Preface

All cells carry out a programme of renewal, continually degrading and synthesizing their components. As each new molecule is synthesized it must find its way to a specific location within the cell. Often the targets are membrane-bound compartments called organelles. The lipid membrane surrounding each organelle serves to keep some macromolecules in — for example, proteins and nucleic acids — while excluding others. This level of cellular organization allows a defined set of biochemical reactions to be carried out within each specific compartment. The synthesis of RNA from its DNA template, for example, takes place within the nucleus of eukaryotic cells, whereas, in plant cells, the biochemical reactions of photosynthesis are carried out within chloroplasts. Protein synthesis takes place within the cytoplasm, whereas RNA is synthesized, for the most part, within the nucleus. Proteins and RNA often carry out their functions within cellular compartments different from those in which they were synthesized and must, therefore, traverse lipid membranes that are normally impermeable. As a result, the cell must be able to transport these macromolecules across lipid membranes to the site where they ultimately function.

The topic of this volume of *Essays in Biochemistry* is molecular trafficking. The 10 review articles that follow discuss the mechanisms and machinery that facilitate the trafficking of proteins and nucleic acids across different organelles within a variety of cell types. The timeliness of this volume is exemplified by the fact that the 1999 Nobel Prize in Physiology or Medicine was awarded to Dr Günter Blobel for the discovery that "proteins have intrinsic signals that govern their transport and localization in the cell". Dr Blobel's Nobel Prize-winning research demonstrated that proteins contain specific intrinsic signals — address tags — which govern their transport to specific intracellular organelles. As illustrated in the following essays, this simple signal hypothesis has been used by cells to solve a diverse set of problems from transport of proteins into the endoplasmic reticulum, chloroplasts or mitochondria, to shuttling of proteins and nucleic acids in and out of the nucleus.

The basic theme — that a specific signal contained within each macromolecule is recognized by a cellular machine to transport that molecule across a pore within the lipid membrane — is first described in Chapter 1 and reiterated in subsequent chapters. There is substantial diversity to this molecular theme. Not only do the signals differ, as would be expected for address tags, but, in addition, the transporters themselves share only a superficial similarity. Membrane pores seem to be a ubiquitous feature, but their characteristics dif-

fer depending on the organelle in which they are present. This is due, in part, to the structural differences between each of the organelles, i.e. the complex lipid bilayer of the nucleus versus the cisternal organization of the mitochondrion. The differences in pore structures may also further regulate the types of molecule that traverse the different membranes and the directionality of the transport. As will be seen in Chapters 7, 8 and 10, the complexity of the nuclear pore and its associated transport machinery may be due to the necessity to transport chemically diverse molecules — proteins and nucleic acids — in a bi-directional manner (in and out of the nucleus). Chloroplasts and mitochondria (Chapters 5 and 6) generally only transport proteins in a single direction; however, these structurally complex organelles have had to solve the problem of targeting proteins across one or several membranes of the cisternae. Although their pore structure appears less complex than the nuclear pore, a unique set of mechanisms and machinery allows for the regulated targeting required by these organelles. The address tags themselves can be modified. In Chapter 3, glycosylation, a post-translational event that specifically allows a subset of proteins to be targeted to different intracellular or extracellular locations, is described. Similarities between molecular targeting and secretion are examined in Chapter 4 in the context of bulk flow. Although pore structures are not involved in secretory vesicle trafficking, some of the principles used to target proteins to specific organelles also apply to the transport of vesicles. Chapters 2 and 9 discuss how molecular trafficking shapes specific biological events, immunological surveillance and gene regulation, respectively.

As each cell and organelle issues its own diverse set of problems in targeting newly synthesized macromolecules, it will be fascinating to learn how the common themes discussed in this volume continue to develop and diverge.

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Authors

Suzanna Meacock studied Biochemistry at the University of Manchester and stayed in Manchester to carry out her Ph.D. in Stephen High's laboratory. Suzanna's work focused on the biogenesis of polytopic integral membrane proteins and she was awarded her Ph.D. in January 2000. Suzanna is presently training to become a patent attorney. **Julie Greenfield** carried out her Ph.D. studies at the Institute of Arable Crops Research, Long Ashton, Bristol, before joining Stephen High's group as a postdoctoral research associate. Julie's postdoctoral research focused on the structure/function of the endoplasmic reticulum and in particular on the subcellular localization of ER translocon components. Julie is now working in biomedical publishing. **Stephen High** has a long-standing interest in membrane-protein biogenesis at the endoplasmic reticulum. This originated from his Ph.D. studies of red-cell membrane proteins and continued during his time as an EMBO fellow with Bernhard Dobberstein. For the past decade Stephen has been studying various aspects of membrane-protein biosynthesis with his own research group in Manchester. His current interests include membrane insertion, chaperone-mediated protein folding and the relationship between the misfolding of membrane proteins and specific diseases. He is currently a Professor of Biochemistry at the University of Manchester.

Christopher Nicchitta received his B.Sc. in Biology at the College of William and Mary in 1981 and his Ph.D. in Biochemistry/Biophysics from the University of Pennsylvania in 1987. He then moved to Rockefeller University, New York, where he was a postdoctoral fellow in Dr Günter Blobel's laboratory from 1988 to 1993. Following his postdoctoral studies, he moved to Duke University as an Assistant Professor of Cell Biology and was promoted to Associate Professor in 2000. **Robyn Reed** received her B.Sc. in Biology at Wake Forest University in 1996. She is currently a fourth-year M.D./Ph.D. student at Duke University, working towards a Ph.D. in Cell Biology.

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ing on ER-Golgi cycling proteins during his postdoctoral studies at EMBL, and is now investigating sorting at the *trans*-Golgi network.

Francis Barr did his Ph.D. with Professor Wieland Huttner in the Cell Biology programme of the EMBL in Heidelberg, looking at the formation of secretory granules from the *trans*-Golgi network in neuroendocrine cells. While working as a postdoc in the laboratory of Graham Warren at the ICRF in London he started to look for proteins involved in establishing the stacked structure of the Golgi apparatus, which lead to the discovery of the GRASP proteins. He then became an independent researcher at the University of Glasgow, and has recently moved to the Max Planck Institute for Biochemistry in Munich to take up a position as a group leader.

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Michael Rout is a Rita Allen Foundation Scholar, a recipient of an Irma T. Hirschl Career Scientist Award, and Assistant Professor and Head of the Laboratory of Cellular and Structural Biology at the Rockefeller University in New York. He obtained his Ph.D. at the MRC Laboratory of Molecular Biology and the University of Cambridge in 1989, and then joined Günter Blobel's laboratory at Rockefeller University for postdoctoral studies. During his Ph.D. he isolated the spindle organizer from yeast, and building on this expertise isolated the yeast nuclear pore complex in Blobel's laboratory. **John Aitchison** is an Assistant Professor and MRC and Heritage Scholar at the University of Alberta in Canada. He obtained his Ph.D. at McMaster University in Hamilton, Canada, in 1992 and then joined Günter Blobel's laboratory at Rockefeller University. During his Ph.D. studies under the direc-

tion of Dr Richard Rachubinski, he developed a molecular assay system to study peroxisomal biogenesis in the yeast. Together in Blobel's laboratory, Drs Aitchison and Rout collaborated on several projects to identify and characterize components of the yeast nuclear pore complex and many novel transport factors that mediate protein import into the nucleus. In their own laboratories, Dr Aitchison is concentrating on the soluble factors while Dr Rout continues to study the structure of the nuclear pore complex.

Dianne Barry received a Ph.D. in Neurobiology from Washington University School of Medicine in 1997 after having completed her thesis work on the molecular correlates of the mammalian cardiac current, I_{to}. She completed postdoctoral training in the laboratory of Dr Susan Wente, where she examined the role of the nuclear pore complex-associated protein, hGle1p, in the vertebrate mRNA-export pathway. She is currently employed by the Bayer Chemical Company. **Susan Wente** is an Associate Professor of Cell Biology and Physiology at Washington University School of Medicine. She received her Ph.D. in Biochemistry from the University of California, Berkeley, in 1988 with Dr Howard Schachman. After a 1-year fellowship with Dr Ora Rosen at the Memorial Sloan Kettering Cancer Center, she began her studies of nuclear transport with Dr Günter Blobel at The Rockefeller University, New York. In 1993, Dr Wente was named an Assistant Professor at the Washington University School of Medicine, and was promoted to Associate Professor in 1998. Recent research efforts have focused on using yeast and vertebrate model systems to understand the mechanism of nuclear transport and the pathway of nuclear pore complex assembly.

Mary Shannon Moore is an Assistant Professor in the Department of Molecular and Cellular Biology at Baylor College of Medicine in Houston. She received her Ph.D. from the University of Texas Southwestern Medical Center in Dallas and did a postdoctoral fellowship at Rockefeller University, New York, prior to joining the Baylor faculty. **Eric D. Schwoebel** received his Ph.D. at Baylor College of Medicine, worked at the Institute for Primate Research in Nairobi, Kenya, as a senior research scientist, and is currently a postdoctoral fellow in Dr Moore's laboratory.

Matthew E. Harris received his Ph.D. from the Biology Department at the University of California, San Diego, in 1999. He received his B.Sc. in Biology from Harvey Mudd College in 1993. Presently, he is a commissioned officer in the United States Army serving at the Walter Reed Army Institute of Research. **Thomas J. Hope** is an Assistant Professor at the Salk Institute for Biological Studies in the Infectious Disease Laboratory. Dr Hope received his Ph.D. from the University of California, Berkeley, in 1988. He was a postdoctoral fellow at the University of California, San Francisco, from 1988 to 1992, where he started his studies of the post-transcriptional regulation of viral gene expression. Presently, his research is directed towards understanding RNA processing and export using viral models on intronless messages.

Abbreviations

cNLS	classical nuclear localization sequence
CTE	constitutive transport element
$\Delta\Psi$	membrane potential
ER	endoplasmic reticulum
ERGIC-53	ER-Golgi intermediate-compartment protein of 53 kDa
GIP	general insertion pore
GR	glucocorticoid receptor
HBV	hepatitis B virus
HIV	human immunodeficiency virus
hnRNP	heterogenous nuclear ribonucleoprotein
HSV	herpes simplex virus
IM	inner membrane
IMS	intermembrane space
LHCP	light-harvesting chlorophyll a/b-binding protein
LMB	leptomycin B
LR-NES	leucine-rich nuclear export sequence
LTD	thylakoid luminal targeting domain
MDCK	Madin–Darby canine kidney
MHC	major histocompatability complex
MPMV	Mason–Pfizer monkey virus
MPP	matrix-processing peptidase
MSF	mitochondrial-import-stimulating factor
mt-Hsp70	mitochondrial Hsp70
NE	nuclear envelope
NES	nuclear export sequence
NLS	nuclear localization sequence
NPC	nuclear pore complex
NSF	*N*-ethylmaleimide-sensitive fusion protein
NUP	nucleoporin
OM	outer membrane
PDI	protein disulphide isomerase
PPE	pre-mRNA processing enhancer
RanBP1	Ran-binding protein 1
RanGAP	Ran-GTPase-activating protein
RNP	ribonucleoprotein
RRE	Rev-responsive element
SNAP	soluble NSF attachment protein
SNARE	soluble NSF attachment protein receptor

snRNA	small nuclear RNA
snRNP	small nuclear ribonucleoprotein
SREBP	sterol regulatory-element-binding protein
SRP	signal-recognition particle
SRP54	54 kDa polypeptide of SRP
STD	stromal-targeting domain
TAP	transporter associated with antigen presentation
TK	thymidine kinase
TRAM protein	translocating-chain-associating membrane protein
VIP36	vesicular integral membrane protein of 36 kDa