Preface

In all organisms, correct development, growth and function depends on the precise and exquisite control of the expression of the many thousands of genes comprising their genomes. The human genome is now estimated to contain around 30 000–40 000 genes and even the 'simple' bacterium, *Escherichia coli*, is encoded in about 4300 genes. Thanks to the heroic efforts of the Human Genome Project and other recent sequencing *tours de force* we now know the complete sequences of nearly all the genes of many different prokaryotic and eukaryotic organisms. However, it is not immediately apparent from these gene sequences how expression is regulated during development and in response to changes in the environment. Elucidating the mechanisms that control the processes leading to protein synthesis in the correct cell, at the precise time and in response to appropriate signals remains a major challenge in this 'post-genomic' era. The answers will not only be relevant to our understanding of the basic processes of gene expression, but will also be of immense practical importance in the application of gene therapy in medicine and the development of novel organisms for agriculture, for example.

The authors of the essays in this volume, all internationally recognized experts in their fields, have addressed many topical questions in gene regulation. The volume starts with a reiteration by Mark Ptashne and Alex Gann of a unifying hypothesis of transcriptional regulation by specific 'locators' or signals, frequently proteins (transcription factors), on the DNA which assist in the location of RNA polymerase(s) to the sites where transcription is to be initiated. More detailed descriptions of the process of transcription initiation and of the proteins that regulate it are given in the subsequent essays by Georgina Lloyd, Paolo Landini and Steve Busby and by Grace Gill. In recent years it has become clear that chromatin plays a fundamental and dynamic role in gene regulation and that alterations in chromatin structure can equip cells with a heritable 'memory' of the control state of particular genes. Hence, in his essay, Alan Wolffe discusses the roles of nucleosome structure and histone modification in the control of transcription, and Richard Meehan and Irina Stancheva provide an excellent illustration of the effects of the methylation state of DNA on gene transcription. Gene expression is a dynamic process that must be regulated in accordance with the needs of the organism in a constantly changing environment and according to the proliferative state of the cell. Melanie Lee and Stephen Goodbourn describe the mechanisms by which extracellular signals are transmitted to the nucleus, resulting in altered gene transcription, and Nick La Thangue and his colleagues review how transcriptional activity is cou-

pled to progression through the cell cycle. Although the regulation of transcription is generally the most significant step in modulating the expression of a gene, control of protein synthesis can also occur at subsequent post-transcriptional stages, including RNA processing and mRNA translation. In this area, Chris Proud provides us with an overview of translational processes that regulate gene expression. Many of the areas highlighted in these earlier essays are touched on by Martyn Link and David Harrison when they describe the cellular decision-making processes that come into play once the cell's DNA has been damaged. Thus extracellular and intracellular signals, post-translational control mechanisms and the proliferative state of the cells are all crucial factors in the cell's decision to proliferate or to undergo programmed cell death. The volume ends with a provocative look to the future by Nick Hastie. He highlights some of the exciting recent developments in gene regulation and points to the areas where dramatic progress in our understanding can be anticipated, generating much future excitement.

We thank all the contributors for their thought-provoking essays and for addressing the brief we gave them in such exciting ways. We are sure this volume will enable senior undergraduate and junior postgraduate students to appreciate the amazing subtlety and diversity of gene regulatory mechanisms and will hopefully encourage them to participate in the challenging research work that lies ahead in the Third Millennium.

Thanks are also due to our production editor, Sophie Dilley, and her colleagues at Portland Press for the high quality of the volume.

Karen Chapman (Edinburgh)
Steve Higgins (Leeds)
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Authors

Alexander Gann is Senior Editor at Cold Spring Harbor Laboratory Press. He received his PhD from Edinburgh University in 1988 before pursuing postdoctoral work at Harvard University and the Ludwig Cancer Research Institute at University College London. He was a Lecturer at Lancaster University for two years before moving to Cold Spring Harbor in 1999. **Mark Ptashne** is a professor at Memorial Sloan-Kettering Cancer Center in New York. He gained his PhD from Harvard in 1968. He was a Junior Fellow there before joining the faculty where he remained until moving to Sloan-Kettering in 1998. His research interests are focused on the basic mechanism of gene regulation

Georgina Lloyd obtained her Ph.D. from the University of Leeds, having worked on the purification and characterization of mammalian regulatory aminopeptidases in the laboratory of Tony Turner. Since 1995 she has pursued postdoctoral studies at the University of Birmingham, working with the *Escherichia coli* cAMP receptor protein and concentrating on the role of the RNA polymerase α subunit in transcriptional regulation. **Paolo Landini** obtained his doctorate from the University of Pavia in Italy, studying the interactions between bacterial DNA topoisomerases and DNA. During postdoctoral fellowships at the University of Massachusetts, and in Birmingham, he focused on the *E. coli* Ada protein, which is responsible for the adaptive response to alkylating mutagens. Paolo's work has aimed to understand the interactions of Ada with the different RNA polymerase subunits. Early in 1999, Paolo moved to the Swiss Institute for Environmental Science and Technology in Dübendorf, where he is working on molecular mechanisms of biofilm formation. **Steve Busby's** doctoral studies were concerned with understanding how protein conformation can be controlled by ligands. He was introduced to the marvels of microbial gene regulation and the intricacies of promoters during postdoctoral fellowships at the Institut Pasteur in Paris and the National Institutes of Health in Bethesda, Maryland. In 1983, Steve joined the University of Birmingham and, since then, he has continued active research in the area of microbial gene regulation. He is currently one of the Professors of Biochemistry in the School of Biosciences and is also the Dean of Science.

Grace Gill received her Ph.D. from Harvard University, where she studied the transcriptional activation function of GAL4 with Mark Ptashne. She was a postdoctoral fellow in the laboratory of Robert Tjian at the University of California, Berkeley, where she continued to investigate transcriptional activation mechanisms. Grace Gill is currently an Assistant Professor in the Department of Pathology at Harvard Medical School. She was an Instructor of the Eukaryotic Gene Expression Course at Cold Spring Harbor Laboratory

from 1997 to 2000. Current research in her laboratory is directed towards understanding how the activity of specific promoters and transcription factors is regulated during development of the nervous system.

Alan P. Wolffe is Senior Vice President and Chief Scientific Officer of Sangamo BioSciences Inc., a biotechnology company that designs transcription factors for therapeutic applications. From 1990 to 2000, Dr Wolffe was Director of the Department of Molecular Embryology at the National Institutes of Health. Dr Wolffe leads a research group that studies the regulation of gene expression. He has published more than 260 research papers on this topic and is currently an editor of: *Chromosoma, Chemtracts, European Journal of Biochemistry, Gene Therapy and Molecular Biology* and *Molecular Biology of the Cell.* He also serves on the Editorial Boards of: *Biochemistry, Biochemical Journal, Biochimica et Biophysica Acta, BioEssays, Current Genomics, Cell Research, Journal of Cell Science, Molecular and Cellular Biology, Nucleic Acids Research* and *Science.* Dr Wolffe has received several prizes for his research, and he has organized AACR, ASCB and ASMB Symposia, FASEB Conferences, Juan March Foundation Workshops, Keystone Symposia and Novartis Foundation Symposia. He has served on numerous Federal and International scientific advisory boards.

Richard Meehan undertook his Ph.D. at Edinburgh on the genetics of drug detoxification systems in mice, with Nick Hastie and Roland Wolffe. He then worked with Adrian Bird in the Institute of Molecular Pathology, Vienna, where he purified methyl-CpG binding protein 2 (MeCP2), which paved the way for the subsequent isolation of other methyl-CpG binding proteins. He returned to Edinburgh where, at the Institute of Cell and Molecular Biology, where his attempts to isolate MeCP1 revealed it to be a multi-component complex. Subsequently, he became a lecturer at the Department of Biomedical Science at Edinburgh, and began a more rewarding analysis of the role of DNA methylation in *Xenopus* development. **Irina Stancheva** graduated from the University of Sofia, and undertook her Masters degree at the Institute of Cell Biology of the Bulgarian Academy of Sciences, under the supervision of Luchezar Kargyozov. Here, she began working on DNA methylation and developed a technique for formaldehyde cross-linking which allows one to distinguish between active and inactive gene loci. This, together with some studies on DNA re-methylation after the passage of the replication fork, became the topic of her Ph.D., which was awarded by the Swiss Federal Institute of Technology where she worked with Theodor Koller and Jose M. Sogo. She is currently working with Richard Meehan on the role of DNA methylation in *Xenopus* development.

Melanie Lee obtained a B.Sc. in Biochemistry from the University of Manchester Institute of Science and Technology in 1993 and a Ph.D. in Biochemistry from St.George's Hospital Medical School, University of London in 1997. She is currently a post-doctoral fellow at the Marie Curie

Cancer Research Institute where, she is studying the control of gene regulation in melanocytes and melanomas. **Stephen Goodbourn** obtained a B.A. in Biochemistry from the University of Oxford in 1979 and a D.Phil. in Clinical Medicine from the University of Oxford in 1983, and was a post-doctoral fellow in the Department of Biochemistry and Molecular Biology at Harvard University from 1983 to 1987. He was head of the Gene Expression Laboratory at the Imperial Cancer Research Fund in London from 1987 to 1994, and since then has been a senior lecturer in Biochemistry and Immunology at St. George's Hospital Medical School, University of London. His research interests include the control of cytokine gene expression and the interactions between viral infections and cell signalling.

Ho Man Chan is a final year student supported by the Wellcome Trust. **Noriko Shikama** is a postdoctoral fellow, supported by an EMBO Fellowship, having completed her graduate studies at the University of Basel. **Nicholas La Thangue** is the Cathcart Professor of Biochemistry at the University of Glasgow, and was previously a staff scientist at the MRC National Institute for Medical Research.

Chris Proud carried out his Ph.D. work at the University of Dundee on the role of protein phosphorylation in the regulation of glycogen metabolism. He was introduced to the field of mRNA translation during his post-doctoral work in Jenny Pain's laboratory at Sussex University and has remained in this research area ever since. During his subsequent research at Bristol and Kent he explored the regulation of a number of translation factors by phosphorylation and studied the protein kinases and phosphatases which act upon them. He now leads a group at the University of Dundee which applies a wide range of techniques to investigate the structure and regulation of a number of translation factor proteins and their roles in the control of gene expression in mammals and fruit flies.

Martyn Link graduated from the University of Edinburgh in 1997, after which he began an MRC studentship investigating the modulation and mechanism of cell death in the pancreatic β-cell. **David Harrison** is Professor of Pathology at the University of Edinburgh. He is interested in the cell biology of apoptosis and the factors that influence why the same injury may cause different effects in different cell lineages in different environmental conditions. He is a graduate of medicine from Edinburgh University and has clinical interests in the diagnosis of liver and pancreatic disease.

Nick Hastie is Director of the Medical Research Council Human Genetics Unit in Edinburgh. Over his career he has worked in several areas, including developmental gene expression, genome organization, telomeres and developmental genetics. During the past decade he has focused on the childhood cancer Wilms' tumour, and the multiple functions of the Wilms' tumour-suppressor gene, *WT1*. From 1990 to 1997 he was the European Editor of *Genes & Development* and he continues to sit on the Editorial Board of this journal.

Abbreviations

Apaf	apoptotic protease-activating factor
APC	adenomatous polyposis coli
ATF	activating transcription factor
BAF	BRG1-associated factor
BH domain	Bcl-2 homology domain
BRG	*Brahma*-related gene
CAP	catabolite gene activator protein
CBP	CREB-binding protein
CDC	cell division cycle
CDK	cyclin-dependent kinase
CREB	cAMP-response-element-binding protein
CRP	cAMP receptor protein
αCTD	C-terminal domain of RNA polymerase α subunit
DAG	diacylglycerol
Dnmt	DNA methyltransferase
DPE	downstream promoter element
dsRNA	double-stranded RNA
4E-BP	eIF4E-binding protein
eEF	eukaryotic elongation factor
eIF	eukaryotic initiation factor
ER	endoplasmic reticulum
ERK	extracellular signal-related protein kinase
FADD	Fas-associated death domain
GEF	GDP/GTP exchange factor
Grb2	growth-factor-receptor-bound protein 2
GSK	glycogen synthase kinase
GTF	general transcription factor
HDAC	histone deacetylase
HNF	hepatocyte nuclear factor
Inr	initiator (of transcription)
IP_3	inositol 1,4,5-trisphosphate
IRE	iron response element
IRF	interferon regulatory factor
IκB	inhibitor of NK-κB
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinase
MAPKK	MAPK kinase

MAPKKK	MAPK kinase kinase
MBD	methylated-DNA-binding domain
^{5}mC	cytosine methylated at position 5
MDM2	murine double minute clone 2 oncoprotein
MeCP	methylated-CpG-binding protein
^{Me}CpG	methylated CpG
MEK-1	MAP kinase/ERK kinase
Met-tRNA	methionyl-tRNA
MPTP	mitochondrial permeability transition pore
NFAT	nuclear factor of activated T-cells
NF-κB	nuclear factor κB
αNTD	N-terminal domain of RNA polymerase α subunit
ORF	open reading frame
PDGF	platelet-derived growth factor
PERK	PKR-like ER-resident kinase
PIP_2	phosphatidylinositol 4,5-bisphosphate
PIP_3	phosphatidylinositol 3,4,5-bisphosphate
PKA	protein kinase A
PKR	dsRNA-activated protein kinase
PLC	phospholipase C
PP	pocket protein
pRb	protein product of the retinoblastoma tumour suppressor gene
PV	polio virus
Rb	retinoblastoma
RNAP	DNA-dependent RNA polymerase holoenzyme
SH	Src homology
SNF	sucrose non-fermenting in *Saccharomyces cervisiae*
SRB	suppressor of RNA polymerase B
SRF	serum response factor
STAT	signal transduction and activator of transcription
SWI	mating-type switching in *Saccharomyces cervisiae*
TAF_{II}	TATA-box-binding-protein-associated factor
TBP	TATA-box-binding protein
TNF	tumour necrosis factor
TOP	tract of pyrimidine
(m)TOR	(mammalian) target of rapamycin
UPE	upstream element
UTR	untranslated region