

Contents

| | |
|--------------------------------------|-----------|
| <i>List of Figures and Tables</i> | xi |
| <i>Series Editor's Foreword</i> | xv |
| <i>Acknowledgments</i> | xvii |
| 1 Visceral Phenomena | 1 |
| 1.1 Blood and guts | 1 |
| 1.2 Aims and themes | 4 |
| 1.3 Plan of the book | 8 |
| Part I | |
| 2 Stem Cell Concepts | 15 |
| 2.1 Introduction | 15 |
| 2.1.1 Overview and aims | 15 |
| 2.1.2 Stem cell basics | 16 |
| 2.2 Consensus definition | 19 |
| 2.2.1 Self-renewal | 20 |
| 2.2.2 Differentiation | 22 |
| 2.3 Models: philosophical accounts | 25 |
| 2.4 Abstract stem cell model | 27 |
| 2.4.1 Structure | 27 |
| 2.4.2 Representational assumptions | 30 |
| 2.4.3 Specifying parameters | 32 |
| 2.4.4 Application | 34 |
| 2.5 Concrete methods | 34 |
| 2.5.1 Induced pluripotent stem cells | 34 |
| 2.5.2 Human embryonic stem cells | 36 |
| 2.5.3 Blood stem cells (1970s–1980s) | 37 |
| 2.6 Results | 39 |
| 2.6.1 Robust framework | 39 |
| 2.6.2 Conceptual divide | 40 |
| 2.7 Models and theories | 42 |
| 2.7.1 Unity and diversity | 42 |
| 2.7.2 Price's equation | 43 |
| 2.7.3 Models without theories | 45 |
| 2.8 Conclusions | 45 |

| | | |
|----------------|---|-----------|
| 3 | Don't Know What You've Got 'Til It's Gone: Evidence in Stem Cell Experiments | 48 |
| 3.1 | Structure of experiments | 48 |
| 3.2 | Exemplars revisited | 49 |
| 3.2.1 | Human embryonic stem cells | 50 |
| 3.2.2 | Mouse blood stem cells | 52 |
| 3.3 | Cells and populations | 53 |
| 3.3.1 | General form of the problem | 54 |
| 3.3.2 | Philosophical accounts | 55 |
| 3.3.3 | Evidential gap | 57 |
| 3.3.4 | Scientific response | 58 |
| 3.4 | Population-level models | 60 |
| 3.4.1 | Stochastic model | 60 |
| 3.4.2 | Spleen colony assay | 61 |
| 3.4.3 | Evidence for population-level models | 62 |
| 3.5 | The 'stem cell uncertainty principle' | 64 |
| 3.6 | Conclusions | 68 |
| 4 | A State of Uncertainty: Stemness and the Roles of Theory | 70 |
| 4.1 | The stemness alternative | 70 |
| 4.2 | Contrasting models | 73 |
| 4.3 | Evaluating models | 77 |
| 4.4 | Philosophical responses | 78 |
| 4.5 | General definition | 80 |
| 4.6 | Evidence for plasticity | 82 |
| 4.7 | Molecular genetic explanation | 85 |
| 4.8 | Conclusions | 87 |
| Part II | | |
| 5 | Mechanistic Explanation: The Joint Account | 91 |
| 5.1 | Introduction | 91 |
| 5.2 | Mechanisms | 92 |
| 5.3 | Law-based explanation | 96 |
| 5.4 | Causal explanation | 99 |
| 5.4.1 | The manipulability theory | 99 |
| 5.4.2 | The causal-mechanical account | 100 |
| 5.5 | Three problems | 100 |
| 5.5.1 | Ambiguity | 101 |
| 5.5.2 | Direction | 102 |
| 5.5.3 | Modularity | 104 |
| 5.5.4 | Motivating a new account | 106 |
| 5.6 | Jointness | 107 |

| | | |
|----------|---|------------|
| 5.7 | Joint account of mechanistic explanation | 110 |
| 5.7.1 | Jointness condition for mechanisms | 110 |
| 5.7.2 | Advantages | 111 |
| 5.7.3 | Jointness and unification | 114 |
| 5.8 | Conclusion | 115 |
| 6 | Genes and Development: The Stem Cell Perspective | 117 |
| 6.1 | Introduction | 117 |
| 6.2 | Genes as difference-makers | 119 |
| 6.3 | Specificity and mechanistic explanation | 121 |
| 6.4 | Cell reprogramming | 123 |
| 6.5 | Waddington's epigenetic landscape | 129 |
| 6.5.1 | Developmental pathways | 130 |
| 6.5.2 | Genetic control | 132 |
| 6.5.3 | Unification | 135 |
| 6.6 | Reprogramming and the landscape | 136 |
| 6.7 | Regulatory genes | 141 |
| 6.8 | Conclusion | 144 |
| 7 | Pluripotent Model Organisms | 146 |
| 7.1 | Introduction | 146 |
| 7.2 | Model organisms in experimental biology | 146 |
| 7.3 | An epistemic challenge | 148 |
| 7.4 | Stem cell lines as model organisms | 151 |
| 7.5 | Origins of pluripotency research | 154 |
| 7.5.1 | Embryonal carcinoma | 154 |
| 7.5.2 | Mouse ESC | 159 |
| 7.5.3 | Human ESC | 161 |
| 7.6 | Model epistemology | 165 |
| 7.7 | Conclusion | 169 |
| 8 | Social Experiments | 171 |
| 8.1 | Introduction | 171 |
| 8.2 | Experiment and theory | 173 |
| 8.3 | Blood stem cells (I) | 175 |
| 8.4 | Resolution of controversy | 179 |
| 8.4.1 | Advance | 179 |
| 8.4.2 | Not the real stem cells | 181 |
| 8.4.3 | Indiscriminate glamourization? | 182 |
| 8.5 | Blood stem cells (II) | 183 |
| 8.5.1 | Division of labor | 183 |
| 8.5.2 | Center of collaboration | 185 |
| 8.6 | Contrast in experimenting communities | 187 |

| | | |
|-----------------|--|------------|
| 8.7 | Further examples | 189 |
| 8.7.1 | Spleen colonies | 190 |
| 8.7.2 | Cancer stem cells | 191 |
| 8.8 | Conclusion | 192 |
| Part III | | |
| 9 | Integrating Stem Cell and Systems Biology | 197 |
| 9.1 | Introduction | 197 |
| 9.2 | Systems biology: overview | 197 |
| 9.3 | Mathematical modeling of cellular systems | 204 |
| 9.3.1 | Molecular mechanism | 204 |
| 9.3.2 | Wiring diagram | 205 |
| 9.3.3 | Formal framework | 206 |
| 9.3.4 | Solutions and derivation | 208 |
| 9.4 | Waddington's landscape revisited | 209 |
| 9.4.1 | Bottom-up regulatory networks | 209 |
| 9.4.2 | Top-side experiments | 211 |
| 9.5 | Explaining cell development | 213 |
| 9.6 | Models and experiments | 216 |
| 9.6.1 | Unifying models | 217 |
| 9.6.2 | Microarray experiments | 217 |
| 9.6.3 | General principles | 219 |
| 9.7 | Conclusion | 222 |
| 10 | Clinical Values | 224 |
| 10.1 | Introduction | 224 |
| 10.2 | Translational research | 224 |
| 10.3 | Value-free science | 227 |
| 10.4 | Values in stem cell biology | 231 |
| 10.5 | Conclusion | 235 |
| | <i>Notes</i> | 239 |
| | <i>Bibliography</i> | 251 |
| | <i>Index</i> | 261 |