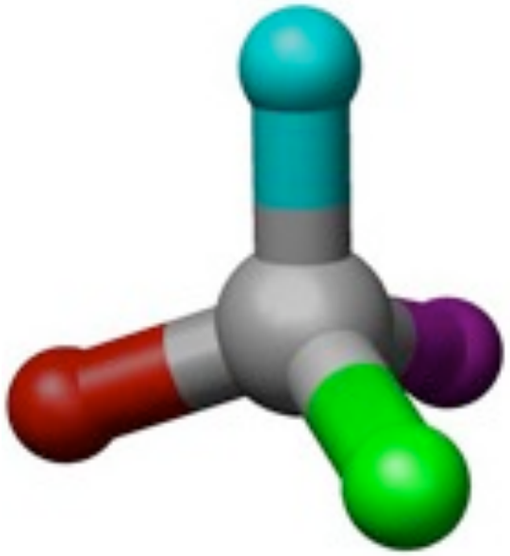
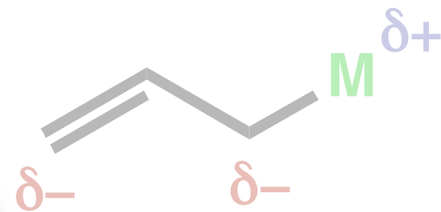


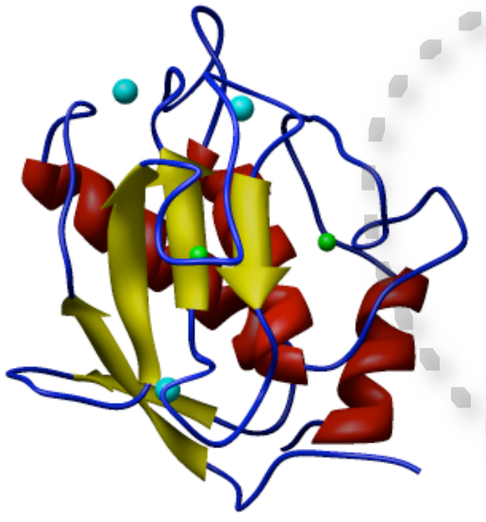
From mechanism to medicne

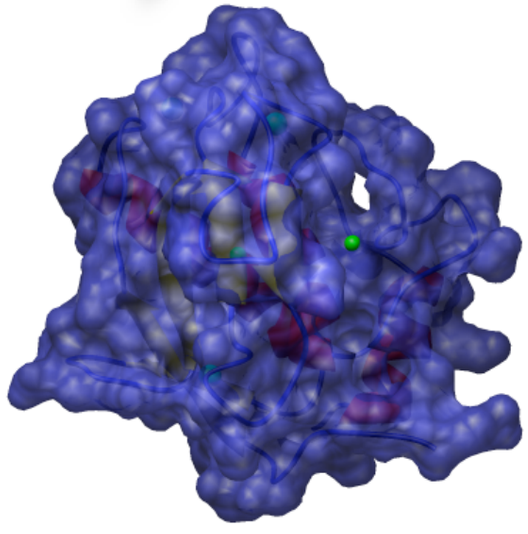
a look at proteins and drug design

Chem 342



2009





Drug Design - an Iterative Approach

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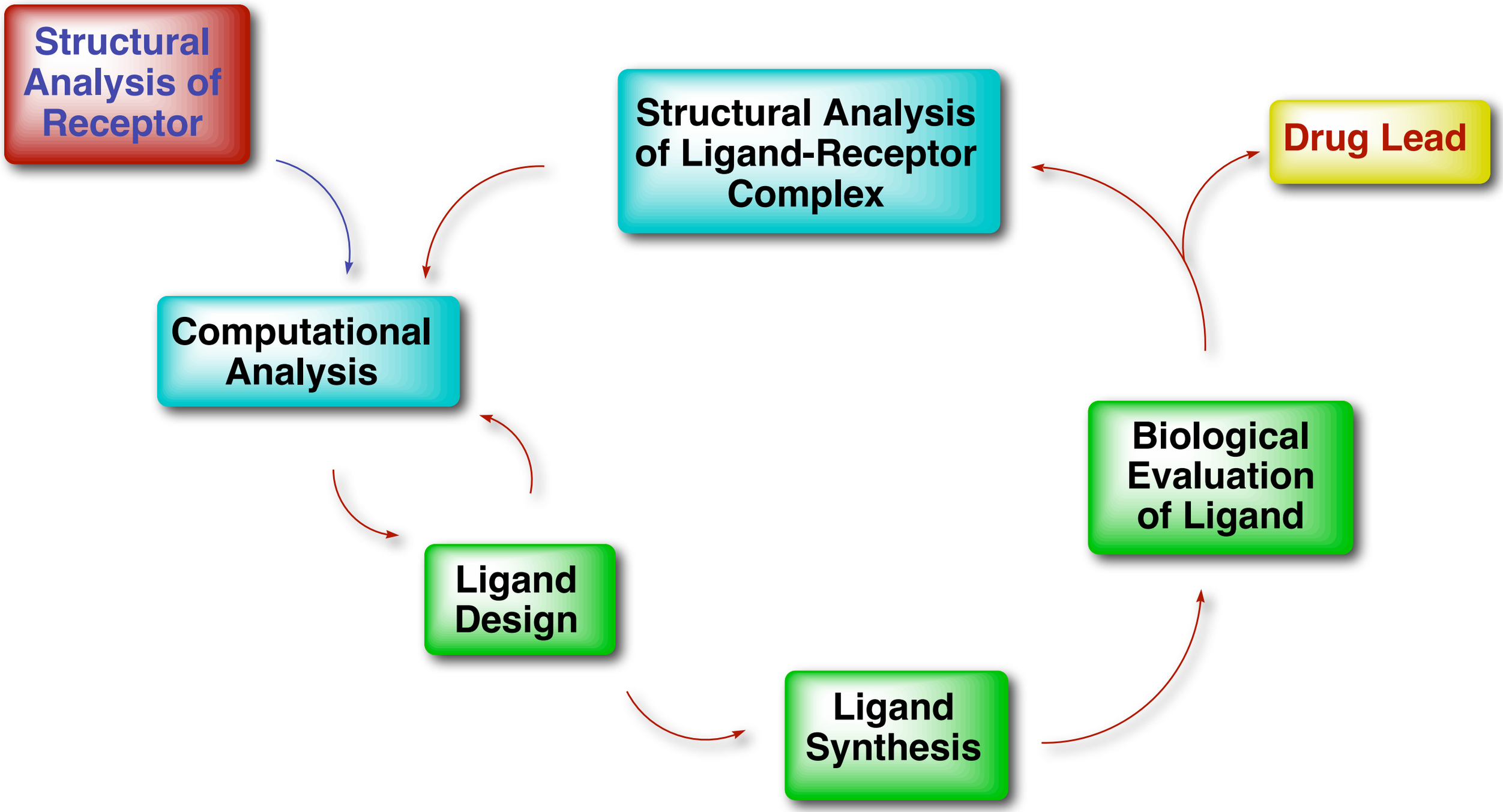

Bringing a Drug to the Market

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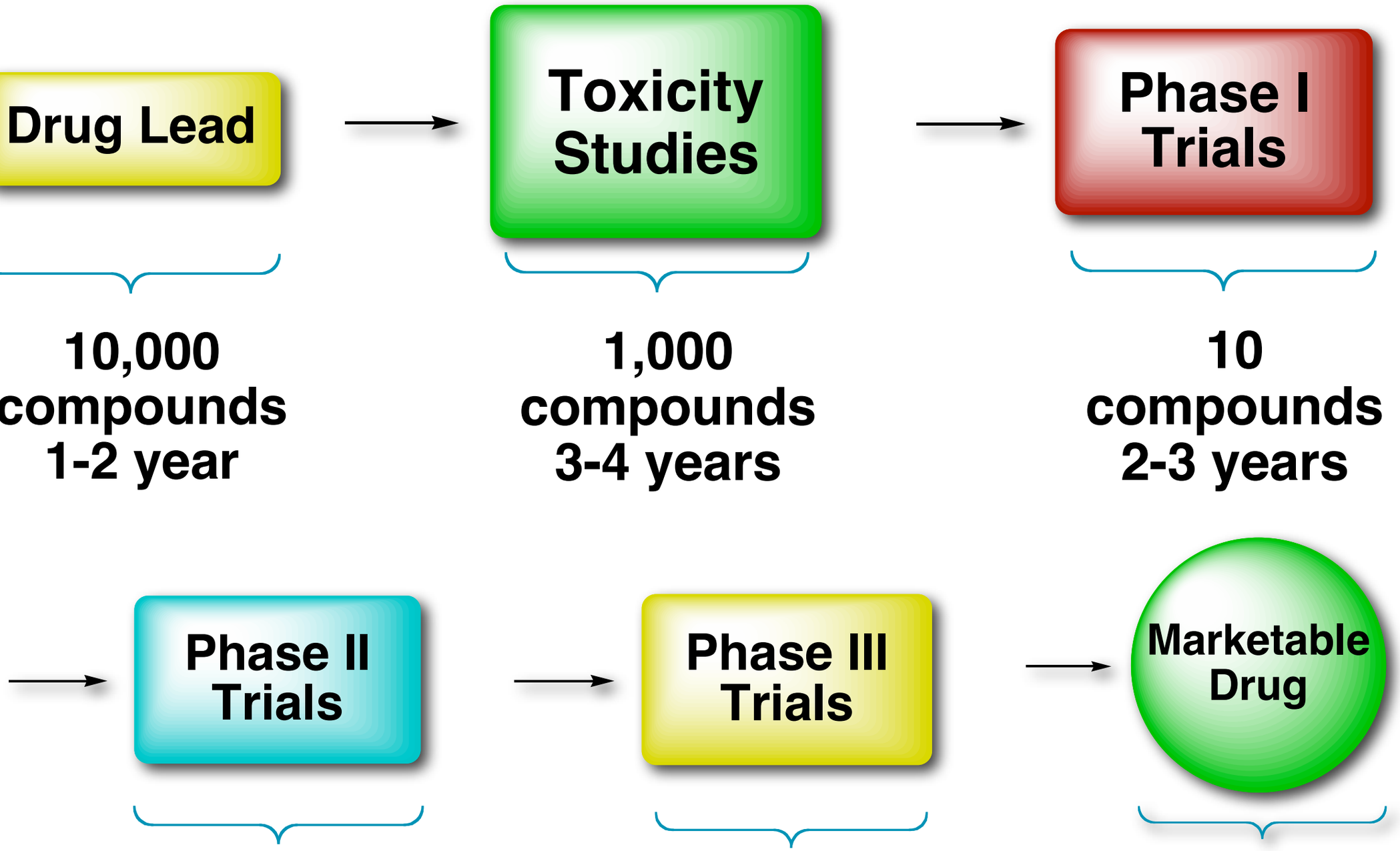
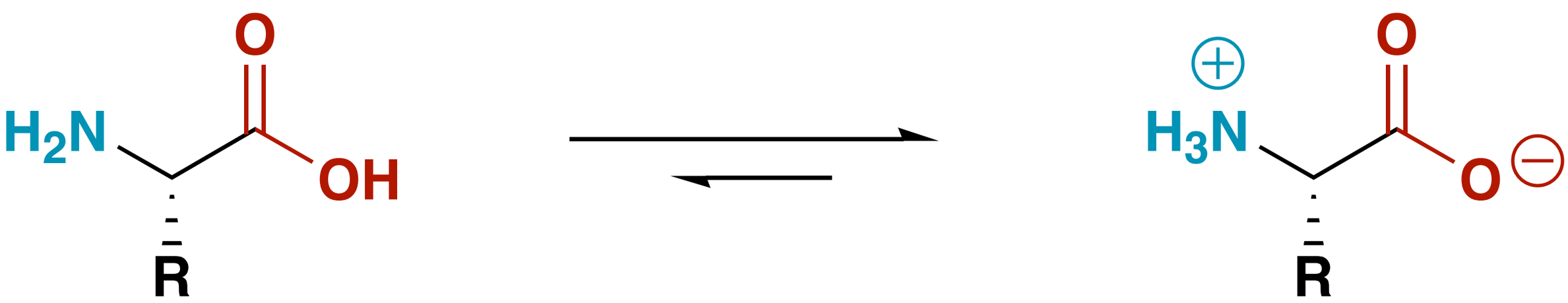


Amino Acids

- Highly polar zwitterions



Amino Acids

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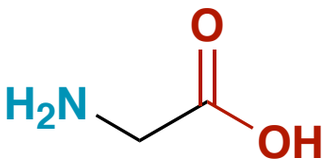
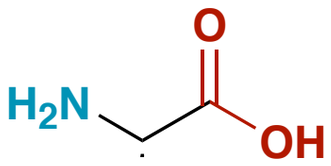
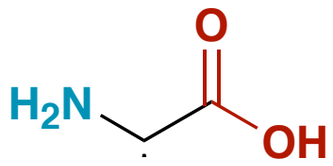
- There are 20 common amino acids - 15 Neutral



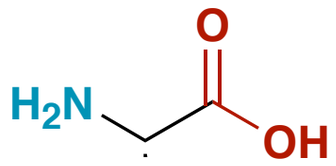
glycine



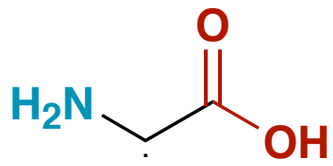
alanine



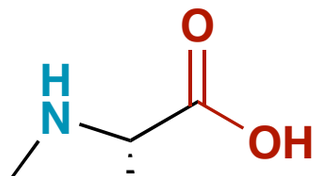
valine



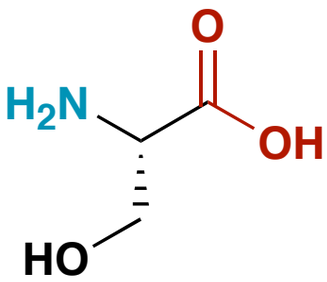
leucine



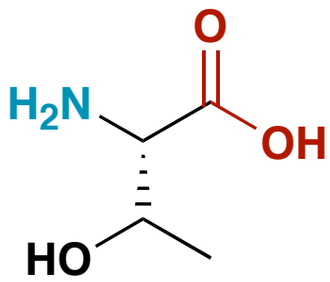
isoleucine



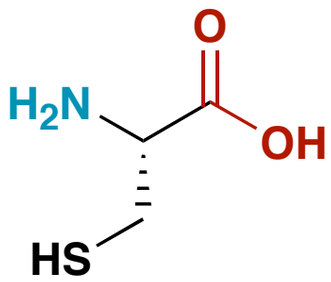
proline



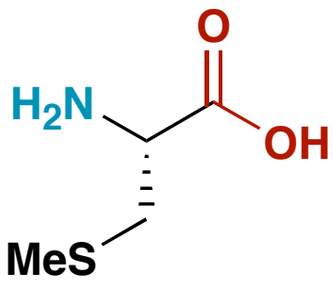
serine



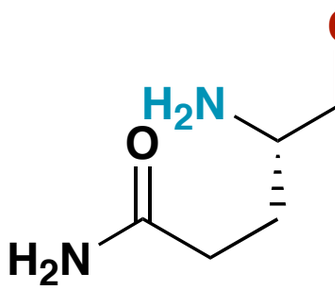
threonine



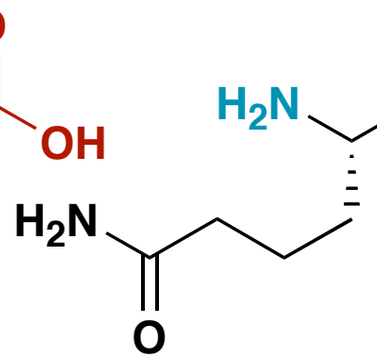
cysteine



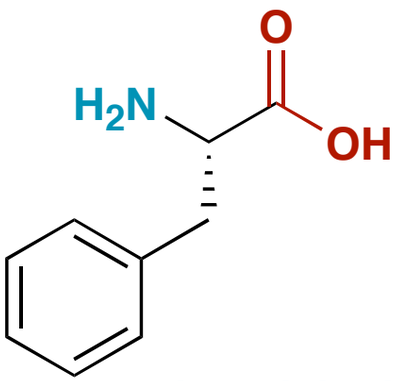
methionine



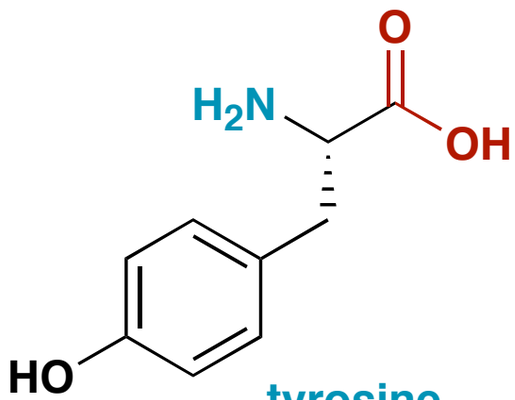
asparagine



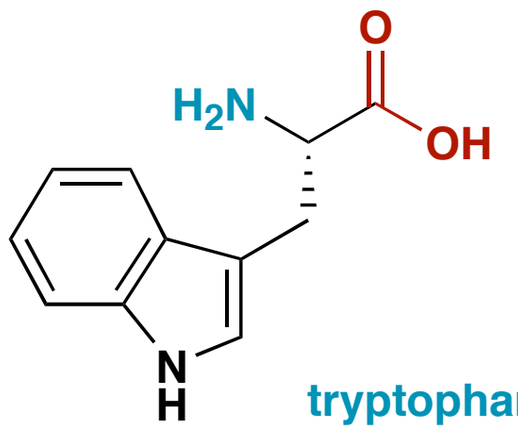
glutamine



phenylalanine



tyrosine



tryptophan

Amino Acids

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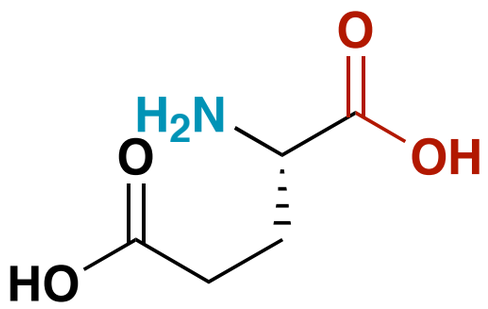
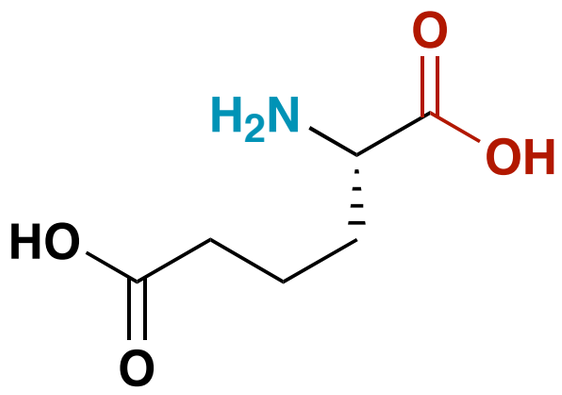
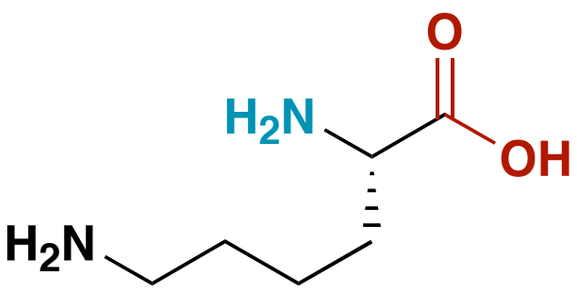
- Acidic and Basic



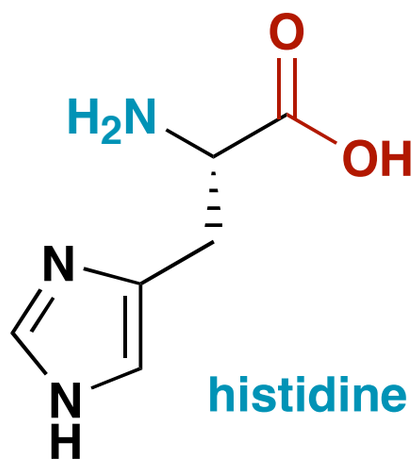
apartic acid



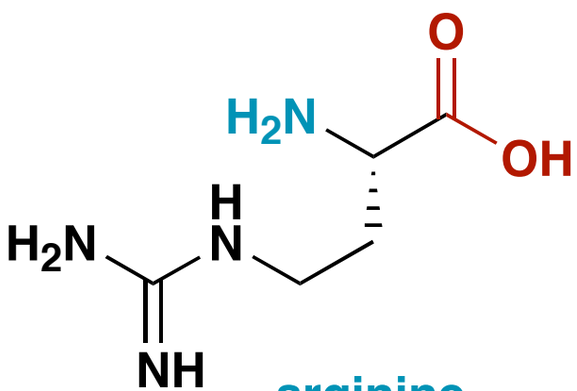
glutamic acid



lysine



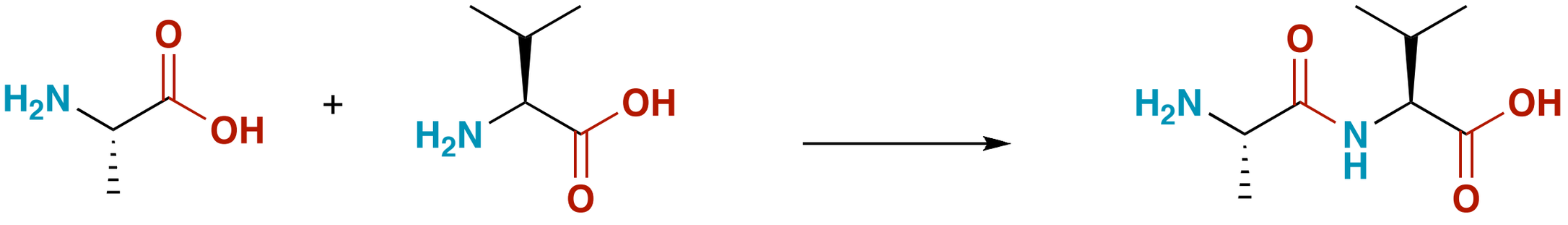
histidine



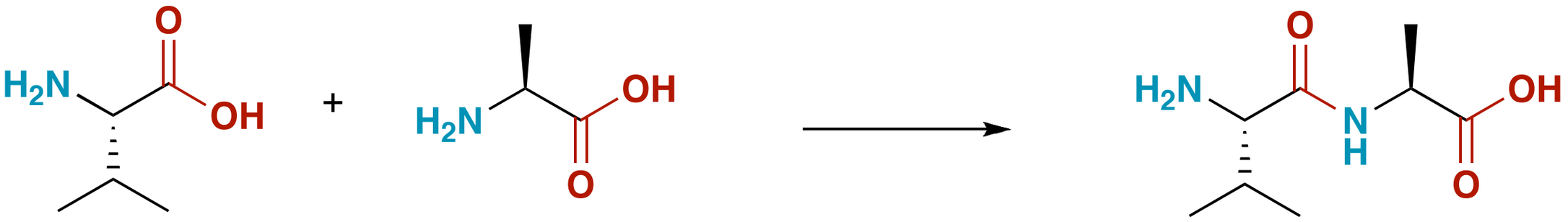
arginine

Peptides - Proteins

- Polymers of Amino Acids



N-terminus C-terminus



Peptide Bonds

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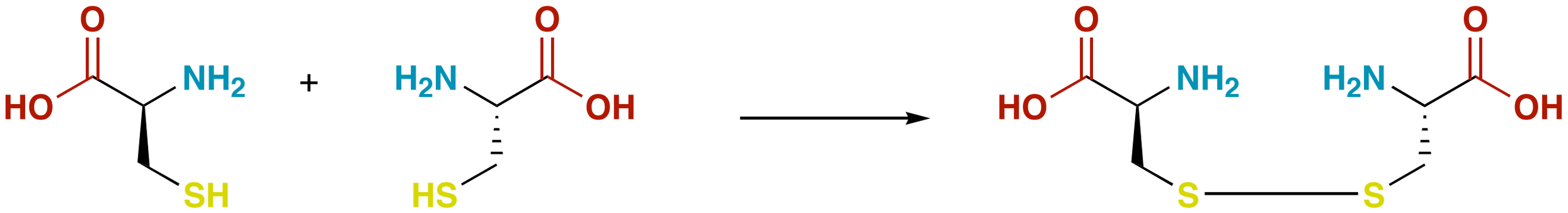
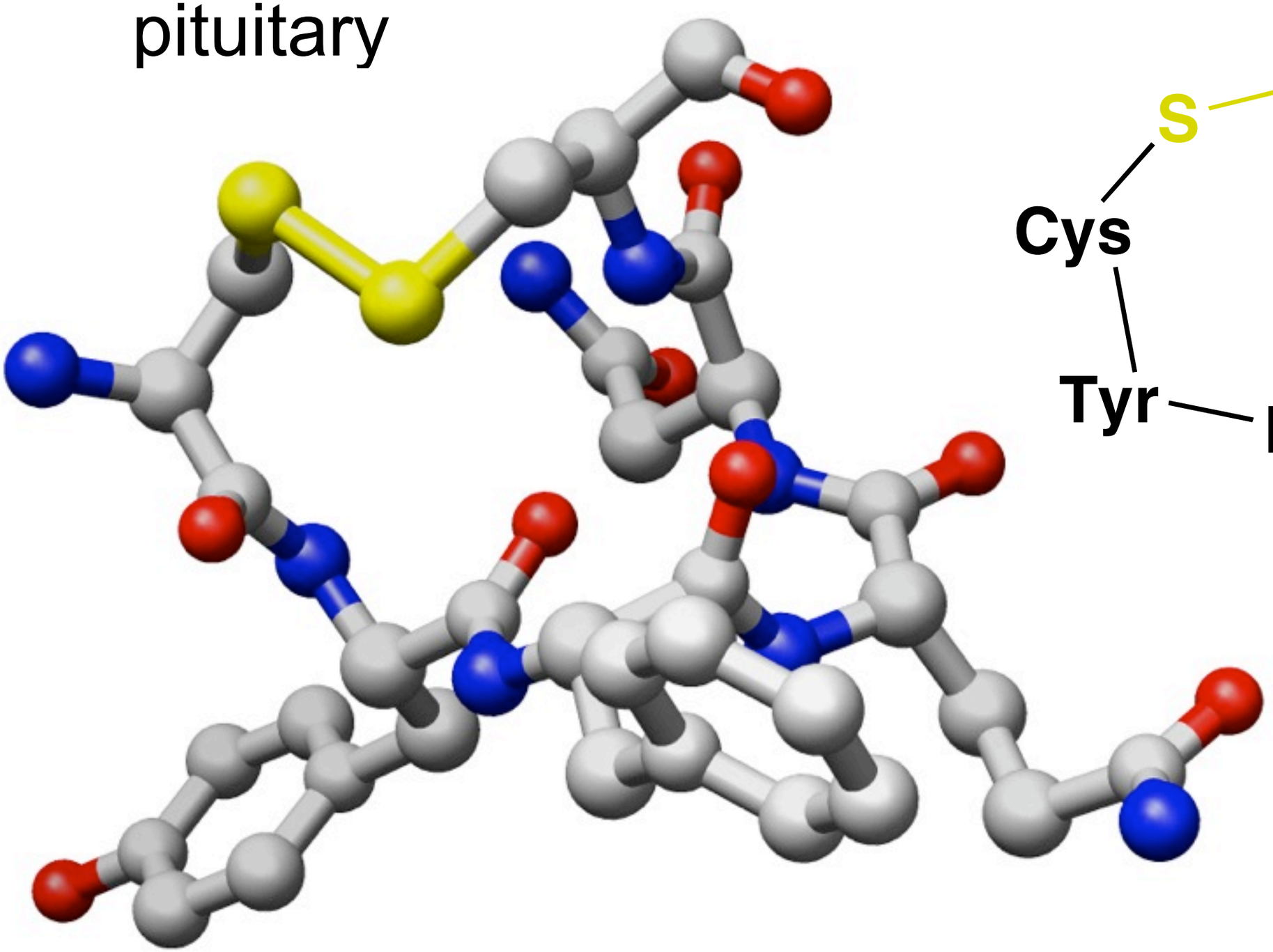
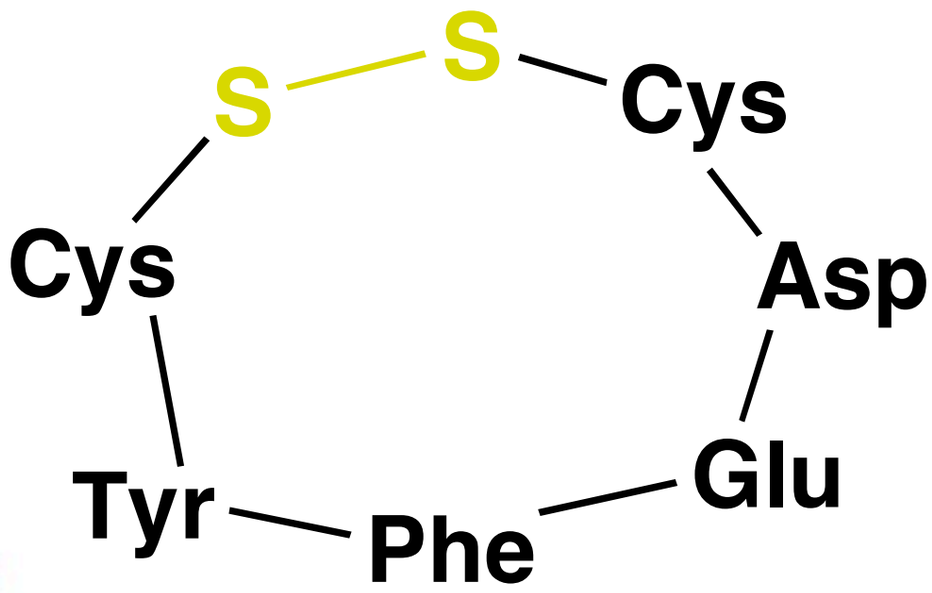
- Amide is the main bond - but can have disulfide bonds



Disulfide in Vasopressin

- Vasopressin - antidiuretic hormone from pituitary



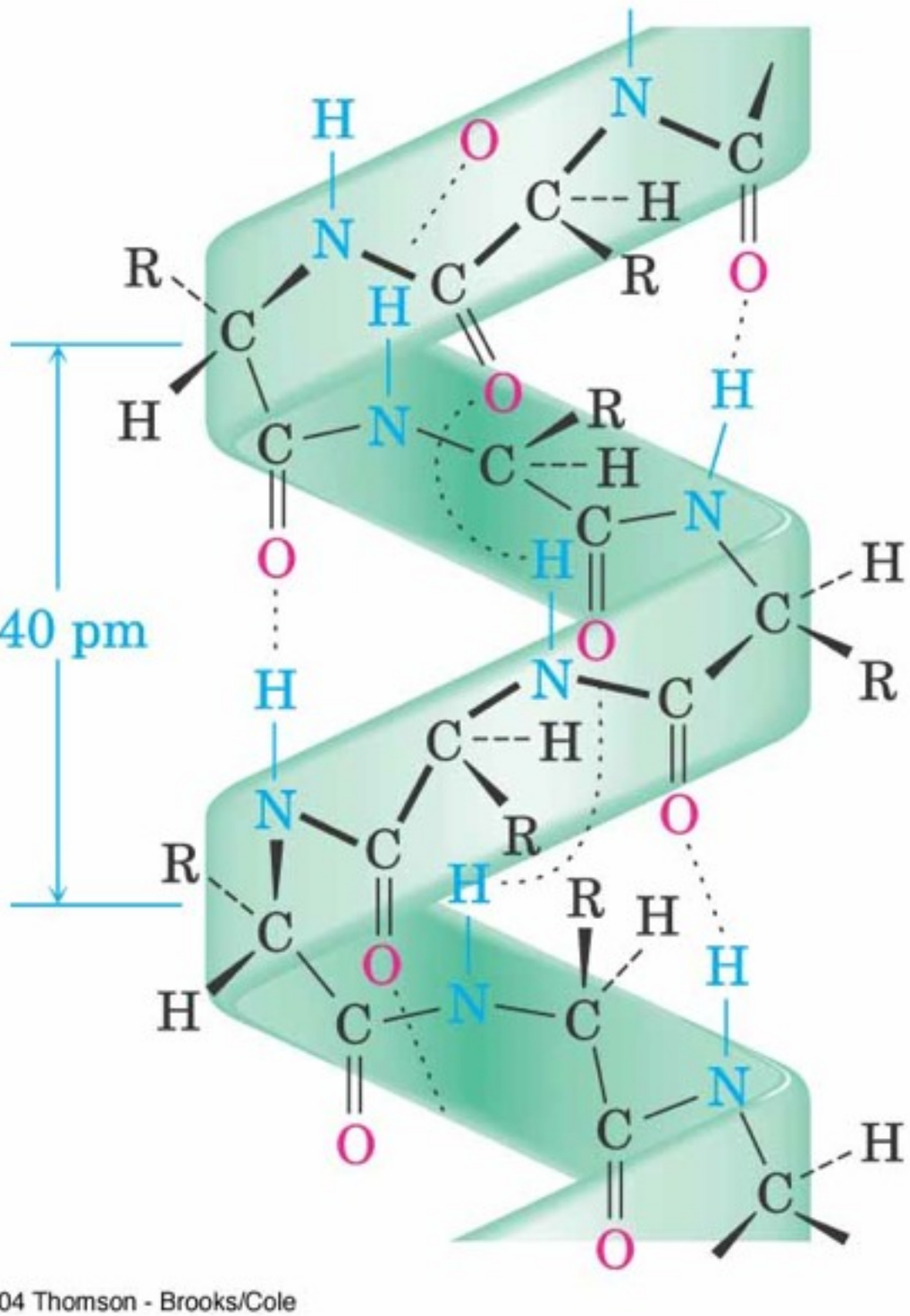


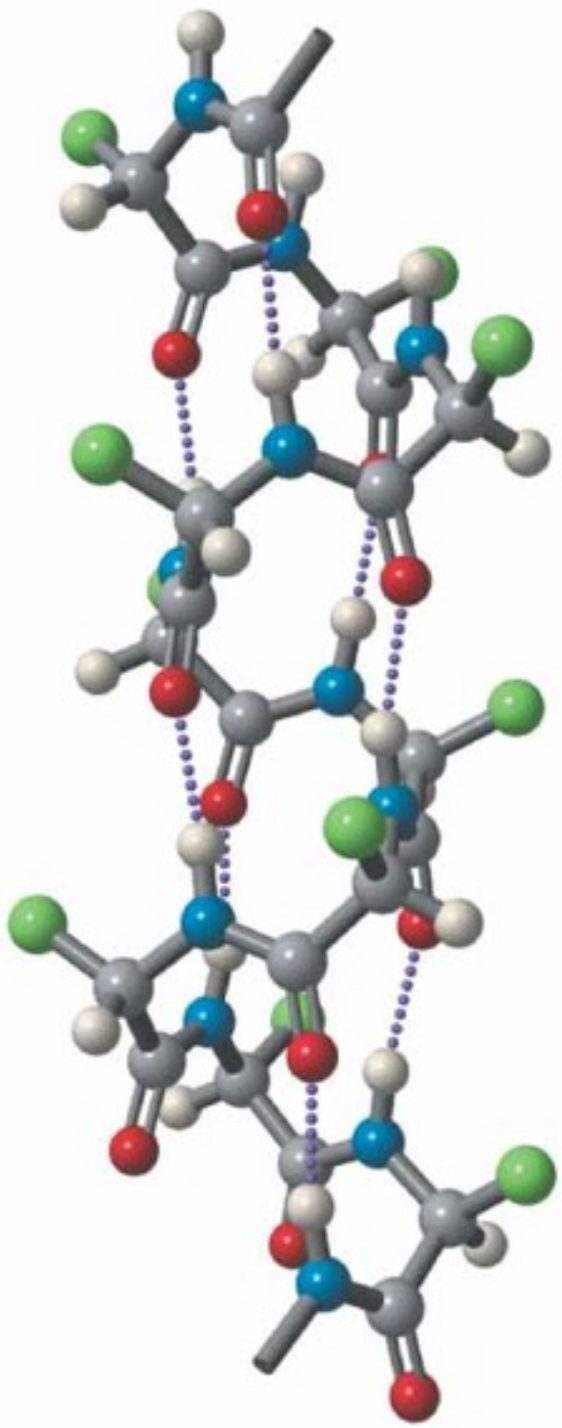
Peptide - Protein Structure

- Primary Structure - amino acid sequence
- Secondary Structure - orientation of segments alpha-helix, beta sheets, loops
- Tertiary Structure - overall shape of the molecule
- Quaternary Structure - overal structure of protein aggregates

Alpha - Helix

- A helical secondary structure from keratin





Beta Sheets

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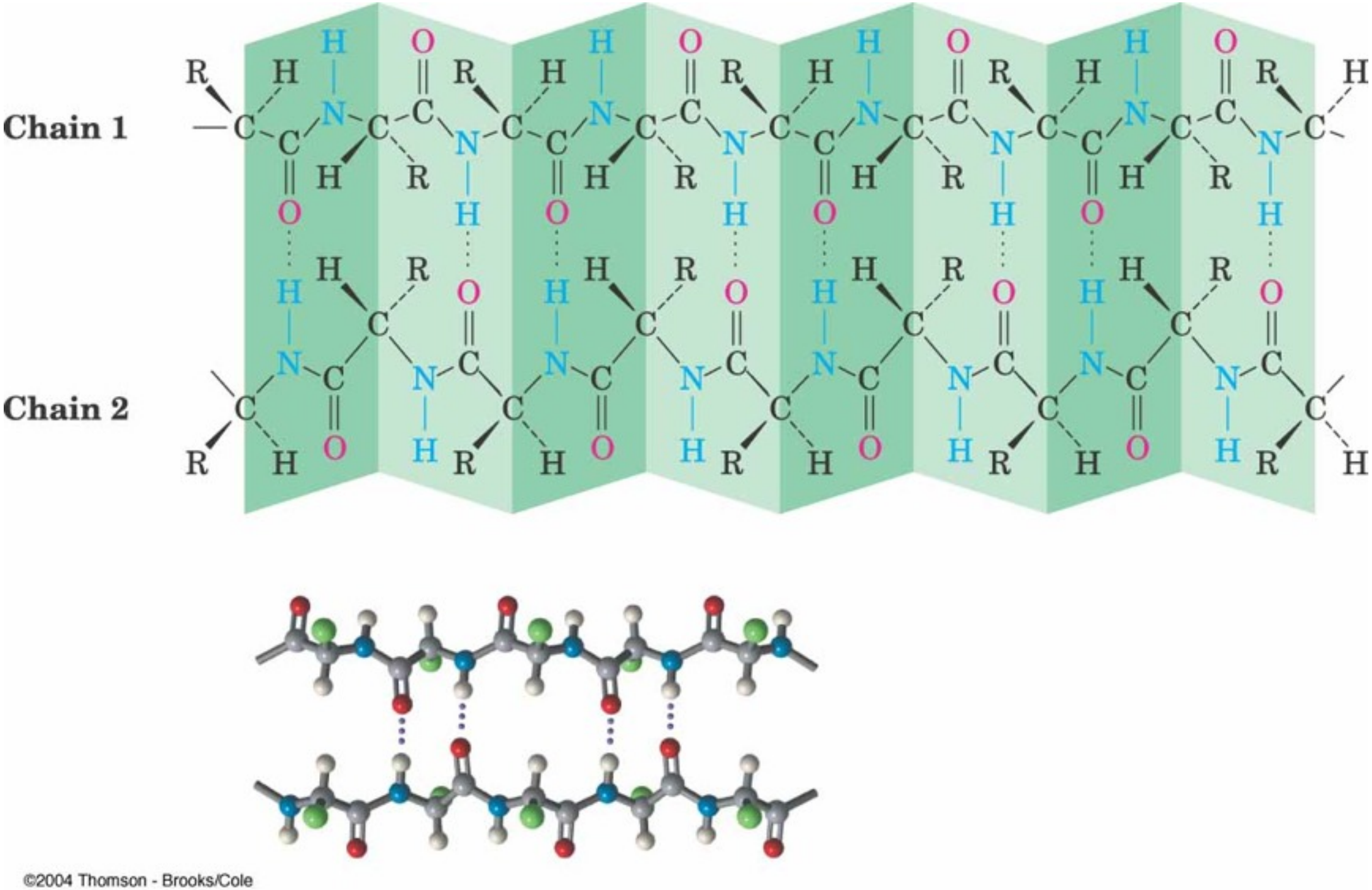
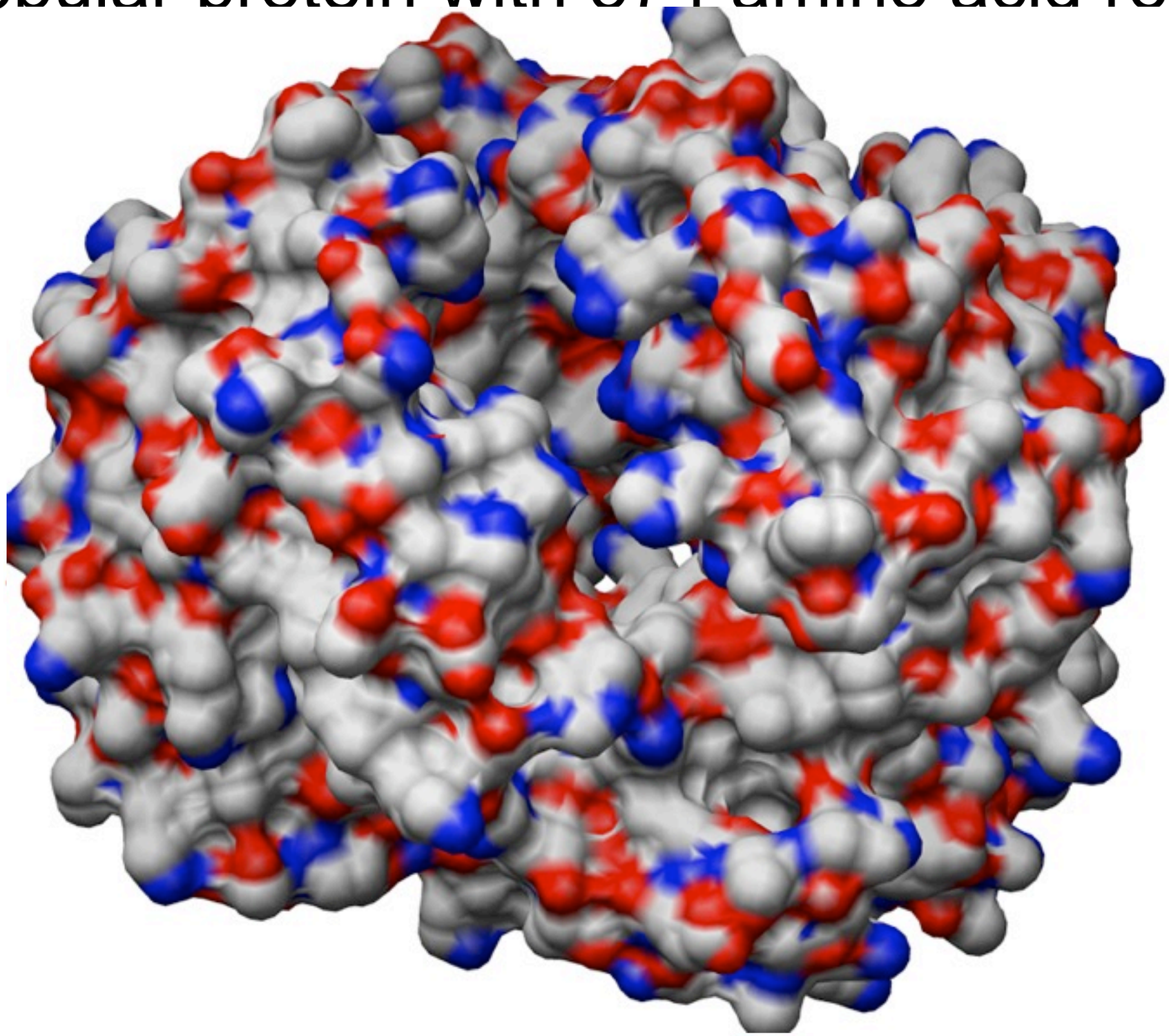
- Beta sheet secondary structure from Silk fibroin



Hemoglobin

- Globular protein with 574 amino acid residues



Types of Proteins

TABLE 26.2 Some Common Fibrous and Globular Proteins

Name	Occurrence and use
Fibrous proteins (insoluble)	
Collagens	Animal hide, tendons, connective tissues
Elastins	Blood vessels, ligaments
Fibrinogen	Necessary for blood clotting
Keratins	Skin, wool, feathers, hooves, silk, fingernails
Myosins	Muscle tissue
Globular proteins (soluble)	
Hemoglobin	Involved in oxygen transport
Immunoglobulins	Involved in immune response
Insulin	Hormone for controlling glucose metabolism
Ribonuclease	Enzyme for controlling RNA synthesis

Enzymes

- Proteins which act as catalysts for chemical reactions.

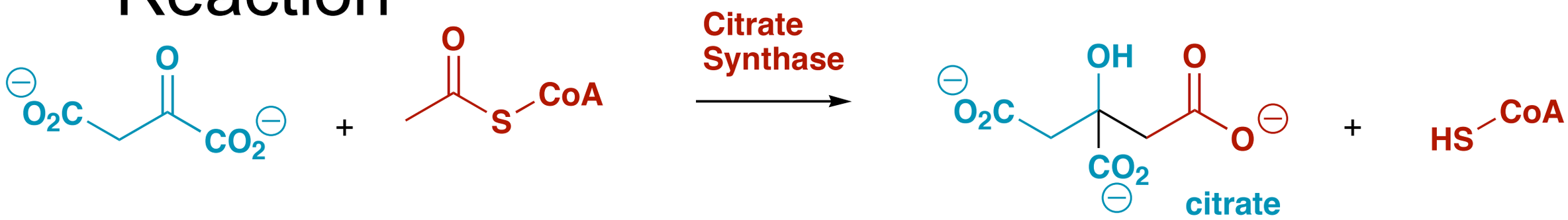
TABLE 26.4 Classification of Enzymes

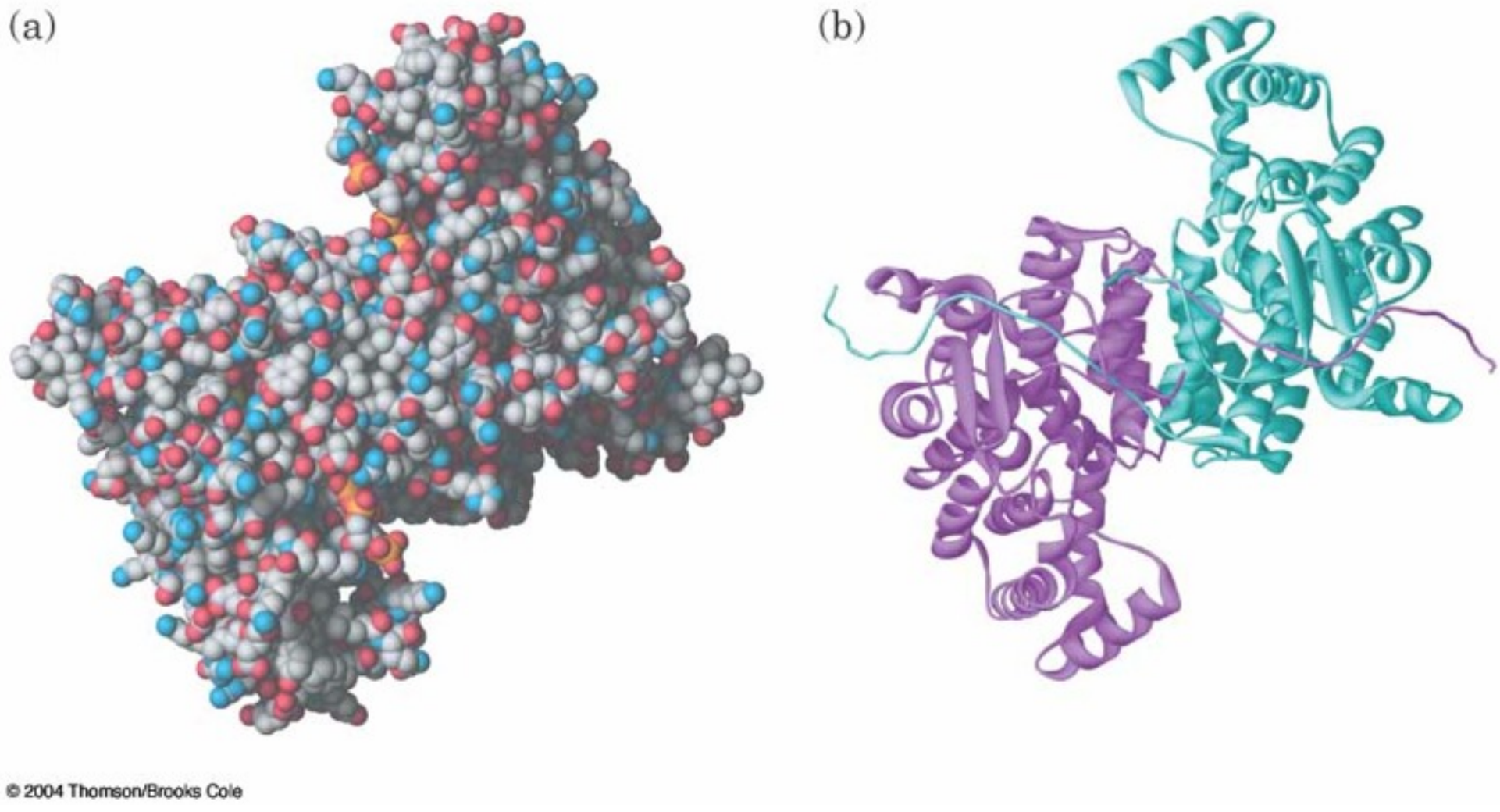
Main class	Some subclasses	Type of reaction catalyzed
Hydrolases	Lipases	Hydrolysis of an ester group
	Nucleases	Hydrolysis of a phosphate group
	Proteases	Hydrolysis of an amide group
Isomerases	Epimerases	Isomerization of a chirality center
Ligases	Carboxylases	Addition of CO_2
	Synthetases	Formation of new bond
Lyases	Decarboxylases	Loss of CO_2
	Dehydrases	Loss of H_2O
Oxidoreductases	Dehydrogenases	Introduction of double bond by removal of H_2
	Oxidases	Oxidation
	Reductases	Reduction
Transferases	Kinases	Transfer of a phosphate group
	Transaminases	Transfer of an amino group

Citrate Synthase

The Cook Group @ NDSU

- A dimeric protein that catalyzes an Aldol Reaction





Citrate Synthase Mechanism

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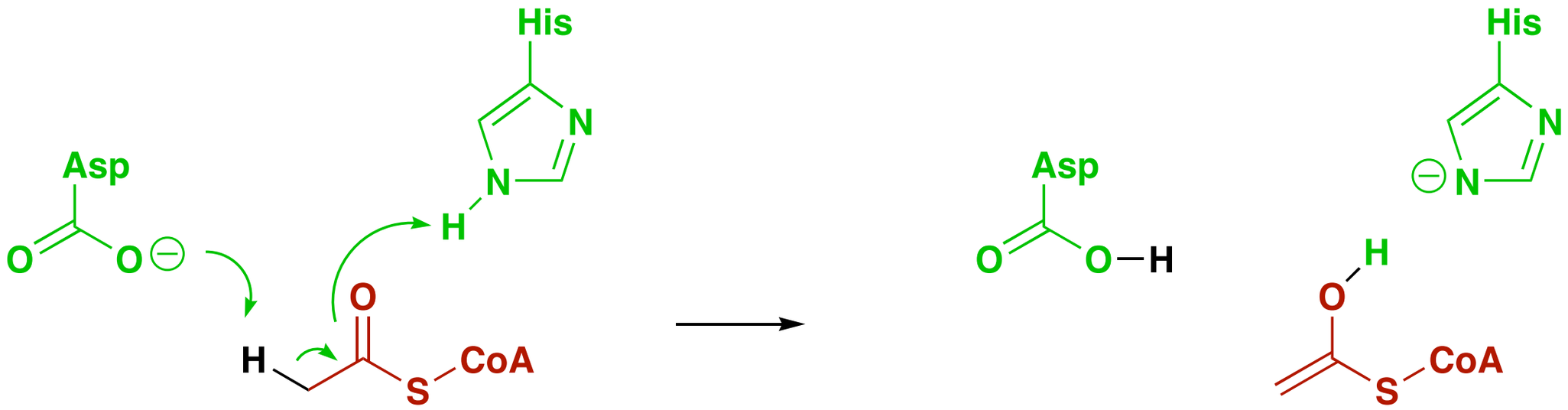
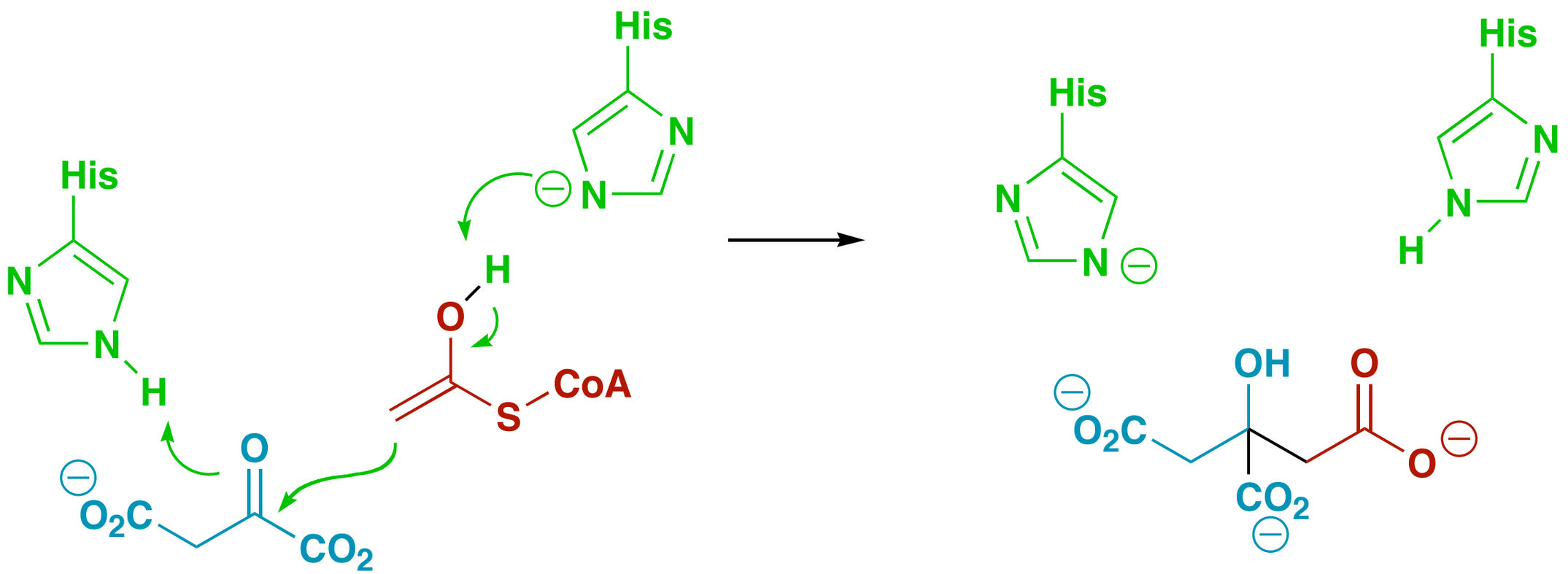
@ NDSU

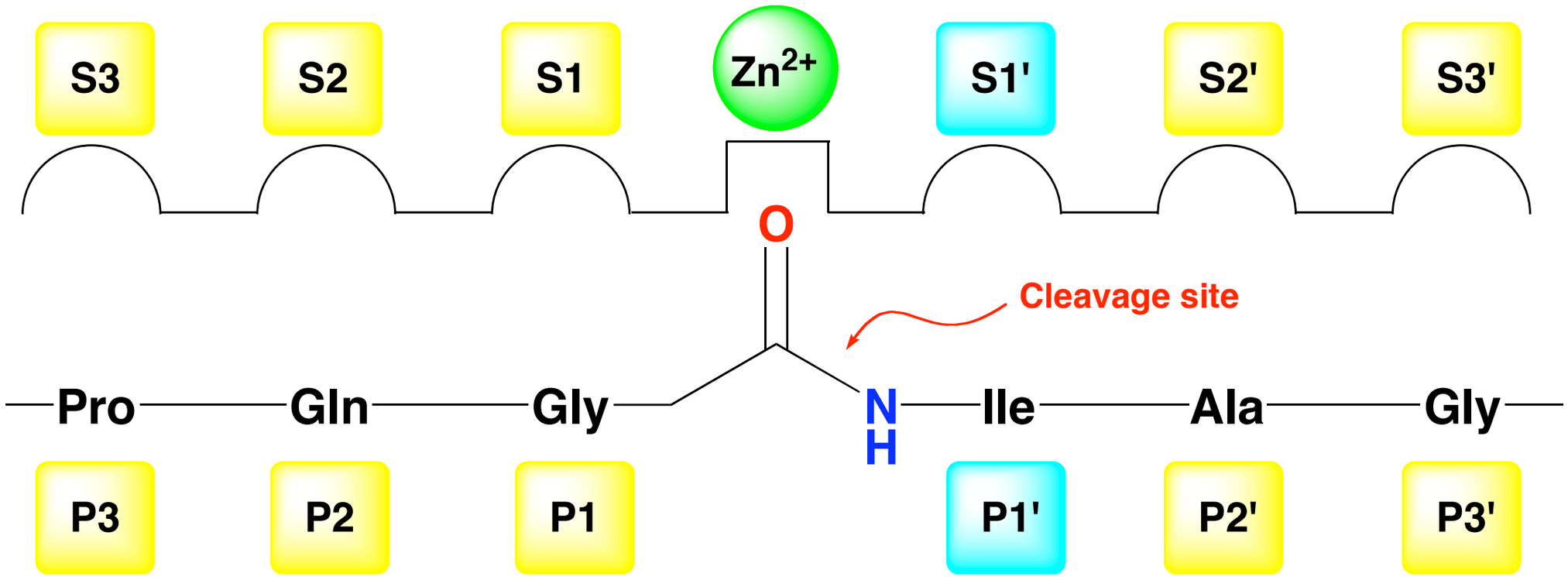




Matrix Metalloproteinases

- Family of Zn-dependent enzymes
  - 26 known MMP's
  - Responsible for maintaining extracellular matrix
- MMP's out of balance in many diseases
  - **CANCER**, Arthritis, Multiple Sclerosis, Stroke Damage, and many more . . .

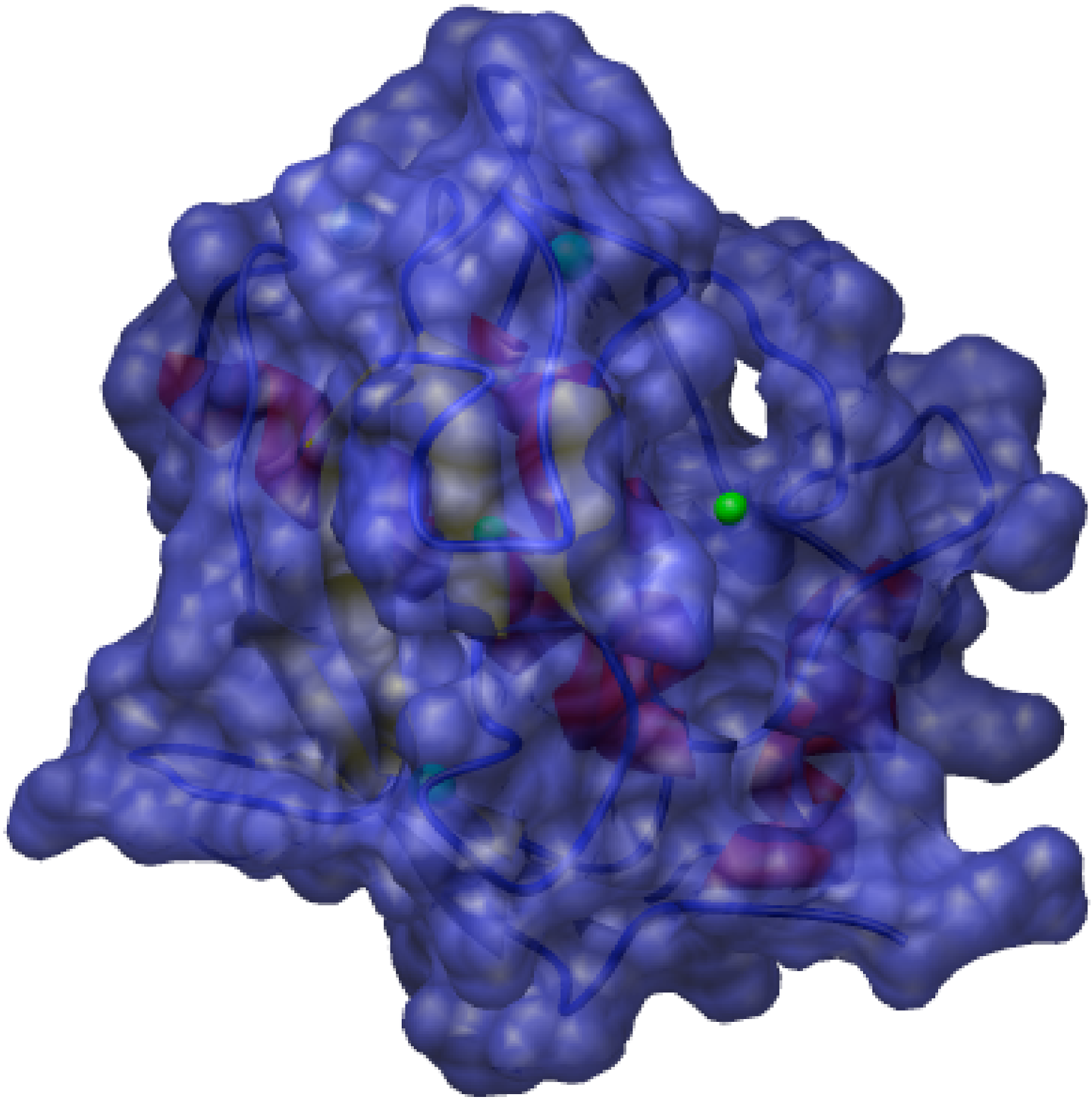
Catalytic Site of MMP-1



Catalytic Site of MMP-1 with natural collagen substrate

MMP Structure

The Cook Group
@ NDSU



hydroxamic acid sar

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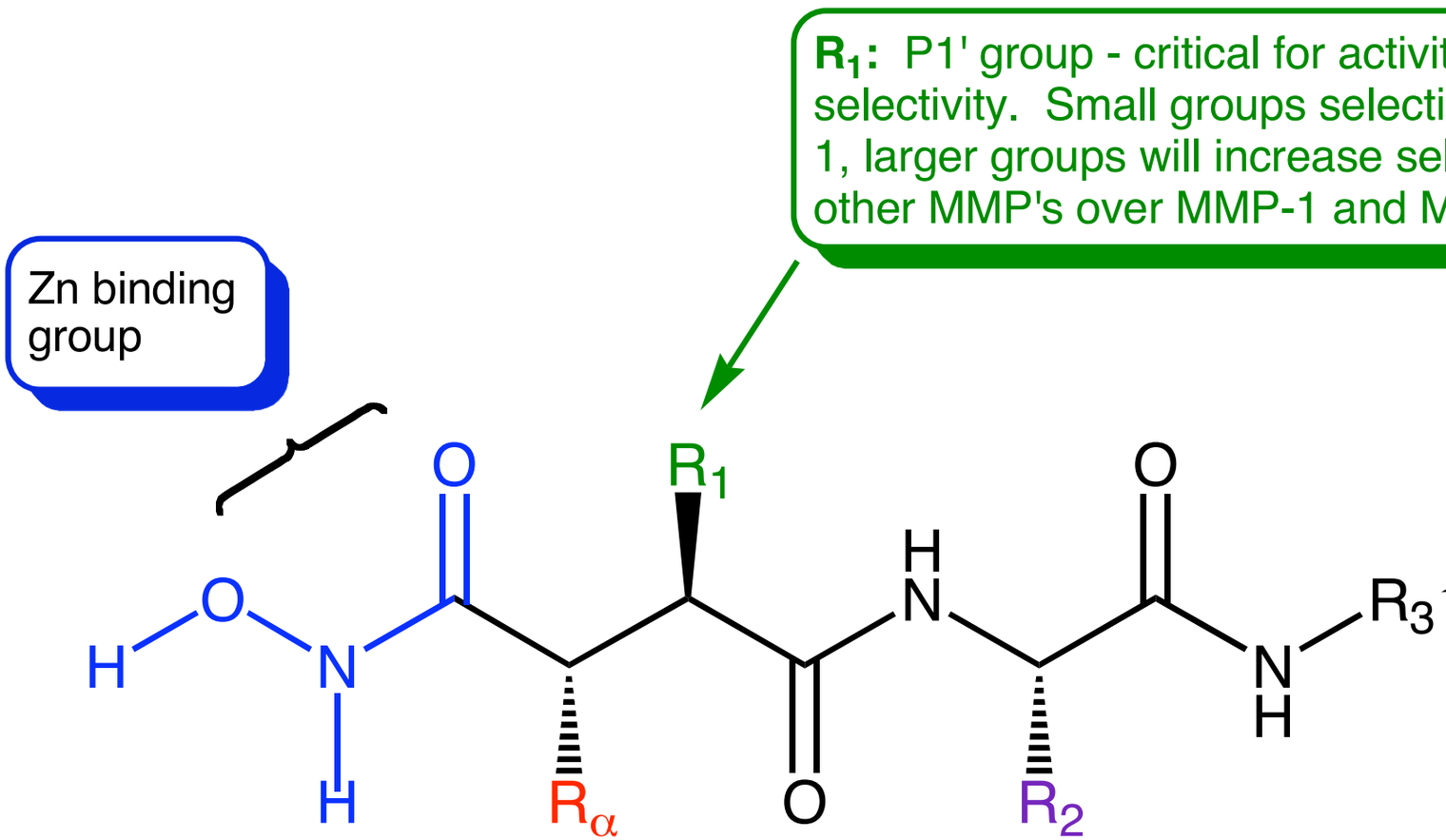


R_1: P1' group - critical for activity and selectivity. Small groups selective for MMP-1, larger groups will increase selectivity of other MMP's over MMP-1 and MMP-7.

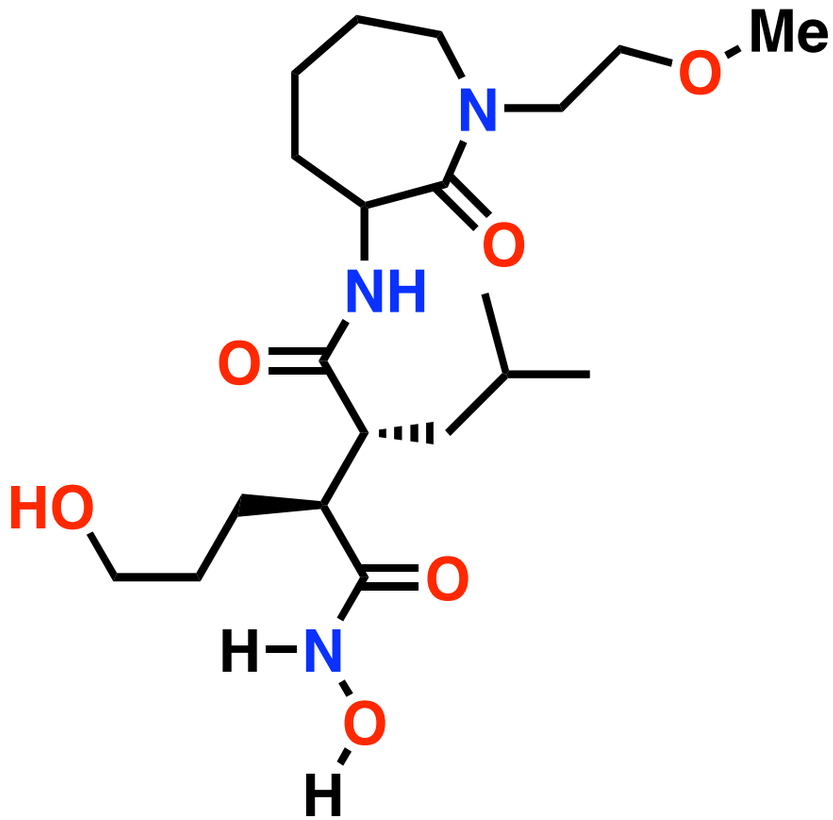
R_3: P3' group - functionality widely tolerated. Aromatic groups increase MMP-3 selectivity.

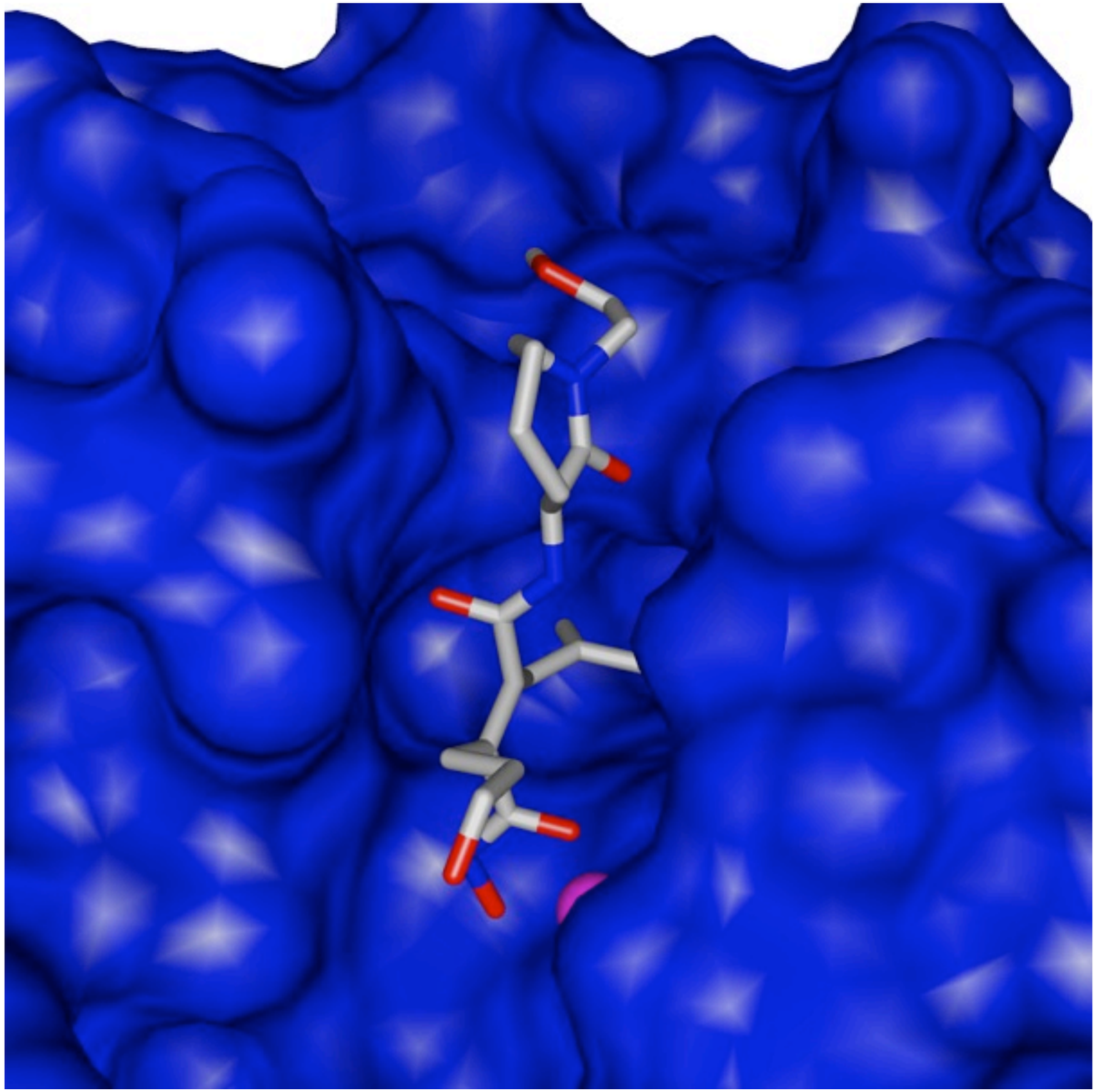
R_α: P1 group - not necessary for activity, but substitution can lead to increased activity of some MMP's.

R_2: P2' group - wide range of substitution tolerated with aromatic groups preferred. More bulky groups increase oral bioavailability by decreasing amide bond scission.

Hydroxamate Bound to MMP-3

- MMP-3 (Stromelysin 1)

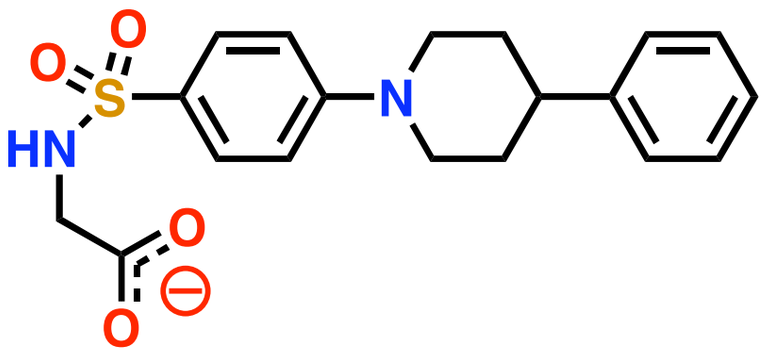


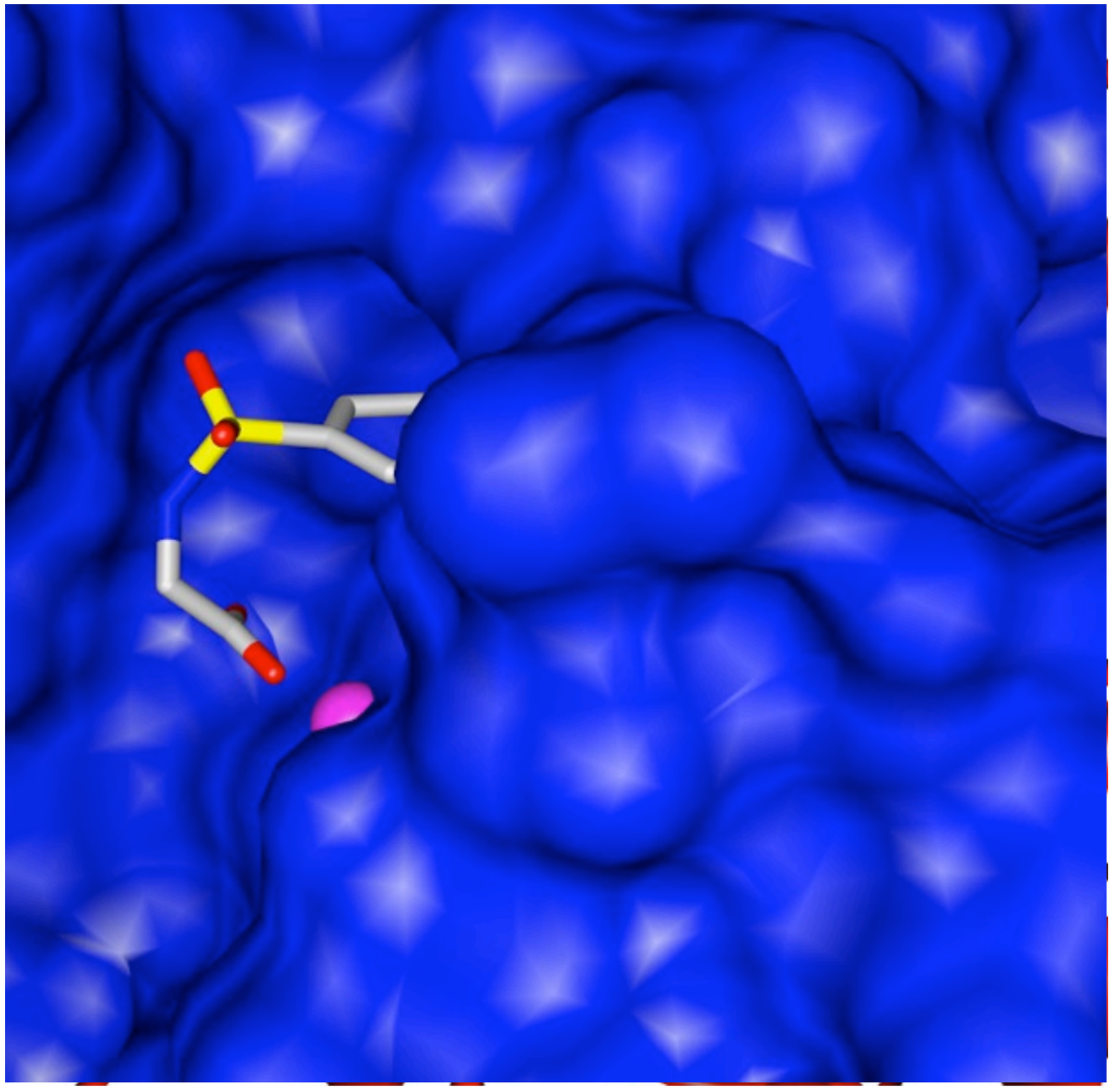


Sulfonamide Bound to MMP-3

The Cook Group @ NDSU

- MMP-3 (Stromelysin 1)





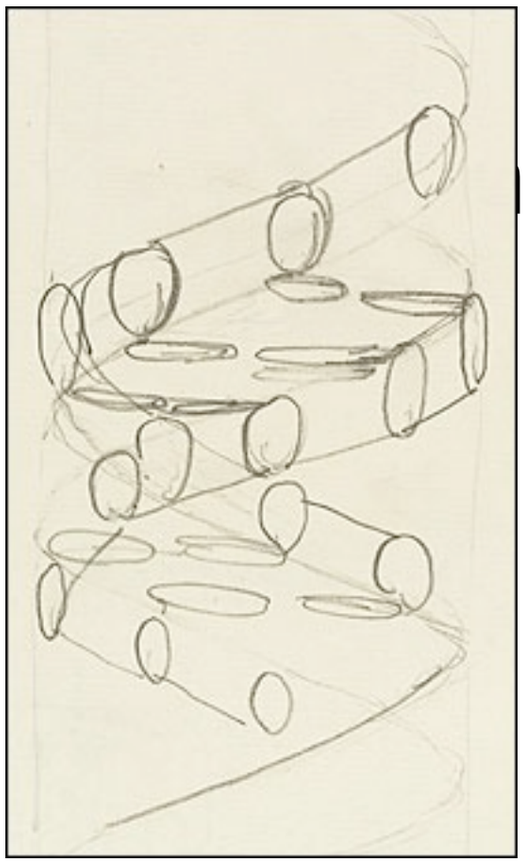
2006 Nobel Prize in Chemistry

"for his studies of the molecular basis of eukaryotic transcription"

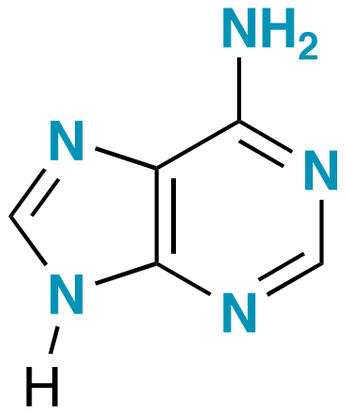
Prof. Roger Kornberg
Dept. of Structural Biology
Stanford University
School of Medicine

DNA Structure

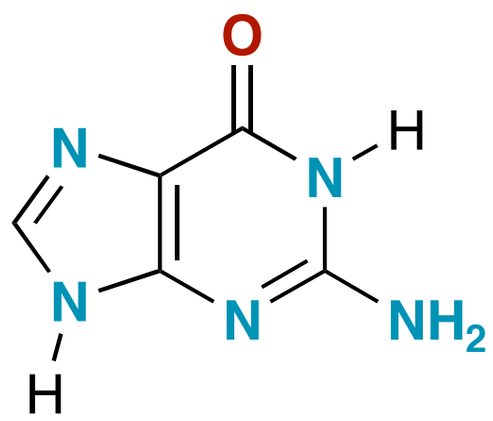
- 1953 - Watson and Crick discovered DNA was made up of two strands running in opposite directions
- The strands are held together by hydrogen bonding from the bases
- Specific bases bind to each other
- The strands are Complementary



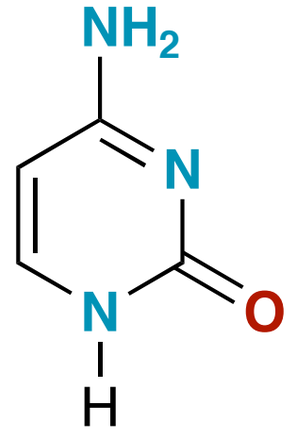
Heterocycles in DNA and RNA



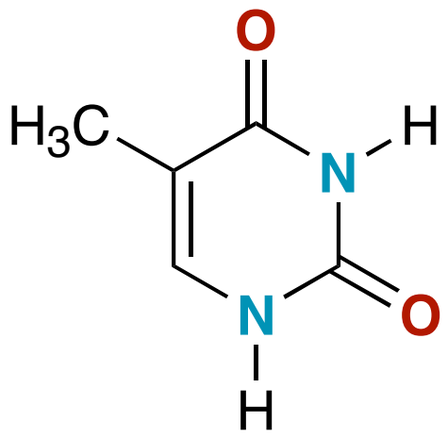
Adenine



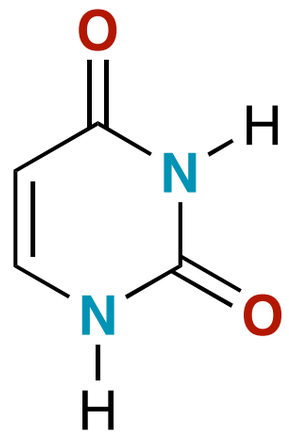
Guanine



Cytosine



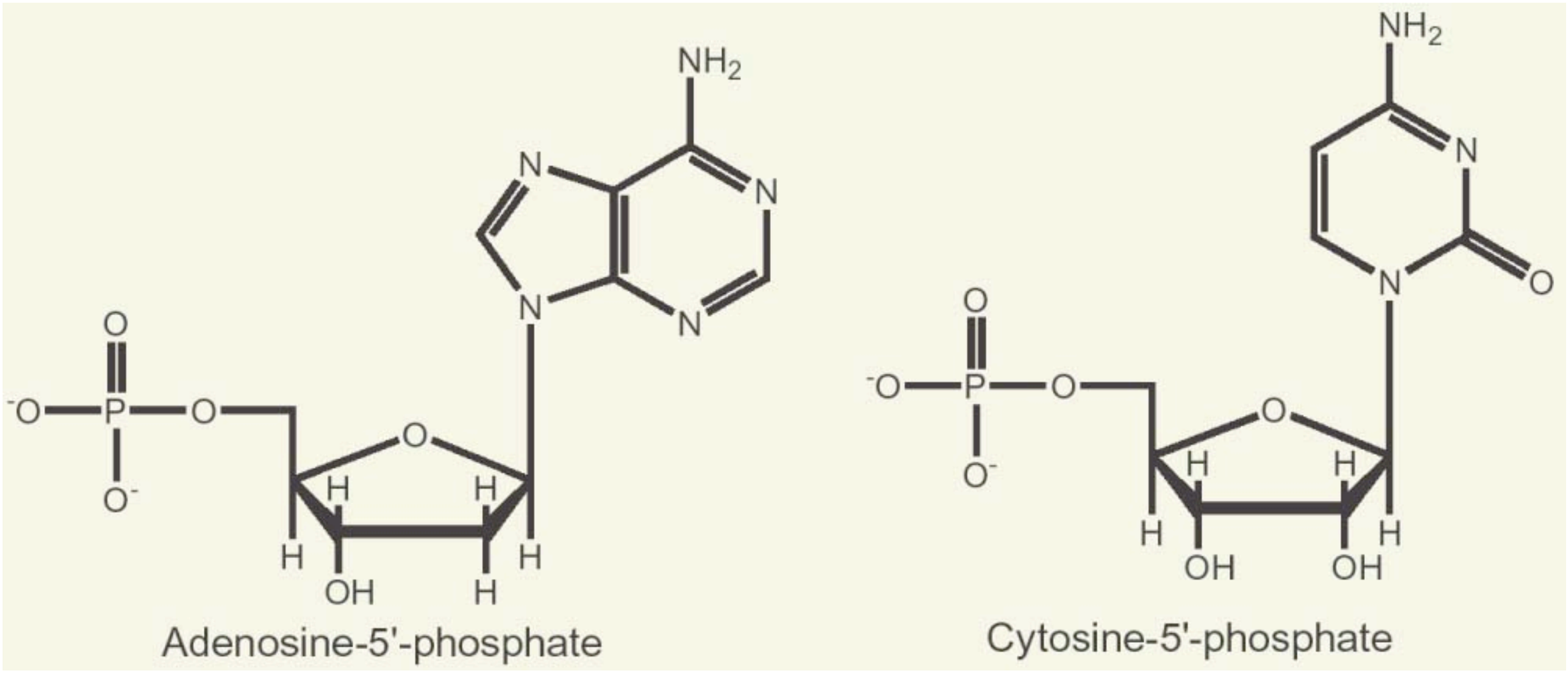
Thymine



Uracil

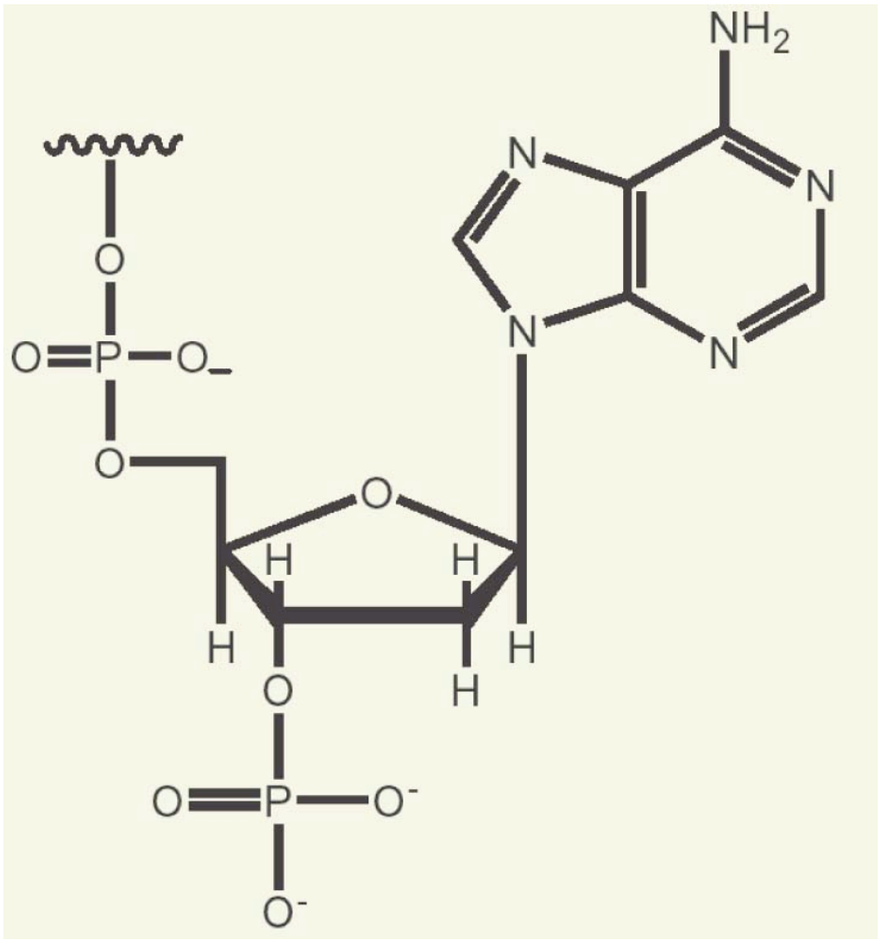
Nucleotides

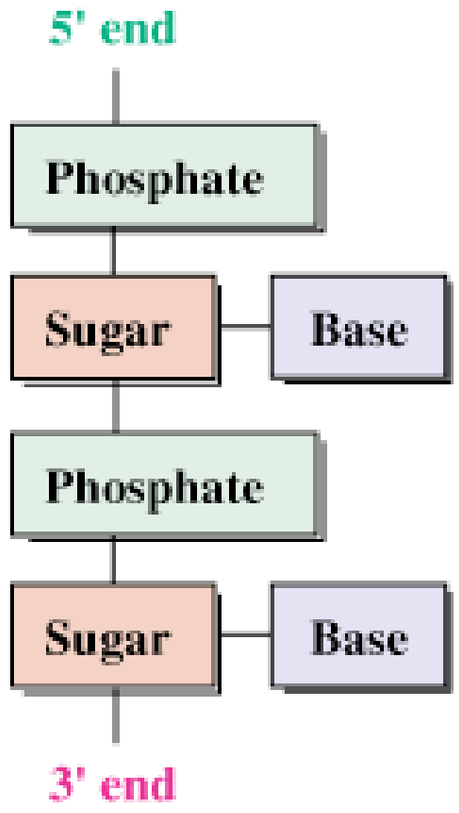
- The DNA/RNA bases are attached to phosphosugars

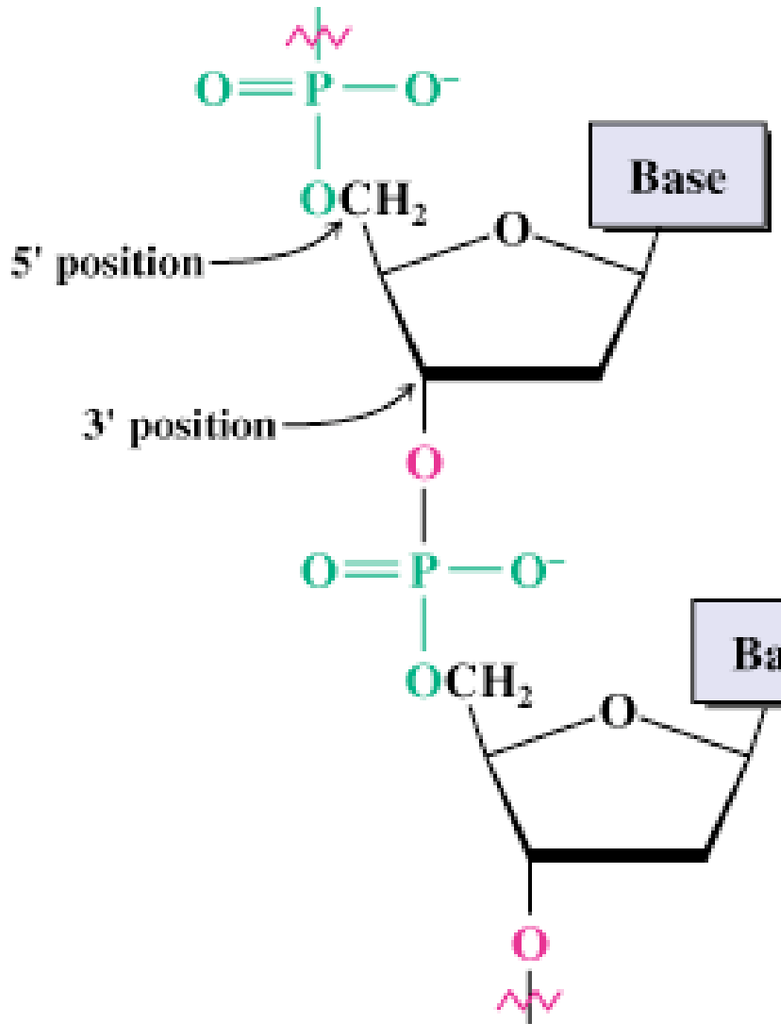


Nucleic Acid Structure

- The nucleotides are connected together by the phosphates on the sugars

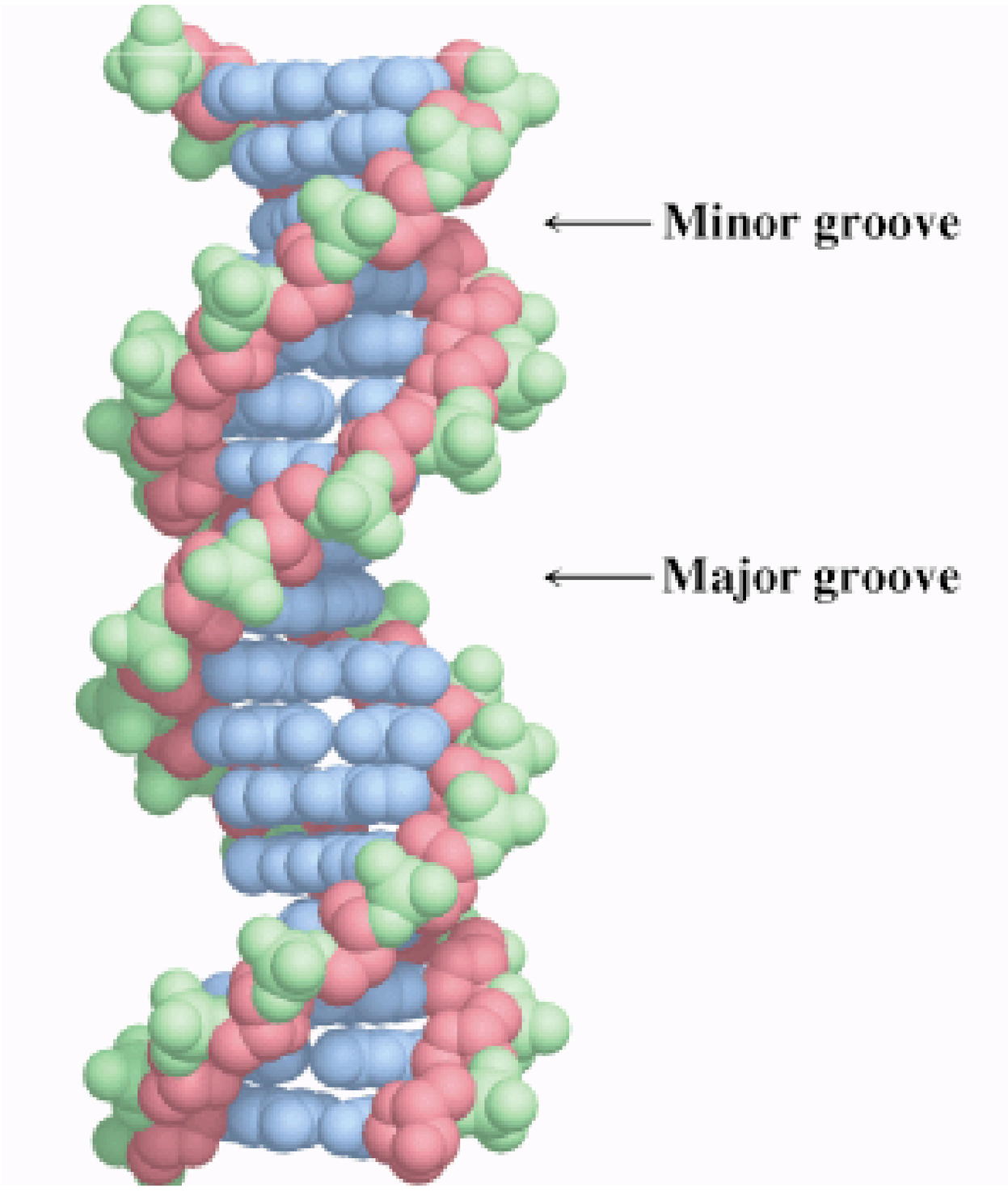






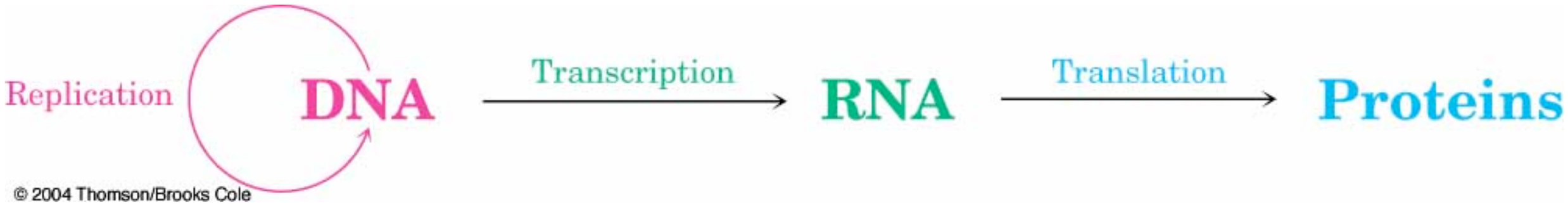
DNA Double Helix

- Two grooves are formed
- Sugar phosphate runs along the outside
- The major groove is slightly bigger and deeper than the minor groove



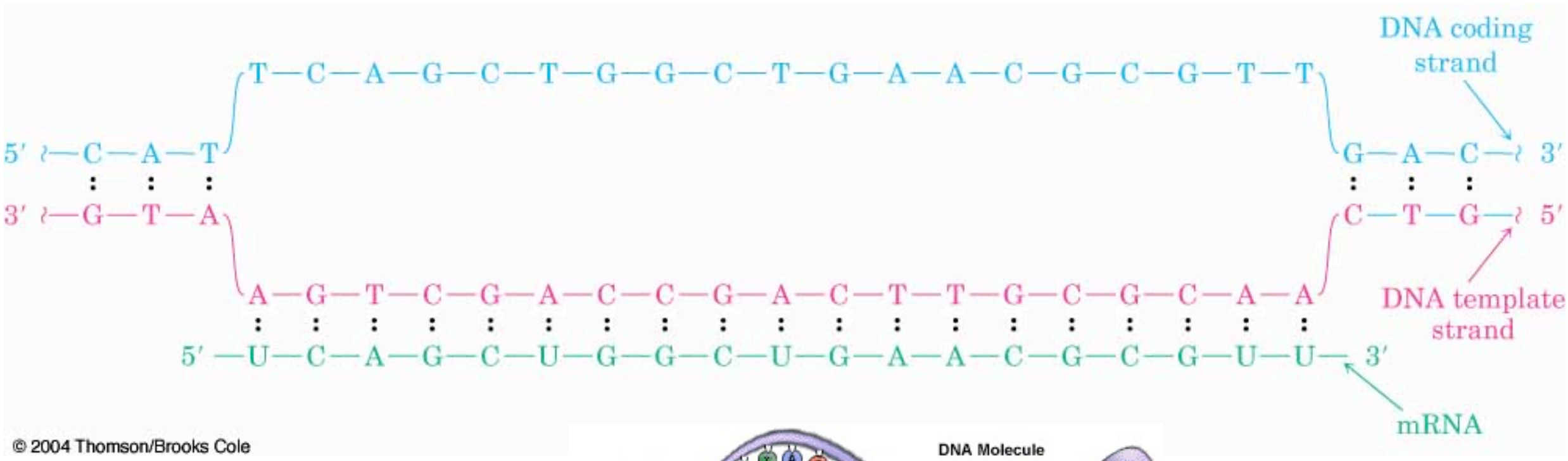
The Genes

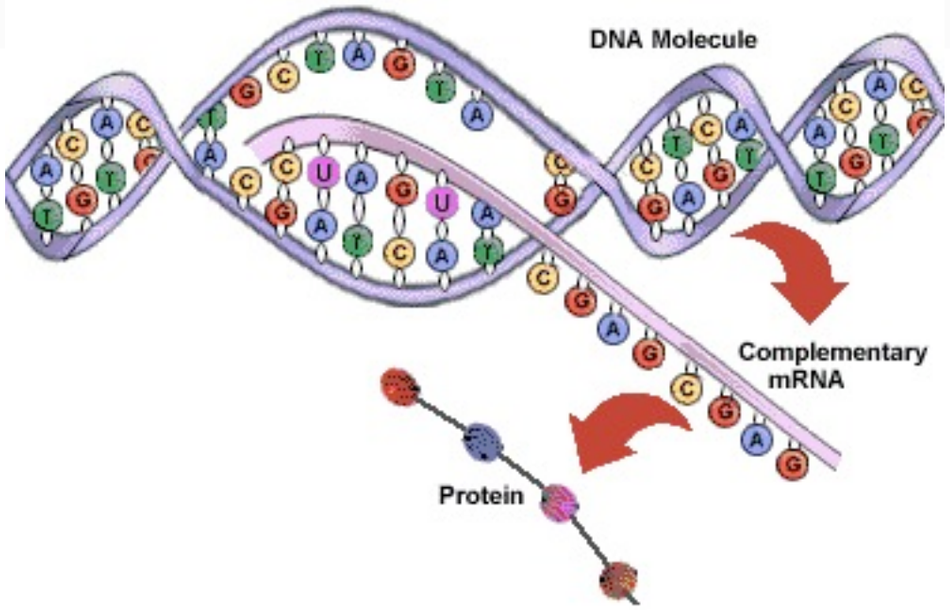
- DNA is a code for the synthesis of proteins. Every 3 base pair sequence is directly correlated with a specific amino acid.



Transcription

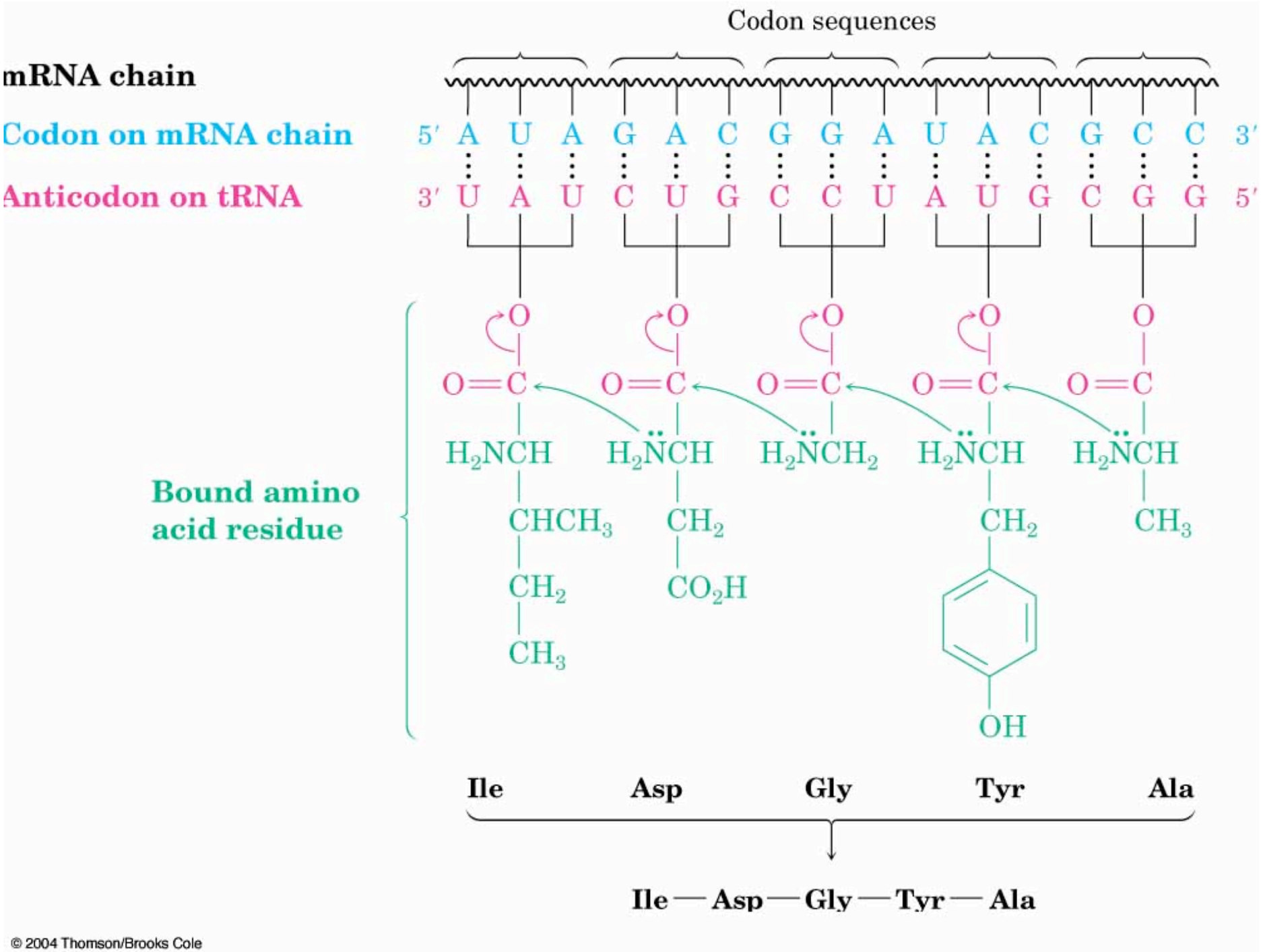
- DNA unwinds and codes an RNA strand
  - RNA Polymerase



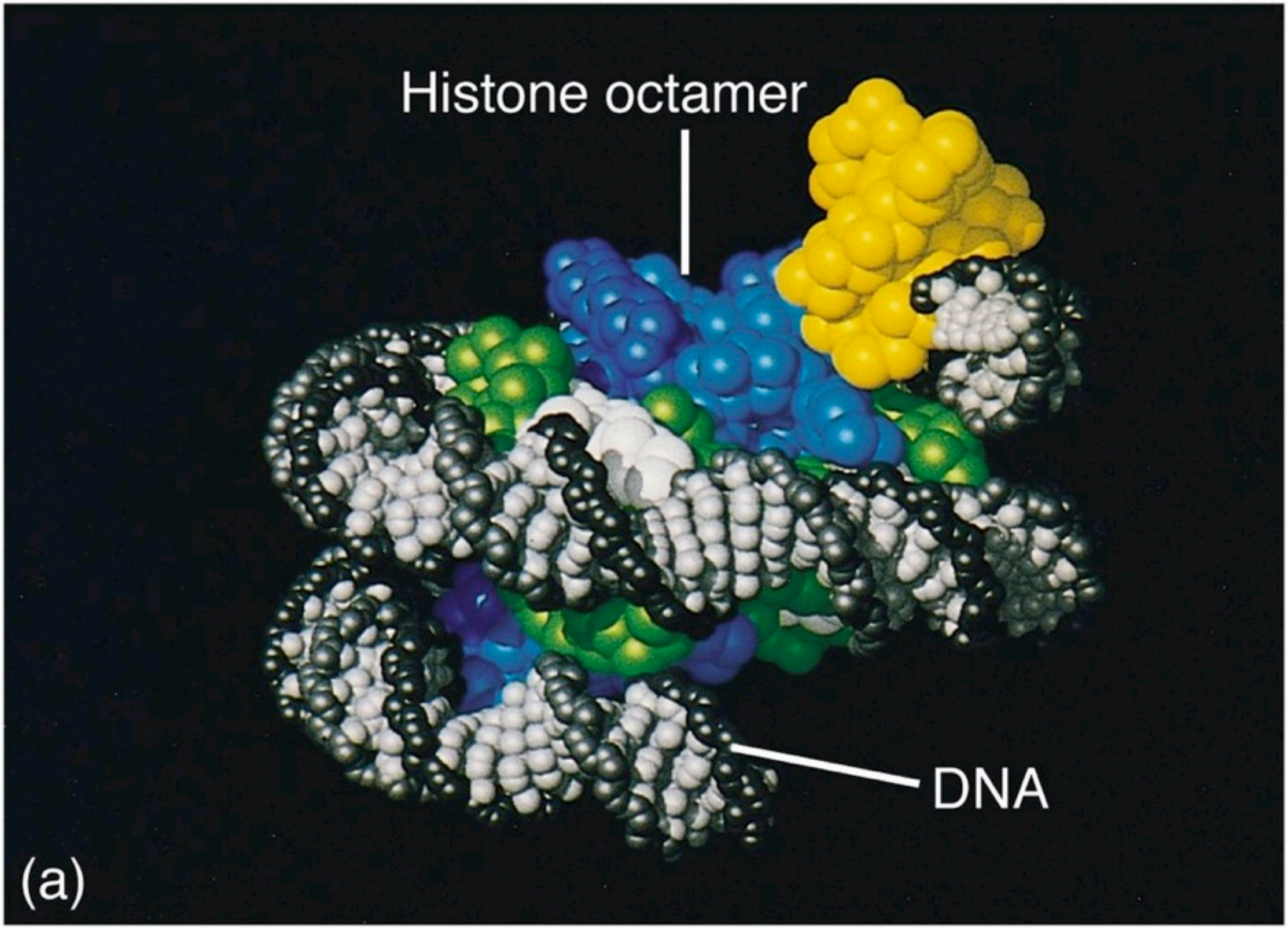


Translation

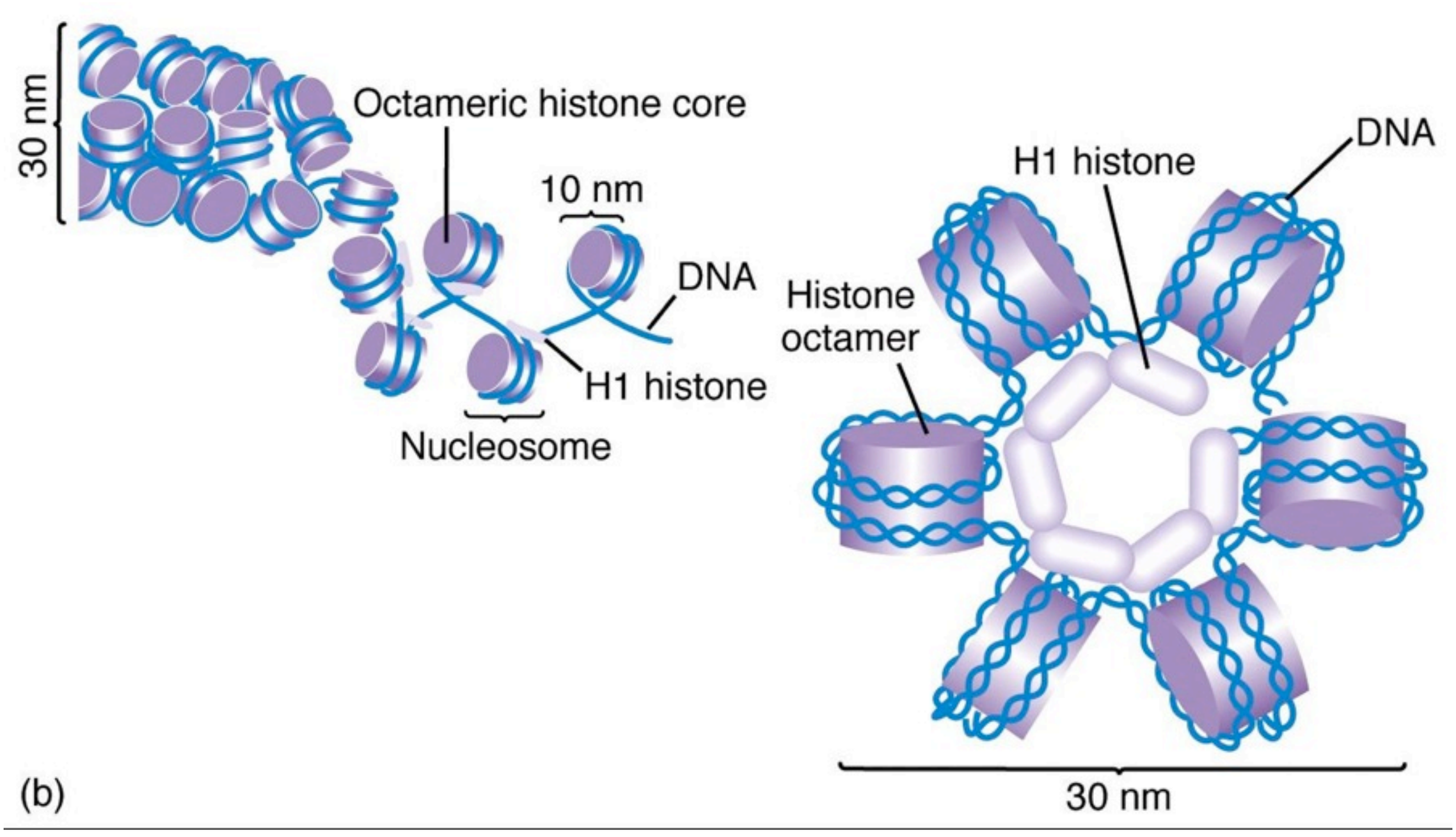
- RNA encodes the amino acid sequence for protein synthesis



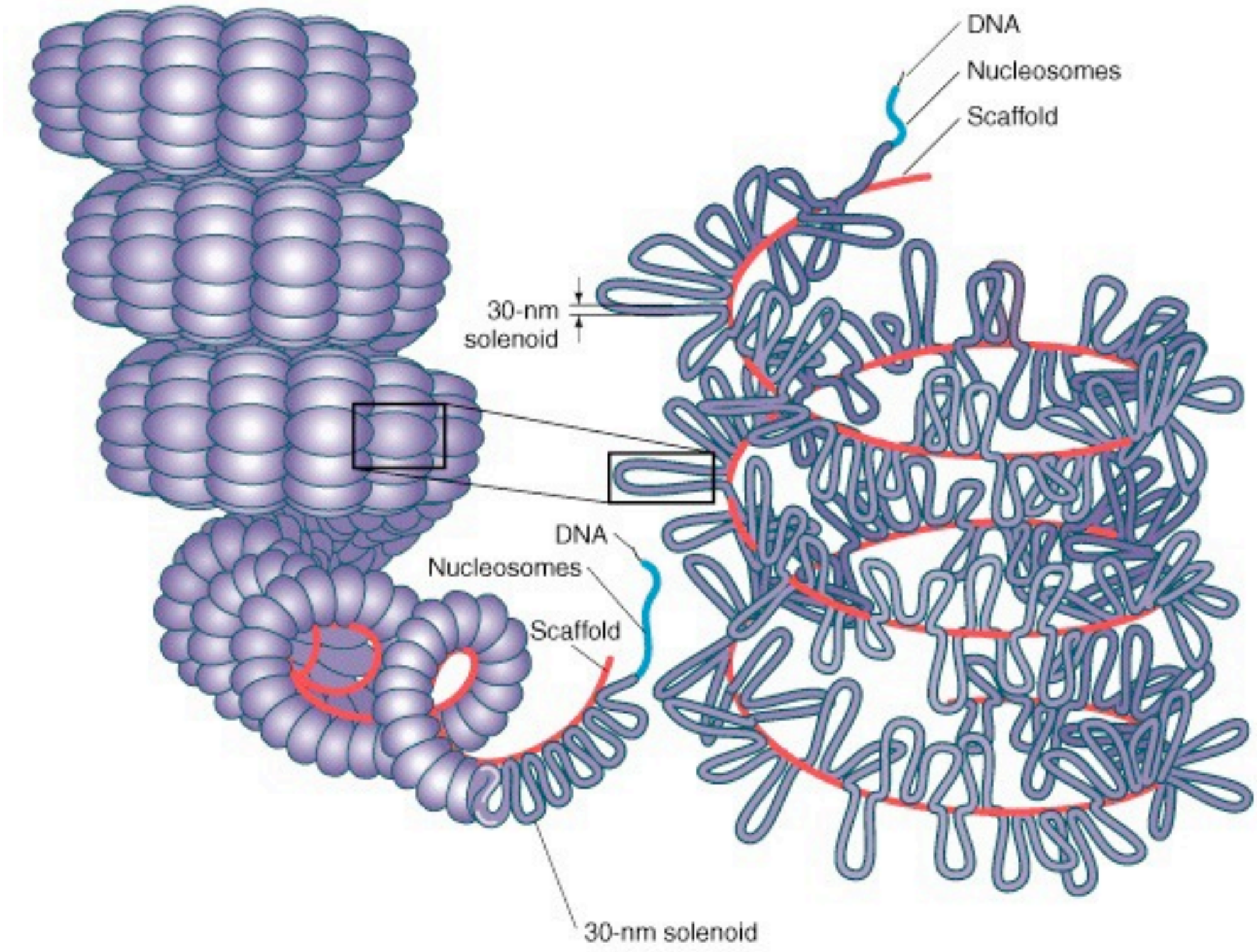
DNA Wraps Around Histone Proteins



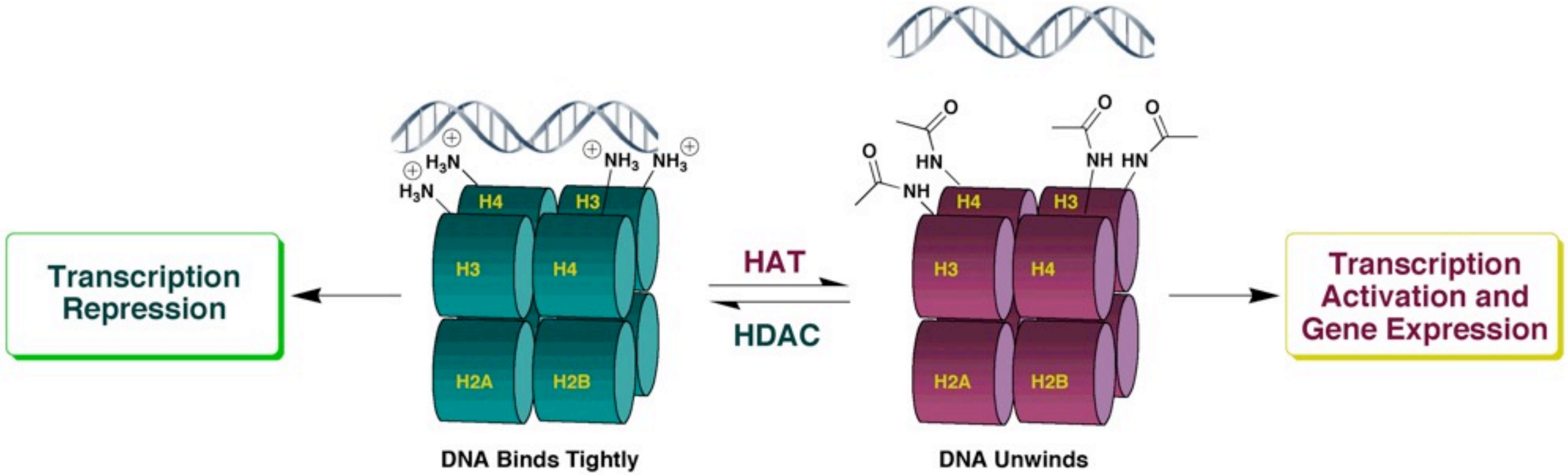
Nucleosomes Coil Up

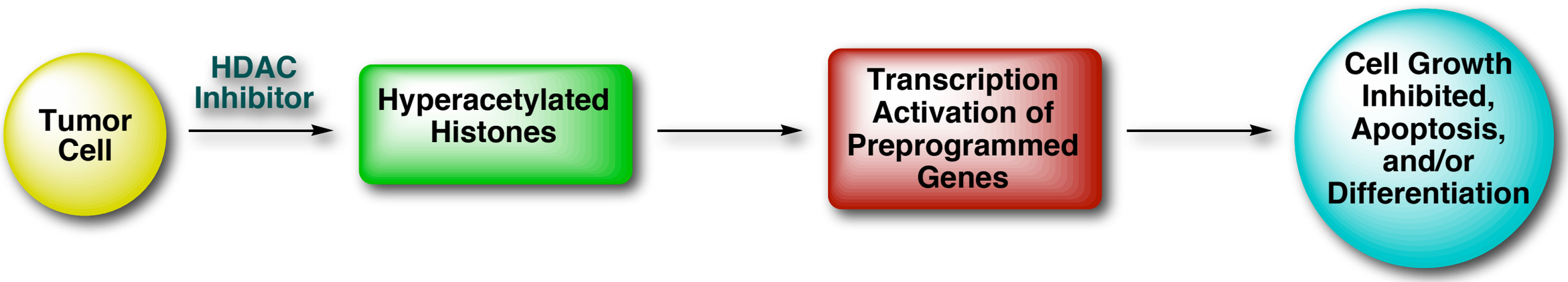


Wrapped Up Tight



Histone Deacetylase





Effectiveness in Clinical Trials

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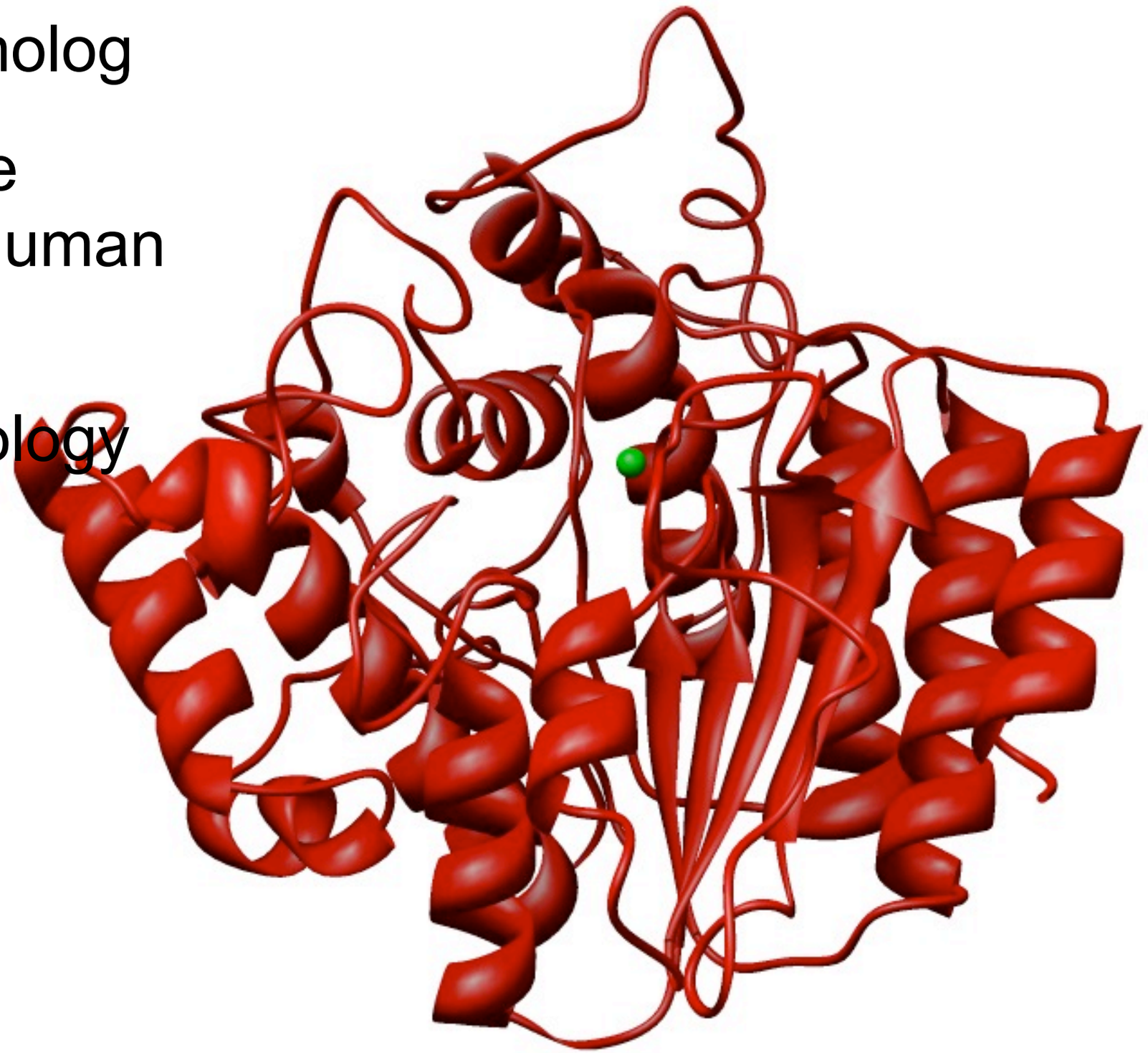
- HDAC Inhibitors show marked effect in the treatment of cutaneous T-cell lymphoma
  - Phase II clinical trials of FK228

HDAC Structure

- HDAC Like Homolog
- 35.2% sequence homology with human HDAC1
- Active site homology much higher



Finnin, et. al. *Nature* 1999, 401, 188.

HDAC Inhibitor Design

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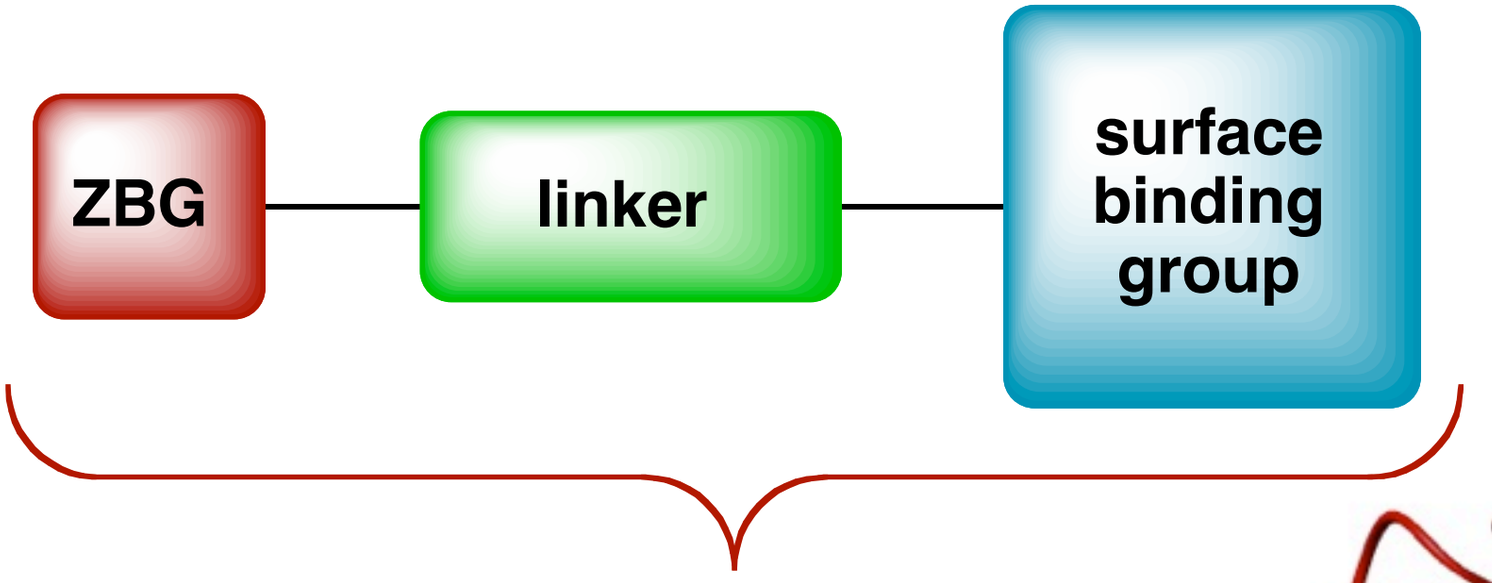
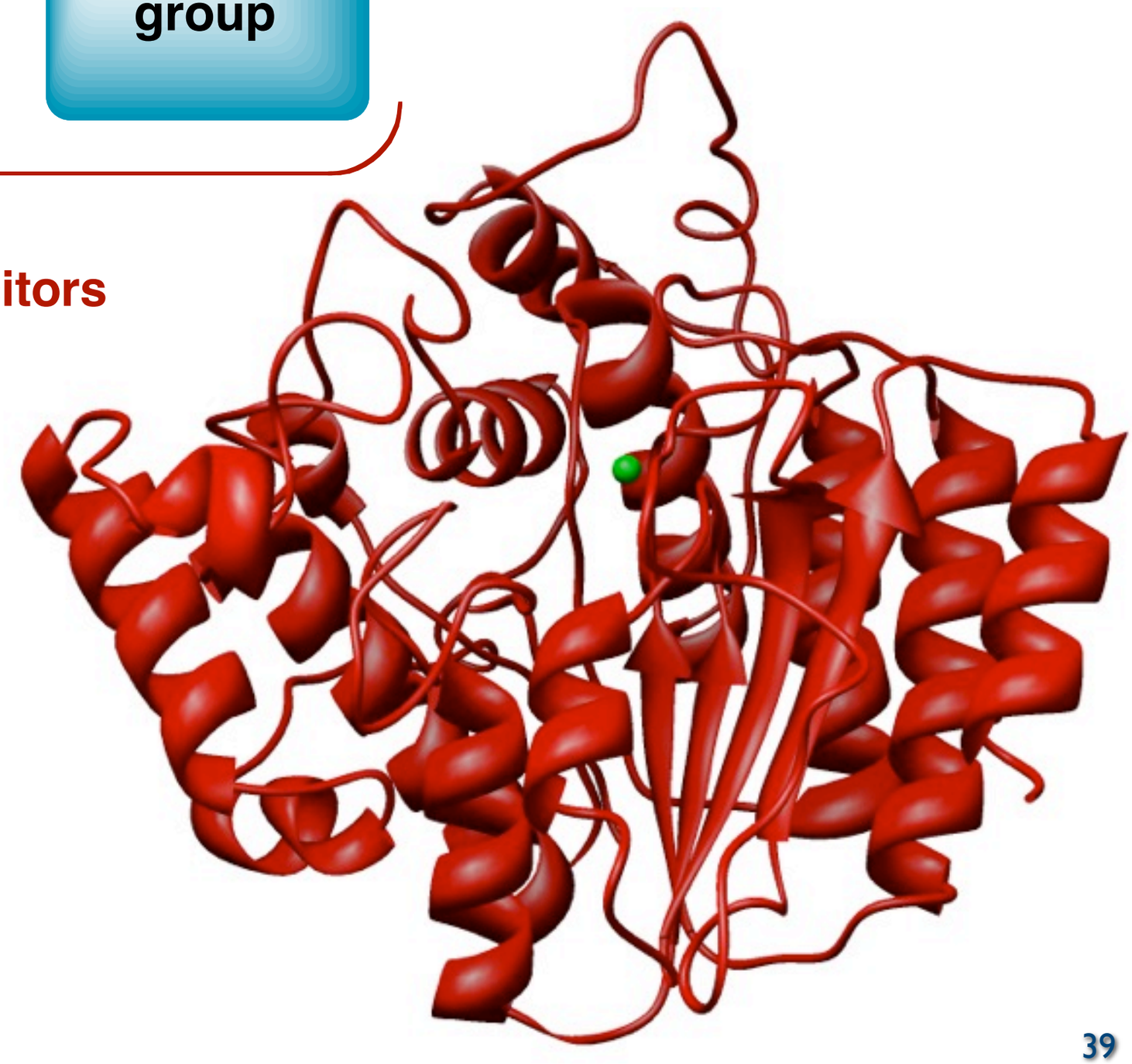


Typical HDAC Inhibitors



HDAC Inhibitors

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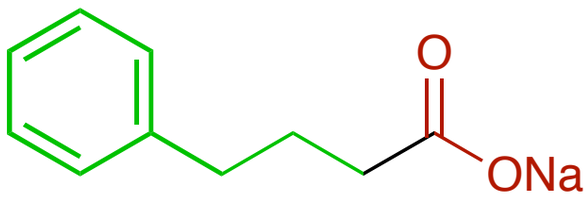
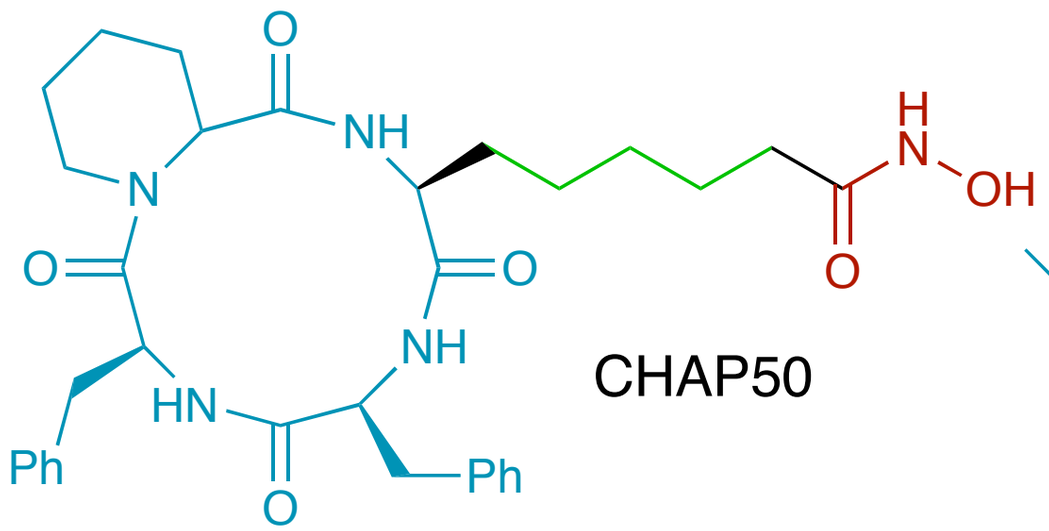
Carboxylates

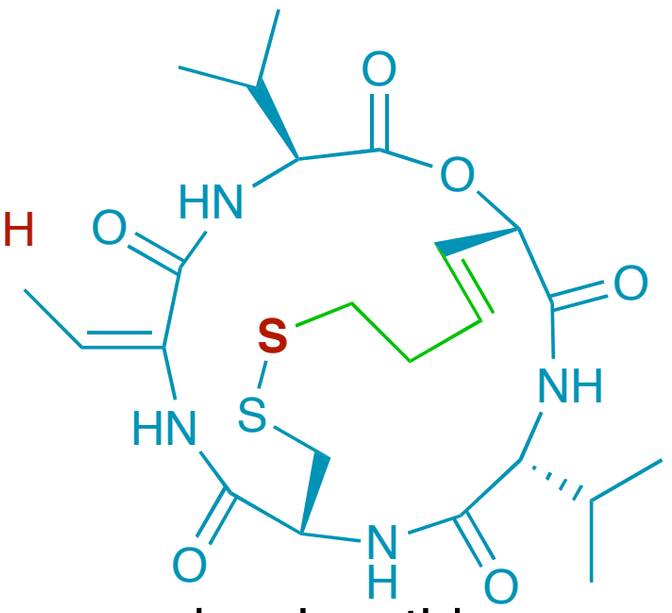


phenylbutyrate
mM

Cyclic Peptides

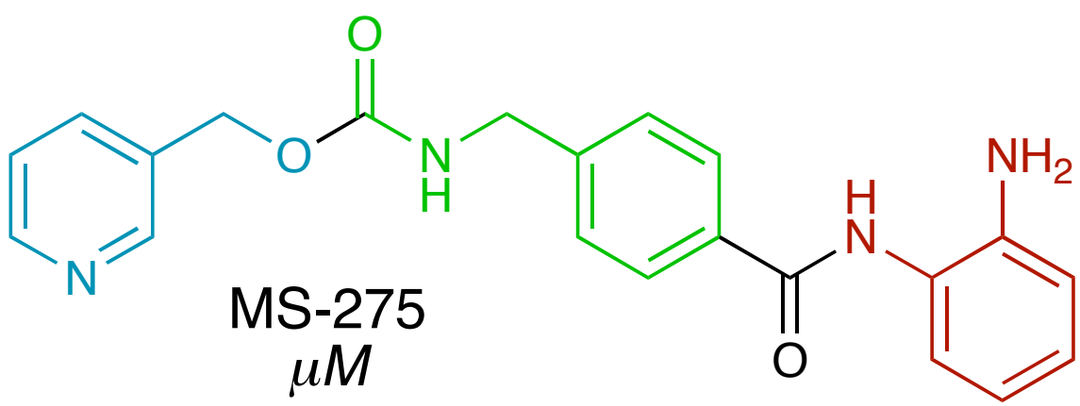


CHAP50



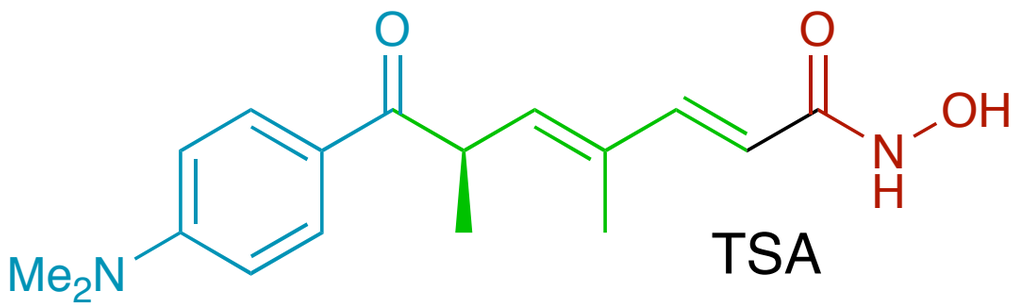
depsipeptide
nM

Benzamides



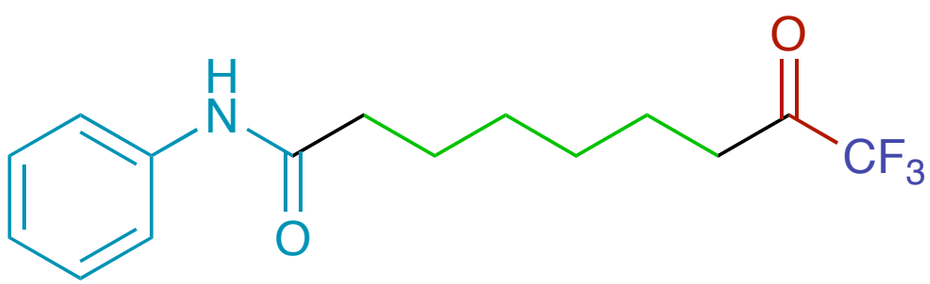
MS-275
μM

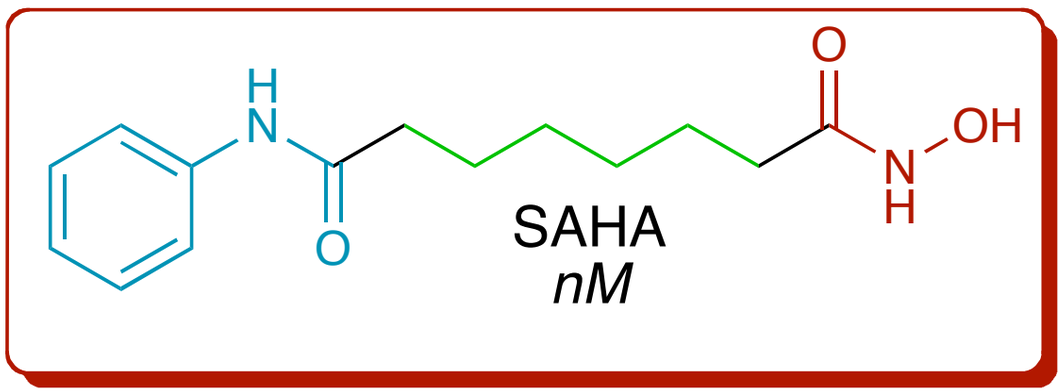
Hydroxamate



TSA

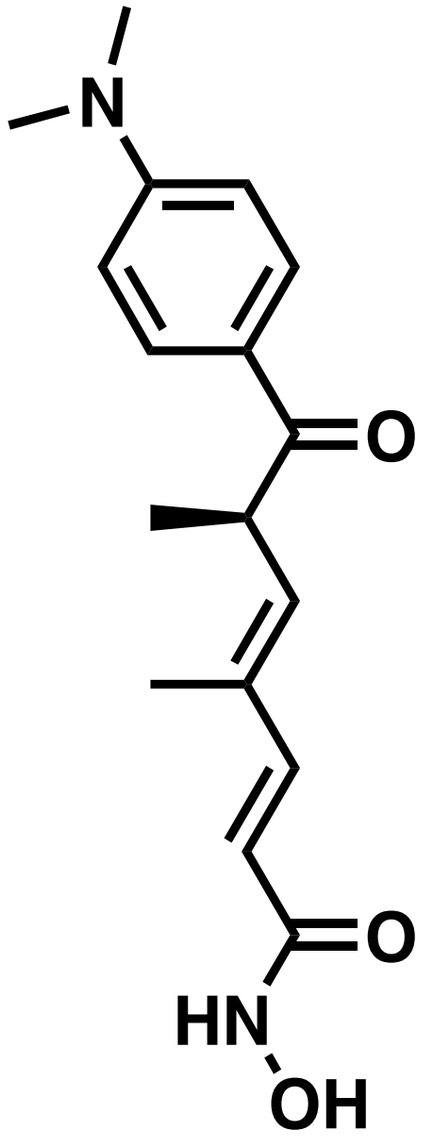
Electrophilic Ketones





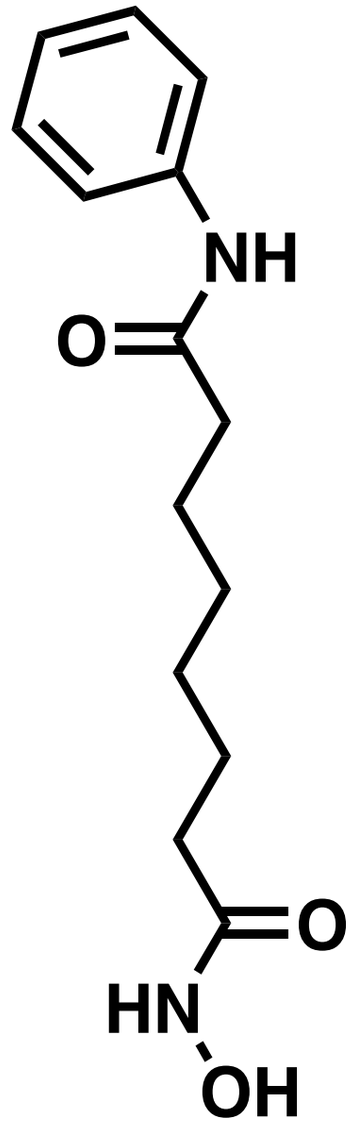
SAHA
nM

TSA and SAHA - Hydroxamic Acids



Trichostatin A
TSA

IC_{50} 12 nm



Suberoylanilide
Hydroxamic Acid
SAHA

IC_{50} 165 nm

Hydroxamic Acid Binding

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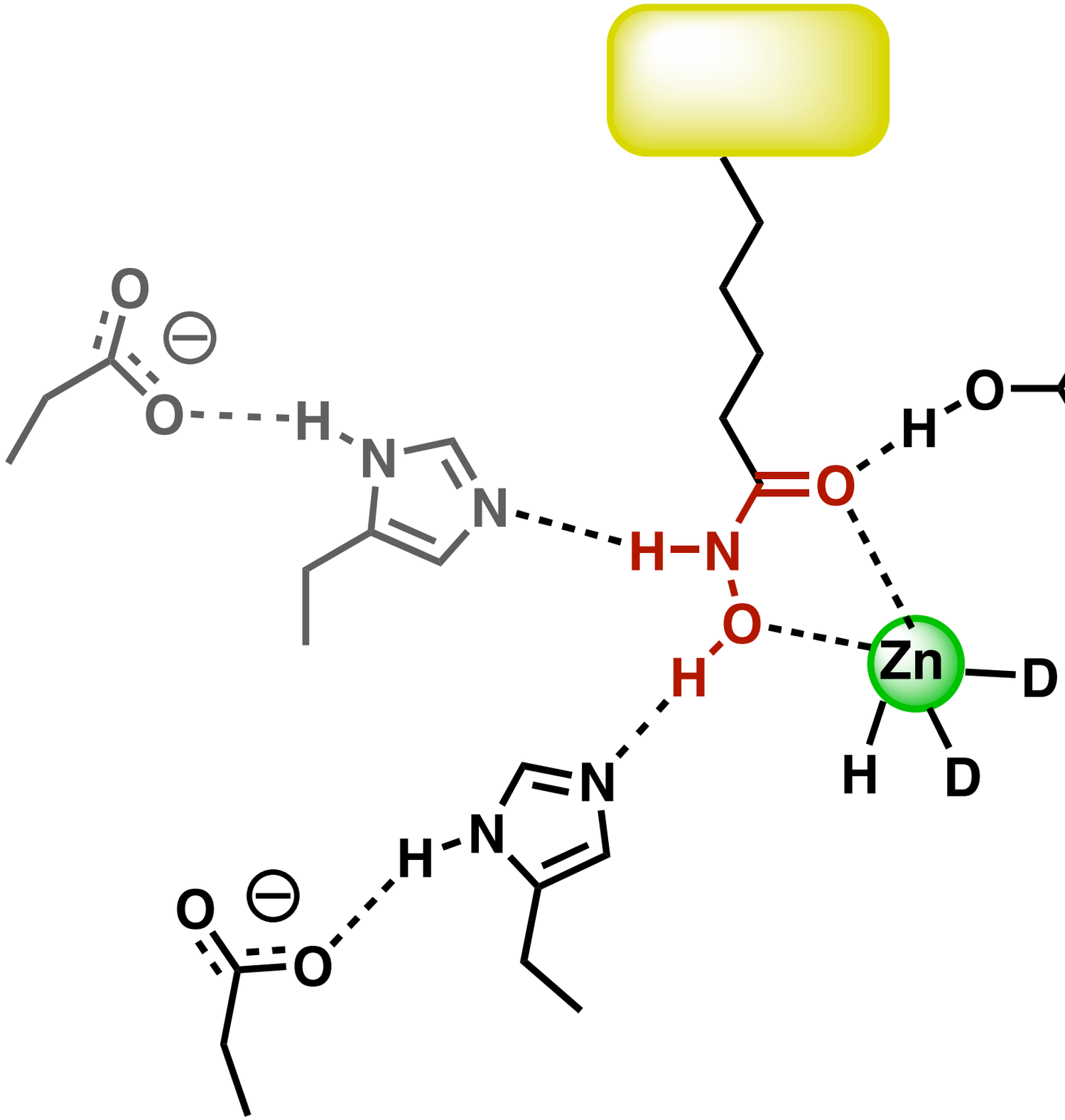
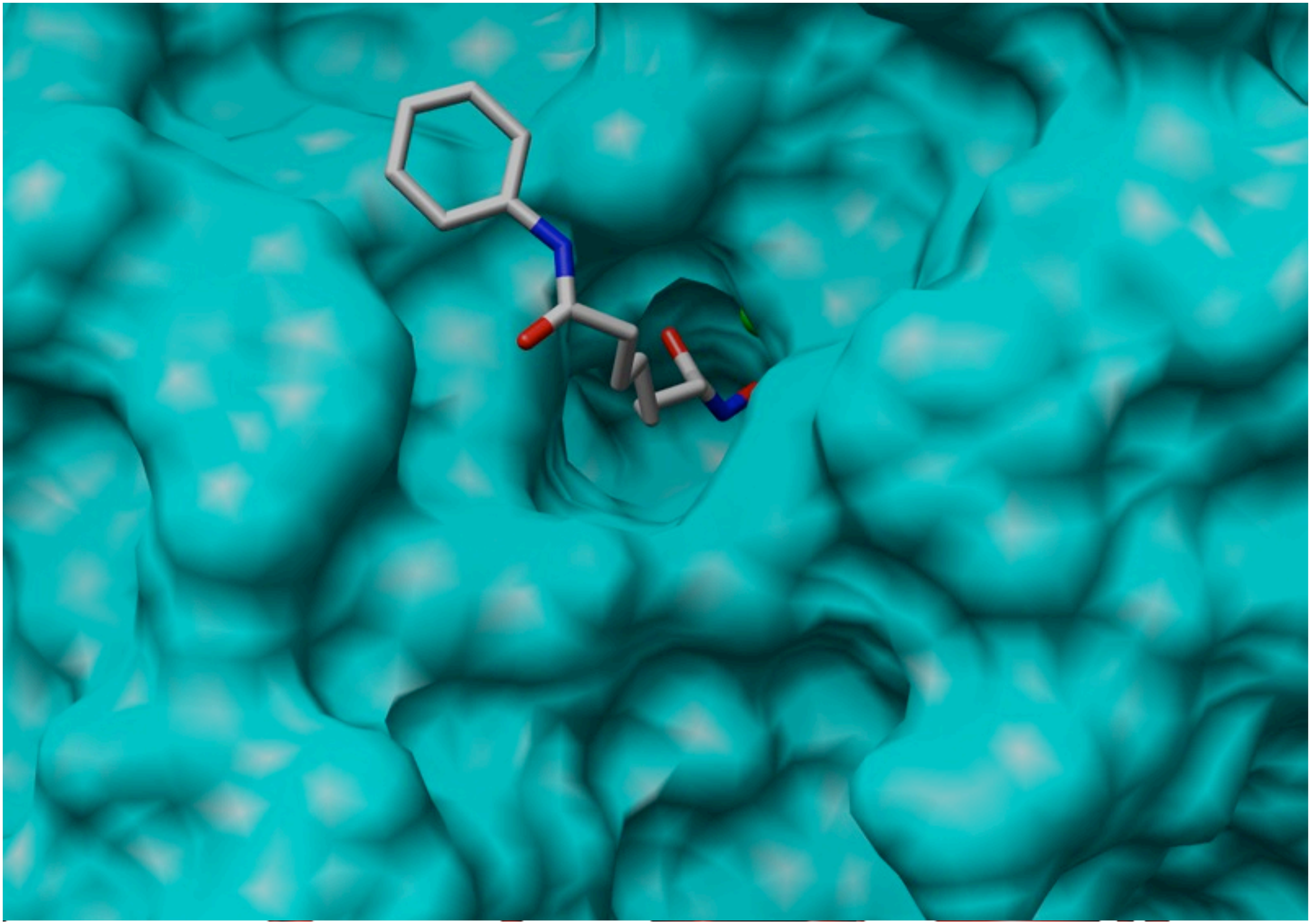


SAHA and HDAC Homolog



Conclusions

- Proteins are the stuff of life.
- DNA encodes amino acid sequence of proteins.
- Ezymes are proteins that catalyze chemical reactions.
- Disease can often be targeted by identifying specific enzymes that is important for the disease state.
- Synthetic chemistry can provide solutions for drug development.