Introduction to Bioorganic Chemistry and Chemical Biology

David Van Vranken and Gregory Weiss
Chapter 1
The Fundamentals of Chemical Biology

Why organize a book on chemical biology around biooligomers?

1.1 THE CENTRAL DOGMA OF MOLECULAR BIOLOGY
The central dogma of molecular biology is an organizing principle for chemical biology.

1.2 GENES
A gene is made up of a promoter and a transcribed sequence.

1.3 GENOMES
We have sequenced the human genome and many others. Now what?

1.4 SOURCES OF DIVERSITY BEYOND GENOMES
The transcriptome is the collection of all of the RNA transcripts in a cell. RNA splicing amplifies the diversity of the transcriptome.

1.6 SOME COMMON TOOLS OF CHEMICAL BIOLOGY
Chromophores reveal invisible molecules.
Assays connect molecular entities to readily visible phenomena.
Powerful microbiological screens reveal interesting chemical phenomena.
Viruses deliver genes efficiently.
Vast libraries of proteins can be screened in vitro using bacteriophages.

Chapter 2
The Chemical Origins of Biology

2.1 MECHANISTIC ARROW-PUSHING IS AN EXPRESSION OF MOLECULAR ORBITAL THEORY
Three properties control chemical reactivity.
Perturbational molecular orbital theory connects arrow-pushing with quantum mechanics.
Six canonical frontier orbitals can be used to predict reactivity.
Electronegativity affects both frontier orbitals and Coulombic interactions.
Curved mechanistic arrows depict the interaction of filled orbitals with unfilled orbitals.
There are three basic rules for mechanistic arrow-pushing.
2.2 HYDROGEN BONDS AND PROTON TRANSFERS
Hydrogen bonds involve three atoms
Proton transfers to and from heteroatoms are usually very fast
Linear geometries are preferred for proton transfers

2.3 PREBIOTIC CHEMISTRY
HCN and CH₂O are key ingredients in the primordial soup
Solutions of HCN contain both nucleophile and electrophile at pH 9.2
HCN forms purines and pyrimidines under prebiotic conditions
Aldol reactions with formaldehyde generate carbohydrates
Cyanide catalyzes the benzoin reaction
Did we arise from a primordial RNA world?
Amino acids arise spontaneously under prebiotic conditions

2.4 NONBONDING INTERACTIONS
Essentially everything taking place in the cell involves nonbonding interactions
The weak energies of nonbonding interactions are not easily calculated using perturbational molecular orbital theory
For nonbonding interactions, the energies can be fitted to a simplified equation
van der Waals interactions can be described by the Lennard-Jones potential
It is helpful to distinguish reversible from irreversible interactions
Entropy makes it difficult to identify favorable states among seemingly endless possibilities
The hydrophobic effect results from a balance between attractive forces and entropy

2.5 THE POWER OF MODULAR DESIGN
Modular design underlies the five basic types of biooligomers
Lability correlates inversely with information longevity
Why are esters more reactive than amides?
Why are phosphate esters less reactive than carboxylic esters?

2.6 SUMMARY

PROBLEMS

Chapter 3
DNA

3.1 FORMS OF DNA
The canonical double helix is one of several forms of DNA
The organization of genomic DNA molecules depends on the type of organism

3.2 THE RIBONUCLEOTIDE SUBUNITS OF DNA
Nucleotides are phosphate esters
DNA and RNA are polymers of nucleotides
Are the heterocyclic DNA bases aromatic?
Nucleic acids are not acidic, and DNA bases are not basic
The missing 2'-hydroxyl group of DNA confers stability to phosphodiester hydrolysis
Modifications to DNA bases are as important as the nucleotide DNA sequence

3.3 ELEMENTARY FORCES IN DNA
Base pairing knits together the two strands of DNA
Some non-natural, isomeric bases form effective base pairs
Hydrogen bonds are not absolutely essential for complementary base pairing
Hoogsteen base pairing is present in triplex DNA
Aromatic π stacking stabilizes the DNA double helix
Intercalation between DNA base pairs involves π stacking
Double-stranded DNA undergoes reversible unfolding and refolding
Complementarity drives self-assembly of DNA
Short stretches of DNA can fold into hairpins

3.4 DNA SUPERSTRUCTURE
Double-stranded DNA forms supercoils
Topoisomerases resolve topological problems with DNA
Bacterial plasmids are rings of DNA
Plasmids contain genes that confer advantageous traits
Eukaryotic DNA is coiled around histone proteins

3.5 THE BIOLOGICAL SYNTHESIS OF DNA BY POLYMERASE ENZYMES
DNA polymerases lengthen existing strands
DNA polymerases copy with high fidelity
Reverse transcriptase lengthens existing DNA strands on an RNA template
DNA polymerase incorporates modified thymidylate residues
The polymerase chain reaction amplifies DNA through iterative doubling

3.6 THE CHEMICAL SYNTHESIS OF DNA
The race to crack the genetic code drove the development of DNA synthesis
The Khorana method of DNA synthesis relies on phosphate coupling chemistry
Letsinger recognized the speed and efficiency of phosphite couplings
Caruthers synthesized DNA by using phosphoramidites on solid phase
Automated oligonucleotide synthesis is performed on glass particles
Modern automated DNA synthesis involves repetitive four-step cycles. The 4,4'-dimethoxytrityl group is deprotected through an Sn1 reaction. Tetrazole serves as an acid catalyst in phosphoramidite couplings. Capping unreacted 5'-hydroxyl groups prevents the propagation of mistakes. Oxidation of unstable phosphites generates stable phosphates. Aqueous ammonium hydroxide cleaves and deprotects synthetic DNA. Microarrays of DNA facilitate screening.

Why are DNA and RNA made up of five-membered ring sugars? 3.7 SEPARATION OF DNA MOLECULES BY ELECTROPHORESIS

Scientists use different criteria for the purity of biological macromolecules versus small, organic molecules. Agarose gel is used for electrophoresis of long DNA molecules. Capillary electrophoresis is used for analytical separation of short DNA molecules. DNA dideoxy sequencing capitalizes on the tolerance of DNA polymerase. Large-scale sequencing methods avoid the need for electrophoresis.

3.8 RECOMBINANT DNA TECHNOLOGY

Molecular biology connects DNA molecules to biological phenotypes. Restriction endonucleases cut DNA at specific sites and facilitate re-ligation. Mutations in DNA can lead to changes in expressed proteins. Site-directed mutagenesis involves labile plasmid templates.

3.9 NUCLEIC ACID PHOTOCHEMISTRY

Ultraviolet radiation promotes [2+2] photodimerization of thymine and uracil bases. Thymine dimers in DNA can be repaired. Psoralens intercalate between DNA base pairs and photocrosslink opposing strands.

3.10 DNA AS A TARGET FOR CYTOTOXIC DRUGS

Cell division is highly controlled in normal human cells. Dividing human cells must pass through checkpoints, or die. Traditional chemotherapy targets DNA in rapidly dividing cells, cancerous or not. Inhibition of thymine biosynthesis triggers apoptosis during the S phase of the cell cycle. Adding the methyl group to thymine is essential for DNA synthesis.

DNA is a nucleophile. Simple alkylation agents are highly mutagenic. Bifunctional alkylation agents that crosslink DNA are highly cytotoxic. Strained rings can bring highly reactive functional groups to DNA. Epoxide alkylators of DNA are highly mutagenic. Aziridinium rings are relatively selective alkylators of DNA. Cyclopropane rings can serve as spring-loaded electrophiles. Free radicals and oxygen conspire to cleave DNA sugars. Enediynes antitumor antibiotics cleave both strands of DNA via para-benzyne diradicals. Some highly reactive enediyne natural products are protected by protein delivery vehicles.

Bleomycin catalyzes the formation of reactive oxygen species. 3.11 SUMMARY

PROBLEMS

Chapter 4 RNA

4.1 RNA STRUCTURE

The nucleotide subunits of RNA are subtly different from those of DNA. The 2'-OH of RNA confers high chemical reactivity. Ubiquitous ribonucleases rapidly degrade RNA. The 5-methyl group of thymine is a form of chemical ID. RNA adopts globular shapes because it is single-stranded.

4.2 RNA SYNTHESIS

RNA polymerases create new strands of RNA. DNA primase is just another RNA polymerase.

4.3 TRANSCRIPTIONAL CONTROL

DNA sequences determine start sites and stop sites for RNA polymerase. Transcription factors bind to DNA with exquisite sequence specificity. Transcription can be controlled by small molecules. Transcription of mRNA in human cells involves many proteins and many regions of DNA. The yeast two-hybrid system provides a transcription-based tool to identify protein–protein interactions.

4.4 mRNA PROCESSING IN EUKARYOTES

After synthesis, eukaryotic organisms modify their mRNA extensively. The ends of the mRNA are capped and polyadenylated. Most eukaryotic genes require mRNA splicing. Some RNA introns undergo self-splicing without a spliceosome.
4.5 CONTROLLED DEGRADATION OF RNA 152
Ribonuclease H degrades RNA–DNA duplexes 152
RNA-induced silencing complexes target specific mRNA sequences 153
RNA interference is a useful laboratory tool 155

4.6 RIBOSOMAL TRANSLATION OF mRNA INTO PROTEIN 156
The ribosome catalyzes oligomerization of α-amino esters 156
The ribosome is a massive molecular machine, half protein and half RNA 157
tRNA molecules are heavily processed and adopt fixed shapes 159
The genetic code allows one to translate from mRNA sequence into protein sequence 161
tRNA synthetases recognize amino acids and nucleotides 162
What controls the beginning and end of translation? 163
Translational initiation is a focal point for control of protein synthesis 165
A protein escorts each aminoacyl-tRNA to the ribosome for fidelity testing 166
The genetic code can be expanded beyond 20 amino acids 167
Ligand-dependent riboswitches control protein expression 169
Many antibiotics target bacterial protein synthesis 170

4.7 FROM OLIGONUCLEOTIDE LIBRARIES TO PROTEIN LIBRARIES 171
Automated oligonucleotide synthesis facilitates generation of both DNA and RNA oligonucleotide libraries 171
RNA libraries can be screened for ribozymes 173
mRNA libraries can be expressed as protein libraries 174

4.8 SUMMARY 175
PROBLEMS 176

Chapter 5
Peptide and Protein Structure 179

5.1 AMINO ACIDS AND PEPTIDES 180
The standard ribosomal amino acids include a broad range of functionalities 180
Amino acids are polymerized into peptides and proteins 181
Amino acid side chains have predictable protonation states 183
Amino acid side chains mediate protein–protein interactions 184

5.2 SOLID-PHASE PEPTIDE SYNTHESIS 185
Peptides can be used as pharmaceuticals 185
Excess reagents and optimized chemistry allow high-throughput peptide synthesis 187

Chemical peptide synthesis involves repeated additions of activated carboxylates to the N terminus 188
The need to remove excess reagents and chemical by-products drove the development of solid-phase peptide synthesis 188
Either acid- or base-labile carbamates are used for the temporary protection of the Nα group 189
Carbodiimides drive condensation to form peptide bonds 190
Side reactions can compete with peptide coupling reactions 190
HOBt minimizes side reactions in carbodiimide couplings 191
Uronium coupling agents provide even faster amide bond formation 192
Resins for solid-phase peptide synthesis are made of plastic 193
Cleavable linkers between the synthesized peptide and solid support provide stable, yet reversible, attachments 193
Side-chain protecting groups come off under acidic conditions 195
Peptide nucleic acids lack phosphate esters and ribofuranose rings 196
Native chemical ligation generates cysteinyl amides through aminolysis of thiol esters 197

5.3 FUNDAMENTAL FORCES THAT CONTROL PROTEIN SECONDARY STRUCTURE 199
Secondary structure involves different patterns of hydrogen bonding between backbone amides 199
α Helices allow effective hydrogen bonding between neighboring amide N-H and C=O 200
β Sheets satisfy hydrogen bonding by backbone amides with linkages between different strands 201
Turn structures have minimal hydrogen bonding between backbone amides 202
Rotation about substituted ethanes, butanes, and pentanes reveals the fundamental forces dictating protein folding 203
Stereoelectronic effects distinguish amides and esters from substituted ethenes 204
Interactions between allylic substituents and alkene substituents limit the conformation of substituted propenes 205
Allylic strain explains the dominance of two types of secondary structures 206

5.4 THE CHEMISTRY OF DISULFIDE CROSSLINKS 207
Cystine disulfides form readily under oxidative conditions 207
Glutathione is an intracellular thiol buffer 207
Cystine disulfides in proteins are in equilibrium with glutathione disulfides 208
Combinatorial crosslinking and protein misfolding can complicate attempts to produce disulfide-containing proteins 209
Concentrations of glutathione depend on location 210

5.5 PROTEIN DOMAINS HAVE STRUCTURAL AND FUNCTIONAL ROLES 210

Biological protein assemblies exhibit hierarchical structures
The tertiary and quaternary structures of proteins access a wide range of different archetypal protein folds
Zinc-finger domains recognize DNA sequences
A number of common domains are based on β-sandwich architectures
Calcium promotes interactions between cadherin domains
WD domains fit together like triangular slices of a cake
Collagen is formed from a three-stranded helix
Protein kinase domains and seven-transmembrane domains have key roles in signal transduction
The RNA recognition motif domain binds to single-stranded RNA
Peptide-binding domains can confer modular functions to proteins

5.6 HIGHER LEVELS OF PROTEIN STRUCTURE 219

The tertiary structure consists of one or more domains
Quaternary structure consists of highly integrated assemblies of independent, folded proteins

5.7 SUMMARY
PROBLEMS

Chapter 6
Protein Function 229

6.1 RECEPTOR–LIGAND INTERACTIONS 229

The thermodynamics and kinetics of receptor–ligand interactions govern all processes in biology
Dose–response curves measure protein function, and correlate with affinity
Highly specific protein–small-molecule interactions are useful

6.2 A QUANTITATIVE VIEW OF ENZYME FUNCTION 236
Enzymes are catalytic receptors
Measurements of enzyme efficiency must account for substrate binding and catalysis

6.3 A MECHANISTIC VIEW OF ENZYMES THAT CATALYZE MULTISTEP REACTIONS 240
Protein kinases and proteases catalyze reactions through multistep mechanisms
Protein kinases share a common motif
Regulation of protein kinase activity requires allosteric binding
Phosphorylation can also activate kinases
Proteases serve roles in degradation and protein signaling
Cysteine proteases catalyze amide hydrolysis by using a nucleophilic cysteine thiolate

Enzymes proceed via mechanisms with the minimum number of different types of transition states 251
Serine proteases cleave amides by using an alkoxide nucleophile
Metalloproteases use Zn²⁺ ions to activate the nucleophilic water and stabilize the tetrahedral intermediate
Activation can control protease activity
Reversible enzyme inhibitors include transition-state analogs with very high affinity
Mechanism-based enzyme inhibitors react with residues at the active site
Cooperative binding requires careful placement of functional groups
Triosephosphate isomerase is nearly a perfect enzyme

6.4 ENZYMES THAT USE ORGANIC COFACTORS 263
Enzyme cofactors extend the capabilities of enzymes
Thiamine pyrophosphate provides a stabilized ylide
The dihydropyridine group of niacin (vitamin B₃) provides a reactive hydride
The pyridoxal cofactor serves as an electron sink

6.5 ENGINEERING IMPROVED PROTEIN FUNCTION 269
Protein engineering provides power tools for the dissection of protein function and the development of hyperfunctional molecules
Alanine scanning assigns function to side chains and motifs
Alanine scanning allows reverse engineering of protein function
Protein engineering enables improvement of protein function
Protein engineering enables a change of protein function
Most random mutations debilitate rather than enhance protein function
Recombination generates new combinations of existing mutations
Screens work well for modest numbers of protein variants, but exceptionally diverse libraries require selections

6.6 SUMMARY
PROBLEMS

Chapter 7
Glycobiology 281

7.1 STRUCTURE 281
There are 10 common monosaccharide building blocks for human glycans
Glycobiology uses a compact form of nomenclature
Polar effects and stereoelectronic effects determine the relative stability of α and β anomers

7.2 THE CHEMISTRY AND ENZYMEOLOGY OF THE GLYCOSIDIC BOND 286
Monosaccharide carbonyl groups form hemiacetals 286
Six- and five-membered ring hemiacetals are common 286
Chemical hydrolysis of glycosidic bonds involves $S_N1$ reactions 289
Enzymatic hydrolysis of glycosidic bonds involves $S_N1$-like $S_N2$ reactions 290
Members of all classes of glycosylhydrolases have two carboxylic acids in the active site 290
Substrate distortion is important in glycosylhydrolase enzymes 291
Inhibiting glycosylhydrolase enzymes from viruses can treat influenza 293
Glycosyltransferases transfer monosaccharides from glycosyl phosphate donors 294
Glycosyltransferases transfer glycosyl groups from phosphates 294
7.3 POLYSACCHARIDES
Diastereomers of glucose polymers have very different properties 296
Chitin is a resilient polymer in insect cuticles 297
Some tissues are cushioned by the polysaccharide hyaluronan 298
Meningococci are coated with polysialic acids like those found on neurons 298
7.4 GLYCOPROTEINS
Glycosylation of human proteins occurs in the vesicles of the secretory pathway 299
Synthesis of O-linked glycoproteins begins with the addition of xylose or $N$-acetylgalactose 300
O-linked proteoglycans are polyanions 301
The carbohydrate moiety of N-linked glycoproteins is initially added as an oligosaccharide 303
An Asn-Xxx-Ser motif adopts a reactive conformation in the N-glycosylation of proteins 304
The processing of glycans occurs during vesicular trafficking 305
A few human proteins are C-mannosylated on tryptophan residues 308
Glycosylation of proteins sometimes, but not always, affects the intrinsic function of the protein 308
Most extracellular signaling proteins are glycosylated with oligosaccharides 310
Many protein pharmaceuticals are glycosylated 310
Cell–cell recognition is often mediated by glycoproteins 311
Introduction of N-glycosylation sites can improve protein pharmaceuticals 312
Modified sugars can carry reactive groups through the glycoprotein biosynthesis pathway 312
7.5 GLYCOLIPIDS
Glycosphingolipids are lipid-like glycoconjugates 314
Glycosylphosphatidylinositol from pathogens are potential vaccines 314
7.6 GLYCOSYLATION IN THE CYTOSOL
O-glycosylation of proteins in the cytosol with $\beta$-GlcNAc is analogous to phosphorylation 316
Drugs are targeted for export by glucuronidation 318
7.7 CHEMICAL SYNTHESIS OF OLIGOSACCHARIDES
Anomeric stereochemistry is controlled by the anomeric leaving group and the 2 substituent 318
Modern oligosaccharide synthesis takes advantage of activatable leaving groups 320
Synthesis of oligosaccharides still requires a skilled synthetic organic chemist 321
7.8 PROTEINS THAT BIND TO CARBOHYDRATE LIGANDS
Glycans differentiate the surfaces of human cells 322
Most carbohydrate-binding proteins are multivalent 322
Human lectins mediate selective adhesion of leukocytes 326
Human blood group antigens are found on glycolipids and glycoproteins 326
Some toxins enter cells through multivalent carbohydrate recognition 327
Microarray technology facilitates the analysis of protein–glycan interactions 328
7.9 GLUCOSE HOMEOSTASIS AND DIABETES
Human metabolism and paper-burning are related transformations 330
Glucose reacts with proteins over time 331
Glucose-derived protein crosslinks are not necessarily permanent 332
There is a big market for artificial ligands for human taste receptors 333
7.10 SUMMARY
PROBLEMS 337
Chapter 8
Polyketides and Terpenes 339
8.1 THE CLAISEN REACTION IN POLYKETIDE BIOSYNTHESIS
The diverse structures of polyketide natural products belie their iterative construction 340
Polyketides are derived from two-carbon and three-carbon building blocks 340
8.2 THE BIOSYNTHESIS OF FATTY ACIDS IS A PARADIGM FOR POLYKETIDE BIOSYNTHESIS
Fatty acids have varying levels of unsaturation 342
Fatty acid/polyketide synthases are categorized on the basis of their supramolecular structure 343
The acyl carrier protein shuttles the growing polyketide chain from one catalytic domain to another 344
A transacylase loads monomeric subunits onto the carrier protein 344
Ketosynthases catalyze a decarboxylative Claisen condensation 345
Ketoreductases catalyze hydride transfer from NADPH 345
Dehydratases catalyze β-elimination 346
Enoyl reductases catalyze a conjugate reduction 346
A thioesterase uses a catalytic triad to cleave the acyl group from the acyl carrier protein 347
Enzymes associated with the endoplasmic reticulum put the finishing touches on fatty acids 348

8.3 THE BIOLOGICAL ROLE OF HUMAN POLYKETIDES 348
Eight categories of lipids are found in biology 348
Lipid membranes are composed of lipids with a polar head group and a nonpolar tail 348
The lipid bilayer entropically favors interactions between embedded molecules 350
Phospholipases generate distinct chemical signals by hydrolyzing various bonds of phospholipids 350
Phospholipase Cβ generates two signaling molecules 351
Arachidonic acids are converted into diverse signaling molecules during inflammation 352
Sphingosine derivatives are important in intracellular signaling 355
Metal-catalyzed hydrogenation of unsaturated fats changed the human diet 357
Some lipids from lower organisms contain cyclopropane rings 358
Acylation of human proteins induces membrane localization 359
Chemical transformation of fats generates useful compounds 361

8.4 NONHUMAN POLYKETIDE NATURAL PRODUCTS 362
Several tricks amplify the potential diversity of polyketide natural products 362
Streptomyces has mastered polyketide biosynthesis 364
The modular genetic organization of type I polyketide synthases facilitates genetic reprogramming 366
Sometimes additional methyl groups are added to the polyketide backbone 369

8.5 NONRIBOSOMAL PEPTIDE SYNTHASES 369
Ribosomal translation is suited to the production of large proteins, not short peptides 369
Most bioactive peptide secondary metabolites are generated by peptide synthases, not by ribosomes 370

8.7 NONHUMAN TERPENE NATURAL PRODUCTS 385
Plants and microorganisms produce a much wider range of terpene natural products than humans 385
Isomerization of geranyl diphosphate to linalyl diphosphate facilitates cyclization 386
The 2-norbornyl cation exhibits exceptional behavior 388
Some terpene cyclases generate medium-sized rings 390
The biosynthesis of some terpenes involves nontraditional [1,3] hydride shifts 391
Plants can also make complex triterpenes from squalene 392

8.8 SUMMARY 393

Chapter 9 Chemical Control of Signal Transduction 397

9.1 SIGNAL TRANSDUCTION 399
Chemical signaling is universal 399
The field of biology is full of cryptic acronyms and ambiguous symbols 399
Fast cellular responses do not involve the production of proteins 401
Cell contraction and vesicle fusion: fast calcium-dependent responses that do not involve changes in transcription 402
Cell signaling can involve pathways within cells and/or between cells 403

9.2 AN OVERVIEW OF SIGNAL TRANSDUCTION PATHWAYS IN HUMAN CELLS 404
There are seven major signal transduction pathways in humans 404
Chemical genetics involves the use of small molecules to understand gene function 405
Screening identifies small molecules for use in chemical genetics 406

9.3 NUCLEAR RECEPTORS 407
Binding of small-molecule ligands activates nuclear receptor transcription factors 407
Some nuclear receptors translocate from cytoplasm to the nucleus, and bind DNA as homodimers 409
Some nuclear receptors are localized in the nucleus and bind to DNA as heterodimers 409
The mode of nuclear receptor dimerization determines DNA sequence selectivity 410
Human cells can be rewired for control by *Drosophila* nuclear receptors 411
Steroids make highly potent pharmaceuticals 412
Nonsteroidal ligands for nuclear receptors are also widely used as drugs 413
Drugs can be designed to target specific mutations of nuclear receptors 414

9.4 CELL-SURFACE RECEPTORS THAT INTERACT DIRECTLY WITH TRANSCRIPTION FACTORS 415
Hematopoietic proliferation and differentiation are controlled by molecular signals 415
Human cytokines can be used as pharmaceuticals 416
The JAK–STAT pathway involves a receptor, a kinase, and a transcription factor 417
Small-molecule dimerizers can be used to demonstrate functional relationships between proteins 418
Other interferons bind to heterodimeric and higher-order receptor assemblies 419
Synthetic N-hydroxysuccinimidyl esters can acylate proteins in aqueous solution 419
Transforming growth factor-β receptors possess built-in serine/threonine kinase domains 421

9.5 RECEPTOR TYROSINE KINASES 421
Receptor tyrosine kinases control tissue growth 421
Growth factors have a role in proliferation of urothelial cells 422
Comparing receptor tyrosine kinases and cytokine receptors reveals useful commonalities 423
The ATP-binding sites of receptor tyrosine kinases are sufficiently different that they can be selectively inhibited by small molecules 424
Transphosphorylation of tyrosine residues is sequential 424
Receptor tyrosine kinases signal growth via a MAP kinase cascade 425
Many signal transduction pathways involve abundant small molecules and scarce proteins 426
Receptor tyrosine kinases turn on calcium signaling pathways via phospholipase C 428
Receptor tyrosine kinases broadcast both proliferative and anti-apoptotic signals via Akt 429
The differences between various receptor tyrosine kinase pathways are less important than the similarities 430
Chemical methods for isolation and identification of kinase substrates 430

9.6 G PROTEIN-COUPLED RECEPTORS 431
Seven-transmembrane domain G protein-coupled receptors can respond to a wide range of ligands with high dynamic range 431

High-affinity ligand–receptor interactions lead to slow response times and low dynamic range 432
G proteins allow low-affinity receptors to have high sensitivity 433
Seven-transmembrane domain G protein-coupled receptors can respond to a wide range of ligands with high dynamic range 434
Heterotrimeric G proteins are designed to generate divergent signals 434
Some elements of signal transduction pathways can integrate inputs 434
Contraction of endothelial smooth muscle is controlled by Ga q 436
Some bacterial toxins reprogram Ga subunits, with deadly results 437
Adenyl cyclase and phospholipase Cβ are the most common mediators of 7TM GPCRs 438
Many pharmaceuticals act on 7TM GPCRs that respond to ligands derived from amino acids 438
Opioids act on 7TM GPCRs that bind to neuropeptides 440
Smell and taste involve 7TM GPCRs 441
How do you bind to a photon? 442
The decision between immortality and destiny involves the protein Wnt and the β-catenin pathway 443
A seven-transmembrane receptor that controls development does not bind to an extracellular ligand 444

9.7 ION CHANNEL RECEPTORS 445
Ion channel receptors provide an ultra-fast response to stimuli 445
A human cell is a bag of potassium in a salty ocean 446
Voltage-gated ion channels are activated by transmembrane differences in ion concentrations 447
Pentameric Cys-loop receptors are gated by neurotransmitters 449
The nicotinic acetylcholine receptor is a popular target for toxins 450
Tetrameric glutamate receptors are defined by their specificity for glutamate analogs 451
9.8 TRIMERIC DEATH RECEPTORS 451
Tumor necrosis factor binding to TNF receptors triggers diverse, cell-dependent responses 451

9.9 PATHWAYS CONTROLLED BY SMALL DIFFUSIBLE GAS MOLECULES 453
Oxygen levels are monitored through HIF-1α 453
A nitric oxide receptor induces the production of cGMP 454

9.10 SUMMARY 455
PROBLEMS 456