MOLECULAR PHARMACOLOGY

From DNA to DRUG DISCOVERY

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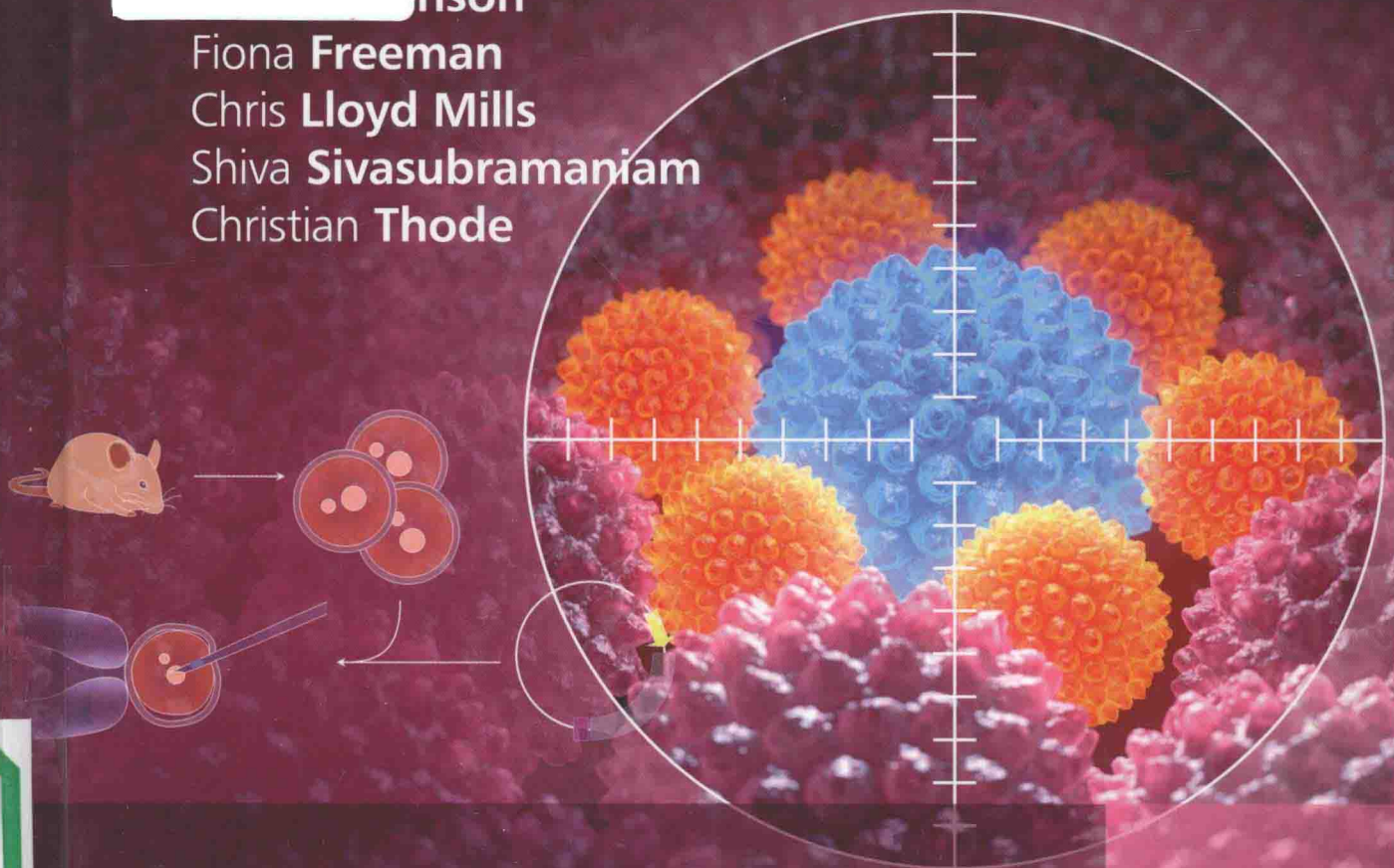
Fiona **Freeman**
Chris **Lloyd Mills**
Shiva **Sivasubramaniam**
Christian **Thode**



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Molecular Pharmacology

From DNA to Drug Discovery

John Dickenson, Fiona Freeman, Chris Lloyd Mills, Shiva Sivasubramaniam and Christian Thode
Nottingham Trent University

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Preface

Nottingham Trent University offers a suite of successful MSc courses in the Biosciences field that are delivered by full-time, part-time and distance (e-learning) teaching. The authors are members of the Pharmacology team at Nottingham Trent University and teach extensively on the MSc Pharmacology and Neuropharmacology courses. The content of this book was inspired by these courses as there is no comparable postgraduate textbook on molecular pharmacology and it is a rapidly expanding subject. The primary aim of this text was to provide a platform to complement our courses and enhance the student experience. Given the breadth and depth of this volume it will be of use to students from other institutions as a teaching aid as well as an invaluable source of background information for post-graduate researchers. The value of this book is enhanced by the research portfolio of the Bioscience Department and individual authors who have research careers spanning over 25 years.

This textbook illustrates how genes can influence our physiology and hence our pharmacological response to drugs used to treat pathological conditions. Tailoring of therapeutic drugs is the future of drug design as it enables physicians to prescribe personalised medical treatments based on an individual's genome. The book utilises a drug target-based approach rather than the traditional organ/system-based viewpoint and reflects the current advances and research trends towards *in silico* drug design based on gene and derived protein structure.

The authors would like to thank Prof Mark Darlison (Napier University, Edinburgh, UK) for providing the initial impetus, inspiration and belief that a book of such magnitude was possible. We would also like to acknowledge the unflagging encouragement and support of the Wiley-Blackwell team (Nicky, Fiona and Clara) during the preparation of this work. Finally thanks should also be given to the helpful, constructive and positive comments provided by the reviewers. We hope that you enjoy this book as much as we enjoyed writing it.

John Dickenson, Fiona Freeman, Chris Lloyd Mills, Shiva Sivasubramaniam and Christian Thode.

Abbreviations

$[Ca^{2+}]_i$	intracellular free ionised calcium concentration
$[Ca^{2+}]_n$	nuclear free ionised calcium concentration
$[Ca^{2+}]_o$	extracellular free ionised calcium concentration
2-APB	2-aminoethoxydiphenyl borate
4EFmut DREAM	4^{th} EF hand mutant DREAM
5F-BAPTA	1,2-bis(2-amino-5,6-diflurophenoxy) ethane-N,N,N′,N′-tretracacetic acid
5-HT	5-hydroxytyrptamine / serotonin
AAV	adeno-associated virus
ABC	ATP-binding cassette (transporter)
AC	adenylyl cyclase
ACC	mitochondrial ADP/ATP carrier (transporter)
ACh	acetylcholine
ACS	anion-cation subfamily
AD	Alzheimer's disease
ADAR	adenosine deaminase acting on RNA (1, 2 or 3)
ADCC	antibody-dependent cellular cytotoxicity
ADEPT	antibody-directed enzyme pro-drug therapy
ADHD	attention deficit hyperactivity disorder
AF1/2	transcriptional activating function (1 or 2)
Ala	alanine (A)
AM	acetoxylmethyl
AMPA	α-amino-3-hydroxy-5-methylis oxazole 4-propionic acid
Apo-	apolipoproteins (A, B or C)
APP	amyloid precursor protein
AQP	aquaporins
ARC channels	arachidonic acid regulated Ca^{2+} channels
Arg	arginine (R)
ASIC	acid sensing ion channels
ASL	airways surface liquid
Asn	asparagine (N)
Asp	aspartic acid (D)
ATF1	activation transcription factor 1
ATP	adenosine triphosphate
AV	adenovirus
Aβ	amyloid β peptide
BAC	bacterial artificial chromosome
BBB	blood brain barrier
BCRP	breast cancer resistant protein
BDNF	brain-derived neurotrophic factor
BK_{Ca}	big conductance Ca^{2+}-activated K^+ channels
BLAST	Basic Local Alignment Search Tool
bp	base pairs
BRET	bioluminescence resonance energy transfer
Brm/brg1	mammalian helicase like proteins
BTF	basal transcription factors
BZ	benzodiazepine
Ca-CaM	Ca^{2+}-calmodulin
CaCC	calcium activated chloride channel
cADPr	cyclic adenosine diphosphoribose
CaM	calmodulin
CaMK	calcium-dependent calmodulin kinase
cAMP	cyclic adenosine 3′,5′ monophsophate
CaRE	calcium responsive element
catSper	cation channels in sperm
Ca_V	voltage-gated Ca^{2+} channels
CBAVD	congenital bilateral absence of the vas deferens

CBP	CREB binding protein
CCCP	carbonyl cyanide *m*-chlorophenylhydrazone
CCK	cholecystokinin
CDAR	cytosine deaminase acting on RNA
cDNA	complementary DNA
CDR	complementarily-determining region
CF	cystic fibrosis
CFP	cyan fluorescent protein
CFS	colony stimulating factors
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	cyclic guanosine 3′,5′ monophosphate
CHF	congestive heart failure
CHO	Chinese hamster ovary cell line
CICR	calcium induced calcium release
CIF	calcium influx factor
CIC	chloride channel
CMV	cytomegalovirus
CNG	cyclic nucleotide-gated channel
CNS	central nervous system
CNT	concentrative nucleoside transporter
COS	CV-1 cell line from Simian kidney cells immortalised with SV40 viral genome
COX	cyclooxygenases (1, 2 or 3)
CPA	monovalent cation/proton antiporter super family
CpG	cytosine-phosphate-guanine regions in DNA
CPP	cell penetrating peptide (transporter)
CRE	cAMP responsive element
CREB	cAMP responsive element binding protein
CREM	CRE modulator
CRF	corticotropin-releasing factor
CRM	chromatin remodelling complex
CRTC	cAMP-regulated transcriptional co-activator family
CSF	cerebral spinal fluid
CTD	C terminal domain
CTL	cytotoxic T lymphocyte
CYP	cytochrome P_{450}
Cys	cysteine (C)
DAG	diacylglycerol
DAX1	dosage-sensitive sex reversal gene/TF
DBD	DNA-binding domain
DC	dicarboxylate
DHA	drug:H^+ antiporter family (transporter)
Dlg1	drosophila disc large tumour suppressor
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
DPE	downstream promoter element
DRE	downstream regulatory element
DREAM	DRE antagonist modulator
dsRNA	double-stranded RNA
EBV	Epstein Barr virus
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGTA	ethylene glycol tetraacetic acid
ELISA	enzyme linked immunosorbent assay
ENaC	epithelial sodium channel
EPO	erythropoietin
ER	endoplasmic reticulum
ERK	extracellular-signal-regulated kinases
eRNA	enhancer RNA
ERTF	oestrogen receptor transcription factor
ES cells	embryonic stem cells
ESE	exon splicing enhancer
ESS	exon splicing silencer
EST	expressed sequence tag
Fab	antibody binding domain
FACS	fluorescent-activated cell sorting
Fc	constant fragment of the monoclonal antibodies
FEV_1	forced expiratory volume in 1 second
FGF-9	fibroblast growth factor
FIH	factor inhibiting HIF
FISH	fluorescence *in situ* hybridisation
FOXL2	fork-head box protein
FRET	fluorescence resonance energy transfer
FXS	fragile-X syndrome
G3P	glucose-3-phosphate
GABA	gamma-aminobutyric acid
GAT	GABA transporters
GC	guanylyl cyclase
GFP	green fluorescent protein
GIRK	G-protein-gated inwardly rectify K^+ channel
Gln	glutamine (Q)
GlpT	sn-glycerol-3-phosphate/phosphate antiporter
GltPh	Pyrococcus horikoshii glutamate transporters
Glu	glutamic acid (E)
GLUT	glucose transporters
Gly	glycine (G)
GLYT	glycine transporters

GMP	guanosine monophosphate
GPCR	G protein coupled receptor
GPN	glycyl-L-phenylalanine-2-napthylamide
GRK	G-protein coupled receptor kinase
GST	Glutathione S-transferase
H^+	hydrogen ion; proton
HAD	histone deacetylases
HAMA	human anti-murine antibodies
HAT	histone acetyltransferases
HCF	host cell factor
HCN	hyperpolarisation-activated cyclic nucleotide-gated channels
HDL	high density lipoprotein
HIF	hypoxia inducible factor
His	histidine (H)
HMG	high mobility group
HMIT	H^+/myo-inositol transporter
hnRNP	nuclear ribonucleoproteins
HOX	homeobox
HPLC	high-performance liquid chromatography
HRE	hypoxia response elements
Hsp70	heat shock protein of the 70 kilodalton family
HSV	herpes simplex virus
HSV-tk	herpes simplex virus thymidine kinase
HTS	high-throughput screening
Htt	Huntingtin
IBMX	3-isobutyl-1-methylxanthine
I_{crac}	calcium release activated Ca^{2+} channel
ICSI	intra-cytoplasmic sperm injection
Ifs	interferons
Ig	immunoglobulins
IGF-1	insulin-like growth factor-I
iGluR	ionotropic glutamate receptor
IHD	ischaemic heart disease
IL-10	interleukin-10
Ile	isoleucine (I)
INN	international non-proprietary names
INR	initiator element
INSL3	insulin-like factor 3
IP_3	inositol 1,4,5-triphosphate
IP_3R	IP_3 receptor
$iPLA_2\beta$	β isoform of Ca^{2+} independent phospholipase A_2
IRT	immunoreactive trypsinogen
I_{sc}	short circuit current
ISE	introns splicing enhancer
ISS	introns splicing silencer
K_{2P}	two-pore potassium channels
K3K4 HMT	histone methyl transferase
K_{ATP}	ATP-sensitive K^+ channels
kb	kilobase
K_{Ca}	Ca^{2+}-activated K^+ channels
KCC	K^+-Cl^- co-transporter
KChIP	K^+ channel interacting protein
KCO	K^+ channel openers
Kd	Ca^{2+} dissociation constant
K_G	G-protein gated K^+ channels
KID	kinase-inducible domain
K_{ir}	inwardly rectifying K^+ channels
K_V	voltage-gated K^+ channel
LacY	lactose:H^+ symporter
LBD	ligand binding domains
LDL	low density lipoprotein
Leu	leucine (L)
LeuTAa	Aquifex aeolicus leucine transporter
LGIC	ligand-gated ion channel
lncRNA	long non-coding RNA
LPS	lipopolysaccharide
lys	lysine (K)
Mab	monoclonal antibodies
MAC	membrane attack complex
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxic compound extrusion superfamily (transporter)
Mb	megabase
MCT	mono carboxylate transporters
MCU	mitochondrial Ca^{2+} uniporter
MDR	multidrug resistance (transporter)
MDR1	multidrug resistant transporter 1
Met	methionine (M)
MFP	periplasmic membrane fusion protein family (transporter)
MFS	major facilitator superfamily (transporter)
MHC	histocompatibility complex
miRNA	microRNA
mPTP	mitochondrial permeability transition pore
mRNA	messenger RNA
MSD	membrane spanning domain
MTF	modulatory transcription factors
Myc	myc oncogene
NAADP	nicotinic acid adenine dinucleotide phosphate
nAChR	nicotinic acetylcholine receptors
NAD^+	nicotinamide adenine dinucleotide
$NADP^+$	nicotinamide adenine dinucleotide phosphate

NALCN	sodium leak channel non-selective protein channel
NAT	natural antisense transcript
Na_V	voltage-gated Na^+ channels
NBD	nucleotide binding domain
ncRNA	non-coding RNA
neoR	neomycin resistance
NES	nuclear endoplasmic space
NFAT	nuclear factor of activated T cells
NFκB	nuclear factor kappa of activated B cells
NHA	Na^+/H^+ antiporters
NhaA	Escherichia coli Na^+/H^+ antiporter
NHE	Na^+/H^+ exchanger
NKCC	sodium potassium 2 chloride cotransporter
NM	nuclear membrane
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic reasonance
NO	nitric oxide
NPA	Asn-Pro-Ala motif
NPC	nuclear pore complex
NR	nucleoplasmic reticulum
NR-HSP	nuclear receptor-heat shock protein complex
NRSE	neuron restrictive silencer element
NSS	neurotransmitter sodium symporter (transporter)
nt	nucleotide
NTD	N- terminal domain
NVGDS	non viral gene delivery systems
OA-	organic anion
OAT	organic anion transporters
OCT	organic cation transporters
Oct/OAP	octomer/octomer associated proteins
OMF	outer membrane factor family (transporter)
ORCC	outwardly rectifying chloride channel
ORF	open-reading frame
OSN	olfactory sensory neurons
OxlT	oxalate:formate antiporter
Pax	paired box gene/TF
pCa	$-\log_{10}$ of the Ca^{2+} concentration
PCR	polymerase chain reaction
PD	potential difference
PDE	phosphodiesterase
PDZ	PSD_{95}-Dlg1-zo-1 (protein motif)
PEPT	dipeptide transporters
PG	prostaglandins
PGC-1α	peroxisome proliferator-activated receptor α, co-activator 1α
PGE_2	prostaglandin E_2
P-gp	permeability glycoprotein (transporter)
Phe	phenylalanine (F)
Pi	inorganic phosphate
PI3	phosphatidylinositol 3-kinases
PIP_2	phosphatidylinositol 4,5-bisphosphate
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PLCβ	β isoform of phospholipase C
pLGICs	pentameric ligand-gated ion channels
PM	plasma membrane
PMCA	plasma membrane Ca^{2+} ATPase
PP1	protein phosphatase 1
PPAR	peroxisome proliferator-activated receptors (α, β, δ, or γ)
PPRE	PPAR response element
pRB	retinoblastoma protein
Pro	proline (P)
PSD_{95}	post synaptic density protein-95
Q1/Q2	glutamine-rich domains (1 or 2)
RaM	rapid mode uptake
RAMP	receptor-activity modifying protein
Ras	rat sarcoma (causing factor)
RBC	red blood cell
REST	repressor element-1 transcription factor
RFLP	restriction fragment length polymorphism
rhDNase	recombinant human DNase
RICs	radio-immunoconjugates
RIP	receptor-interacting protein
RISC	RNA-induced silencing complex
RLF	relaxin-like factor
RNA pol	RNA polymerases
RNA	ribonucleic acid
RNAi	RNA interference
RND	resistance-nodulation-cell division (transporter)
ROS	reactive oxygen species
rRNA	ribosomal RNA
RSPO1	R-spondin-1
RT-PCR	reverse-transcription polymerase chain reaction
RXR	retinoic acid receptor
RyR	ryanodine receptors
SAM	intraluminal sterile α motif
SBP	substrate binding protein
Ser	serine (S)

SERCA	sarco/endoplasmic reticulum Ca^{2+} ATPase
Shh	sonic hedgehog homolog gene/TF
siRNA	short interfering RNA
SK_{Ca}	small conductance Ca^{2+}-activated K^+ channels
SLC	solute carrier superfamily (transporter)
SMN	survival of motor neurons protein
SMR	small multidrug resistance superfamily (transporter)
snoRNA	small nucleolar RNA
SNP	single nucleotide polymorphism
snRNA	spliceosomal small nuclear RNA
SOC	store operated Ca^{2+} channel
Sox9	SRY-related HMG box-9 gene/factor
SR	sarcoplasmic reticulum
SRC-1	steroid receptor co-activator-1.
SREBP	sterol regulatory element-binding proteins
SRY	sex-determining region Y
SSS	solute sodium symporter (transporter)
STAT	signal transducer and activator of transcription (1, 2 or 3)
STIM	stromal interaction molecule
SUG-1	suppressor of gal4D lesions −1
SUMO	small ubiquitin like modifier
SUR	sulfonylureas receptor
SW1/SNF	switching mating type/sucrose non-fermenting proteins
TAD	transactivation domain
TAP	transporters associated with antigen processing
TCA	tricarboxlyic acid
TCR	T cell receptor
TDF	testis-determining factor
TEAD	TEA domain proteins
TEF	transcription enhancer factor
TESCO	testis-specific enhancer of Sox9
TGF	transforming growth factor
TGN	trans-Golgi network
TH	tyrosine hydroxylase
Thr	threonine (T)
TIF-1	transcription intermediary factor
TIRF	total internal reflection fluorescence imaging
TMAO	trimethylamine N-oxide
TMD	transmembrane domain
TMS	transmembrane segments
TNFs	tumour necrosis factors
TPC	two pore calcium channels
TPEN	N,N,N′,N′-tetrakis(2-pyridylmethyl)ethylenediamine
Trk	tyrosine kinase receptor (A, B or C)
tRNA	transfer RNA
TRP	transient receptor potential channels
Trp	tryptophan (W)
TTX	tetrodotoxin
Tyr	tyrosine (Y)
TZD	thiazolidinedione
Ubi	ubiquitination
UTR	untranslated region
Val	valine (V)
VDAC	voltage dependent anion channel
VEGF	vasculoendothelial growth facto
VFT	venus flytrap
vGLUT	vesicular glutamate transporter
VHL	von Hippel-Lindau protein
VIP	vasoactive intestinal peptide
VLDL	very low density lipoprotein
V_m	membrane potential
VOCC	voltage-operated calcium channels
WNT4	wingless-type mouse mammary tumour virus integration site
YAC	yeast artificial chromosome
YFP	yellow fluorescent protein
YORK	yeast outward rectifying K^+ channel
ZAC	zinc-activated channel
Zo-1	zonula occludens-1 protein

POST-FIXes

Chimeric antibodies – *xiMabs*
Human antibodies – *muMbs*
Humanised antibodies – *zumab*
Monoclonal antibodies – *oMabs*

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Contents

1 Introduction to Drug Targets and Molecular Pharmacology

1.1 Introduction to molecular pharmacology

During the past 30 years there have been significant advances and developments in the discipline of molecular pharmacology – an area of pharmacology that is concerned with the study of drugs and their targets at the molecular or chemical level. Major landmarks during this time include the cloning of the first G-protein coupled receptor (GPCR) namely the β_2-adrenergic receptor in 1986 (Dixon et al., 1986). This was quickly followed by the cloning of additional adrenergic receptor family genes and ultimately other GPCRs. The molecular biology explosion during the 1980s also resulted in the cloning of genes encoding ion channel subunits (e.g. the nicotinic acetylcholine receptor and voltage-gated Na^+ channel) and nuclear receptors. The cloning of numerous drug targets continued at a pace during the 1990s but it was not until the completion of the human genome project in 2001 that the numbers of genes for each major drug target family could be determined and fully appreciated. As would be expected, the cloning of the human genome also resulted in the identification of many potentially new drug targets. The completion of genome projects for widely used model organisms such as mouse (2002) and rat (2004) has also been of great benefit to the drug discovery process.

The capacity to clone and express genes opened up access to a wealth of information that was simply not available from traditional pharmacology-based approaches using isolated animal tissue preparations. In the case of GPCRs detailed expression pattern analysis could be performed using a range of molecular biology techniques such as *in situ* hybridisation, RT-PCR (reverse transcriptase-polymerase chain reaction) and Northern blotting. Furthermore having a cloned GPCR gene in a simple DNA plasmid made it possible for the first time to transfect and express GPCRs in cultured cell lines. This permitted detailed pharmacological and functional analysis (e.g. second messenger pathways) of specific receptor subtypes in cells not expressing related subtypes, which was often a problem when using tissue preparations. Techniques such as site-directed mutagenesis enable pharmacologists to investigate complex structure-function relationships aimed at understanding, for example, which amino acid residues are crucial for ligand binding to the receptor. As cloning and expression techniques developed further it became possible to manipulate gene expression *in vivo*. It is now common practice to explore the consequences of deleting a

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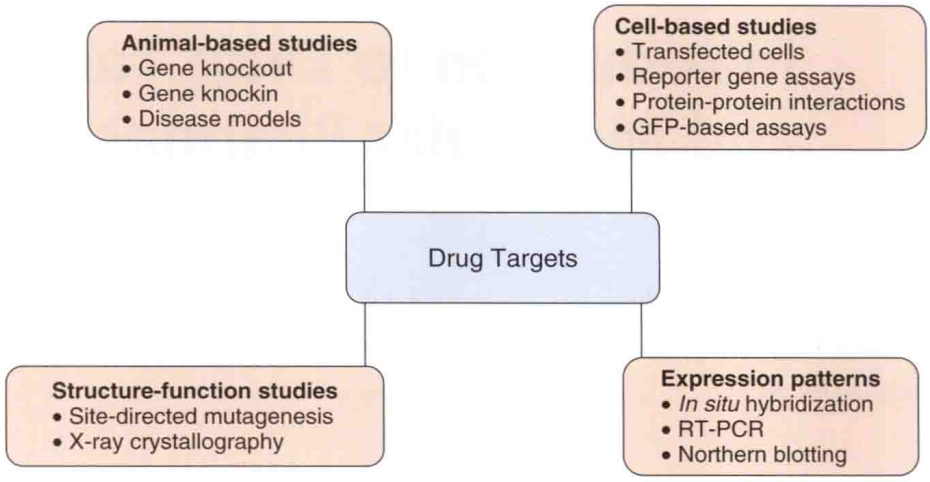

Figure 1.1 Molecular pharmacology-based methods used to interrogate drug targets.

specific gene either from an entire genome (knockout) or from a specific tissue/organ (conditional knockout). It is also possible to insert mutated forms of genes into an organism's genome using knockin technology. These transgenic approaches allow molecular pharmacologists to study developmental and physiological aspects of gene function *in vivo* and in the case of gene knockin techniques to develop disease models.

The molecular biology revolution also enabled the development of novel approaches for studying the complex signal transduction characteristics of pharmacologically important proteins such as receptors and ion channels. These include reporter gene assays, green fluorescent protein (GFP) based techniques for visualising proteins in living cells and yeast two hybrid-based assays for exploring protein-protein interactions. You will find detailed explanations of these and other current molecular-based techniques throughout this textbook. Another major breakthrough in the 2000s was the development of methods that allowed high resolution structural images of membrane-associated proteins to be obtained from X-ray crystallography. During this time the first X-ray structures of GPCRs and ion channels were reported enabling scientists to understand how such proteins function at the molecular level. Indeed crystallography is an important tool in the drug discovery process since crystal structures can be used for *in silico* drug design. More recently researchers have used NMR spectroscopy to obtain a high-resolution structural information of the β_2-adrenergic receptor (Bokoch et al., 2010). A distinct advantage of NMR-based structural studies, which are already used for structural studies of other drug targets such as kinases, would be the ability to obtain GPCR dynamics and ligand activation data which is not possible using X-ray based methods. Some of the molecular pharmacology based approaches used to interrogate drug targets are outlined in Figure 1.1.

Despite this increased knowledge of drug targets obtained during the molecular biology revolution, there has been a clear slowdown in the number of new drugs reaching the market (Betz, 2005). However, since it takes approximately 15 years to bring a new drug to market it may be too early to assess the impact of the human genome project on drug discovery. In 2009 the global pharmaceutical market was worth an estimated $815 billion. However during the next few years a major problem facing the pharmaceutical industry is the loss of drug patents on key blockbusters. The hope for the future is that the advances in molecular pharmacology witnessed during the last decade or so will start to deliver new blockbuster therapeutics for the twenty-first century.

1.2 Scope of this textbook

As briefly detailed above there have been numerous exciting developments in the field of molecular pharmacology. The scope of this textbook is to explore aspects of molecular pharmacology in greater depth than covered in traditional pharmacology textbooks (summarised in Figure 1.2). Recent advances and developments in the four major human drug target families (GPCRs, ion channels, nuclear receptors and transporters) are

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