Preface

Life and death, even at the level of the cell, are but opposite sides of the same coin. Just as the cell-generating process of mitosis is tightly regulated at the genetic and molecular level, so too is the cell-death process of apoptosis. Much of our understanding of programmed cell death, or apoptosis, of cells has come from a deluge of research output during the last decade of the 20th century. However, there are still considerable gaps in our knowledge and I expect that these will be filled slowly over the coming years. The excitement generated by research in the field stems mainly from the broad implications of our understanding of how the process is regulated, and how it may be manipulated in diseases and in developmental and commercial processes. The timely award of the Nobel Prize to Robert Horvitz from his seminal work on the regulation of programmed cell death in *Caenorhabditis elegans* indicates a certain maturity in the field.

I hope that this volume of essays, which covers most of the exciting areas of research in the field of apoptosis, will provide a snapshot of our knowledge at the beginning of the 21st Century. The volume begins with a historical view of the field from my own laboratory indicating when key discoveries were made and how they subsequently influenced the development of the field. This is followed by chapters from Justin McCarthy and Boris Zhivotovsky who explore the role of apoptosis in development and the function of the caspase enzyme cascade, both areas of sustained interest at present. Philippe Parone and colleagues document the role of the mitochondrion as a pivotal point in the execution phase of apoptosis and discuss the Jekyll-and-Hyde-type role played by cytochrome c. The chapter by Harald Wajant takes a look at the initiation phase of the whole process and the roles played by death receptors, in particular members of the tumour necrosis factor family.

Peter Daniel and colleagues look at the enigmatic Bcl-2 family of proteins and the controlling role they play in apoptosis. This is followed by three chapters from the laboratories of Andrew Phillips, Peter Henson and Thomas Brunner on the central role played by apoptosis in a frightening array of disease processes. In the Henson chapter, the focus is on the how the dead cells are removed, which in the scheme of things, is the last piece of the apoptosis jigsaw. The final two chapters from the Ian Hayes and Ian Dransfield laboratories attempt quite elegantly to peer into the future and see what it holds for this exciting field of research.

With a short volume of this sort on a subject as broad as apoptosis, there will invariably be gaps, but if the interest of the reader is sufficiently stimulated by what has been written, then perhaps these gaps can be filled by further reading in this exciting area of science. Material will not be a limitation!
Finally, my thanks go not only to the authors of each essay, but also to the staff of Portland Press, and in particular, Rhonda Oliver and Mike Cunningham who have steered me through the whole process. It has been an education!

Tom Cotter
Cork, Ireland,
July 2003
Tom Cotter is Professor and Chair of Biochemistry in University College Cork (Ireland). He graduated with a D.Phil. from the University of Oxford and studied as a postdoctoral fellow in Colorado, California and Germany before moving back to Ireland. He became interested in the field of apoptosis in 1990 and has worked to understand the role played by apoptosis in disease ever since. At present, he is the principle investigator of a large research group that studies apoptosis-inducing signalling in cancer and neurodegenerative disorders.

James Curtin obtained a B.Sc. in Biochemistry at University College Cork in 1999. He stayed in Cork to study Fas-receptor-mediated apoptosis in prostate cancer under the supervision of Tom Cotter and was awarded his Ph.D. in Biochemistry recently. James has accepted a postdoctoral fellowship in the Gene Therapeutics Research Institute, Los Angeles, CA. Here he will study the potential of gene therapy directed against brain tumours and neurodegenerative disorders.

Justin McCarthy obtained a Ph.D. in Biochemistry from University College Cork (Ireland) in 1996. He then undertook postdoctoral research on the cloning and characterization of genes and proteins involved in apoptosis in the laboratory of Vishva M. Dixit at the University of Michigan and Genentech Inc., South San Francisco, CA. Subsequently, he held a position as Senior Scientist at a biotechnology company, Scios Inc., Sunnyvale, CA. He was appointed as a Lecturer in Biochemistry at University College Cork in 2002. His present research interests involve the Presenilin genes and their involvement in neurodegeneration and the pathogenesis and progression of Alzheimer’s disease.

Boris Zhivotovsky received his Ph.D. in Biochemistry and Radiobiology in 1975 and his Dr. Sci. in 1989 in St. Petersburg (Russia). In 1991, he joined the group of Sten Orrenius at the Karolinska Institutet, Stockholm, Sweden, where he was later appointed Professor of Toxicology. His initial work on mechanisms of radiation-induced lymphoid cell death led to continued interest in understanding how radiation kills cells. At present, his general research interests are focused on cell death mechanisms of importance for the elimination of cancer cells; in particular, on deficiencies in apoptotic machinery of tumour cells resistant to treatment. His group made a notable contribution to characterization of caspases and their localization and translocation during apoptosis.

Philippe Parone obtained his doctoral thesis from the University of Cambridge (U.K.), following work on the role of the interaction between Bcl-2 family members in the regulation of neuronal apoptosis. He is currently
investigating the importance of mitochondrial fission in apoptosis and cell-cycle regulation. **Muriel Priault** obtained her doctoral thesis from the University of Bordeaux (France) following work on mitochondria and apoptosis, and, in the meantime, benefitted from a training in electrophysiology at the New York University. She then joined Jean-Claude Martinou’s laboratory where she works on the role of mitochondria in autophagy. **Dominic James** initially worked at EMBL exploring limb-pattern formation and the role of fibroblast growth factor-2 in embryonic development. His research focus shifted towards apoptosis and he undertook a Ph.D. at Manchester University (U.K.) studying the molecular mechanisms of apoptosis following growth factor withdrawal in blood cells. His work currently involves investigating the impact of mitochondrial fission on apoptotic pathways. **Steve Nothwehr** performed graduate work at Washington University in the laboratory of Jeffrey I. Gordon, where he studied signal peptidase processing of secretory proteins. After postdoctoral work with Tom H. Stevens at the University of Oregon he started his own laboratory at the University of Missouri where he has studied membrane trafficking in yeast. He is currently on research leave in the laboratory of Jean-Claude Martinou at the University of Geneva. **Jean-Claude Martinou** is Professor in the Department of Cell Biology at the University of Geneva. He is interested in the mechanisms of action of Bcl-2 family members and the role of mitochondria in cell death and in the processes that underlie mitochondrial fission and fusion.

**Harald Wajant** is Full Professor and Head of the Department of Internal Molecular Medicine at the Medical Polyclinic of the University of Wuerzburg (Germany). He received his Ph.D. degree in Biology from the University of Stuttgart in 1993. His current research interests are in the areas of apoptotic and non-apoptotic signalling by death receptors, and the development of death-ligand derivatives with cell-surface target-restricted activity for cancer treatment.

**Peter Daniel** was born on 16 December 1960 in Reutlingen, Germany. He undertook medical studies at the Eberhard Karls University in Tübingen, Germany, after which he became a post-doc at the Institute for Tumor Immunology, German Cancer Research Center, Heidelberg. He is a consultant in haematology and oncology. At present, he is group leader of the Molecular Hematology and Oncology Section at the University Medical Center Charité, Humboldt University, Berlin, Germany. His research focuses on the role of the CD95 death receptor in immune homoeostasis; the identification of defects in caspases and pro-apoptotic Bcl-2 family members in cancer; functional genomic analysis of apoptosis defects in human malignant tumours and their relevance to disease prognosis and the predictive value for responses to anti-cancer therapy. **Klaus Schulze-Osthoff** was born on 26 August 1960 in Münster, Germany. He studied biochemistry at the Westphalian Wilhelms University in Münster and became a post-doc at the Vlaams Institute of Biotechnology, Gent, Belgium. He was a group leader at
the Institute for Tumor Immunology, German Cancer Research Center in Heidelberg and at the Institute for Biochemistry, University of Freiburg, Germany. He also held the post of Associate Professor at the Universities of Tübingen and Münster. At presently, he is Director of the Institute for Molecular Medicine at the Heinrich Heine University, Düsseldorf, Germany. His research focuses on death-receptor signalling and the roles of caspases in apoptosis. **Claus Belka** was born on 15 May 1967 in Gelsenkirchen, Germany. He studied medicine at the University of Essen. He is a consultant in radiation oncology and group leader of Experimental Radiation Oncology Section at the Radiation Oncology Department of the Eberhard Karls University of Tübingen, Germany. Experimental work focuses on the role of Bcl-2 family members in radiation-induced apoptosis and the role of the endoplasmic reticulum. **Dilek Güner** was born on 2 November 1969 in Eskesehir, Turkey. She studied medicine at Hannover University and is now a specialist in radiation oncology at the Department of Radiation Oncology, University Medical Center Charité, Humboldt University, Berlin, Germany. Her research deals with apoptosis defects and Rb pathway cell-cycle deregulation in human malignant tumors and their relevance to disease prognosis and the predictive value for responses to radiation therapy.

**Mohamed Labazi** obtained a B.Sc. from the My Ismail University (Morocco), a Masters Degree from the St. Petersberg State Technical University, Russia and a Ph.D. from the University of Barcelona, Spain. After post-doctoral training with William S. Dynan, he took up a position as a research fellow in laboratory the laboratory of Andrew Phillips at the Institute of Molecular Medicine and Genetics, Augusta, GA. **Andrew C. Phillips** studied for a B.Sc. in genetics at the University of Nottingham (U.K.) and completed his Ph.D. at the Beatson Institute for Cancer Research in Glasgow (U.K.) After post-doctoral training with Karen H. Vousden at the Ludwig Institute, London and at the National Cancer Institute, Frederick, U.S.A., he took up a position as an Assistant Professor at the Institute of Molecular Medicine and Genetics, Augusta, GA. He is a Georgia Cancer Coalition Distinguished Scholar.

**Aimee M. deCathelineau** received her B.Sc. in Genetics and Cell Biology from the University of Minnesota, Twin Cities, MN, and her Ph.D. in Experimental Pathology from the University of Colorado Health Sciences in Denver, CO. She is currently a postdoctoral fellow with Dr Gary Bokoch at the Scripps Research Institute in La Jolla, CA. **Peter M. Henson** received his Veterinary degree from the University of Edinburgh and a Ph.D. in Immunology from the University of Cambridge. He spent 10 years as first a postdoctoral fellow and then faculty member at the Scripps Clinic and Research Foundation in La Jolla, CA, and since 1977 has been on the Faculty of the National Jewish Medical and Research Center and the University of Colorado Health Sciences Center in Denver, CO.
Thomas Brunner is Assistant Professor in Experimental Pathology at the Institute of Pathology, University of Bern, Switzerland. He has a long-standing research interest in the regulation of T-cell apoptosis and cytotoxicity in the pathogenesis of inflammatory diseases. Christoph Mueller is Associate Professor at the Institute of Pathology, University of Bern, Switzerland. His research focus has been in various fields of immunopathology, including the role of cell-mediated cytotoxicity in transplant rejection, auto-immune diabetes and inflammatory bowel disease.

Finbarr J. Murphy is Head of Apoptosis Biology at EiRx Therapeutics, an apoptosis drug discovery company based in Cork (Ireland). Before taking up a position at EiRx, he held a number of postdoctoral positions both in Ireland and the U.S.A., including an ORISE fellowship at the Food and Drug Administration, Bethesda, MD, where he examined the regulation of interleukin-12 secretion. He holds a Ph.D. from University College Dublin in the area of inflammation biology. His current research interests are survival pathways in inflammatory and transformed cells. Liam T. Seery is Head of BioInformatics and Discovery Biology at EiRx Therapeutics. Current research interests include the integration of genomic and proteomic data and development of systems solutions for in silico modelling of genetic regulatory networks. Ian Hayes is the Chief Executive Officer of EiRx Therapeutics. Over a number of years, he has pioneered the application of large-scale gene-transcription analysis (genomics) to the discovery of molecular control points in disease processes, including cancer (leukaemia/lymphoma) and inflammatory disease (asthma and arteriosclerosis). His interests include identification of novel apoptosis pathways.

Carol Ward received her Ph.D. in 1998 from the Department of Medicine, University of Edinburgh. She is currently undertaking postdoctoral research work in the Centre for Inflammation Research, University of Edinburgh, investigating mechanisms underlying the control of granulocyte apoptosis in the resolution of inflammation. Adriano G. Rossi completed his Ph.D. in 1987 at the Department of Pharmacology, University of Glasgow. After a post-doctoral fellowship at Wake Forest University, NC, he joined the National Heart and Lung Institute, Imperial College, London. He is currently a Senior Lecturer at the Centre for Inflammation Research, University of Edinburgh Medical School and throughout his career, has investigated the mechanisms that regulate inflammatory cell biology and the induction and resolution of inflammation. Chris Haslett is currently Head of the MRC Centre for Inflammation Research, Director of Research for the College of Medicine and Veterinary Medicine at the University of Edinburgh and Professor of Respiratory Medicine. He moved to Edinburgh in 1990 from the Royal Postgraduate Medical School at the Hammersmith Hospital, London to become Head of the Department of Respiratory Medicine. He later became the Head of the Division of Clinical Science and Community Health and was Associate Dean of
Research in the Faculty of Medicine. He is a Fellow of the Royal Society of Edinburgh and of the Royal College of Physicians. **Ian Dransfield** obtained his Ph.D. in 1988 from the University of Sheffield after studying monocyte functional and phenotypic heterogeneity. His postdoctoral research at the Imperial Cancer Research Fund, London, contributed to the characterization of a novel antibody that defined functional activity of these adhesion receptors. Ongoing studies, at the University of Edinburgh, of the intracellular signalling events in granulocytes, apoptotic-cell clearance by phagocytes and surface molecular changes associated with neutrophil apoptosis have revealed new ways in which inflammatory cell function can be controlled, which has profound implications for the control of inflammatory diseases.
**Abbreviations**

- ACAMP: apoptotic-cell-associated molecular pattern
- AIF: apoptosis-inducing factor
- ANT: adenine nucleotide translocase
- Apaf-1: apoptotic protease-activating factor 1
- APL: acute promyelocytic leukaemia
- ARF: alternative reading frame
- BH: Bcl-2 homology
- CDK: cyclin-dependent kinase
- cFLIP: cellular Flice-like inhibitory protein
- cIAP: cellular inhibitor of apoptosis protein
- CML: chronic myelogenous leukaemia
- DED: death effector domain
- Diablo: direct inhibitor-of-apoptosis-protein-binding protein
- DISC: death-inducing signalling complex
- DR: death receptor
- EAE: experimental allergic encephalomyelitis
- EDAR: ectodermal dysplasia receptor
- EGF: epidermal growth factor
- EGFR: epidermal growth factor receptor
- ER: endoplasmic reticulum
- FADD: Fas-associated death domain
- FcR: Fc receptor
- FDA: U.S. Food and Drug Administration
- FLIP: Flice-like inhibitory protein
- FMK: fluoromethylketone
- GFP: green fluorescent protein
- HDAC: histone deactylase
- HSP: heat-shock protein
- IkB: inhibitory κB
- IAP: inhibitor of apoptosis protein
- ICAM-3: intercellular cell-adhesion molecule 3
- ICE: interleukin-1β-converting enzyme
- IKK: inhibitory κB kinase
- IL: interleukin
- JNK: c-Jun N-terminal kinase
- MAPK: mitogen-activated protein kinase
- MEF: mouse embryo fibroblast
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-κB</td>
<td>nuclear factor κB</td>
</tr>
<tr>
<td>p75-NGFR</td>
<td>p75-nerve growth factor receptor</td>
</tr>
<tr>
<td>PARP</td>
<td>polyADP-ribose polymerase</td>
</tr>
<tr>
<td>PI 3-kinase</td>
<td>phosphoinositide 3-kinase</td>
</tr>
<tr>
<td>PLAD</td>
<td>pre-ligand-binding assembly domain</td>
</tr>
<tr>
<td>PS</td>
<td>phosphatidyserine</td>
</tr>
<tr>
<td>PSR</td>
<td>PS receptor</td>
</tr>
<tr>
<td>PTP</td>
<td>permeability transition pore</td>
</tr>
<tr>
<td>RAR</td>
<td>retinoic acid receptor</td>
</tr>
<tr>
<td>RIP</td>
<td>receptor-interacting protein</td>
</tr>
<tr>
<td>RXR</td>
<td>retinoid X receptor</td>
</tr>
<tr>
<td>Smac</td>
<td>second mitochondrial activator of caspases</td>
</tr>
<tr>
<td>SV40</td>
<td>simian virus 40</td>
</tr>
<tr>
<td>TCR</td>
<td>T-cell receptor</td>
</tr>
<tr>
<td>TNFα</td>
<td>tumour necrosis factor α</td>
</tr>
<tr>
<td>TNF-R</td>
<td>tumour necrosis factor receptor</td>
</tr>
<tr>
<td>TRADD</td>
<td>tumour necrosis factor receptor 1-associated death domain protein</td>
</tr>
<tr>
<td>TRAF</td>
<td>tumour necrosis factor receptor-associated factor</td>
</tr>
<tr>
<td>TRAIL</td>
<td>tumour necrosis factor-related apoptosis-inducing ligand</td>
</tr>
<tr>
<td>TRAIL-R</td>
<td>tumour necrosis factor-related apoptosis-inducing ligand receptor</td>
</tr>
<tr>
<td>VDAC</td>
<td>voltage-dependent anion channel</td>
</tr>
<tr>
<td>v-FLIP</td>
<td>viral Flice-like inhibitory protein</td>
</tr>
</tbody>
</table>