Screening 158
- 4.5.2 Chemoprevention 159
- 4.6 Conclusion 160
- References 160

**Part Two Exposures that Could Alter the Risk of Cancer Occurrence, and Impact Its Indolent or Aggressive Behavior and Progression Over Time 171**

**5 Diet Factors in Cancer Risk 173**

*Lynnette R. Ferguson*

- 5.1 Introduction 173
- 5.2 Obesity 174
- 5.3 Macronutrients 175
- 5.3.1 Protein 176
- 5.3.2 Lipids 177
- 5.3.3 Carbohydrates 178
- 5.4 Micronutrients 181
- 5.4.1 Vitamins 181
- 5.4.2 Minerals 184
- 5.5 Phytochemicals 184
- 5.5.1 Phytoestrogens 185
- 5.5.2 Other Phytochemicals 186
- 5.6 Conclusions 188
- References 188

**6 Voluntary Exposures: Natural Herbs, Supplements, and Substances of Abuse – What Evidence Distinguishes Therapeutic from Adverse Responses? 199**

*Eli P. Crapper, Kylie Wasser, Katelyn J. Foster, and Warren G. Foster*

- 6.1 Introduction 199
- 6.1.1 Alcohol 200
- 6.1.2 Cigarette Smoking 201
- 6.1.3 Herbs and Supplements 202
- 6.1.3.1 Melatonin 202

- 6.1.3.2 Resveratrol 204
- 6.1.3.3 Dong Quai 205
- 6.1.3.4 Eleutherococcus 206
- 6.1.3.5 Saw Palmetto 206
- 6.1.3.6 Stinging Nettle 207
- 6.2 Summary and Conclusions 207
- References 207
  
- 7 Voluntary Exposures: Pharmaceutical Chemicals in Prescription and Over-the-Counter Drugs – Passing the Testing Gauntlet 213**  
*Ronald D. Snyder*
- 7.1 Introduction 213
- 7.2 Testing of New Drug Entities for Genotoxicity 214
- 7.3 Relationship between Genotoxicity Testing and Rodent Carcinogenicity 217
- 7.4 Can Drug-Induced Human Cancer Be Predicted? 218
- 7.5 What Can Rodent Carcinogenicity Tell Us about Human Cancer Risk? 220
- 7.6 Genotoxicity Prediction Using “Traditional” *In Silico* Approaches 222
- 7.7 Covalent versus Noncovalent DNA Interaction 223
- 7.8 Use of New Technologies to Predict Toxicity and Cancer Risk: High-Throughput Methods 224
- 7.9 Transcriptomics 225
- 7.10 Single-Nucleotide Polymorphisms (SNPs) 226
- 7.11 Conclusions 227
- Appendix A 228
- References 253
  
- 8 Children’s and Adult Involuntary and Occupational Exposures and Cancer 259**  
*Annamaria Colacci and Monica Vaccari*
- 8.1 Introduction 259
- 8.2 Occupational Exposures and Cancer 262
- 8.2.1 Occupational Cancer in the Twenty-First Century 262
- 8.2.2 Past and Present Occupational Exposure to Asbestos 263
- 8.2.3 Toxicology of Fibers: What We Have Learned from the Asbestos Lesson 265
- 8.2.3.1 Mechanism and Mode of Action of Asbestos and Asbestos-Like Fibers in Carcinogenesis: The Role of Inflammation and Immune System to Sustain the Cancer Process 268
- 8.2.4 Occupational Exposures and Rare Tumors 270
- 8.3 Environmental Exposures and Cancer 271

8.3.1	Environmental Exposures and Disease: Is This the Pandemic of the Twenty-First Century?	271
8.3.2	The Complexity of Environmental Exposures	272
8.3.3	Environmental Impact on Early Stages of Life: Are Our Children at Risk?	274
8.3.4	Environmental Endocrine Disruptors: The Steps Set Out to Recover Our Stolen Future	277
8.3.5	From Occupational to Environmental Exposures: Asbestos and Other Chemicals of Concern	279
8.3.5.1	Asbestos	279
8.3.5.2	Arsenic and Arsenic Compounds	280
8.3.5.3	Phthalates	282
8.3.5.4	Pesticides	283
8.3.5.5	Mycotoxins	286
8.3.6	Air Pollution and Airborne Particulate Matter: The Paradigmatic Example of Environmental Mixtures	288
8.3.6.1	Characteristics of PM and PM Exposures	289
8.3.6.2	PM Exposures and Cancer	291
8.3.6.3	Possible Mechanisms of PM Toxicity	293
8.3.6.4	The Role of PM Exposures in the Fetal Origin of the Disease	294
8.4	Conclusions and Future Perspectives	296
	References	299

### **Part Three Gene–Environment Interactions 317**

<b>9</b>	<b>Ethnicity, Geographic Location, and Cancer</b>	<b>319</b>
	<i>Fengyu Zhang</i>	
9.1	Introduction	319
9.2	Classification of Cancer	320
9.2.1	Classification by Histology	320
9.2.2	Classification by Primary Location	322
9.3	Ethnicity and Cancer	323
9.3.1	Cancer Death and Incidence	323
9.3.2	Site-Specific Cancer Incidence	326
9.3.3	Site-Specific Cancer Incidence between the United States and China	328
9.4	Geographic Location and Cancer	331
9.4.1	Mapping Human Diseases to Geographic Location	331
9.4.2	Geographic Variation and Cancer in the United States	332
9.5	Ethnicity, Geographic Location, and Lung Cancer	334
9.5.1	Ethnic Differences	334
9.5.2	Geographic Variation	335

9.5.3	Individual Risk Factors	335
9.6	Common Cancers in China	338
9.6.1	Liver Cancer	339
9.6.1.1	Geographic Variation	339
9.6.1.2	Urban Residence and Sex	340
9.6.1.3	Hepatitis B Virus Infection	340
9.6.1.4	Familial Aggregation and Genetic Variants	341
9.6.2	Gastric Cancer	342
9.6.2.1	<i>H. pylori</i>	342
9.6.2.2	Familial Aggregation	343
9.6.2.3	Genetic Susceptibility Factors	343
9.6.3	Esophageal Cancer	344
9.6.3.1	Geographic Variation	344
9.6.3.2	Viral Infections	344
9.6.3.3	Familial Aggregation	345
9.6.3.4	Genetic Susceptibility Factors	345
9.6.4	Lung Cancer	346
9.6.5	Genetic Susceptibility Factors	347
9.6.6	Cervical Cancer	348
9.7	Cancer Risk Factors and Prevention	348
9.7.1	Environmental Chemical Exposure	348
9.7.2	Infectious Agents	349
9.7.3	Psychosocial Stress and Social Network	349
9.7.4	The Developmental Origin of Adult-Onset Cancer	350
9.7.5	Cancer Prevention and Intervention	351
	References	353
<b>10</b>	<b>Dietary/Supplemental Interventions and Personal Dietary Preferences for Cancer: Translational Toxicology Therapeutic Portfolio for Cancer Risk Reduction</b>	<b>363</b>
	<i>Sandeep Kaur, Elaine Trujillo, and Harold Seifried</i>	
10.1	Introduction	363
10.2	Gene Expression and Epigenetics	364
10.3	Environmental Lifestyle Factors Affecting Cancer Prevention and Risk	366
10.3.1	Obesity	366
10.3.2	Weight Loss	368
10.3.3	Physical Activity	369
10.4	Dietary Patterns	370
10.5	Complementary and Integrative Oncology Interventions/Restorative Therapeutics	373
10.6	Special and Alternative Diets	377
10.7	Popular Anticancer Diets	378

- 10.7.1 Macrobiotic Diet 378
- 10.7.2 The Ketogenic Diet 382
- 10.7.3 Fasting Diet 383
- 10.8 Conclusion 384
- Acknowledgment 384
- References 385

**11 Social Determinants of Health and the Environmental Exposures: A Promising Partnership 395**

*Lauren Fordyce, David Berrigan, and Shobha Srinivasan*

- 11.1 Introduction 395
- 11.1.1 Conceptual Model 397
- 11.1.2 Difference versus Disparity 398
- 11.2 Social Determinants of Health 399
- 11.2.1 Race/Ethnicity 399
- 11.2.2 Social Determinants of Health: “Place” and Its Correlates 402
- 11.2.3 Gender and Sexuality 405
- 11.3 Conclusions: Social Determinants of Health and Windows of Susceptibility 407
- Acknowledgments 408
- References 408

**Part Four Categorical and Pleiotropic Nonmutagenic Modes of Action of Toxicants: Causality 415**

**12 Bisphenol A and Nongenotoxic Drivers of Cancer 417**

*Natalie R. Gassman and Samuel H. Wilson*

- 12.1 Introduction 417
- 12.2 Dosing 420
- 12.3 Receptor-mediated Signaling 421
- 12.4 Epigenetic Reprogramming 422
- 12.5 Oxidative stress 424
- 12.6 Inflammation and Immune Response 425
- 12.7 BPA-Induced Carcinogenesis 426
- 12.8 Fresh Opportunities in BPA Research 428
- References 429

**13 Toxicoeugenetics and Effects on Life Course Disease Susceptibility 439**

*Luke Montrose, Jaclyn M. Goodrich, and Dana C. Dolinoy*

- 13.1 Introduction to the Field of Toxicoeugenetics 439
- 13.1.1 The Epigenome 440

- 13.1.2 Epigenetic Marks are Heritable and Reversible 440
- 13.1.3 DNA Methylation 441
- 13.1.4 Histone Modifications and Chromatin Packaging 442
- 13.1.5 Noncoding RNAs 443
- 13.1.6 Key Windows for Exposure-Related Epigenetic Changes 443
- 13.1.7 Evaluation of Environmentally Induced Epigenetic Changes in Animal Models and Humans 444
- 13.2 Exposures that Influence the Epigenome 444
  - 13.2.1 Air Pollution 445
  - 13.2.2 Metals 447
  - 13.2.3 Endocrine Disrupting Chemicals (EDCs) 448
  - 13.2.4 Diet 451
  - 13.2.5 Stress 453
- 13.3 Intergenerational Exposures and Epigenetic Effects 454
- 13.4 Special Considerations and Future Directions for the Field of Toxicogenetics 456
  - 13.4.1 Tissue Specificity 456
  - 13.4.2 The Dynamic Nature of DNA Methylation 458
- 13.5 Future Directions 459
- 13.6 Conclusions 460
  - Acknowledgments 461
  - References 461
  
- 14 Tumor-Promoting/Associated Inflammation and the Microenvironment: A State of the Science and New Horizons 473**  
*William H. Bisson, Amedeo Amedei, Lorenzo Memeo, Stefano Forte, and Dean W. Felsner*
  - 14.1 Introduction 473
  - 14.2 The Immune System 475
    - 14.2.1 Innate Immune Response 475
    - 14.2.2 Adaptive Immune Response 478
  - 14.3 Prioritized Chemicals 482
    - 14.3.1 Bisphenol A 482
    - 14.3.2 Polybrominated Diphenyl Ethers 483
    - 14.3.3 4-Nonylphenol 485
    - 14.3.4 Atrazine 485
    - 14.3.5 Phthalates 486
  - 14.4 Experimental Models of Carcinogenesis through Inflammation and Immune System Deregulation 487
  - 14.5 Antioxidants and Translational Opportunities 493
  - 14.6 Tumor Control of the Microenvironment 495
    - Acknowledgments 497
    - References 497

- 15 Metabolic Dysregulation in Environmental Carcinogenesis and Toxicology 511**  
*R. Brooks Robey*
- 15.1 Introduction 511
  - 15.2 Metabolic Reprogramming and Dysregulation in Cancer 513
    - 15.2.1 Carbohydrate Metabolism in Cancer 515
    - 15.2.2 Lipid Metabolism in Cancer 519
    - 15.2.3 Protein Metabolism in Cancer 521
  - 15.3 Moonlighting Functions 523
  - 15.4 Cancer Metabolism in Context 523
    - 15.4.1 The Gestalt of Intermediary Metabolism 523
    - 15.4.2 Cancer Tissues, Cells, and Organelles as Open Systems 527
    - 15.4.3 The Endosymbiotic Nature of Cancer 527
    - 15.4.4 Catabolic and Anabolic Support of Cell Proliferation 528
    - 15.4.5 Cancer Heterogeneity 529
    - 15.4.6 Phenotypic Relationships between Cancer Cells and Their Parental Cell Origins 532
    - 15.4.7 Evolutionary Perspectives of Metabolic Fitness and Selection in Cancer Development 533
  - 15.5 Dual Roles for Metabolism in Both the Generation and Mitigation of Cellular Stress 536
    - 15.5.1 Metabolism and Oxidative Stress 537
    - 15.5.2 Metabolism and Hypoxic Stress 539
    - 15.5.3 Nutritional Stress and Metabolism 539
    - 15.5.4 Metabolism and Physical Stress 540
    - 15.5.5 Metabolism and Other Forms of Cellular Stress 541
  - 15.6 Models of Carcinogenesis 541
    - 15.6.1 Traditional Multistage Models of Cancer Development 542
    - 15.6.2 Role of Replicative Mutagenesis in Cancer Development 543
    - 15.6.3 Acquired Mismatch Model of Carcinogenesis 543
  - 15.7 Potential Metabolic Targets for Environmental Exposures 546
    - 15.7.1 Conceptual Overview of Potential Metabolic Targets 546
    - 15.7.2 Identification of Key Targetable Contributors to Metabolic Dysregulation and Selection 549
      - 15.7.2.1 Glycolysis 555
      - 15.7.2.2 Lipogenesis, Lipolysis, and the PPP 555
      - 15.7.2.3 Citric Acid Cycle 556
      - 15.7.2.4 Organizational or Compartmental Targets 556
      - 15.7.2.5 Metabolite Transport Mechanisms 557
      - 15.7.2.6 Signal Transduction Effectors 558
  - 15.8 Metabolic Changes Associated with Exposures to Selected Agents 559

- 15.8.1 Selected Agents Classified by the World Health Organization's International Agency for Research on Cancer (IARC) 559
  - 15.8.1.1 IARC Group 1 (Carcinogenic to Humans) 560
  - 15.8.1.2 IARC Group 2A (Probably Carcinogenic to Humans) 564
  - 15.8.1.3 IARC Group 2B (Possibly Carcinogenic to Humans) 565
  - 15.8.1.4 Other Agents 565
- 15.8.2 Environmentally Relevant Combinatorial Exposures 567
  - 15.8.2.1 Occupational and Common Environmental Exposures 567
  - 15.8.2.2 Environmentally Relevant Low-Dose Combinatorial Exposures 568
  - 15.8.2.3 The Halifax Project 570
- 15.9 A Conceptual Overview of Traditional and Emerging Toxicological Approaches to the Problem of Cancer Metabolism: Implications for Future Research 571
  - 15.9.1 General Experimental Considerations in the Study of Metabolism *In Vitro* 571
  - 15.9.2 Systems Biology and Current Approaches to *In Vitro* Toxicology Screening 573
- 15.10 The Nosology of Cancer and Cancer Development 577
- 15.11 Discussion 579
  - Acknowledgments 583
  - References 583

**Part Five Biomarkers for Detecting Premalignant Effects and Responses to Protective Therapies during Critical Windows of Development 607**

- 16 Circulating Molecular and Cellular Biomarkers in Cancer 609**  
*Ilaria Chiodi, A. Ivana Scovassi, and Chiara Mondello*
  - 16.1 Introduction 609
  - 16.2 Proteins in Body Fluids: Potential Biomarkers 610
    - 16.2.1 Diagnostic Protein Biomarkers 612
    - 16.2.2 Prognostic Protein Biomarkers 613
    - 16.2.3 Protein Biomarkers of Drug Response 615
  - 16.3 Circulating Cell-Free Nucleic Acids 615
    - 16.3.1 Circulating Cell-Free Tumor DNA 616
      - 16.3.1.1 Cf-DNA Integrity, Microsatellite Instability, and LOH 617
      - 16.3.1.2 Tumor-Specific Genetic Alterations 617
      - 16.3.1.3 Tumor Genetic Alterations and Therapy Resistance 619
      - 16.3.1.4 Tumor Epigenetic Alterations: DNA Methylation 620
    - 16.3.2 Circulating Cell-Free RNA 621
      - 16.3.2.1 Circulating Cell-Free microRNA 621
  - 16.4 Extracellular Vesicles: General Features 624



- 16.4.1 Classification of EVs 624
- 16.4.2 EVs and Cancer 625
- 16.4.3 EVs as Mediators of Cell-To-Cell Communication 627
- 16.5 Circulating Tumor Cells 628
- 16.5.1 Two-Step Processing of Blood Samples: Enrichment and Identification of Circulating Tumor Cells 628
  - 16.5.1.1 CTC Number as a Cancer Biomarker 630
  - 16.5.2 Characterization of CTCs 630
    - 16.5.2.1 Molecular Characterization of CTCs 630
    - 16.5.2.2 Functional Characterization of CTCs 632
  - 16.5.3 Single CTCs *versus* CTC Clusters 634
  - 16.5.4 In Hiding Before Getting Home, the Long Journey of CTCs 635
- 16.6 Conclusions 635
- References 637
  
- 17 Global Profiling Platforms and Data Integration to Inform Systems Biology and Translational Toxicology 657**  
*Barbara A. Wetmore*
  - 17.1 Introduction 657
  - 17.2 Global Omics Profiling Platforms 659
    - 17.2.1 Genomics 659
    - 17.2.2 Epigenomics 661
    - 17.2.3 Transcriptomics 662
    - 17.2.4 Proteomics 665
    - 17.2.5 Metabolomics 668
  - 17.3 High-Throughput Bioactivity Profiling 669
    - 17.3.1 High-Throughput Bioactivity and Toxicity Screening 669
    - 17.3.2 *In Vitro*–*In Vivo* Extrapolation 671
  - 17.4 Biomarkers 672
  - 17.5 Exposomics 673
  - 17.6 Bioinformatics to Support and Data Integration and Multiomics Efforts 674
  - 17.7 Data Integration: Multiomics and High-Dimensional Biology Efforts 676
  - 17.8 Conclusion 679
  - References 679
  
- 18 Developing a Translational Toxicology Therapeutic Portfolio for Cancer Risk Reduction 691**  
*Rebecca Johnson and David Kerr*
  - 18.1 Introduction 691
  - 18.2 The Identification of Novel Predictors of Adverse Events 693
    - 18.2.1 Candidate Gene Studies 693
    - 18.2.2 Genome-wide Associations 694

18.2.3	Next-Generation Sequencing	695
18.3	Proof of Principle Toxgnostics	696
18.4	Proposed Protocol	698
18.4.1	Integration within Randomized Control Trials	698
18.4.2	Biobanking and Future-Proofing Samples	699
18.4.3	Data Protection and Full Consent	702
18.4.4	The Need for a Collaborative Approach	703
18.4.5	Open Access to Results	704
18.4.6	Translation from Bench to Bedside	705
18.5	Fiscal Matters	706
18.6	The Future of Toxgnostics	706
	References	707
<b>19</b>	<b>Ethical Considerations in Developing Strategies for Protecting Fetuses, Neonates, Children, and Adolescents from Exposures to Hazardous Environmental Agents</b>	<b>711</b>
	<i>David B. Resnik and Melissa J. Mills</i>	
19.1	Introduction	711
19.2	What Is Ethics?	712
19.2.1	Some Fundamental Ethical Values	712
19.2.1.1	Benefits and Costs	712
19.2.1.2	Individual Rights and Responsibilities	713
19.2.1.3	Justice	713
19.2.2	Value Conflicts and Ethical Decision-Making	713
19.3	Ethical Considerations for Strategies Used to Protect Fetuses, Neonates, Children, and Adolescents from Exposures to Harmful Environmental Agents	715
19.3.1	Education	715
19.3.2	Testing/Screening/Monitoring	717
19.3.3	Worker Protection	720
19.3.4	Government Regulation	722
19.3.5	Taxation	725
19.3.6	Civil Liability	726
19.3.7	Criminal Liability	729
19.4	Research with Human Participants	730
19.4.1	Return of Individualized Research Results	732
19.4.2	Protecting Privacy and Confidentiality	733
19.4.3	Interventional Studies	734
19.4.4	Intentional Exposure Studies	736
19.4.5	Protecting Vulnerable Participants	739
19.5	Conclusion	742
	References	742
	<b>Index</b>	<b>751</b>



## List of Contributors

***Amedeo Amedei***

Department of Experimental and  
Clinical Medicine  
University of Florence  
Firenze  
Italy

***David Berrigan***

Division of Cancer Control and  
Population Sciences  
National Cancer Institute  
National Institutes of Health  
Rockville, MD  
USA

***William H. Bisson***

Knight Cancer Institute  
Oregon Health & Science University  
Portland, OR  
USA

***Ilaria Chiodi***

Institute of Molecular Genetics  
Pavia  
Italy

***Annamaria Colacci***

Center for Environmental  
Toxicology and Risk Assessment  
Regional Agency for Prevention  
Environment and Energy  
Emilia Romagna Region  
Italy

***Eli P. Crapper***

Department of Obstetrics &  
Gynaecology  
McMaster University  
Hamilton  
Ontario  
Canada

***Dana C. Dolinoy***

Department of Environmental  
Health Sciences  
University of Michigan School of  
Public Health  
Ann Arbor, MI  
USA

Department of Nutritional Sciences  
University of Michigan School of  
Public Health, Ann Arbor, MI  
USA

**Dean W. Felsher**

Division of Oncology  
Departments of Medicine and  
Pathology  
Stanford University School of  
Medicine  
Stanford, CA  
USA

**Lynnette R. Ferguson**

Discipline of Nutrition and Dietetics  
and Auckland Cancer Society  
Research Centre  
Faculty of Medical and Health  
Sciences  
The University of Auckland  
Auckland  
New Zealand

**Lauren Fordyce**

Office of Behavioral and Social  
Sciences Research  
Office of the Director  
National Institutes of Health  
Bethesda, MD  
USA

**Stefano Forte**

Department of Experimental  
Oncology  
Mediterranean Institute of Oncology  
Viagrande (CT)  
Italy

**Katelyn J. Foster**

Department of Obstetrics &  
Gynaecology  
McMaster University  
Hamilton  
Ontario  
Canada

**Warren G. Foster**

Department of Obstetrics &  
Gynaecology  
McMaster University  
Hamilton  
Ontario  
Canada

Department of Reproductive Medicine  
University of California San Diego  
San Diego, CA  
USA

**Natalie R. Gassman**

Department of Oncologic Sciences  
University of South Alabama  
Mitchell Cancer Institute  
Mobile, AL  
USA

**Jaclyn M. Goodrich**

Department of Environmental  
Health Sciences, University of  
Michigan School of Public  
Health, Ann Arbor, MI  
USA

**Claude L. Hughes**

Therapeutic Science and Strategy Unit  
QuintilesIMS Inc.  
Morrisville, NC  
USA

Department of Obstetrics and  
Gynecology  
Duke University Medical Center  
Durham, NC  
USA

Department of Mathematics  
North Carolina State University  
Raleigh, NC  
USA

**Rebecca Johnson**

Nuffield Division of Clinical  
Laboratory Sciences  
Radcliffe Department of Medicine  
University of Oxford  
John Radcliffe Infirmary  
Headington  
Oxford  
UK

**Sandeep Kaur**

Nutritional Science Research Group  
Division of Cancer Prevention  
National Cancer Institute  
National Institutes of Health  
Rockville, MD  
USA

**David Kerr**

Nuffield Division of Clinical  
Laboratory Sciences  
Radcliffe Department of Medicine  
University of Oxford  
John Radcliffe Infirmary  
Headington  
Oxford  
UK

**Lorenzo Memeo**

Department of Experimental  
Oncology  
Mediterranean Institute of Oncology  
Viagrande (CT)  
Italy

**Melissa J. Mills**

Mills Consulting  
LLC  
Durham, NC  
USA

**Chiara Mondello**

Institute of Molecular Genetics  
Pavia  
Italy

**Luke Montrose**

Department of Environmental  
Health Sciences, University of  
Michigan School of Public Health,  
Ann Arbor, MI  
USA

**David B. Resnik**

National Institute of Environmental  
Health Sciences (NIEHS)  
Research Triangle Park, NC  
USA

**R. Brooks Robey**

White River Junction Veterans  
Affairs Medical Center  
White River Junction, VT  
USA

Geisel School of Medicine at  
Dartmouth  
Hanover, NH  
USA

**John M. Rogers**

Toxicity Assessment Division  
National Health and Environmental  
Effects Research Laboratory  
Office of Research and Development  
United States Environmental  
Protection Agency  
Research Triangle Park, NC  
USA

**A. Ivana Scovassi**

Institute of Molecular Genetics  
Pavia  
Italy

**Harold Seifried**

Nutritional Science Research Group  
Division of Cancer Prevention  
National Cancer Institute  
National Institutes of Health  
Rockville, MD  
USA

**Ronald D. Snyder**

RDS Consulting Services  
Mason, OH  
USA

**Shobha Srinivasan**

Division of Cancer Control and  
Population Sciences  
National Cancer Institute  
National Institutes of Health  
Rockville, MD  
USA

**Bernard W. Stewart**

Cancer Control Program  
South Eastern Sydney Public Health  
Unit and Faculty of Medicine  
University of New South Wales  
Sydney  
Australia

**Elaine Trujillo**

Nutritional Science Research Group  
Division of Cancer Prevention  
National Cancer Institute  
National Institutes of Health  
Rockville, MD  
USA

**Monica Vaccari**

Center for Environmental  
Toxicology and Risk Assessment  
Regional Agency for Prevention  
Environment and Energy  
Emilia Romagna Region  
Italy

**Suryanarayana V. Vulimiri**

National Center for Environmental  
Assessment  
Office of Research and Development  
United States Environmental  
Protection Agency  
Washington, DC  
USA

**Kylie Wasser**

Department of Human Kinetics  
Western University  
London  
Ontario  
Canada

**Michael D. Waters**

Michael Waters Consulting USA  
Hillsborough, NC  
USA

**Barbara A. Wetmore**

Office of Research and Development  
U.S. Environmental Protection  
Agency  
Research Triangle Park, NC  
USA

**Samuel H. Wilson**

Genome Integrity and Structural  
Biology Laboratory  
National Institute of Environmental  
Health Sciences (NIEHS)  
Research Triangle Park, NC  
USA

**Fengyu Zhang**

Global Clinical and Translational  
Research Institute  
Bethesda, MD  
USA

## **Part One**

**Introduction: The Case for Concern about Mutation and Cancer Susceptibility during Critical Windows of Development and the Opportunity to Translate Toxicology into a Therapeutic Discipline**



