Chem 452 - Lecture 2
Protein Structure
110928

Proteins are the workhorses of a living cell and involve themselves in nearly all of the activities that take place in a cell. Their wide range of structures are manifested by the wide range of 3-dimensional structures that they are able to possess. Proteins are linear polymers of amino acids, whose sequence is determined by the sequence of DNA base pairs in their corresponding gene. The connection between this linear sequence of amino acids for a protein and its 3-dimensional structure will be the focus of this lecture.

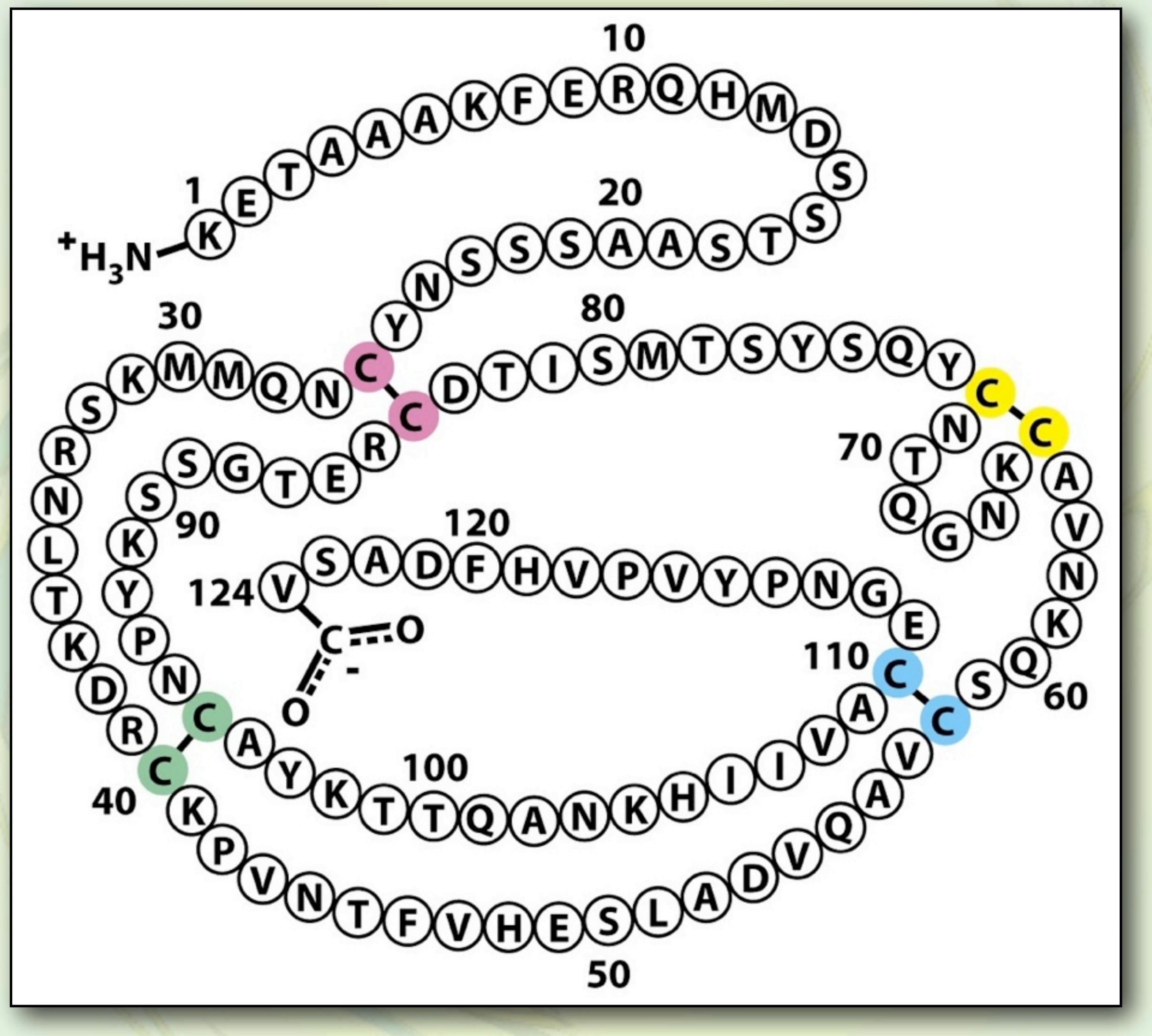
Protein Folding

- The primary structure determines the other levels of structure.
  - Christian Anfinsen demonstrated this in the 1950's

Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein Folding

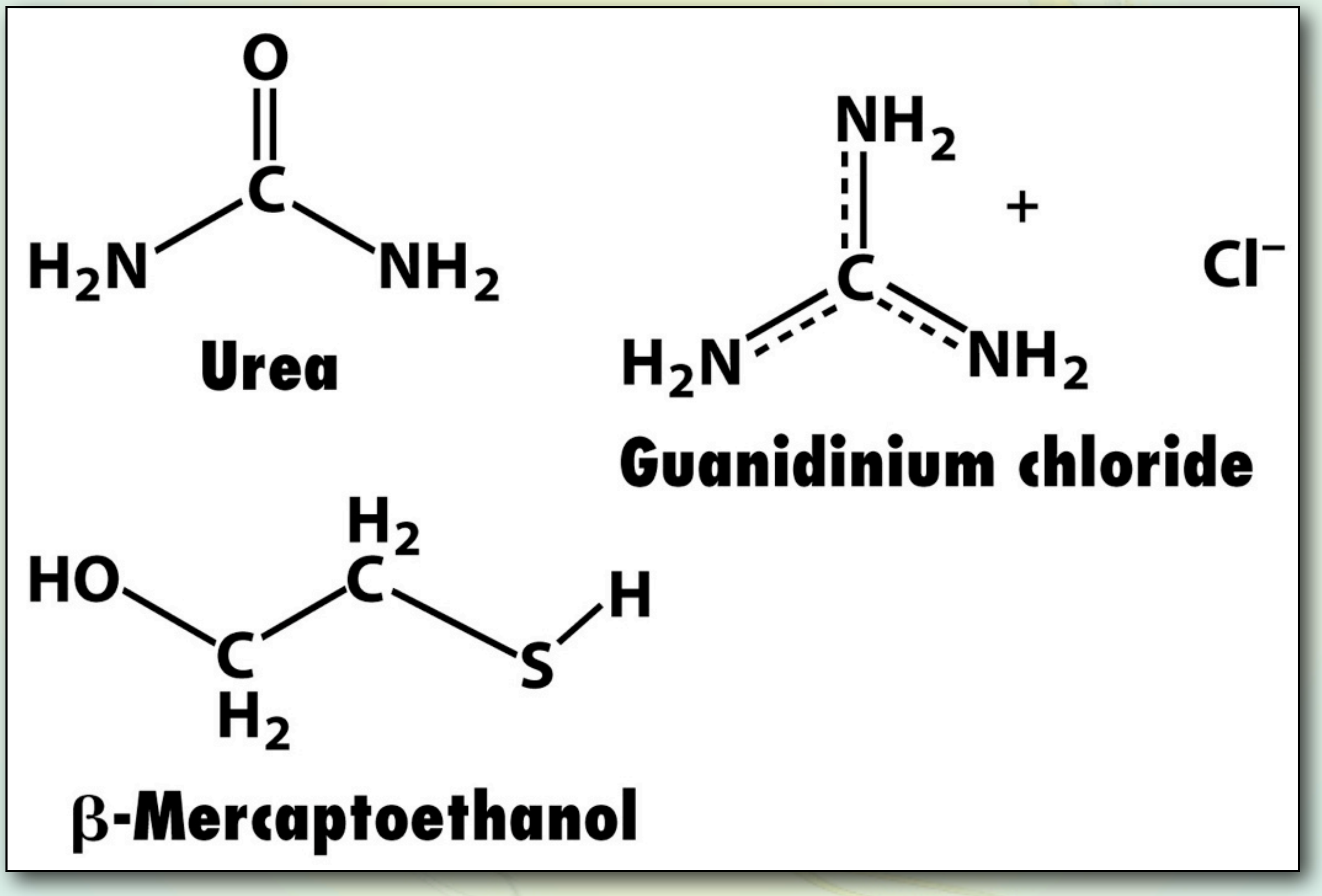
- Anfinsen's Experiment



Bovine Ribonuclease A

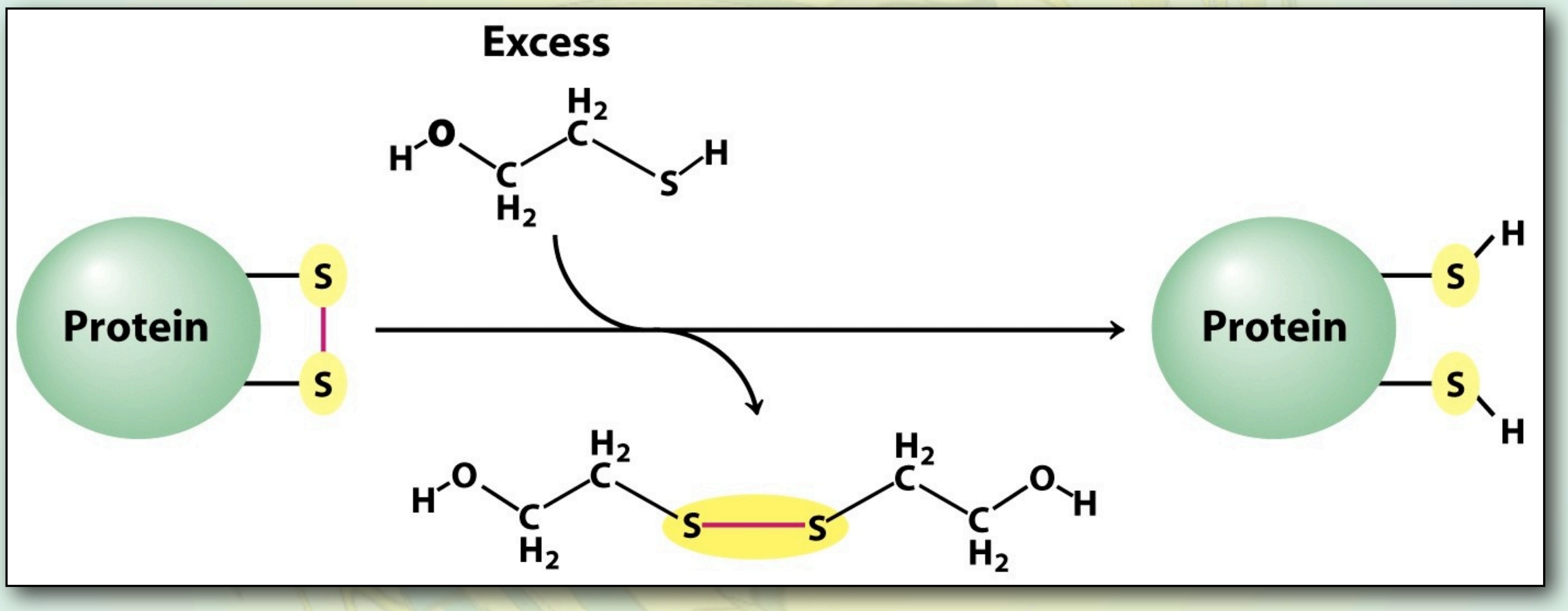
Protein Folding

- Anfinsen's Experiment



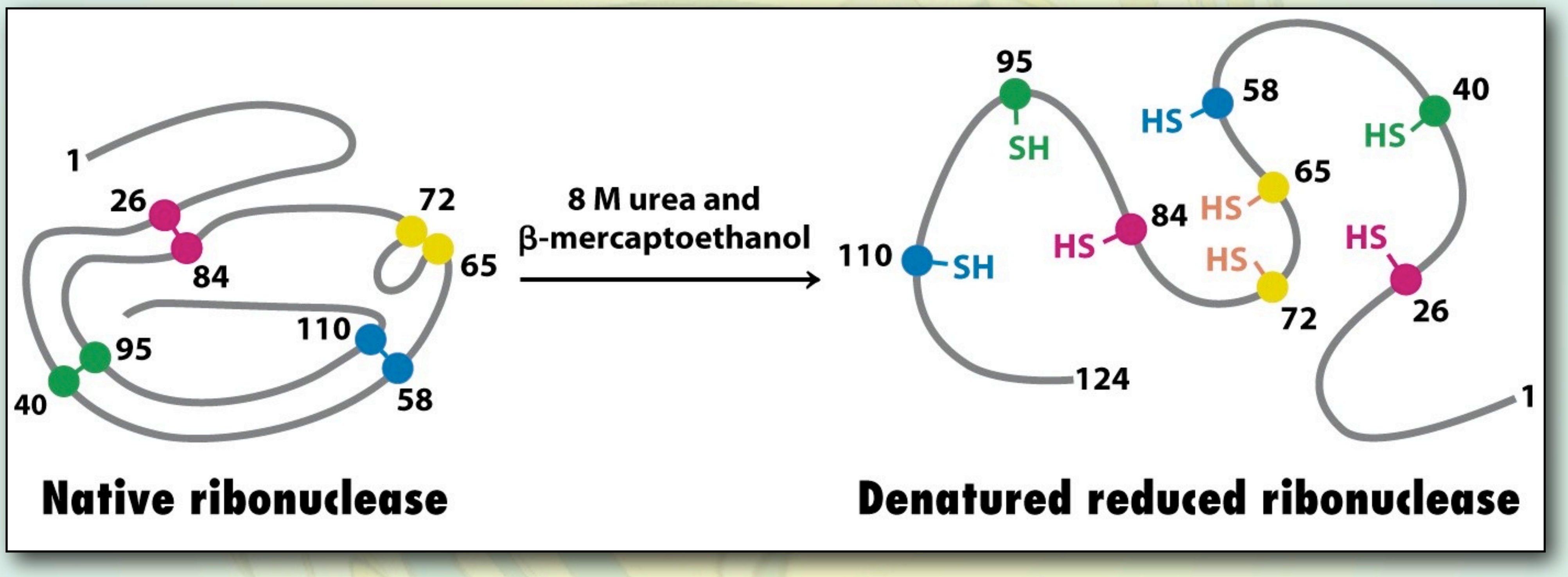
Protein Folding

- Anfinsen's Experiment



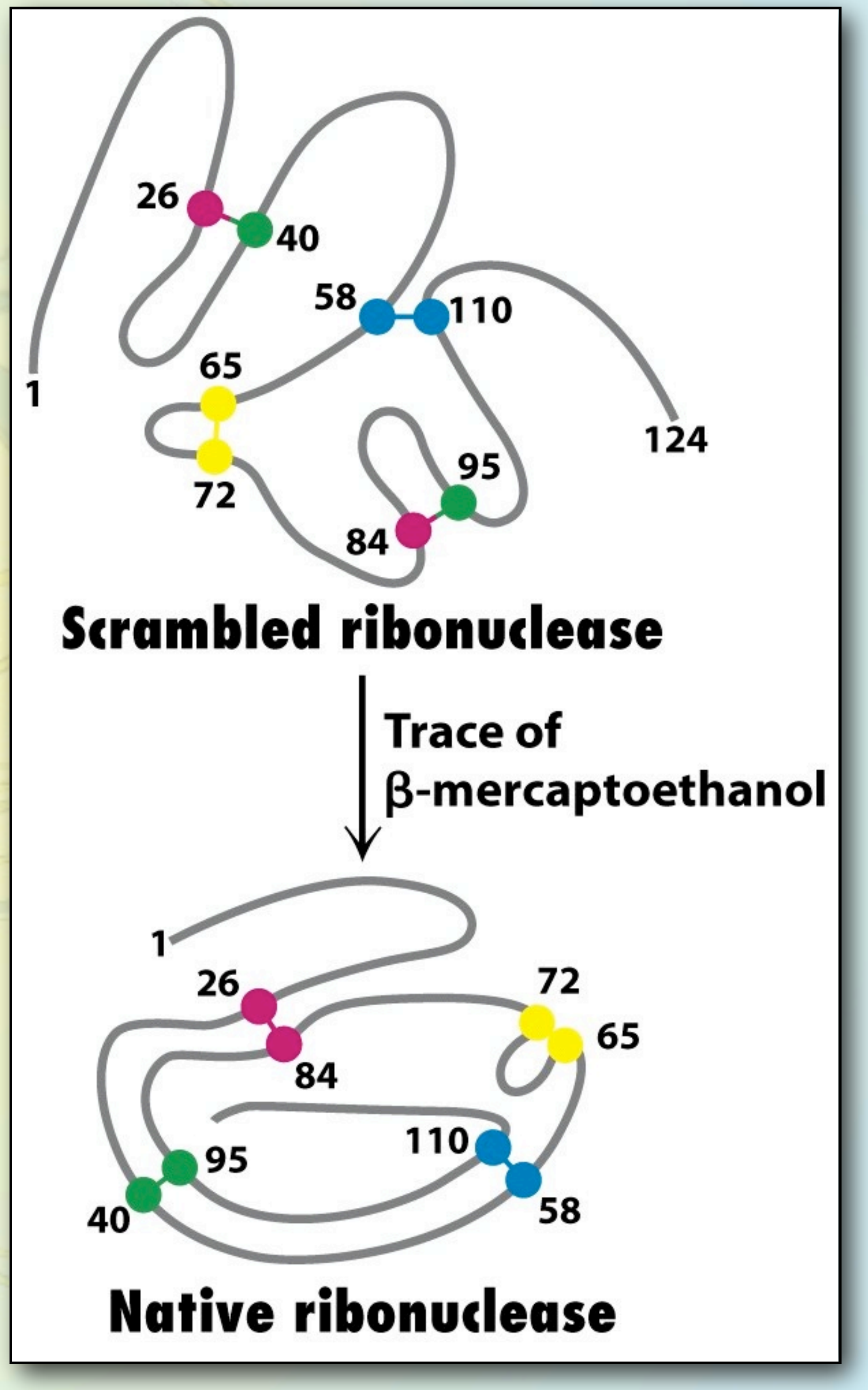
Protein Folding

- Anfinsen's Experiment



Protein Folding

- Anfinsen's Experiment



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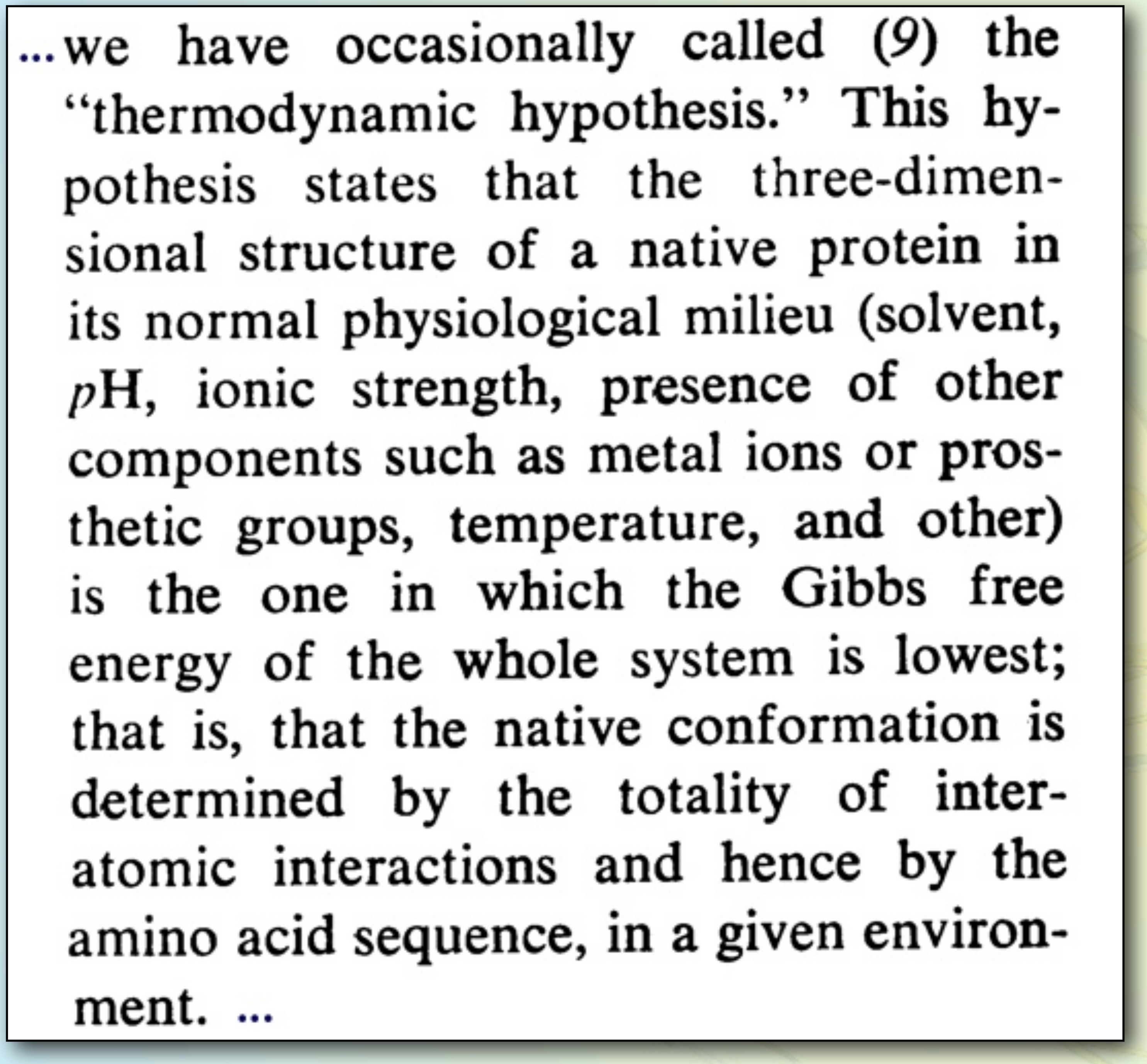
Protein Folding



...we have occasionally called (*9*) the "thermodynamic hypothesis." This hypothesis states that the three-dimensional structure of a native protein in its normal physiological milieu (solvent, *p*H, ionic strength, presence of other components such as metal ions or prosthetic groups, temperature, and other) is the one in which the Gibbs free energy of the whole system is lowest; that is, that the native conformation is determined by the totality of interatomic interactions and hence by the amino acid sequence, in a given environment. ...

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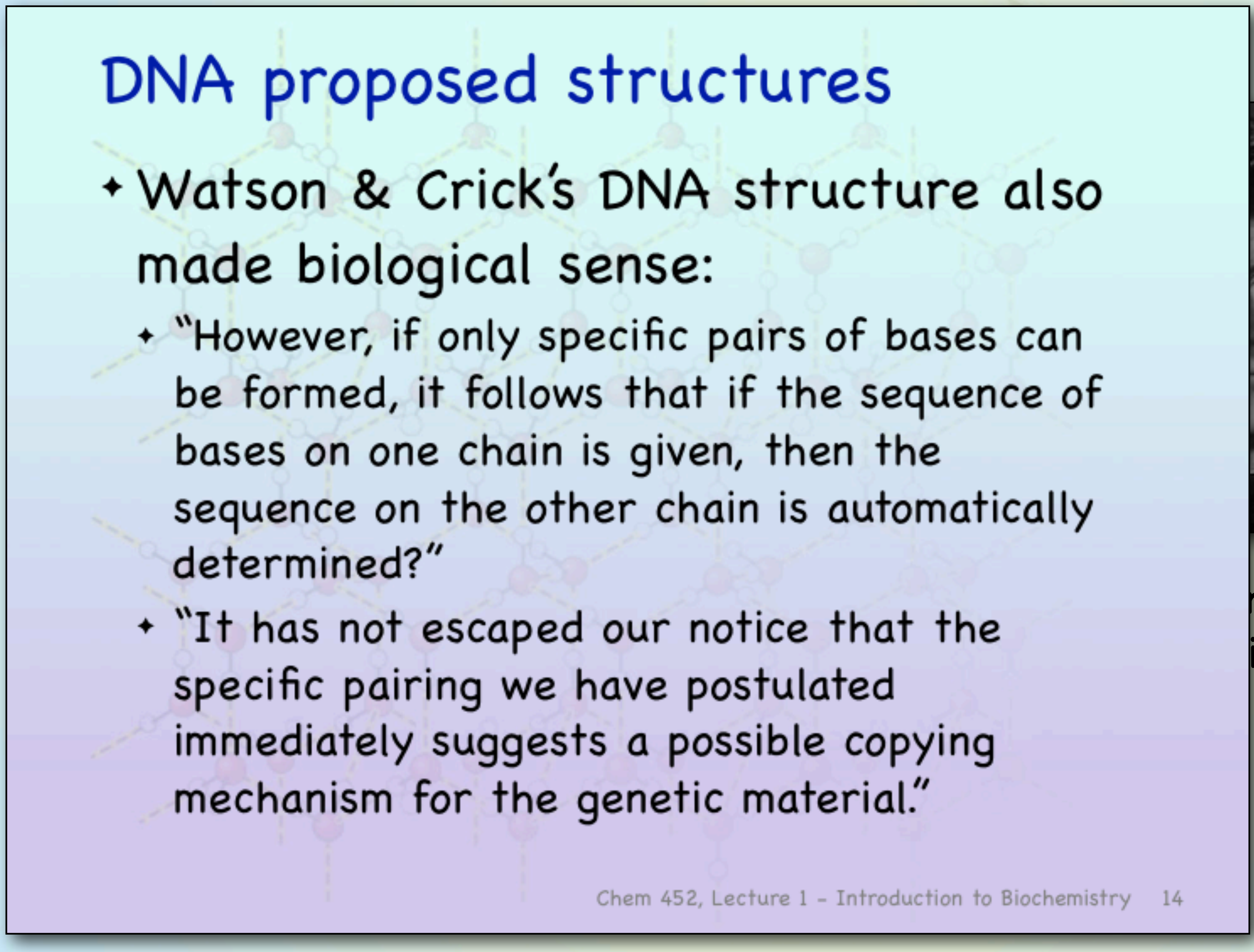
Protein Folding



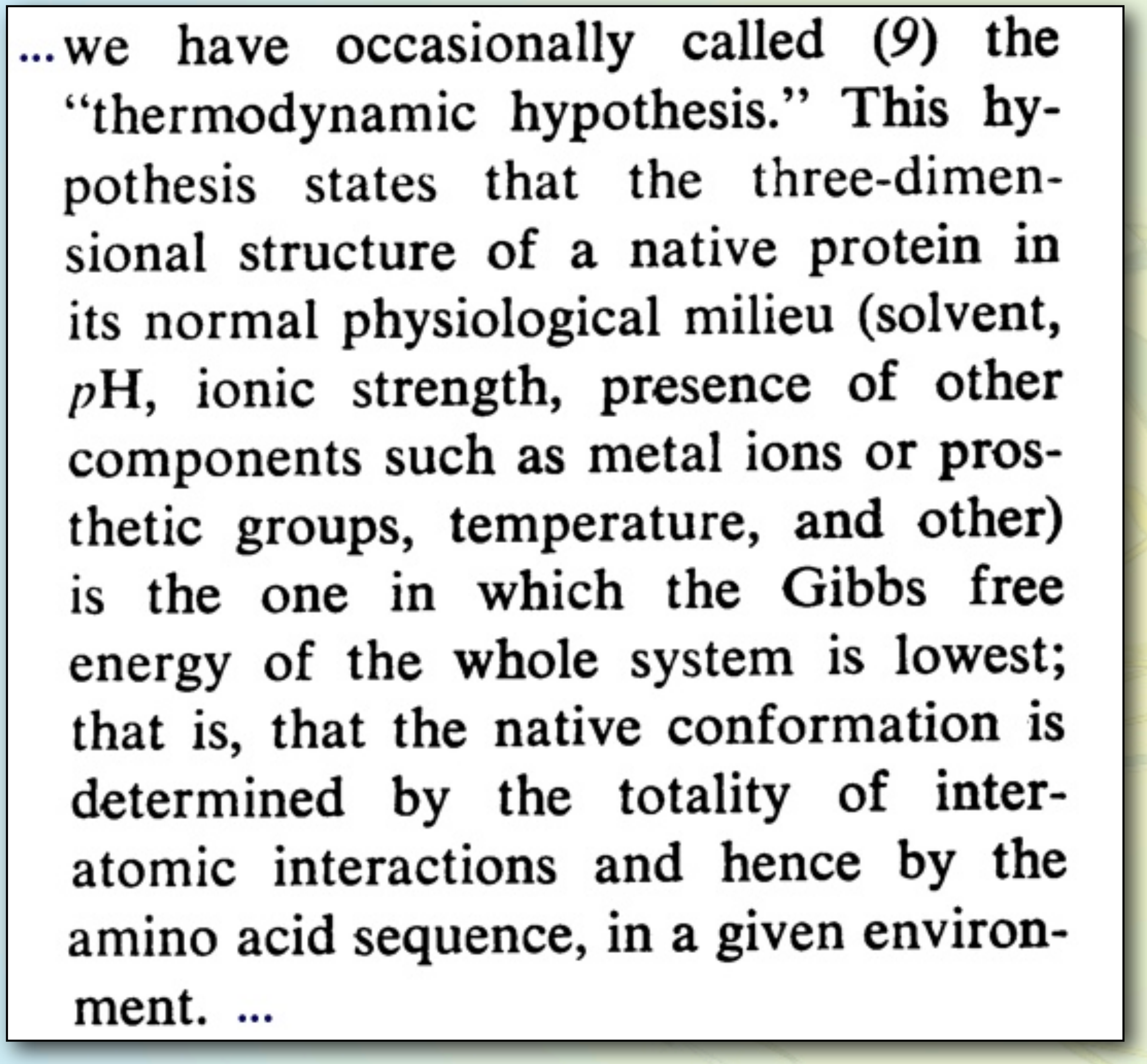
DNA proposed structures

- Watson & Crick's DNA structure also made biological sense:
  - "However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined?"
  - "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

Chem 452, Lecture 1 - Introduction to Biochemistry 14

n Anfinsen
ize in Chemistry

Protein Folding



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Protein Folding

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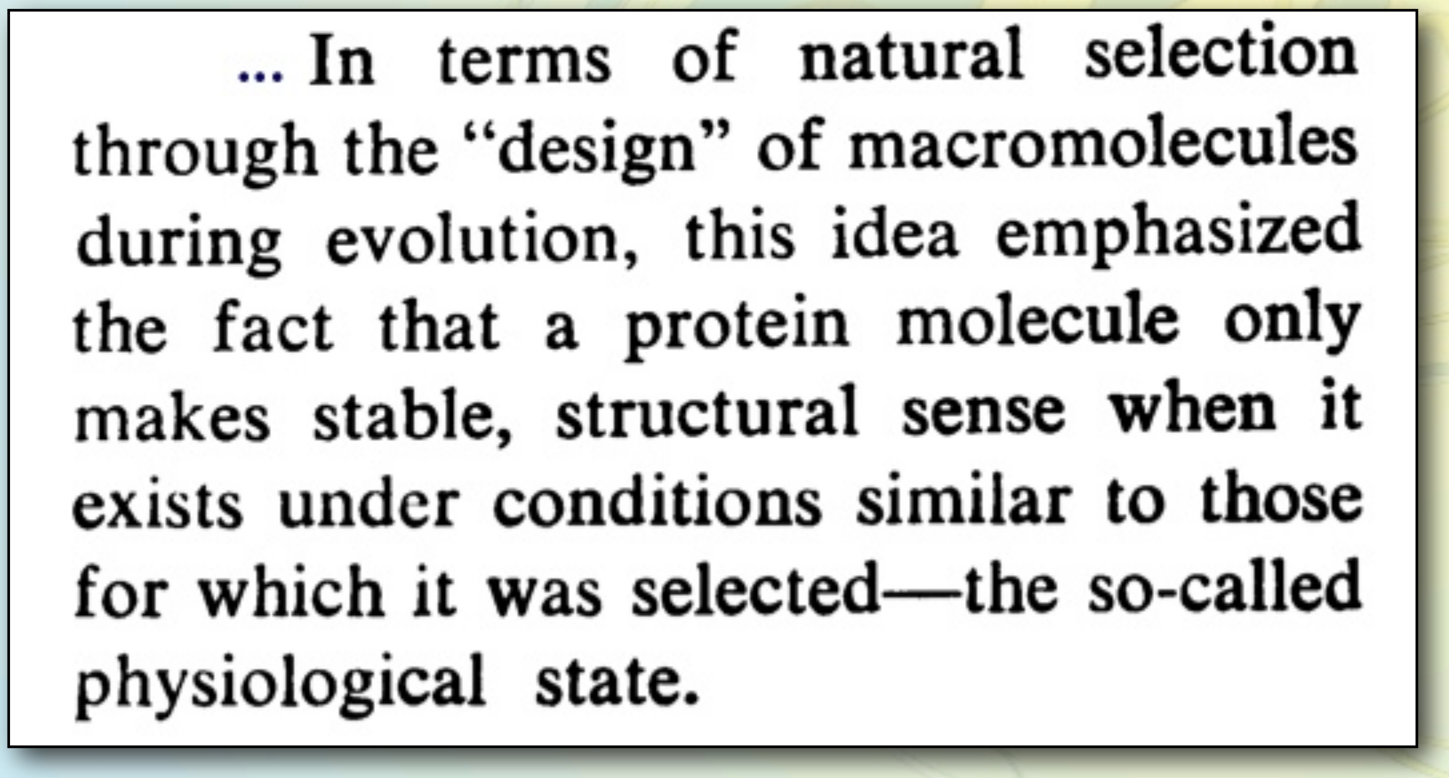

... In terms of natural selection through the "design" of macromolecules during evolution, this idea emphasized the fact that a protein molecule only makes stable, structural sense when it exists under conditions similar to those for which it was selected—the so-called physiological state.

Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein Folding

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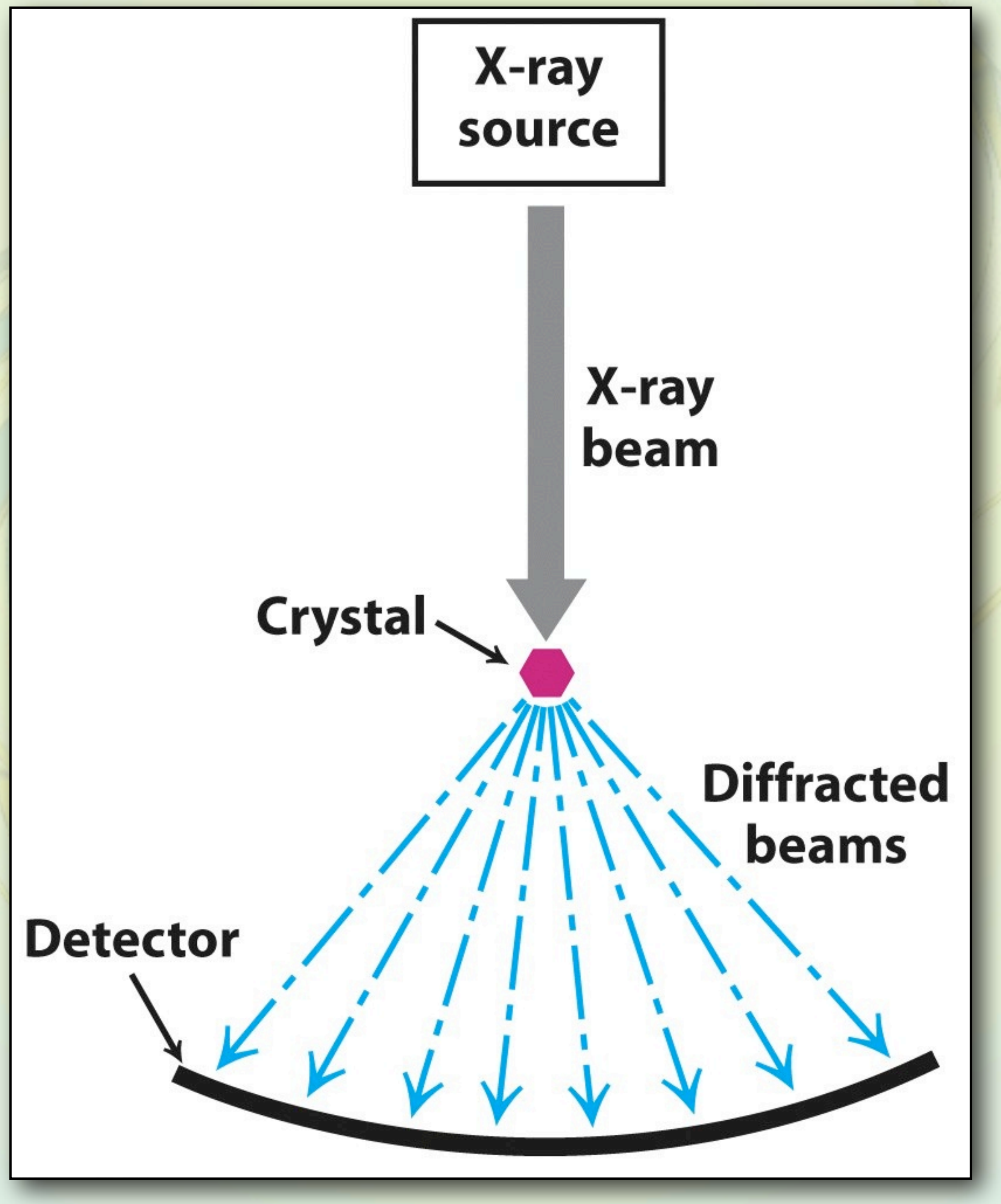
Protein 3-Dimensional Structures

- The first proteins to have their 3-D structures determined were determined in the late 1950‘s myoglobin and hemoglobin.

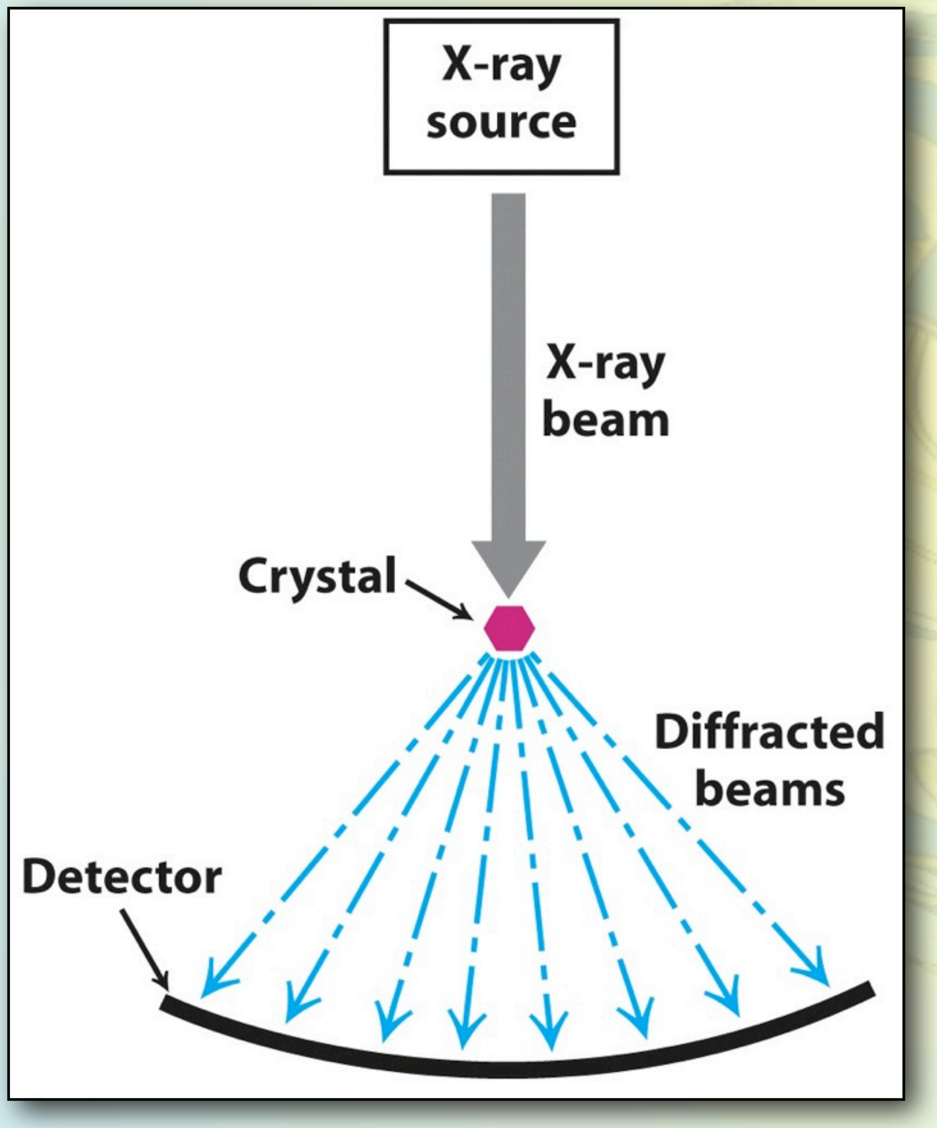
Protein 3-Dimensional Structures

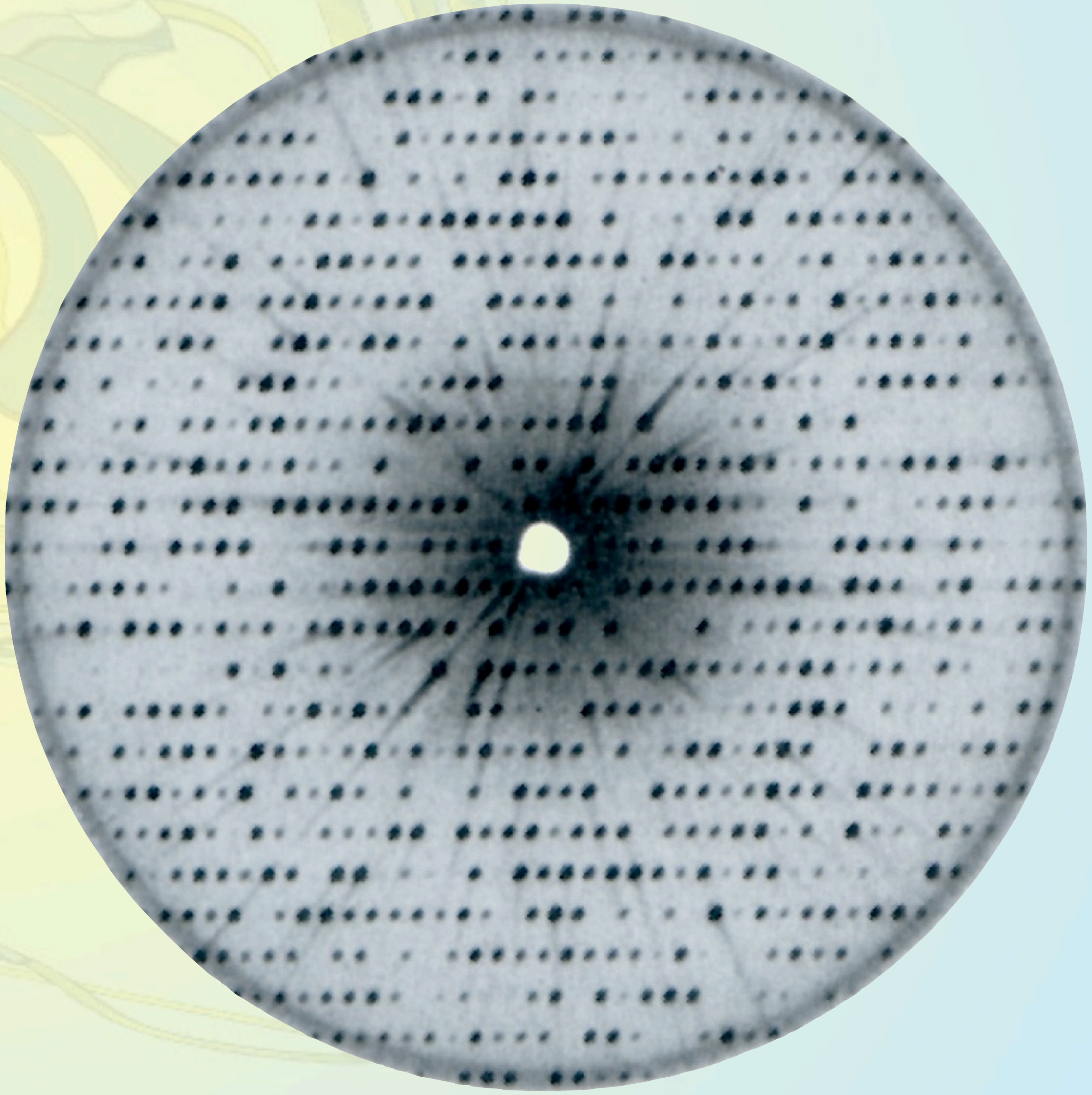
- X-ray crystallography (Section 3.6)



Protein 3-Dimensional Structures

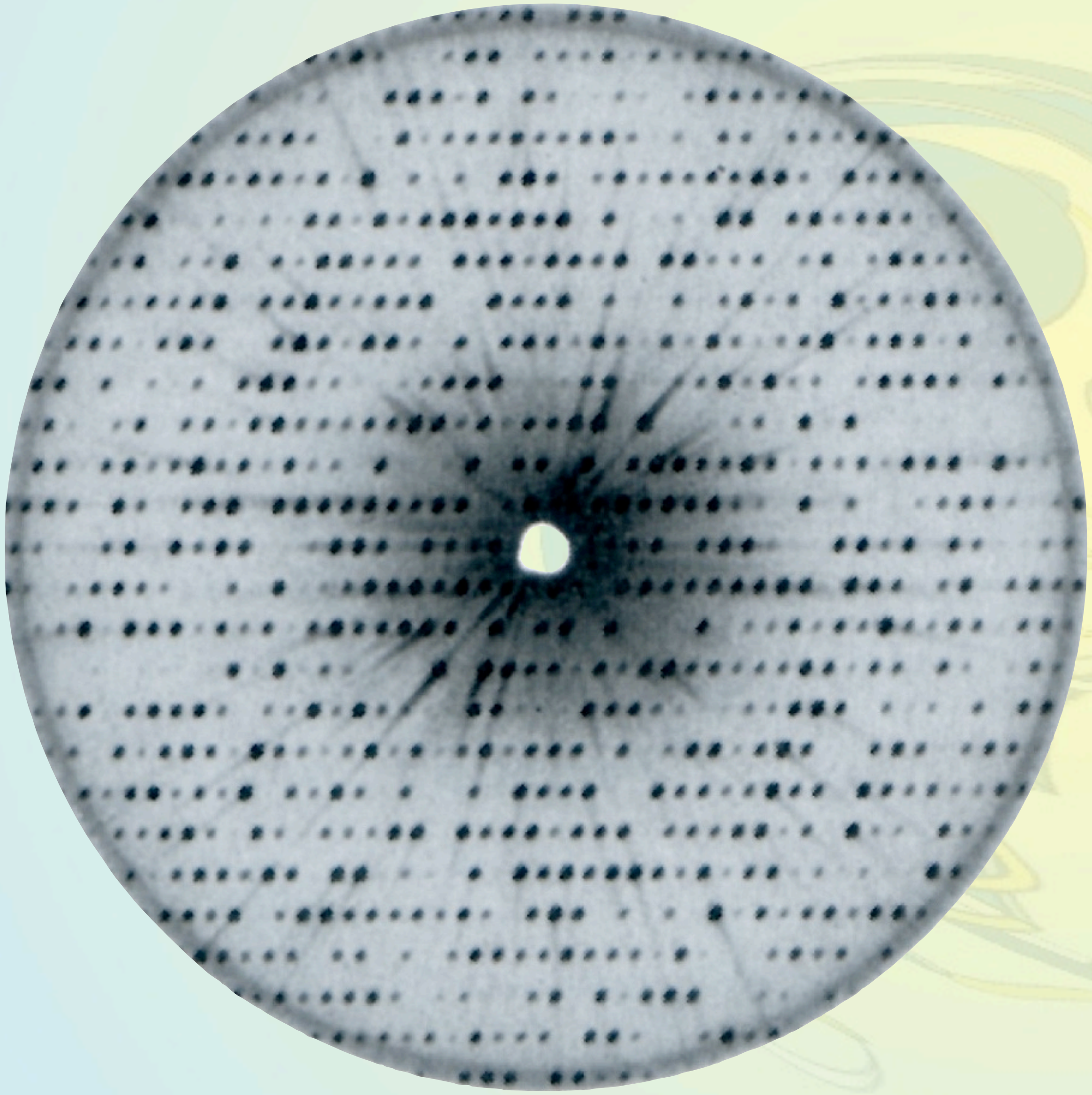
- X-ray crystallography (Section 3.6)

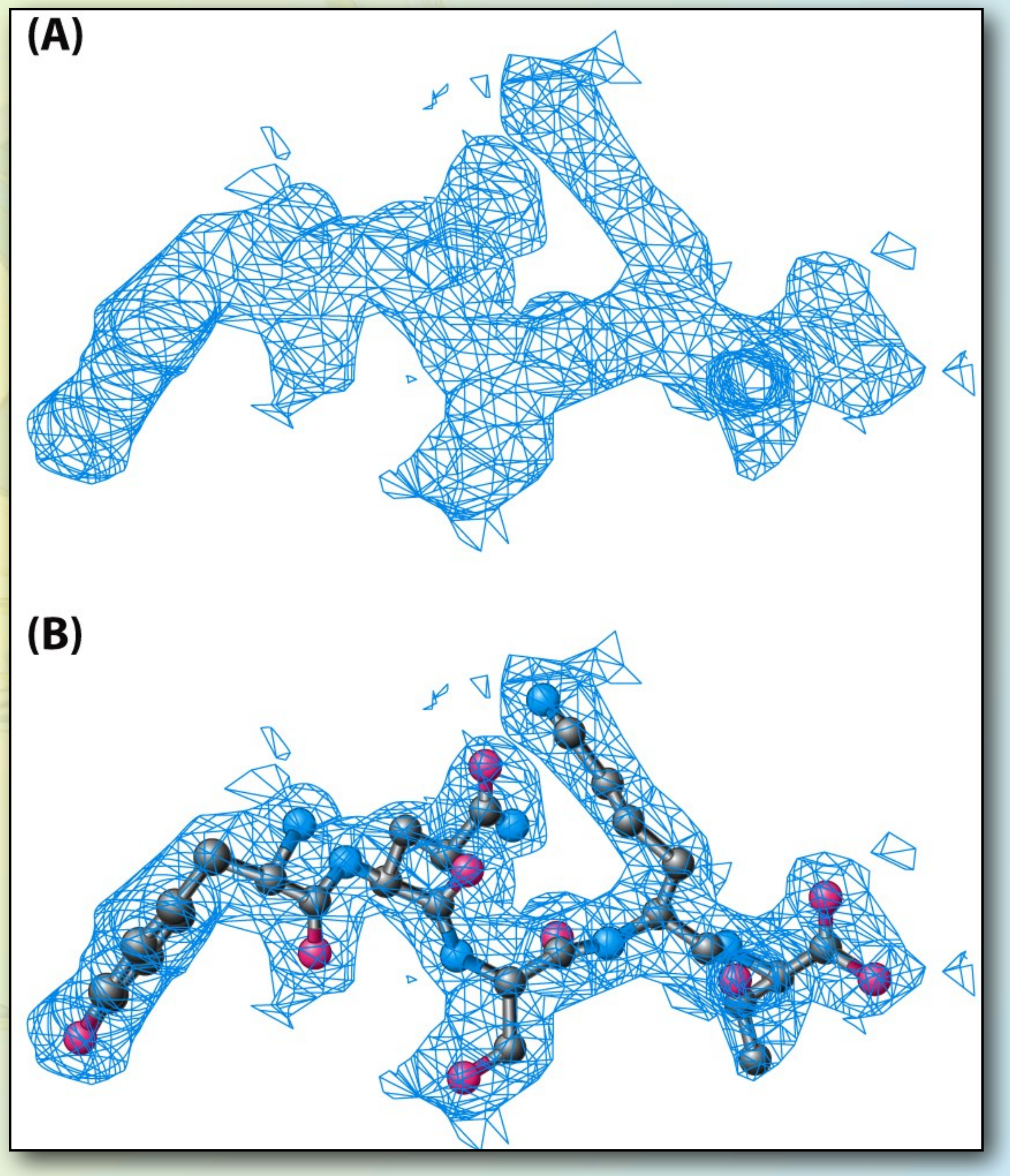




Protein 3-Dimensional Structures

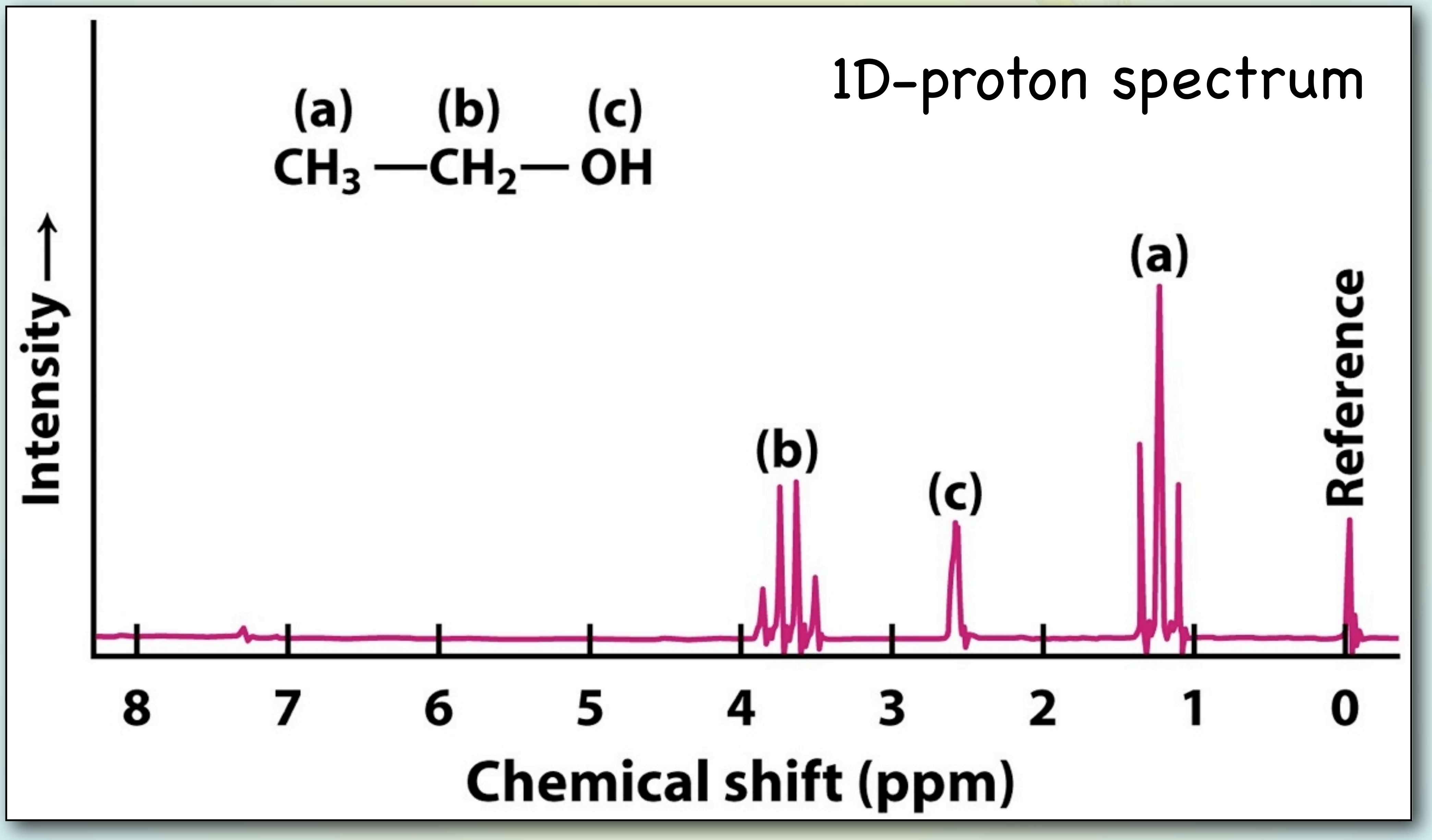
- X-ray crystallography (Section 3.6)





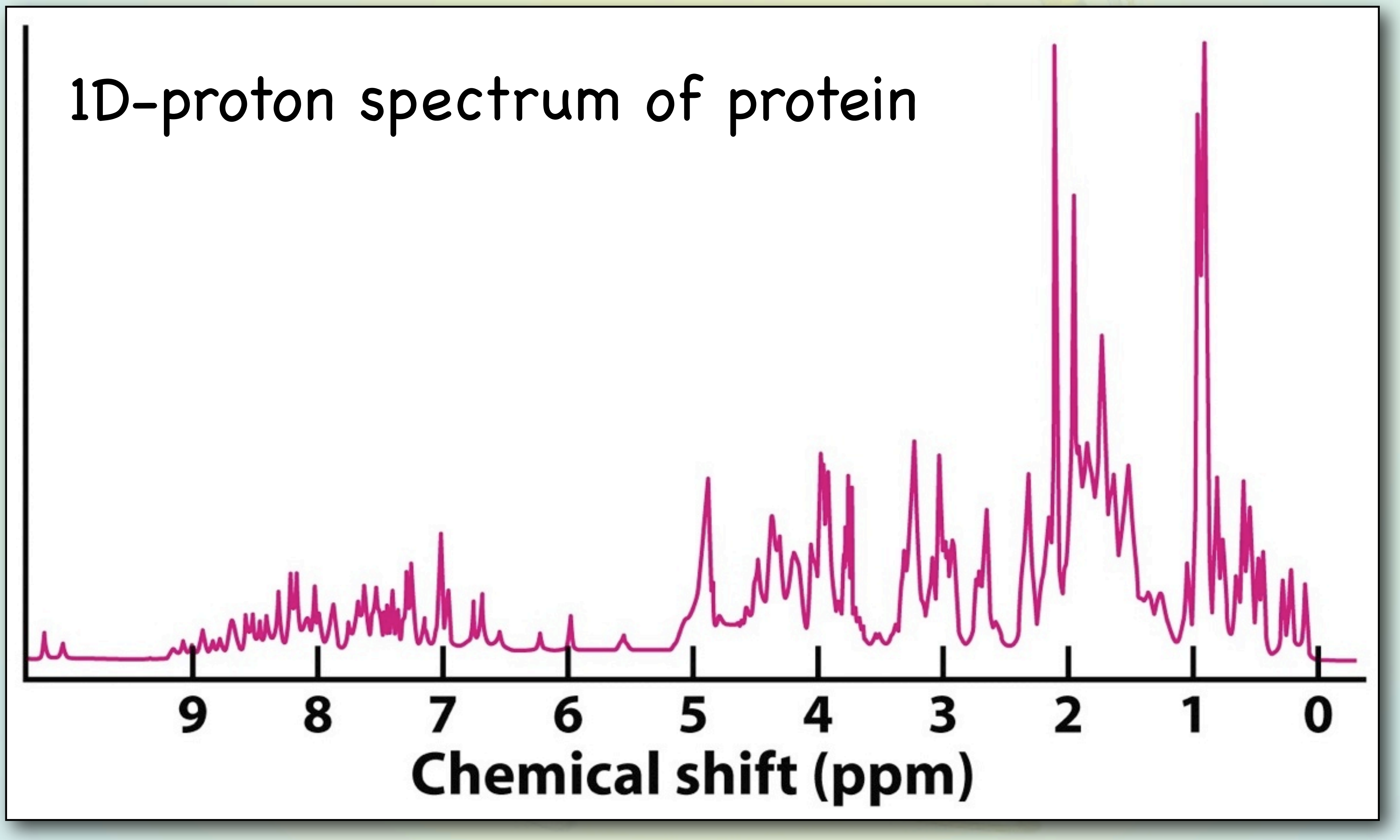
Protein 3-Dimensional Structures

- NMR Spectroscopy (Section 3.6)



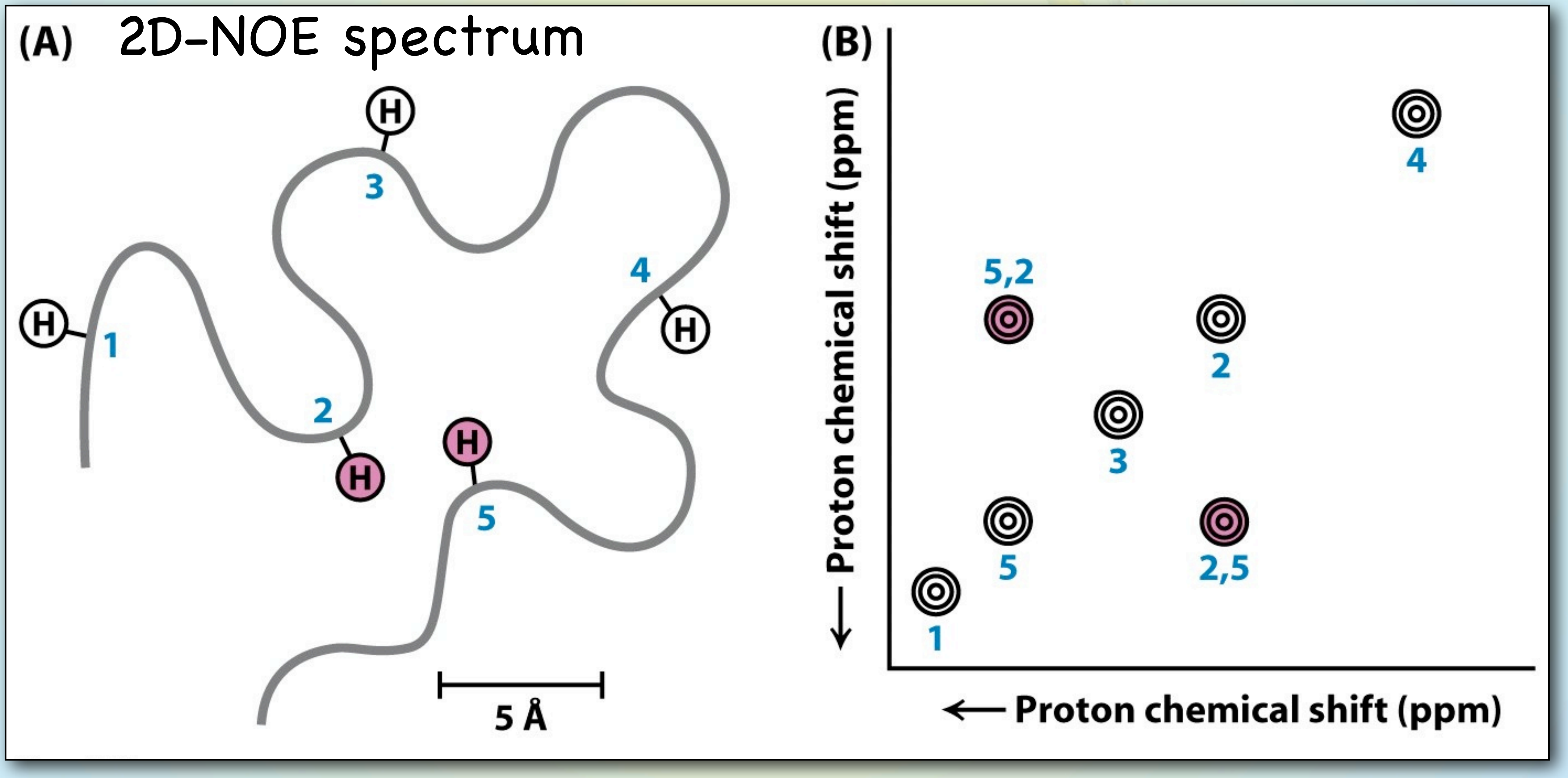
Protein 3-Dimensional Structures

- NMR Spectroscopy (Section 3.6)



Protein 3-Dimensional Structures

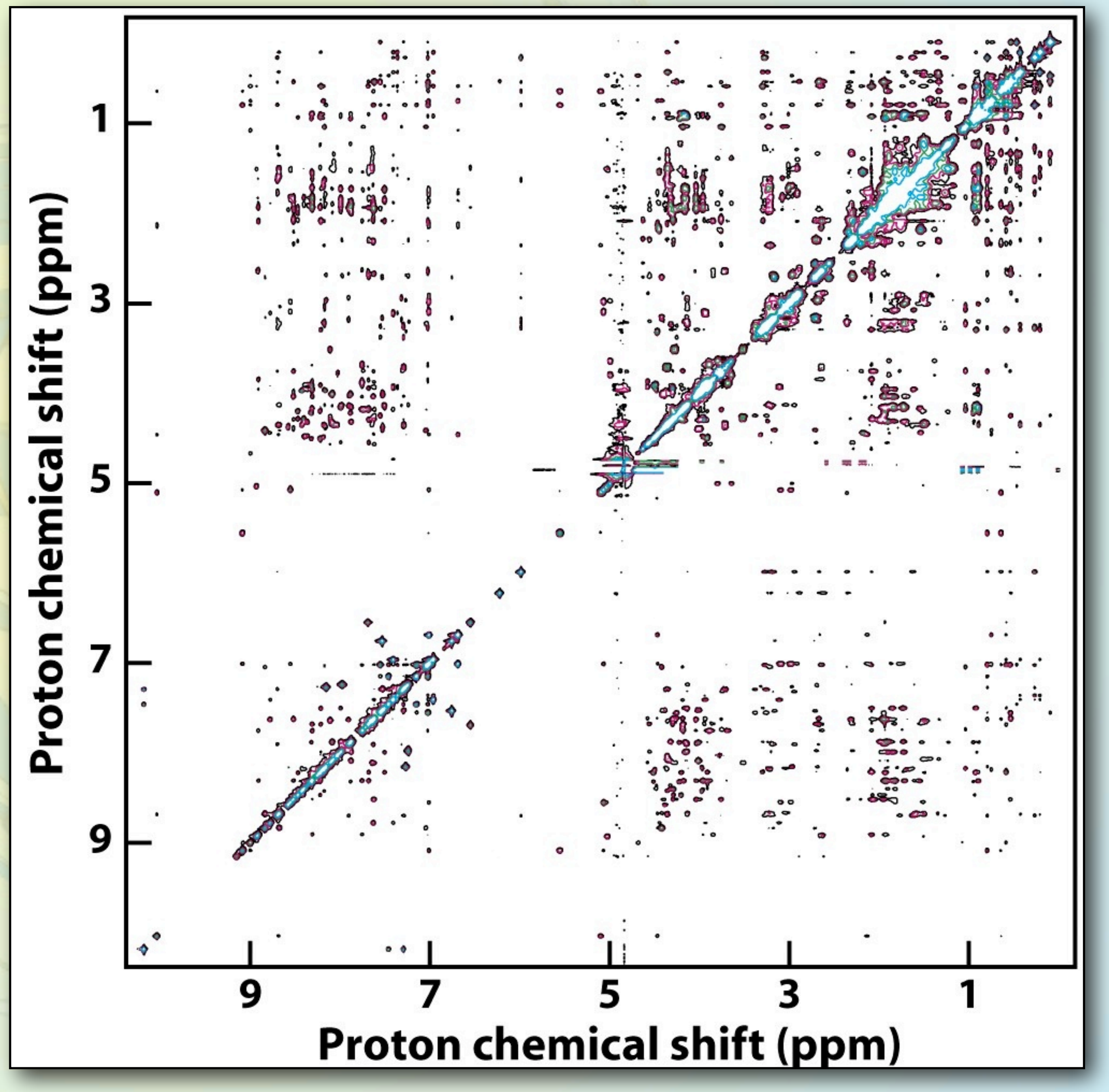
- NMR Spectroscopy (Section 3.6)



Protein 3-Dimensional Structures

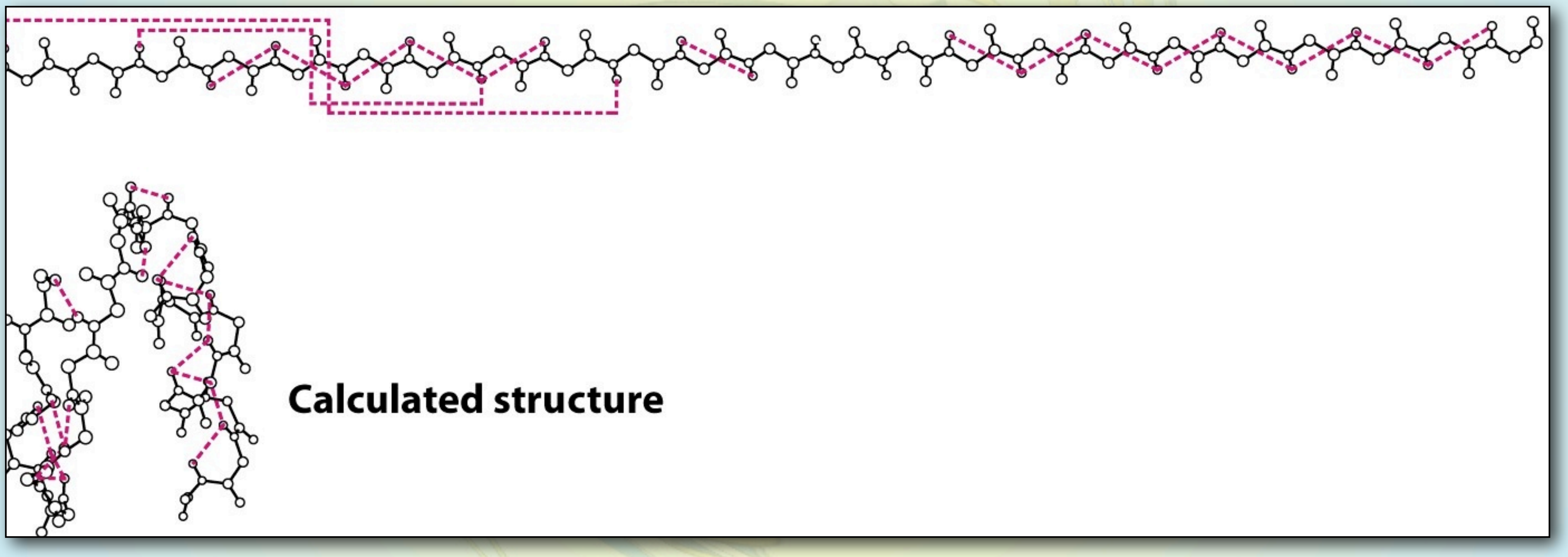
- NMR Spectroscopy (Section 3.6)

2D-NOE spectrum



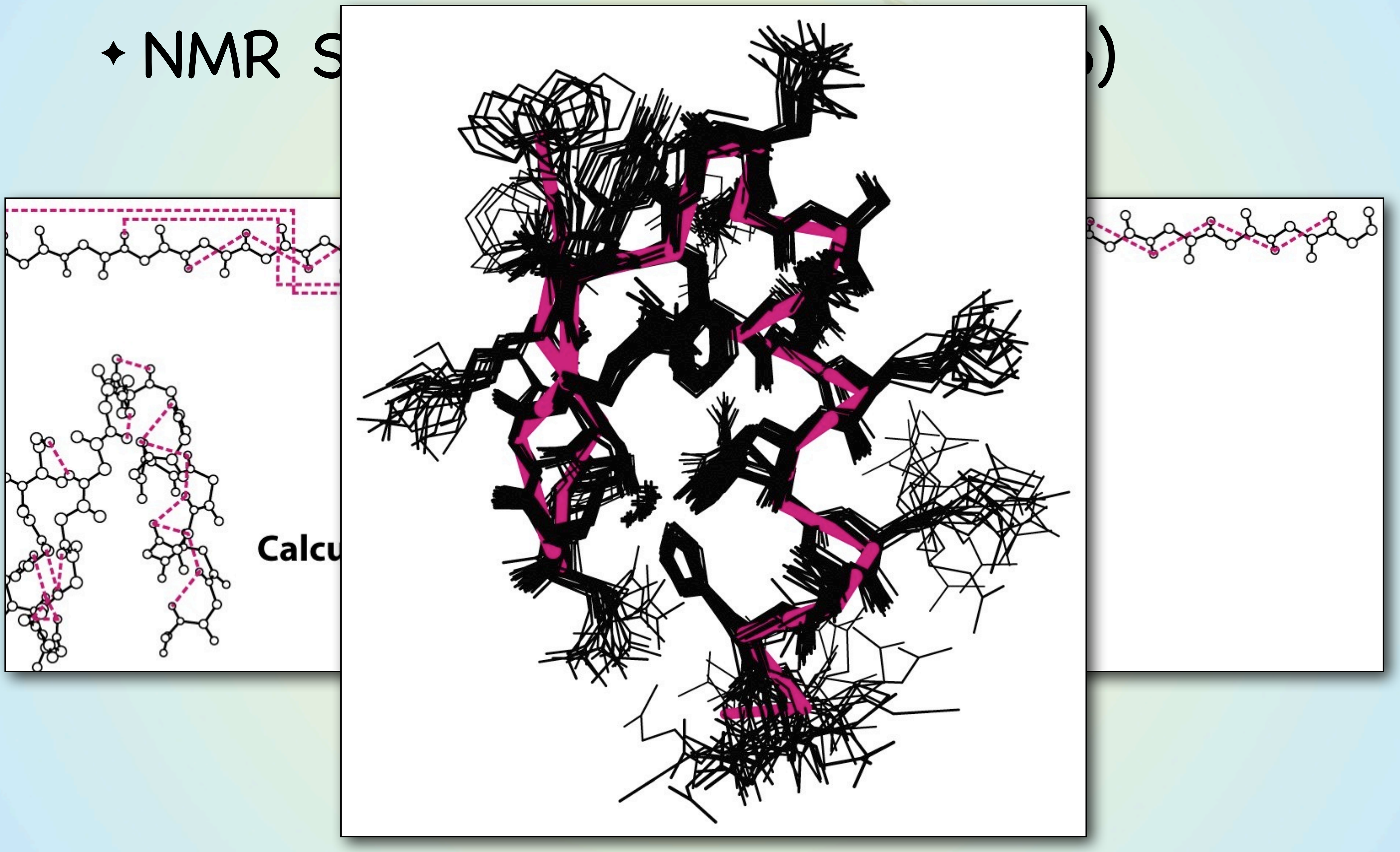
Protein 3-Dimensional Structures

- NMR Spectroscopy (Section 3.6)



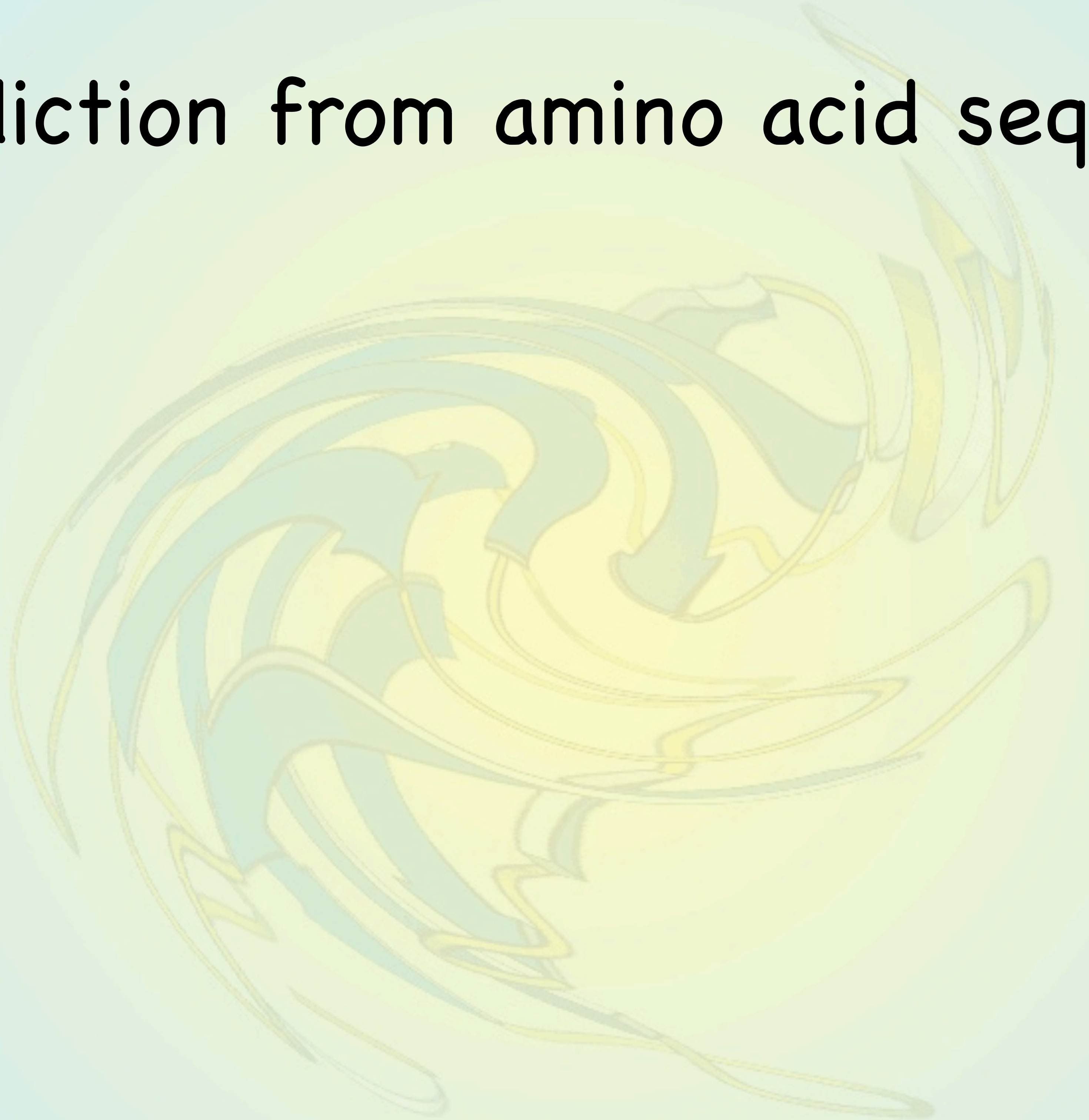
Protein 3-Dimensional Structures

- NMR S)



Protein 3-Dimensional Structures

- Prediction from amino acid sequence



Protein 3-Dimensional Structures

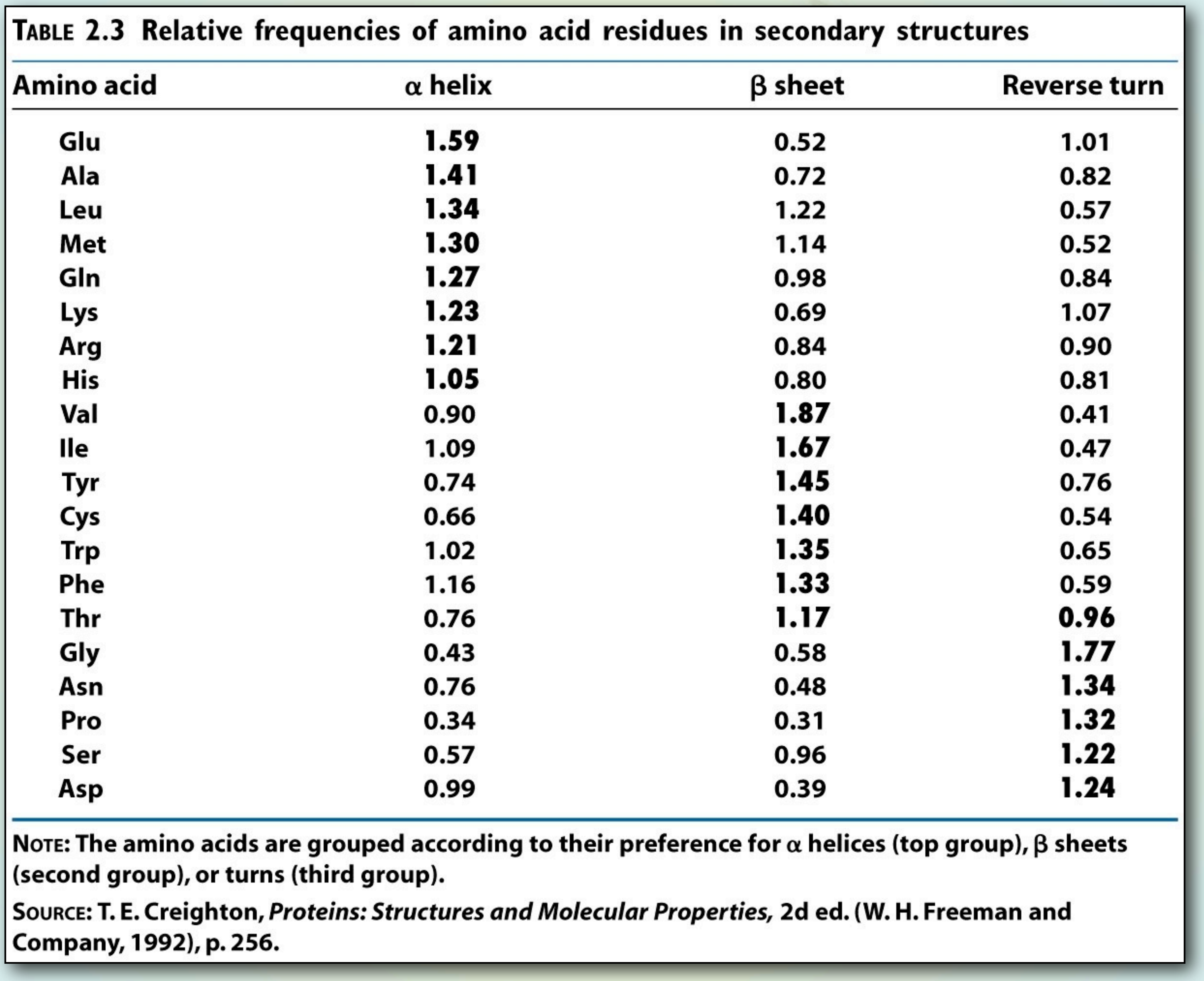


Table 2.3 Relative frequencies of amino acid residues in secondary structures

Amino acid	α helix	β sheet	Reverse turn
Glu	**1.59**	0.52	1.01
Ala	**1.41**	0.72	0.82
Leu	**1.34**	1.22	0.57
Met	**1.30**	1.14	0.52
Gln	**1.27**	0.98	0.84
Lys	**1.23**	0.69	1.07
Arg	**1.21**	0.84	0.90
His	**1.05**	0.80	0.81
Val	0.90	**1.87**	0.41
Ile	1.09	**1.67**	0.47
Tyr	0.74	**1.45**	0.76
Cys	0.66	**1.40**	0.54
Trp	1.02	**1.35**	0.65
Phe	1.16	**1.33**	0.59
Thr	0.76	**1.17**	**0.96**
Gly	0.43	0.58	**1.77**
Asn	0.76	0.48	**1.34**
Pro	0.34	0.31	**1.32**
Ser	0.57	0.96	**1.22**
Asp	0.99	0.39	**1.24**

Note: The amino acids are grouped according to their preference for α helices (top group), β sheets (second group), or turns (third group).

Source: T. E. Creighton, *Proteins: Structures and Molecular Properties,* 2d ed. (W. H. Freeman and Company, 1992), p. 256.

Protein 3-Dimensional Structures

- Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)
  - By comparison to structures found in the protein data bank.

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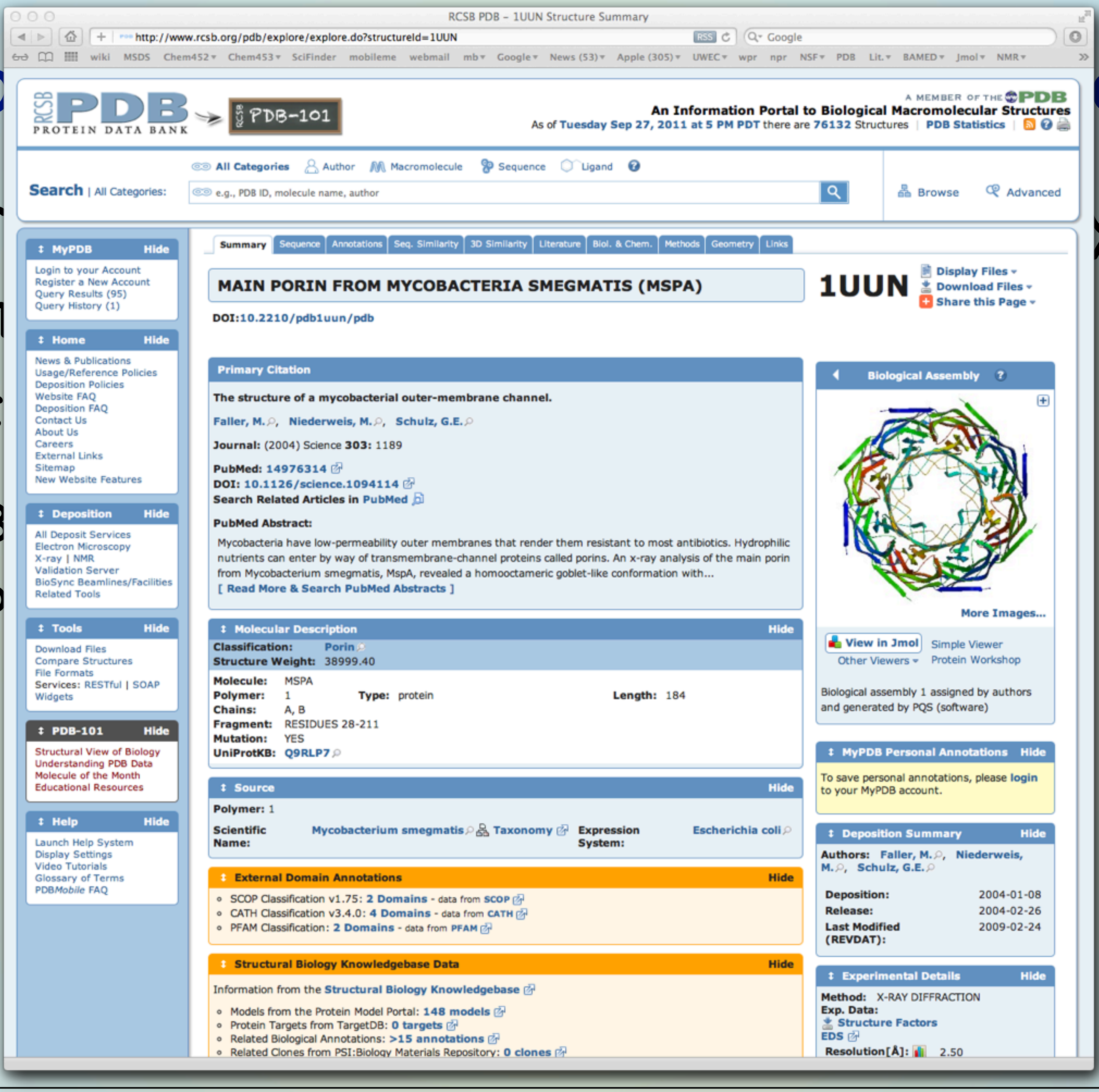

An Information Portal to Biological Macromolecular Structures

As of Tuesday Sep 27, 2011 at 5 PM PDT there are 76132 Structures | PDB Statistics

MAIN PORIN FROM MYCOBACTERIA SMEGMATIS (MSPA)

1UUN

DOI: 10.2210/pdb1uun/pdb

Primary Citation

The structure of a mycobacterial outer-membrane channel.

Faller, M., Niederweis, M., Schulz, G.E.

Journal: (2004) Science **303:** 1189

PubMed: 14976314
DOI: 10.1126/science.1094114
Search Related Articles in PubMed

PubMed Abstract:

Mycobacteria have low-permeability outer membranes that render them resistant to most antibiotics. Hydrophilic nutrients can enter by way of transmembrane-channel proteins called porins. An x-ray analysis of the main porin from Mycobacterium smegmatis, MspA, revealed a homooctameric goblet-like conformation with...
[Read More & Search PubMed Abstracts]

Biological assembly 1 assigned by authors and generated by PQS (software)

Molecular Description

Classification: Porin
Structure Weight: 38999.40

Molecule: MSPA
Polymer: 1 **Type:** protein **Length:** 184
Chains: A, B
Fragment: RESIDUES 28-211
Mutation: YES
UniProtKB: Q9RLP7

MyPDB Personal Annotations

To save personal annotations, please login to your MyPDB account.

Source

Polymer: 1

Scientific Name: Mycobacterium smegmatis Taxonomy **Expression System:** Escherichia coli

Deposition Summary

Authors: Faller, M., Niederweis, M., Schulz, G.E.

Deposition:	2004-01-08
Release:	2004-02-26
Last Modified (REVDAT):	2009-02-24

External Domain Annotations

- SCOP Classification v1.75: 2 Domains - data from SCOP
- CATH Classification v3.4.0: 4 Domains - data from CATH
- PFAM Classification: 2 Domains - data from PFAM

Experimental Details

Method: X-RAY DIFFRACTION
Exp. Data:
Structure Factors
EDS
Resolution[Å]: 2.50

Structural Biology Knowledgebase Data

Information from the Structural Biology Knowledgebase

- Models from the Protein Model Portal: 148 models
- Protein Targets from TargetDB: 0 targets
- Related Biological Annotations: >15 annotations
- Related Clones from PSI:Biology Materials Repository: 0 clones

Protein 3-Dimensional Structures

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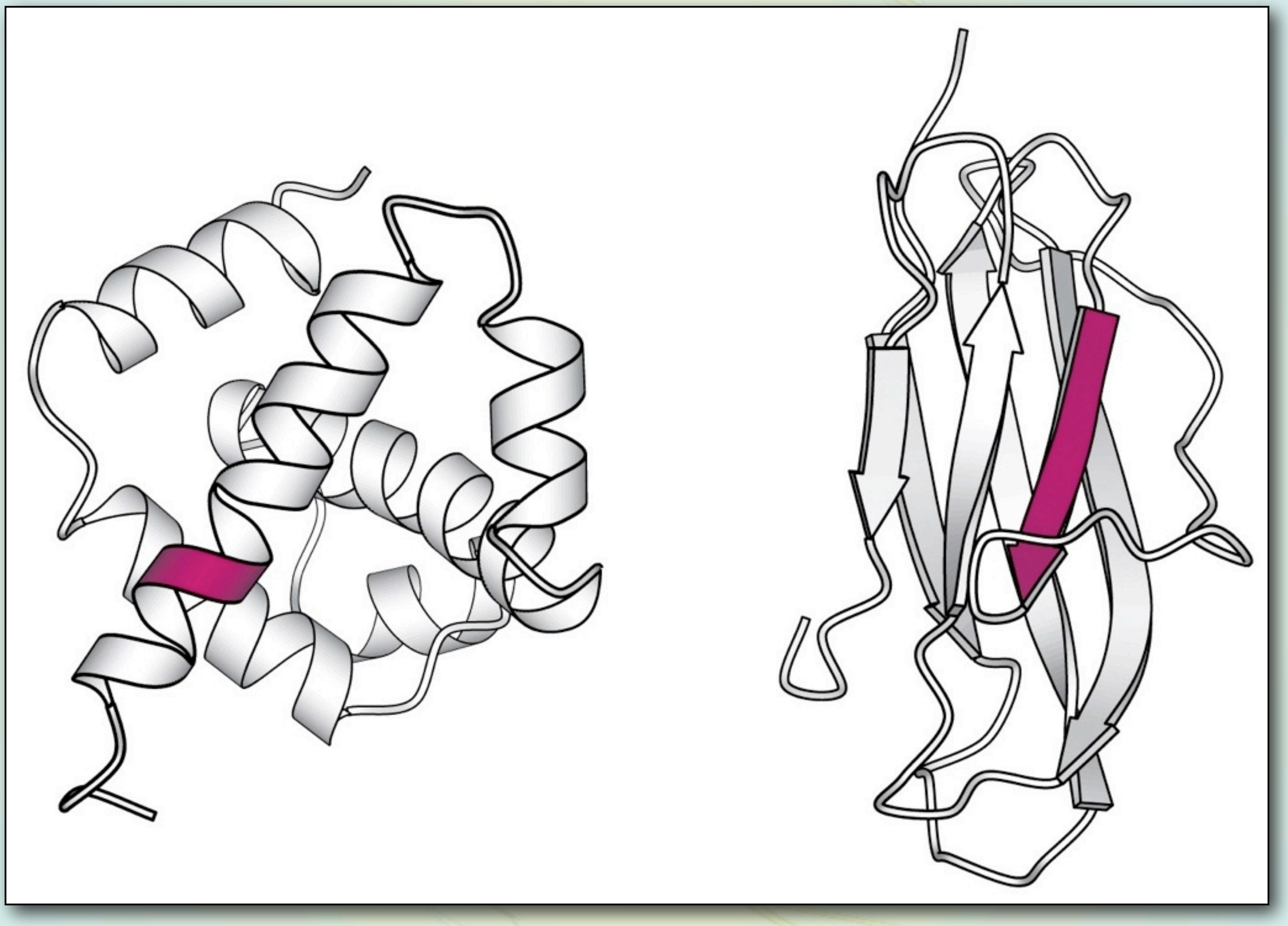
Protein 3-Dimensional Structures



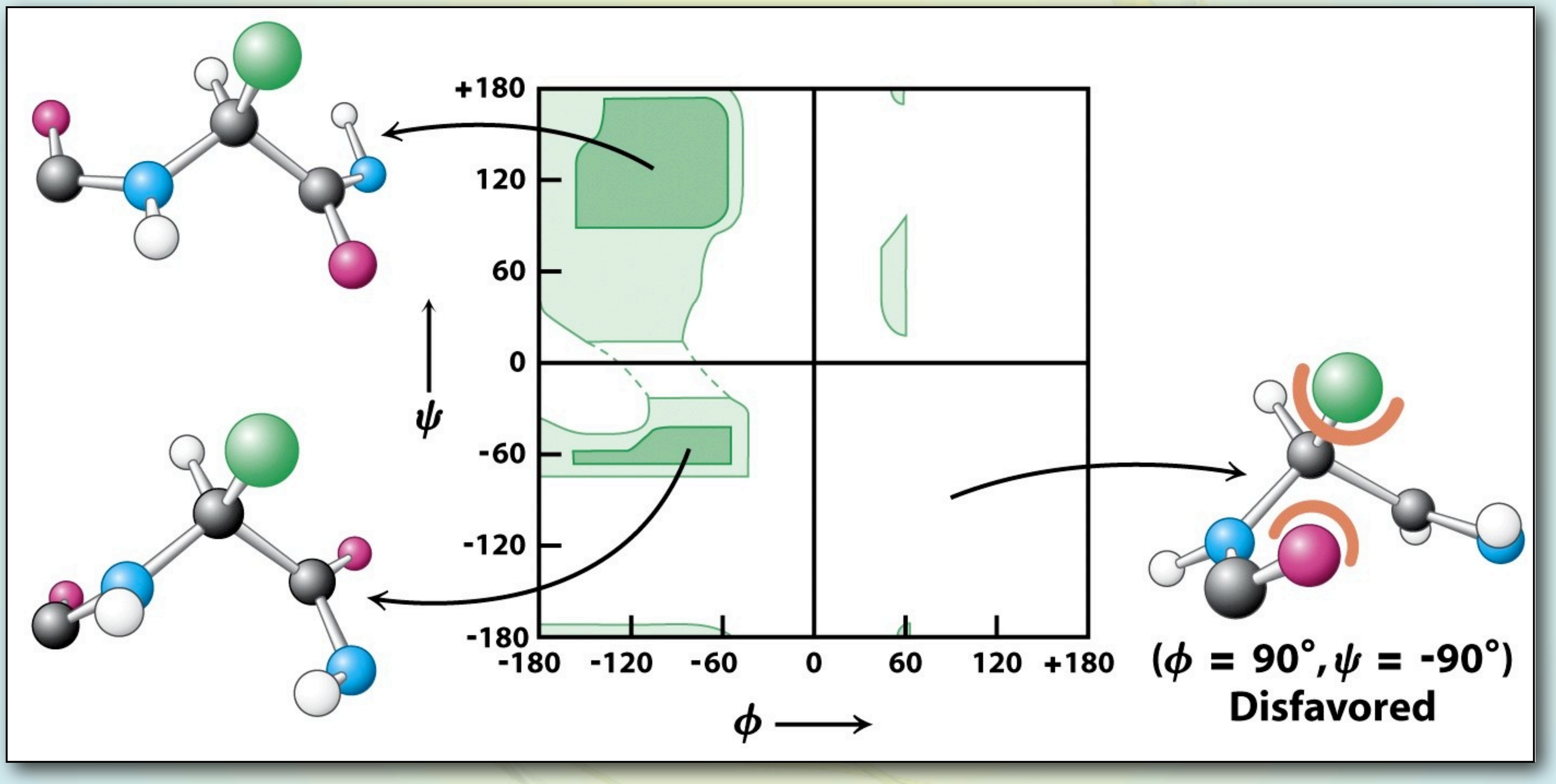
The sequence VDLLKN

Protein 3-Dimensional Structures

- Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)
  - By comparison to structures found in the protein data bank.
  - By searching for the structure with the lowest free energy.
    - Rosetta@Home

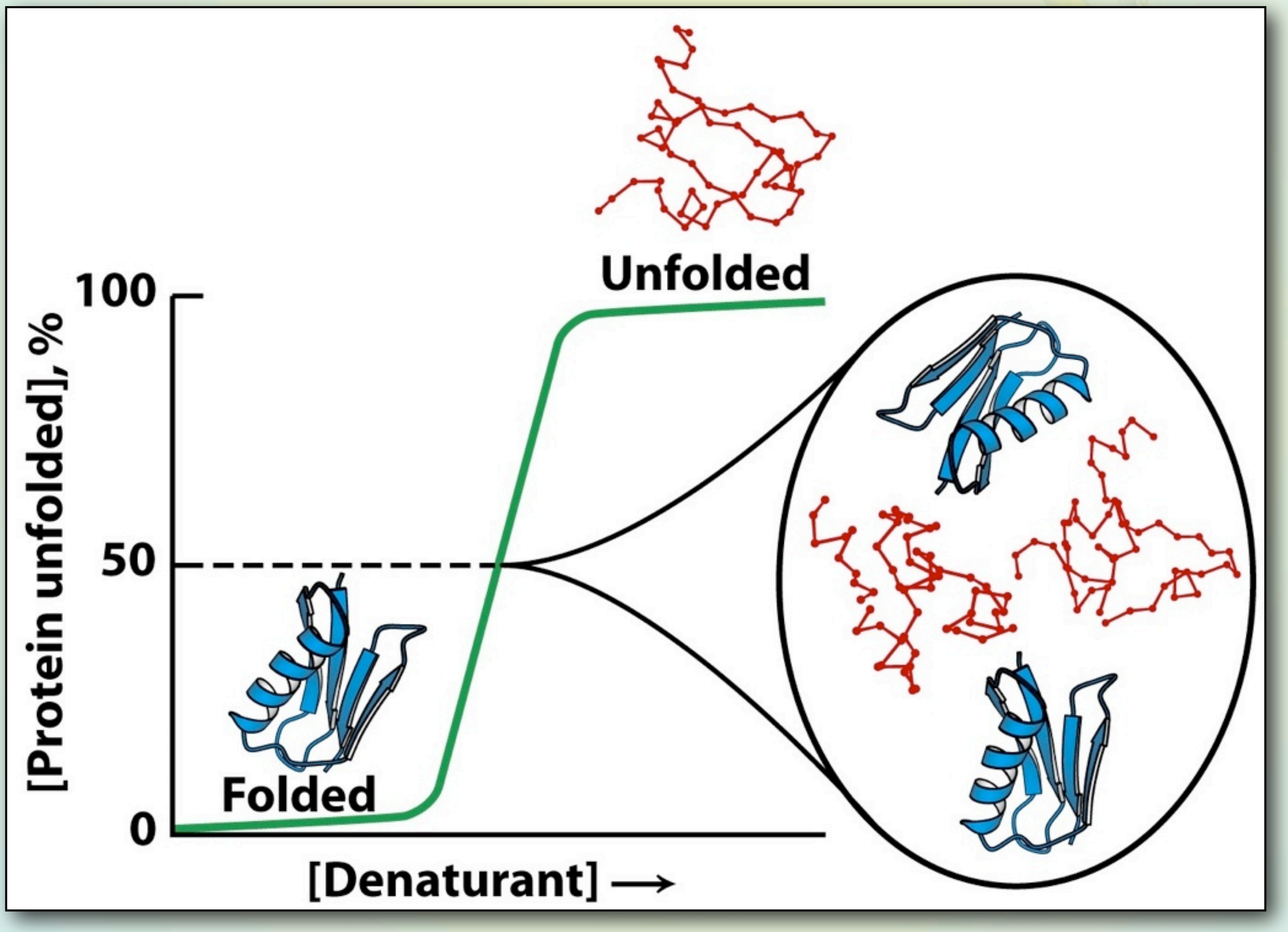
Protein 3-Dimensional Structures

- The Levinthal Paradox



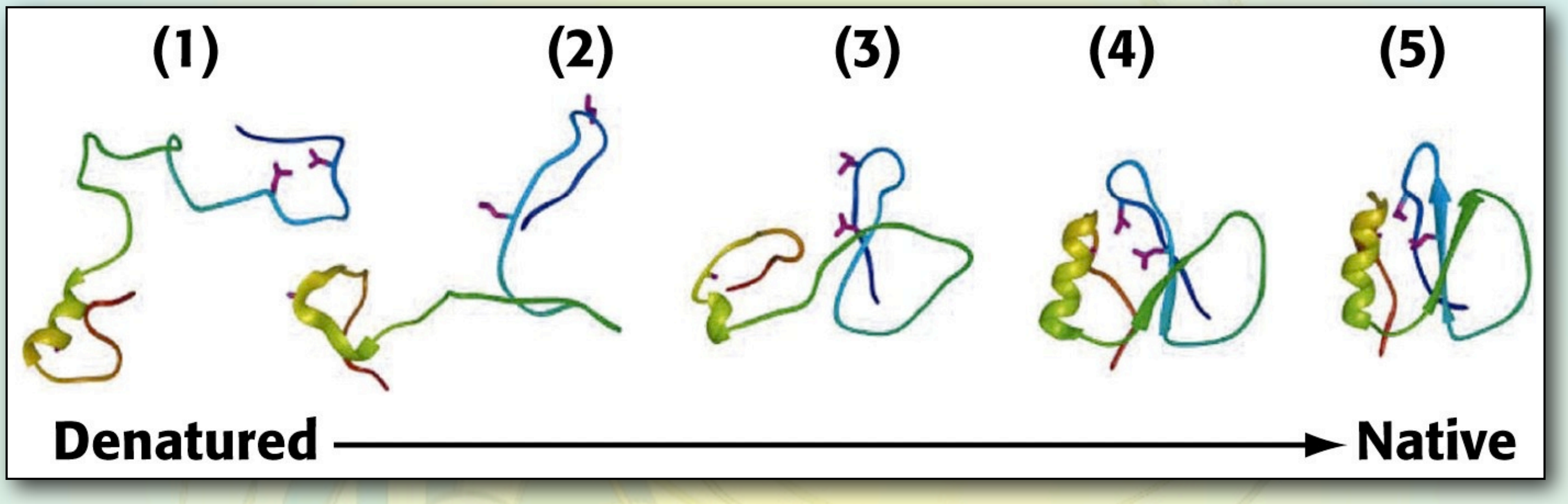
Protein Folding

- Proteins folding is highly cooperative



Protein 3-Dimensional Structures

- Successive Stabilization



Protein 3-Dimensional Structures

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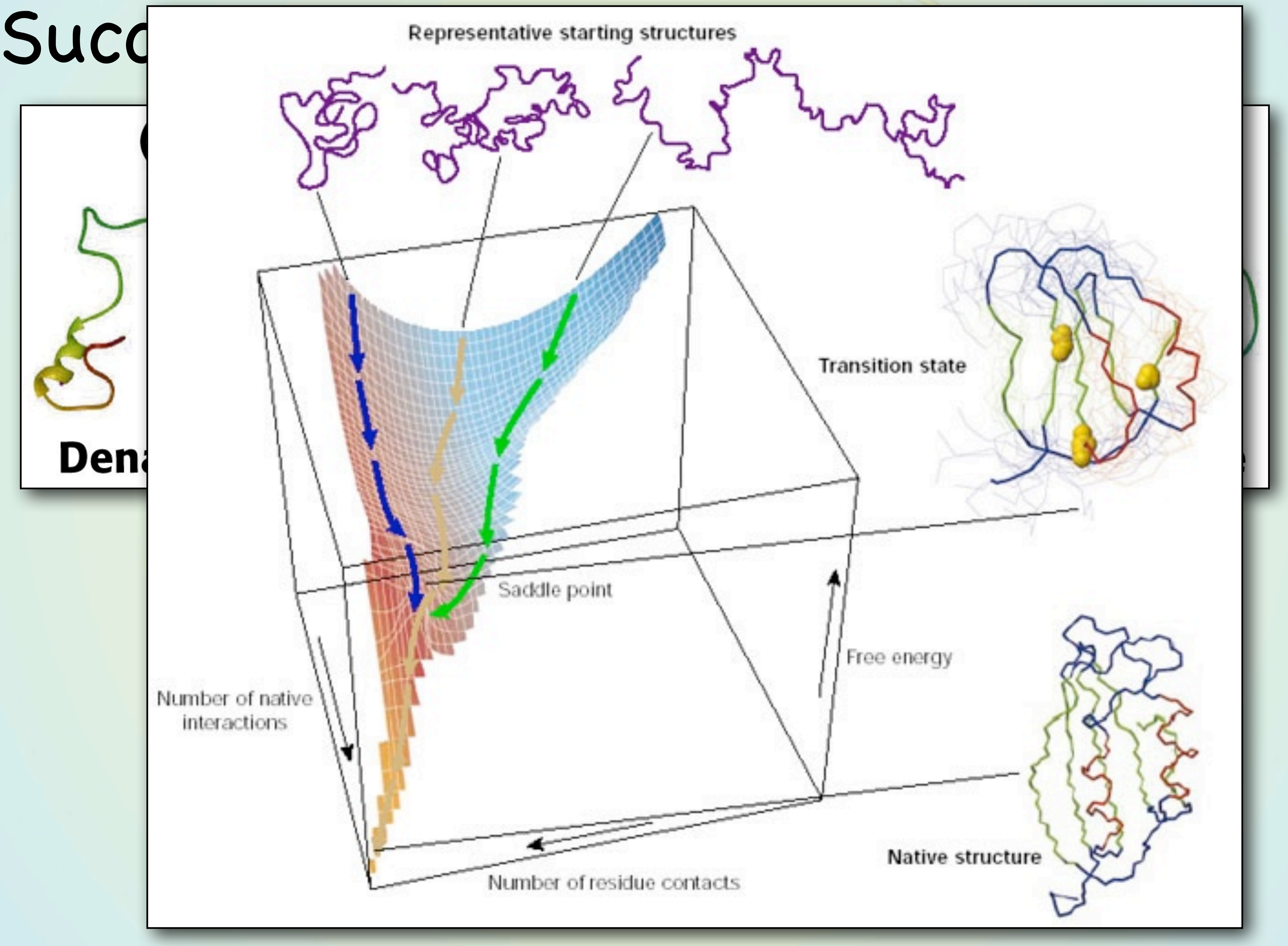

Protein 3-Dimensional Structures

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Protein 3-Dimensional Structures

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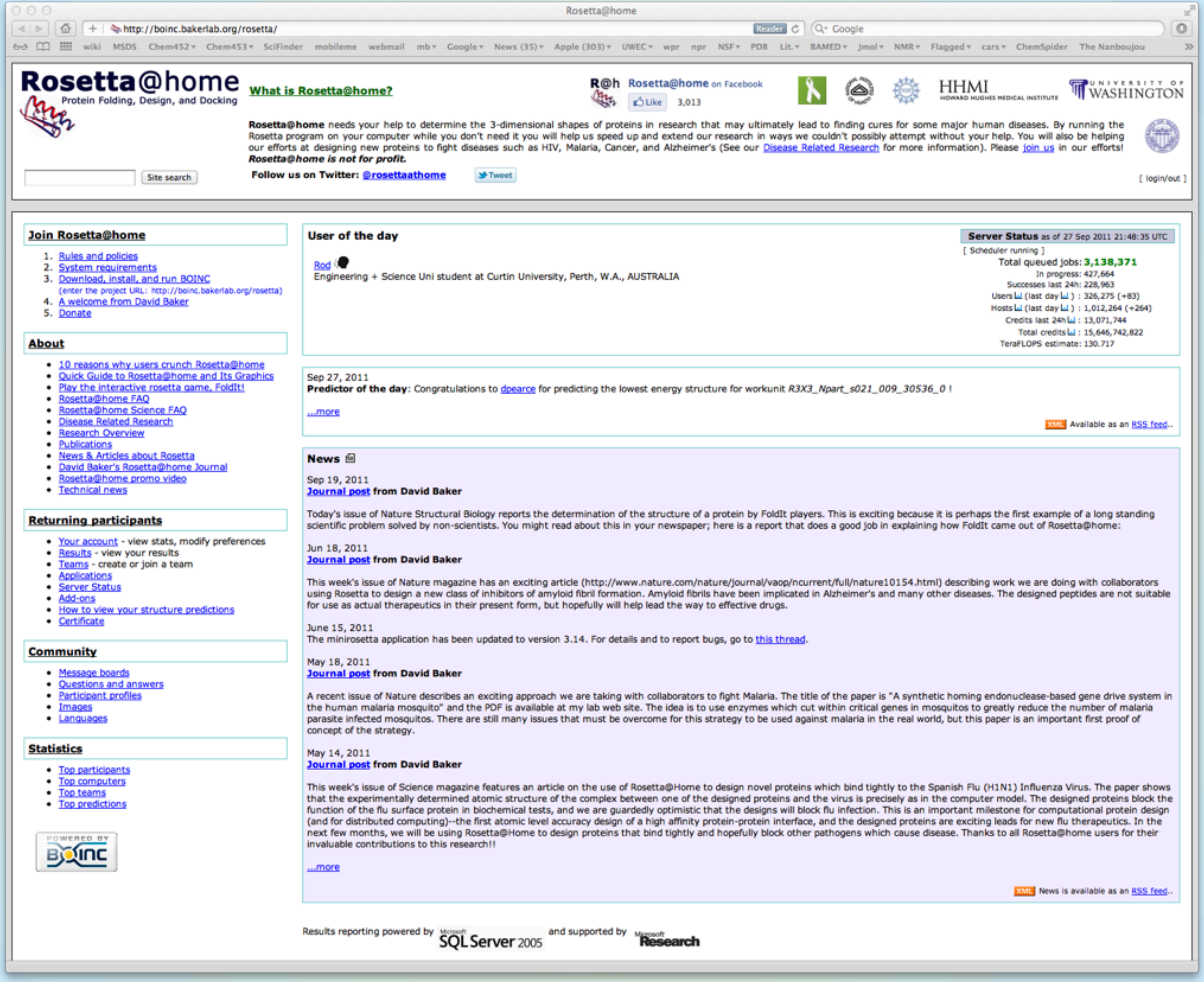

Rosetta@home

Protein Folding, Design, and Docking

What is Rosetta@home?

Rosetta@home on Facebook

Rosetta@home needs your help to determine the 3-dimensional shapes of proteins in research that may ultimately lead to finding cures for some major human diseases. By running the Rosetta program on your computer while you don't need it you will help us speed up and extend our research in ways we couldn't possibly attempt without your help. You will also be helping our efforts at designing new proteins to fight diseases such as HIV, Malaria, Cancer, and Alzheimer's (See our Disease Related Research for more information). Please join us in our efforts! ***Rosetta@home is not for profit.***

Follow us on Twitter: @rosettaathome

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Join Rosetta@home

1. Rules and policies
2. System requirements
3. Download, install, and run BOINC
   (enter the project URL: http://boinc.bakerlab.org/rosetta)
4. A welcome from David Baker
5. Donate

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- Participant profiles
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- Languages

Statistics

- Top participants
- Top computers
- Top teams
- Top predictions

User of the day

Rod
Engineering + Science Uni student at Curtin University, Perth, W.A., AUSTRALIA

Server Status as of 27 Sep 2011 21:48:35 UTC

[Scheduler running]

Total queued jobs: **3,138,371**
In progress: 427,664
Successes last 24h: 228,963
Users (last day) : 326,275 (+83)
Hosts (last day) : 1,012,264 (+264)
Credits last 24h : 13,071,744
Total credits : 15,646,742,822
TeraFLOPS estimate: 130.717

Sep 27, 2011
Predictor of the day: Congratulations to dpearce for predicting the lowest energy structure for workunit *R3X3_Npart_s021_009_30536_0* !

...more

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News

Sep 19, 2011
Journal post from David Baker

Today's issue of Nature Structural Biology reports the determination of the structure of a protein by FoldIt players. This is exciting because it is perhaps the first example of a long standing scientific problem solved by non-scientists. You might read about this in your newspaper; here is a report that does a good job in explaining how FoldIt came out of Rosetta@home:

Jun 18, 2011
Journal post from David Baker

This week's issue of Nature magazine has an exciting article (http://www.nature.com/nature/journal/vaop/ncurrent/full/nature10154.html) describing work we are doing with collaborators using Rosetta to design a new class of inhibitors of amyloid fibril formation. Amyloid fibrils have been implicated in Alzheimer's and many other diseases. The designed peptides are not suitable for use as actual therapeutics in their present form, but hopefully will help lead the way to effective drugs.

June 15, 2011
The minirosetta application has been updated to version 3.14. For details and to report bugs, go to this thread.

May 18, 2011
Journal post from David Baker

A recent issue of Nature describes an exciting approach we are taking with collaborators to fight Malaria. The title of the paper is "A synthetic homing endonuclease-based gene drive system in the human malaria mosquito" and the PDF is available at my lab web site. The idea is to use enzymes which cut within critical genes in mosquitos to greatly reduce the number of malaria parasite infected mosquitos. There are still many issues that must be overcome for this strategy to be used against malaria in the real world, but this paper is an important first proof of concept of the strategy.

May 14, 2011
Journal post from David Baker

This week's issue of Science magazine features an article on the use of Rosetta@Home to design novel proteins which bind tightly to the Spanish Flu (H1N1) Influenza Virus. The paper shows that the experimentally determined atomic structure of the complex between one of the designed proteins and the virus is precisely as in the computer model. The designed proteins block the function of the flu surface protein in biochemical tests, and we are guardedly optimistic that the designs will block flu infection. This is an important milestone for computational protein design (and for distributed computing)--the first atomic level accuracy design of a high affinity protein-protein interface, and the designed proteins are exciting leads for new flu therapeutics. In the next few months, we will be using Rosetta@Home to design proteins that bind tightly and hopefully block other pathogens which cause disease. Thanks to all Rosetta@home users for their invaluable contributions to this research!!

...more

XML News is available as an RSS feed..

Results reporting powered by Microsoft SQL Server 2005 and supported by Microsoft Research

Protein 3-Dimensional Structures

- Taking Rosetta one step further with Foldit, by turning structure prediction into an online video game!!

Pr s

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22:13:31 GMT

Click to learn how you contribute to science by playing Foldit.

GET STARTED: DOWNLOAD

Win Beta	Mac Beta	Linux Beta
Windows XP/Vista/7	Intel OSX 10.4 or later	Linux

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USER LOGIN

Username: *

Password: *

Log in

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- Request new password
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What's New

Small Update

We've posted a small update today that should improve some of the introductory levels!

(Sun, 09/25/2011 - 01:25 | 6 comments) Share

Puzzle deadlines extended, global chat help

We have extended the deadlines for the Beginner Puzzle and Puzzle 459 by 3 days (due to all the new visitors to the site).

Again, welcome to all the new Foldit players. We are working on improving the server response time. If you are having trouble with global chat, you may want to use an IRC client to access chat: http://foldit.wikia.com/wiki/Fold.it_IRC_(chat)_Information

(Thu, 09/22/2011 - 10:25 | 2 comments) Share

Server status

Due to the high volume of new visitors to the site, response times from the server are slow and some features of the site are disabled. We're working on improving the server response time. Thanks for your patience!

(Mon, 09/19/2011 - 19:37 | 3 comments) Share

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PLAYER			PUZZLE	SCORE
Cake or&nb...	108	3332	460 (<150): Que...ein	10,066
mrhaandi	108	337	460 (<15): Ques...ein	10,172
wudooAl	108	1150	460: Quest to t...ein	10,410
rvhonorato	108	1220	Beginner Puzzle...ein	9,792
zorkmid	108	5611	Beginner Puzzle...ein	9,767
Enzyme	108	36	Beginner Puzzle...ein	9,812
Incongruous	108	238	459 (<150): Mul...zle	10,710
Kuwaga	108	343	459 (<15): Mult...zle	10,775
Junker	108	173	459: Multi-Star...zle	10,948

FULL

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Protein 3-Dimensional Structures

- Protein Data Bank
  - An online repository for 3-D biological structures.

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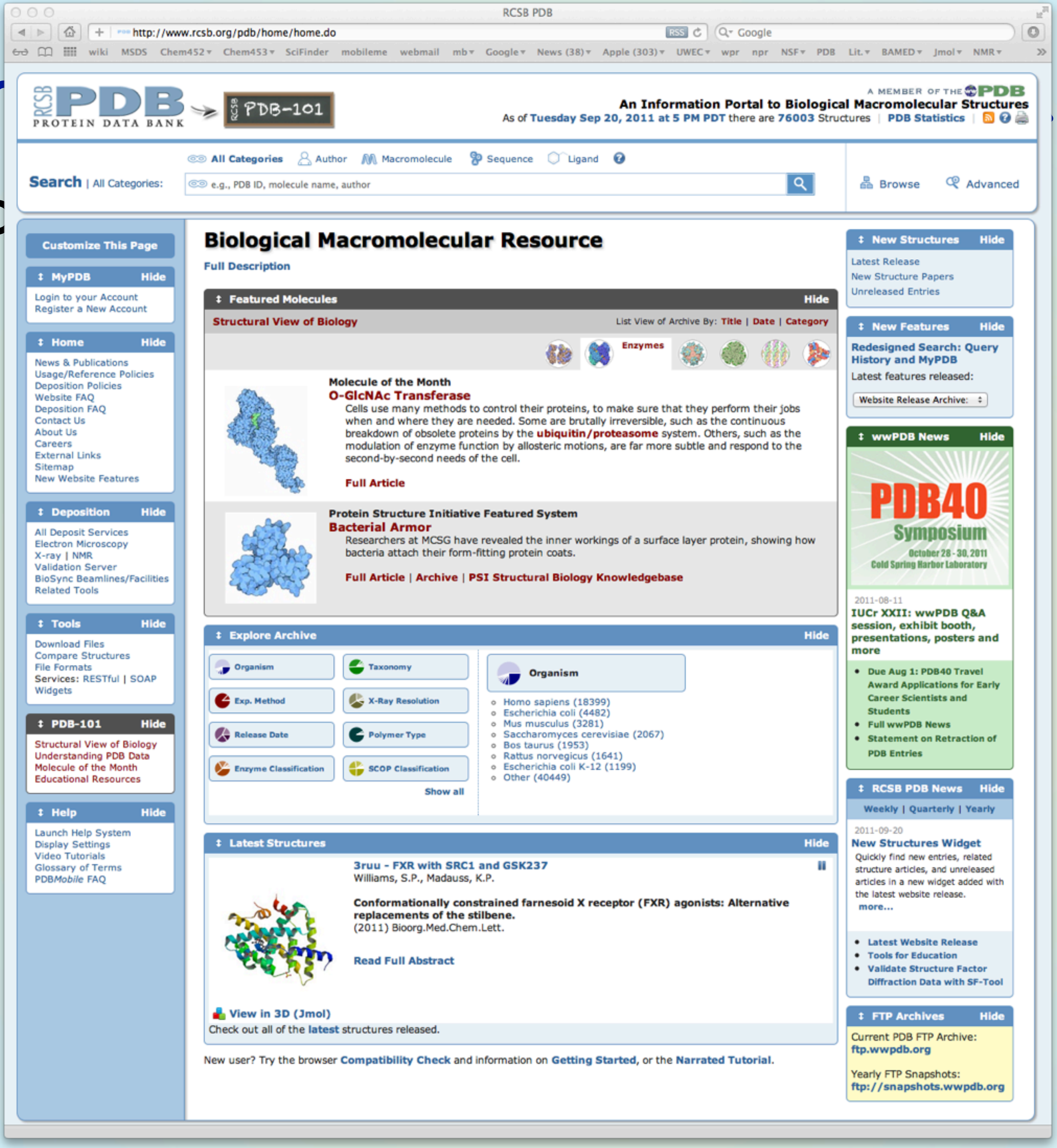

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Molecule of the Month
O-GlcNAc Transferase
Cells use many methods to control their proteins, to make sure that they perform their jobs when and where they are needed. Some are brutally irreversible, such as the continuous breakdown of obsolete proteins by the **ubiquitin/proteasome** system. Others, such as the modulation of enzyme function by allosteric motions, are far more subtle and respond to the second-by-second needs of the cell.

Full Article

Protein Structure Initiative Featured System
Bacterial Armor
Researchers at MCSG have revealed the inner workings of a surface layer protein, showing how bacteria attach their form-fitting protein coats.

Full Article | **Archive** | **PSI Structural Biology Knowledgebase**

Explore Archive Hide

Organism
Taxonomy
Exp. Method
X-Ray Resolution
Release Date
Polymer Type
Enzyme Classification
SCOP Classification
Show all

Organism

- Homo sapiens (18399)
- Escherichia coli (4482)
- Mus musculus (3281)
- Saccharomyces cerevisiae (2067)
- Bos taurus (1953)
- Rattus norvegicus (1641)
- Escherichia coli K-12 (1199)
- Other (40449)

Latest Structures Hide

3ruu - FXR with SRC1 and GSK237
Williams, S.P., Madauss, K.P.

Conformationally constrained farnesoid X receptor (FXR) agonists: Alternative replacements of the stilbene.
(2011) Bioorg.Med.Chem.Lett.

Read Full Abstract

View in 3D (Jmol)
Check out all of the **latest** structures released.

New user? Try the browser **Compatibility Check** and information on **Getting Started**, or the **Narrated Tutorial**.

New Structures Hide

Latest Release
New Structure Papers
Unreleased Entries

New Features Hide

Redesigned Search: Query History and MyPDB
Latest features released:
Website Release Archive:

wwPDB News Hide

PDB40 Symposium
October 28 - 30, 2011
Cold Spring Harbor Laboratory

2011-08-11
IUCr XXII: wwPDB Q&A session, exhibit booth, presentations, posters and more

- Due Aug 1: PDB40 Travel Award Applications for Early Career Scientists and Students
- Full wwPDB News
- Statement on Retraction of PDB Entries

RCSB PDB News Hide

Weekly | **Quarterly** | **Yearly**

2011-09-20
New Structures Widget
Quickly find new entries, related structure articles, and unreleased articles in a new widget added with the latest website release.
more...

- Latest Website Release
- Tools for Education
- Validate Structure Factor Diffraction Data with SF-Tool

FTP Archives Hide

Current PDB FTP Archive:
ftp.wwpdb.org

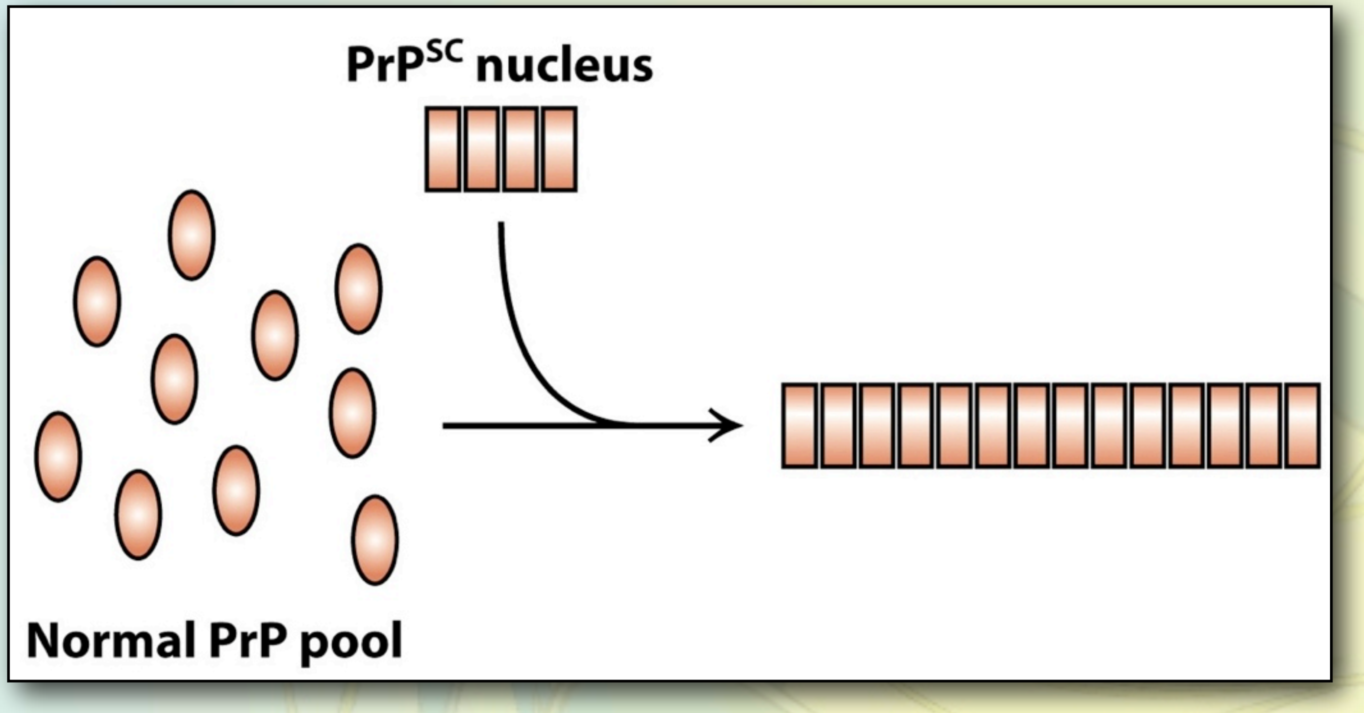
Yearly FTP Snapshots:
ftp://snapshots.wwpdb.org

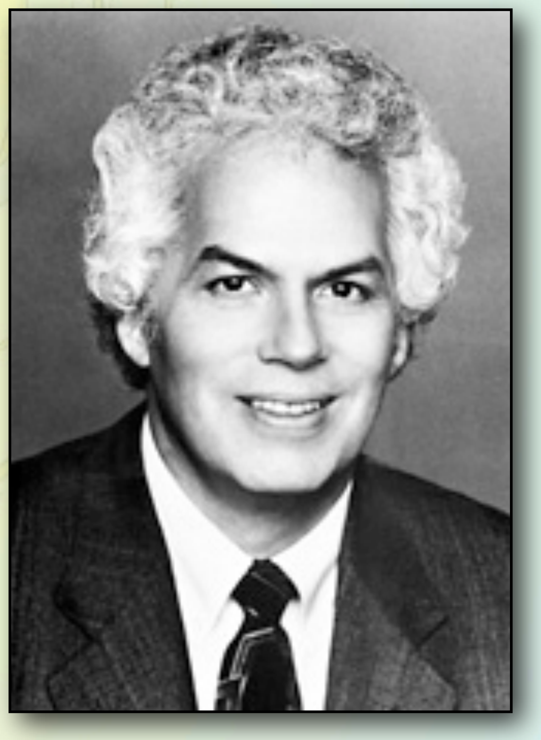
Protein Misfolding

- What happens when a protein misbehave and misfold.
  - Prions
    - Mad Cow Disease (Bovine spongiform encephalopathy, BSE)
    - Creutzfeld-Jakob disease (CJD)
    - Scrapies
    - Chronic Wasting Disease (CWD)
  - Alzheimer's Disease

Protein Misfolding

- Prions

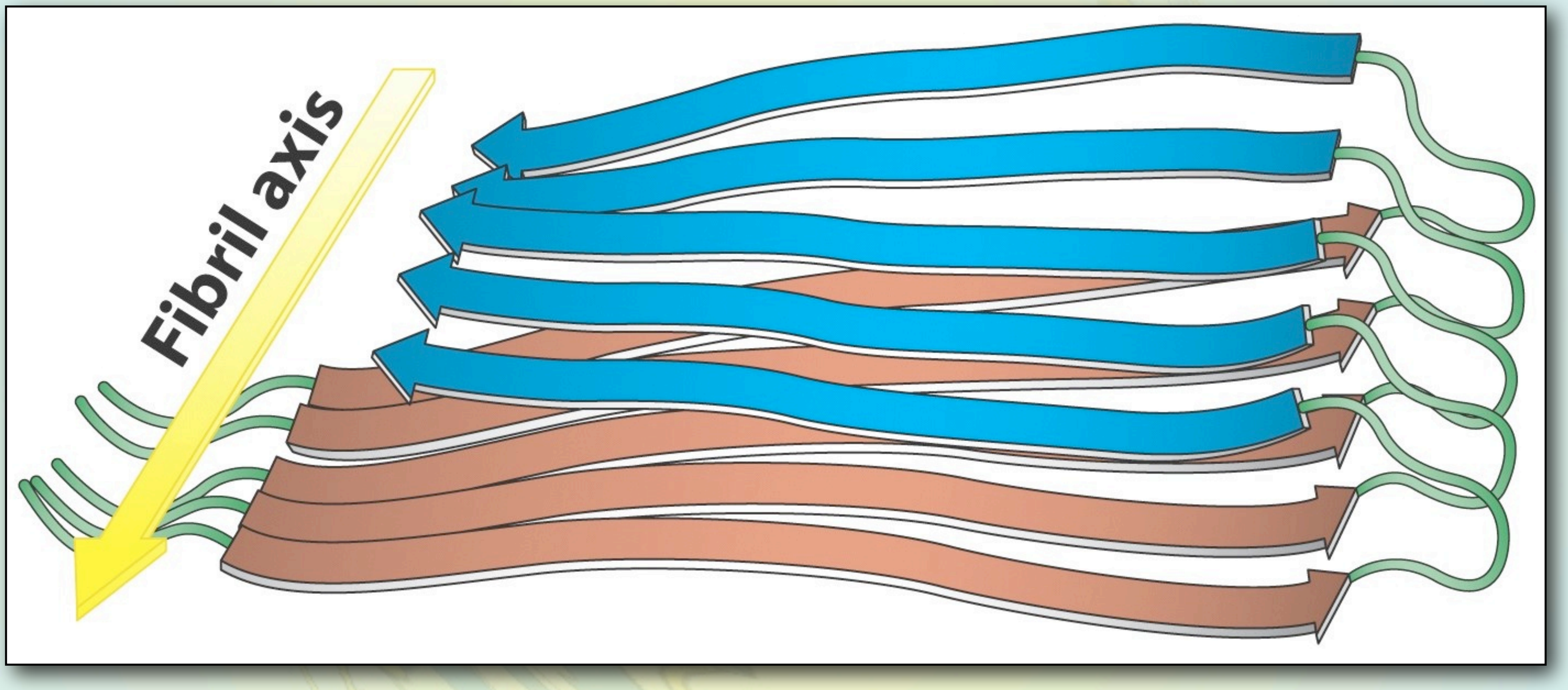




Stanley Prusiner
1997 Nobel Prize in Medicine

Protein Misfolding

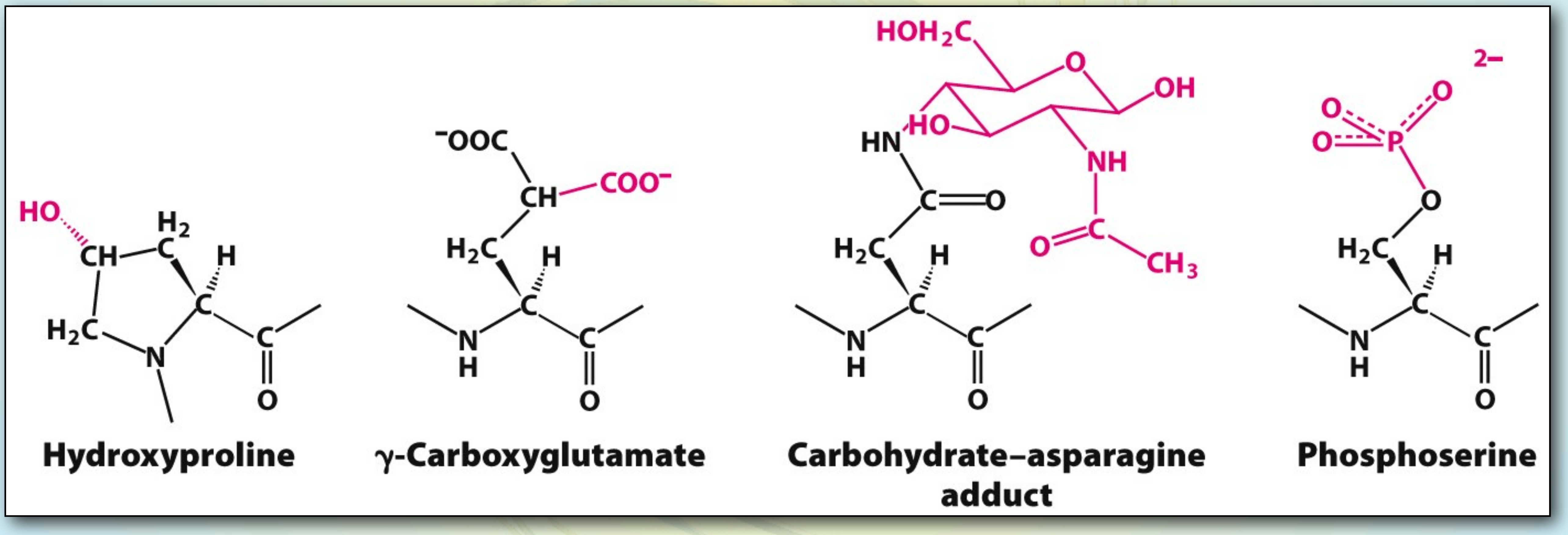
- Alzheimer's Disease



Amyloid β-fibrils

Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



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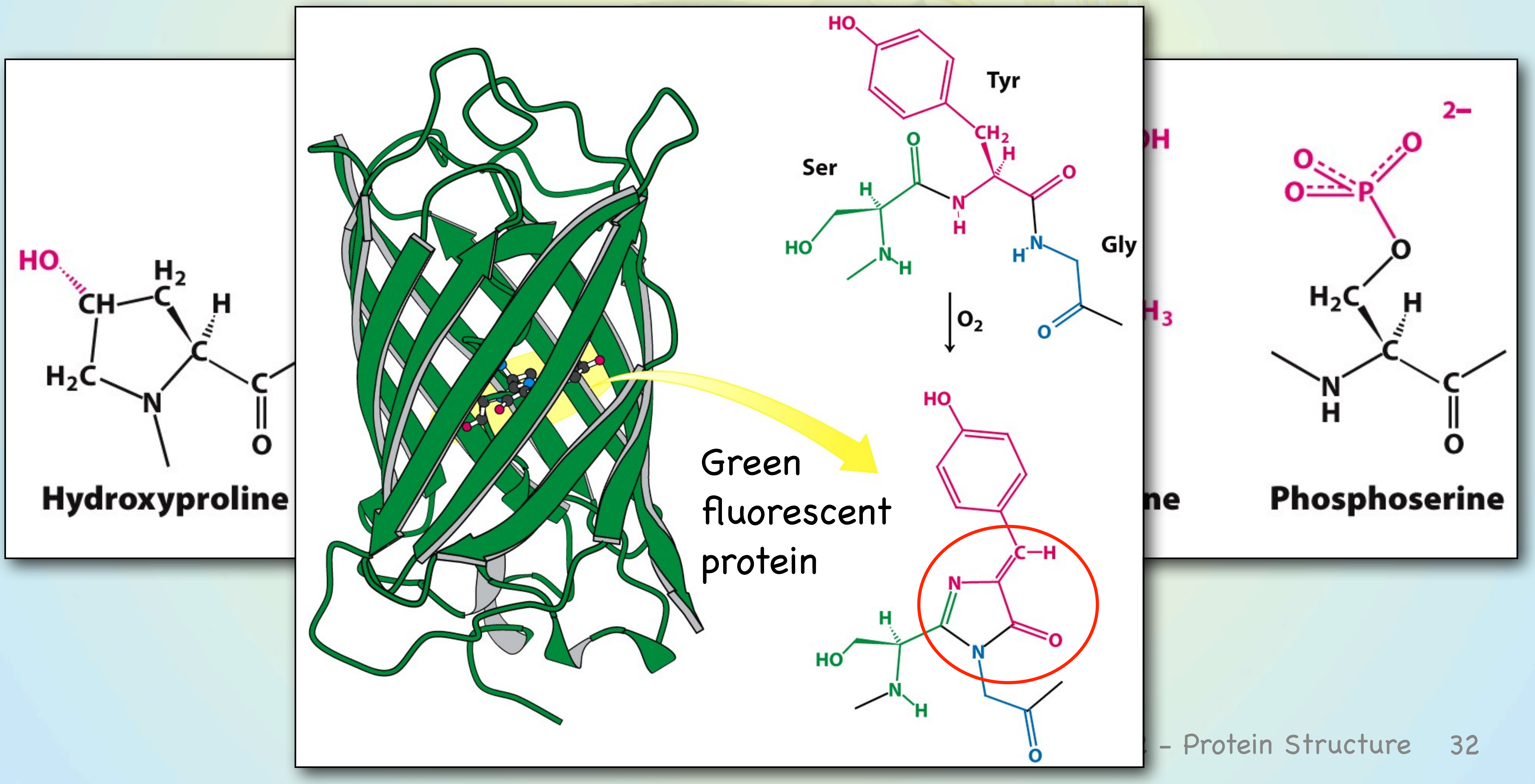
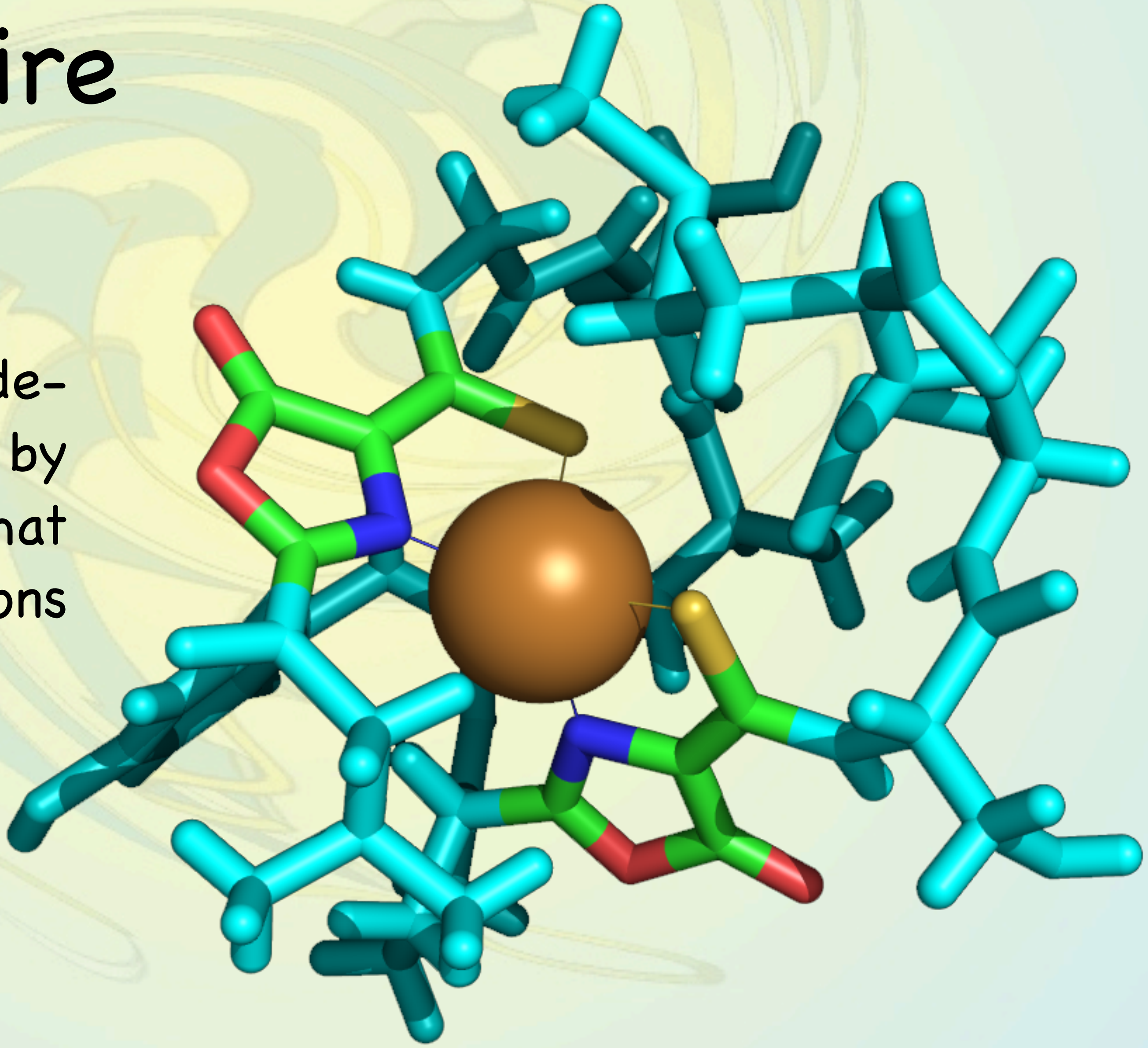


Green fluorescent protein

Modifications to the Primary

- Some post translational modifications that we have discovered here at UW-Eau Claire



Methanobactins are peptide-derived molecules produced by methane oxidizing bacteria that are scavengers for copper ions

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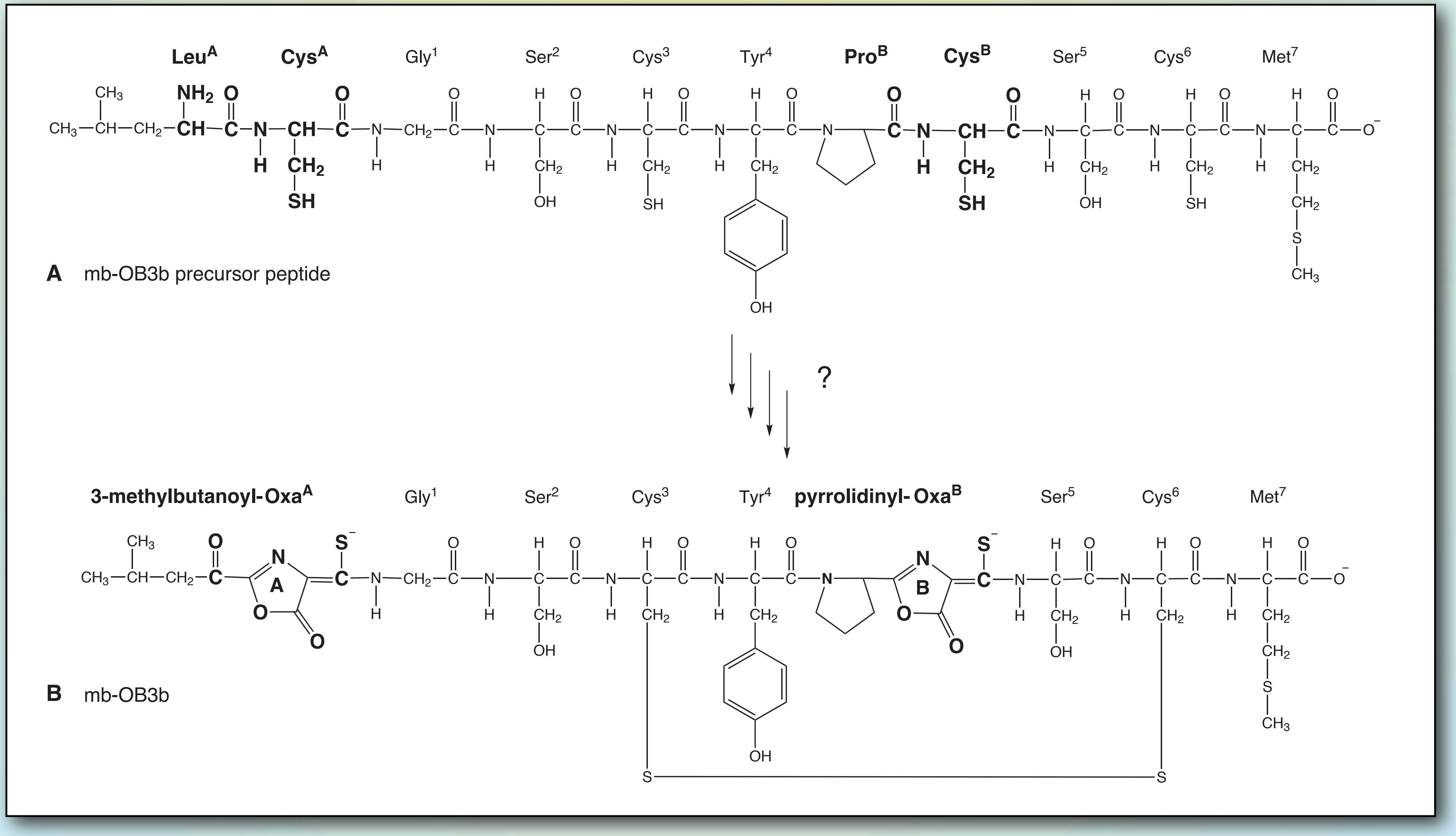

A mb-OB3b precursor peptide

B mb-OB3b

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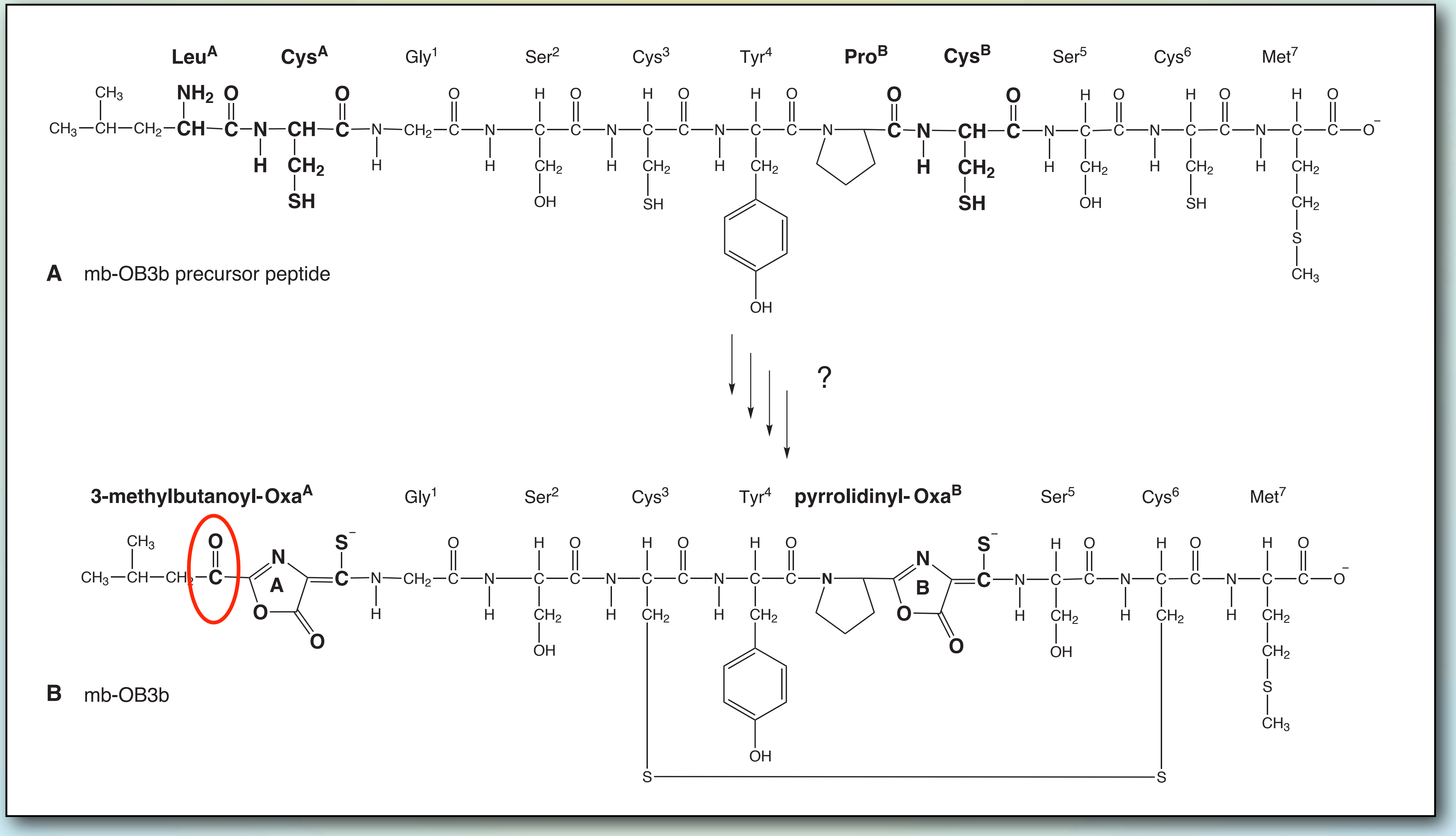

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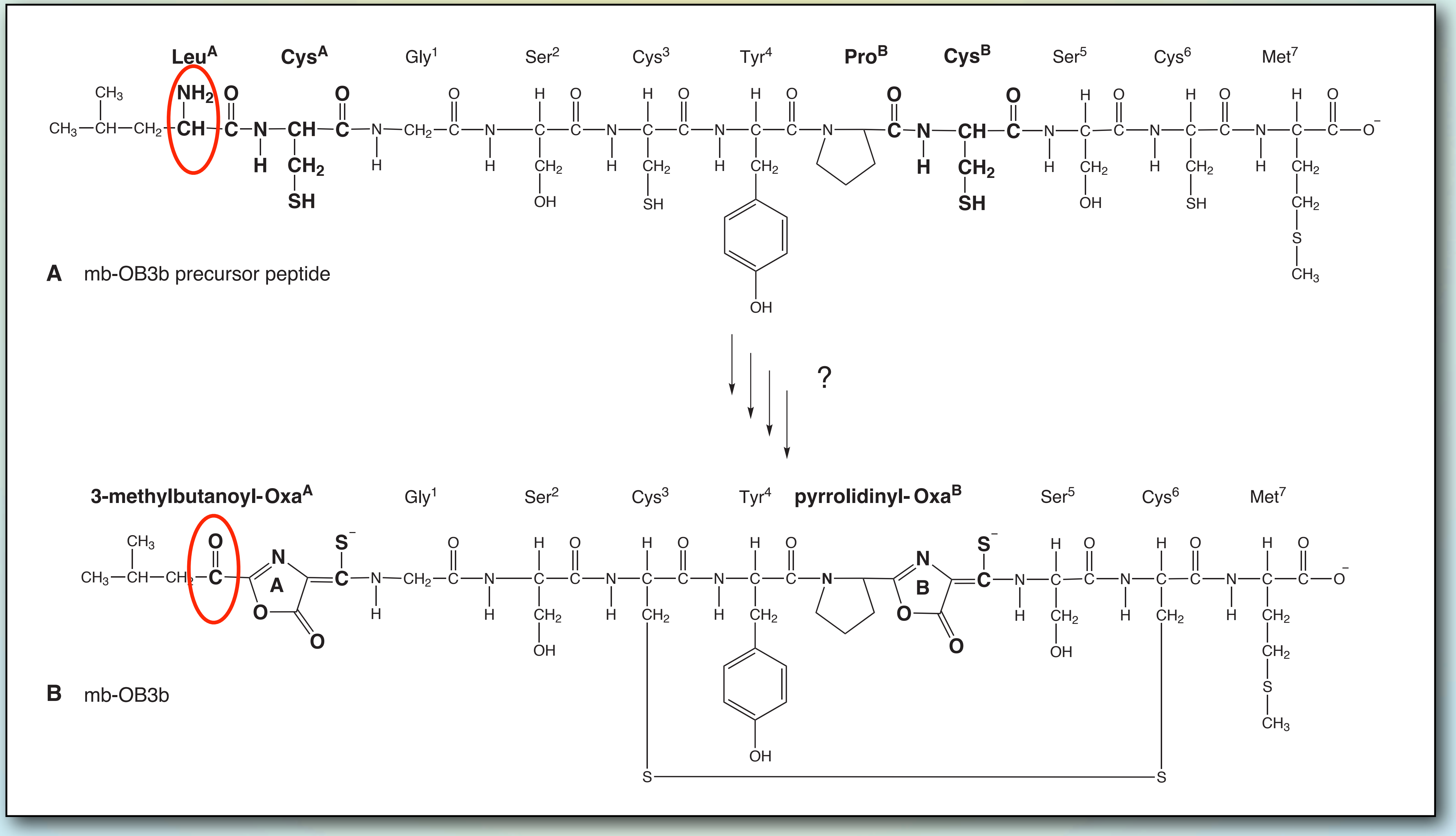

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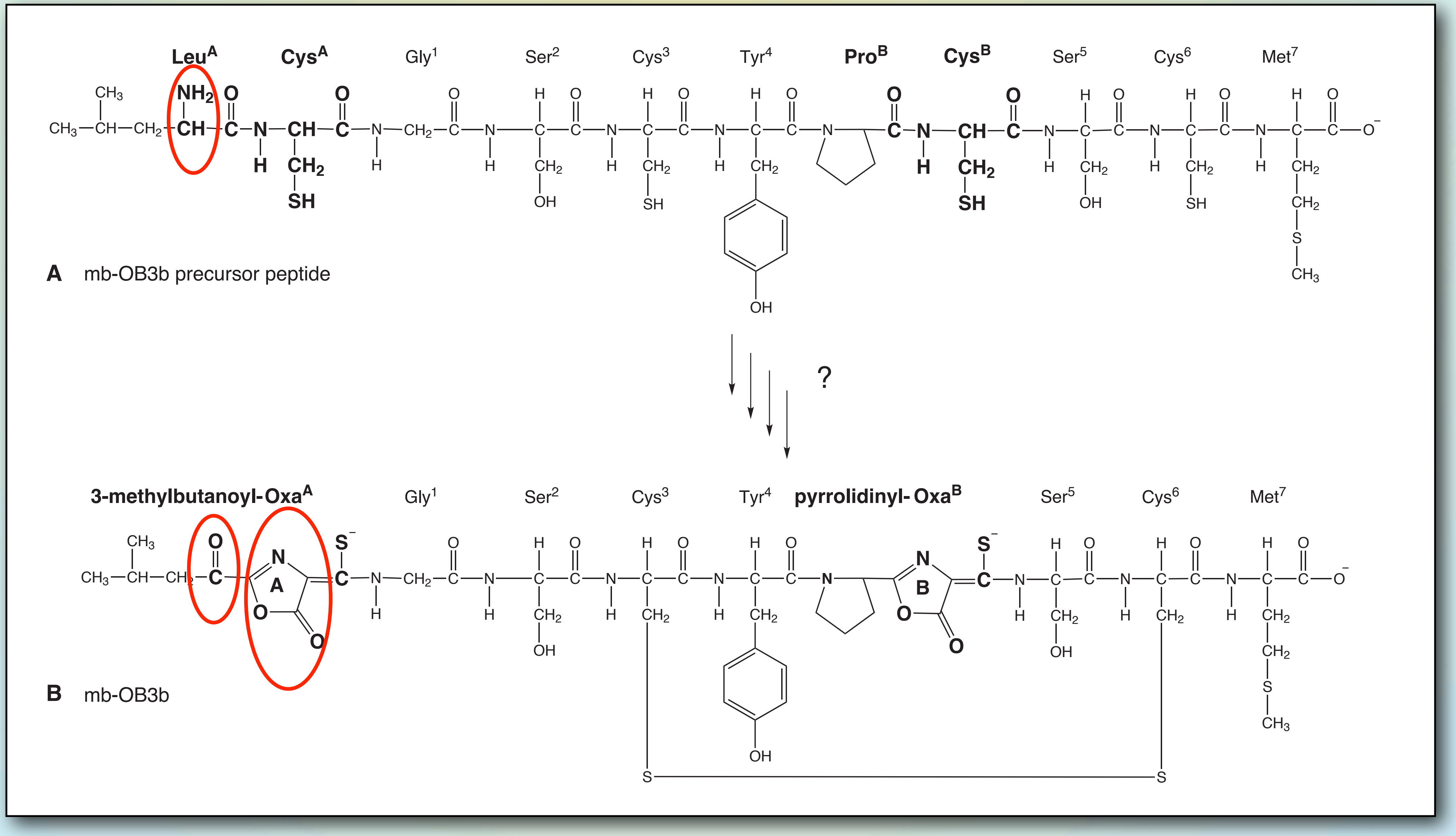

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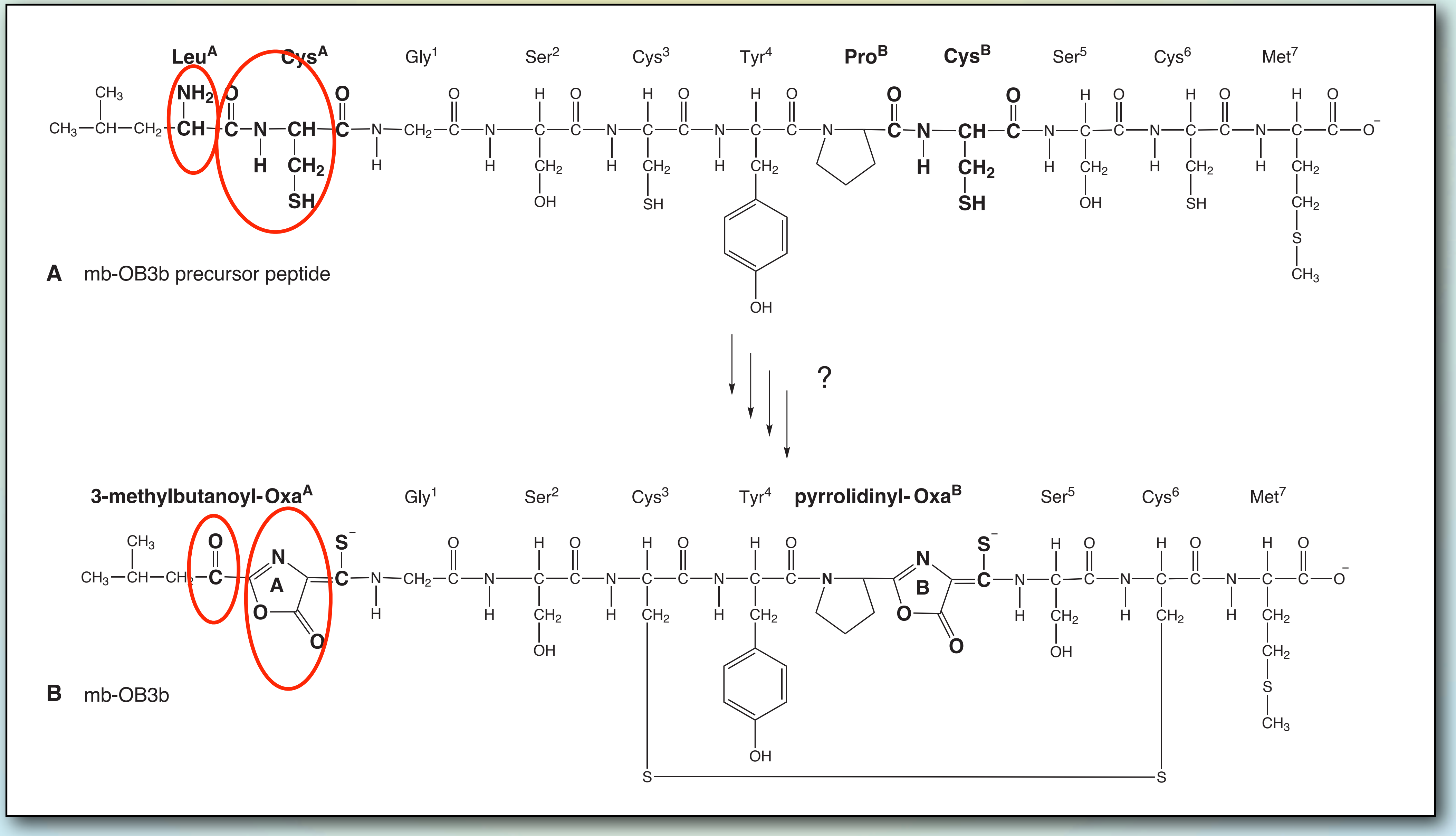

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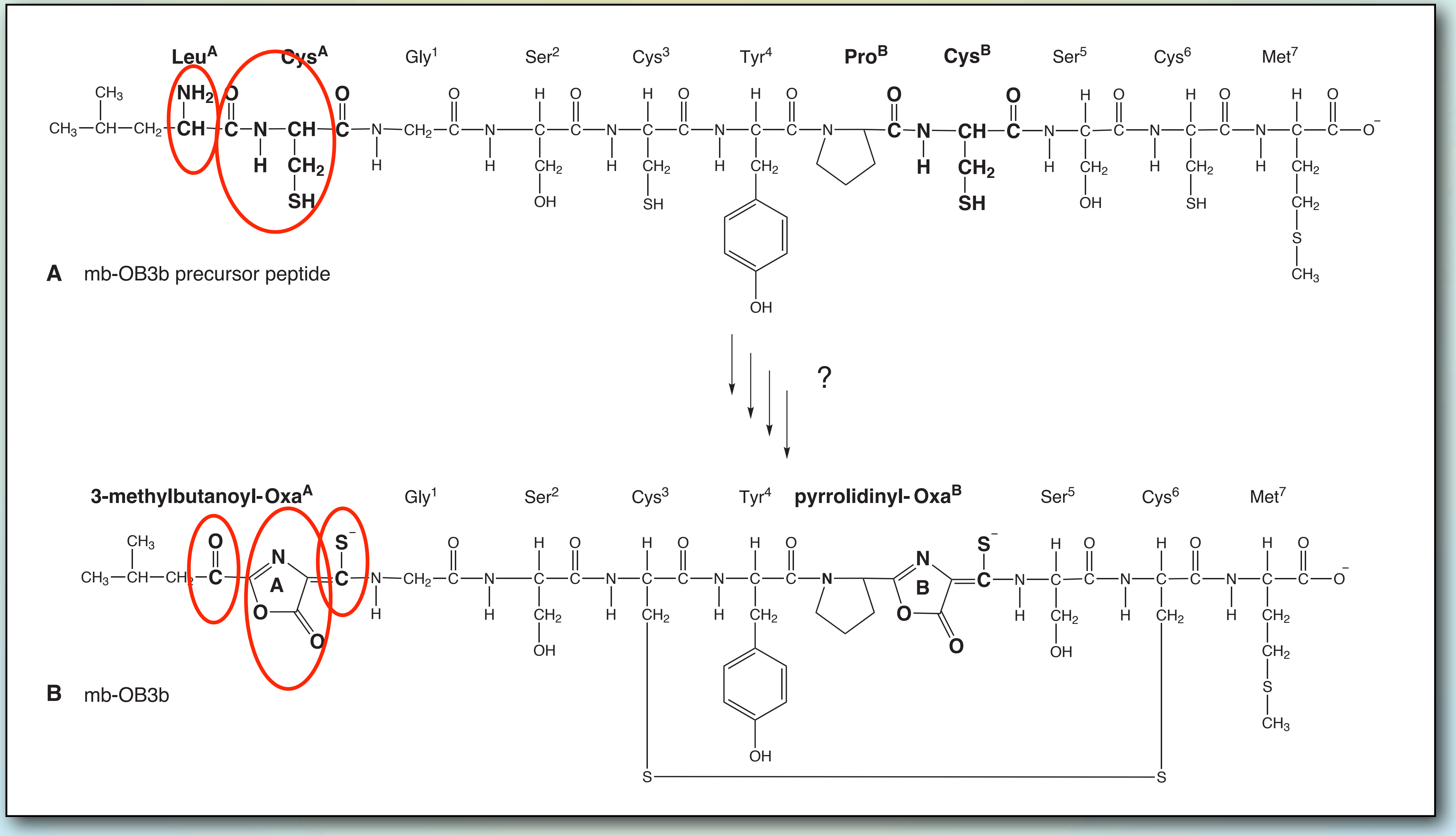

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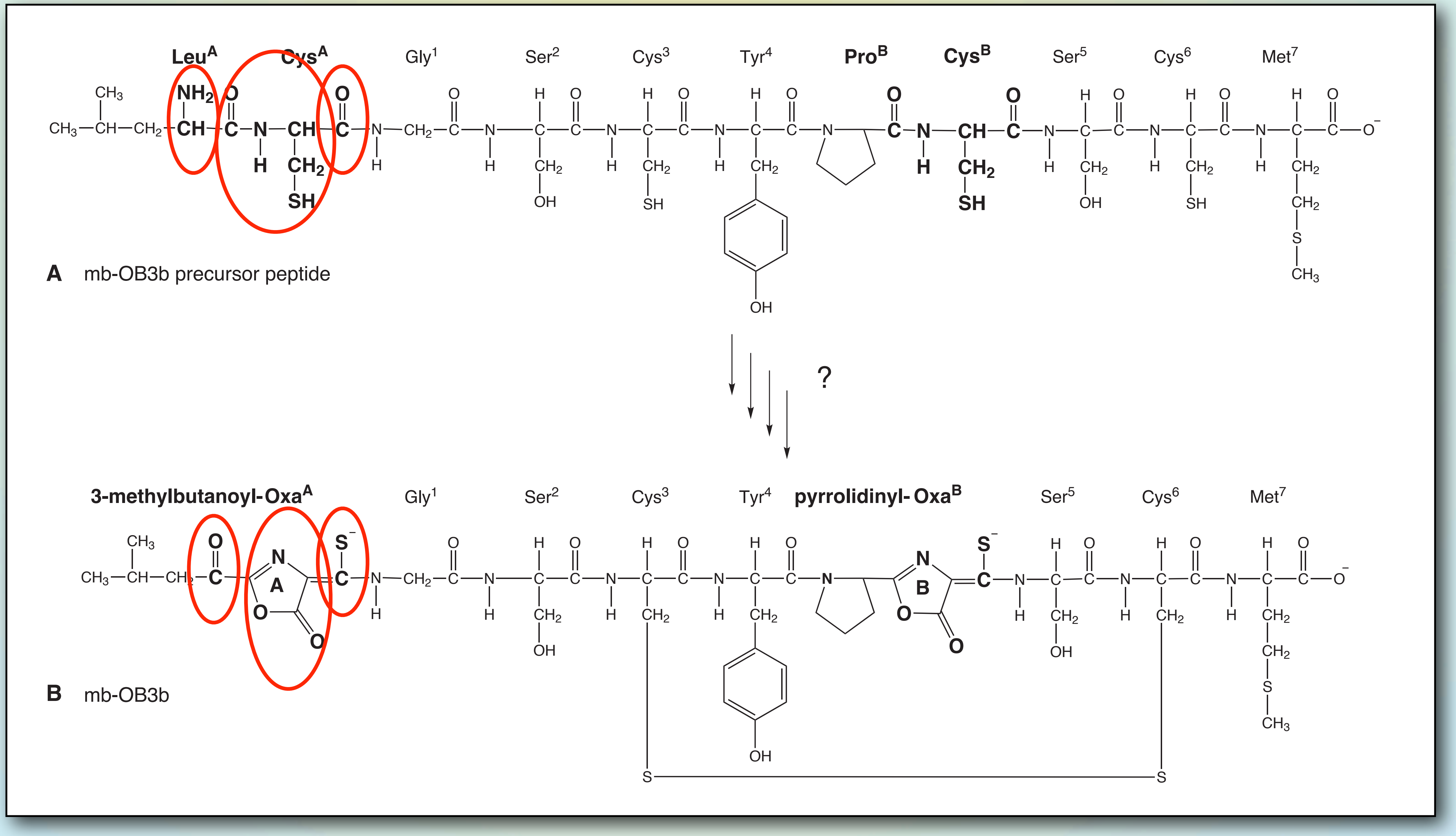

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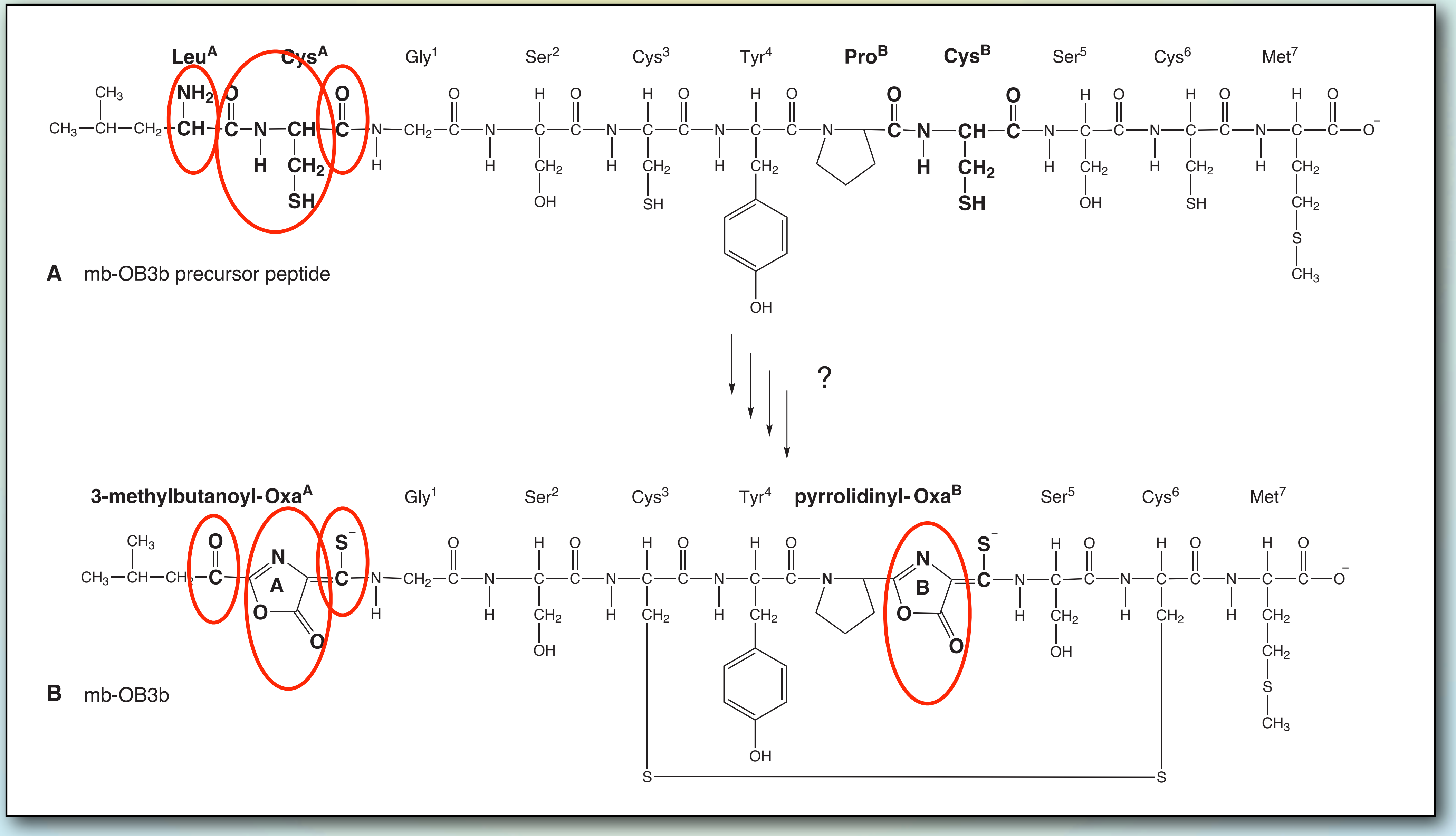

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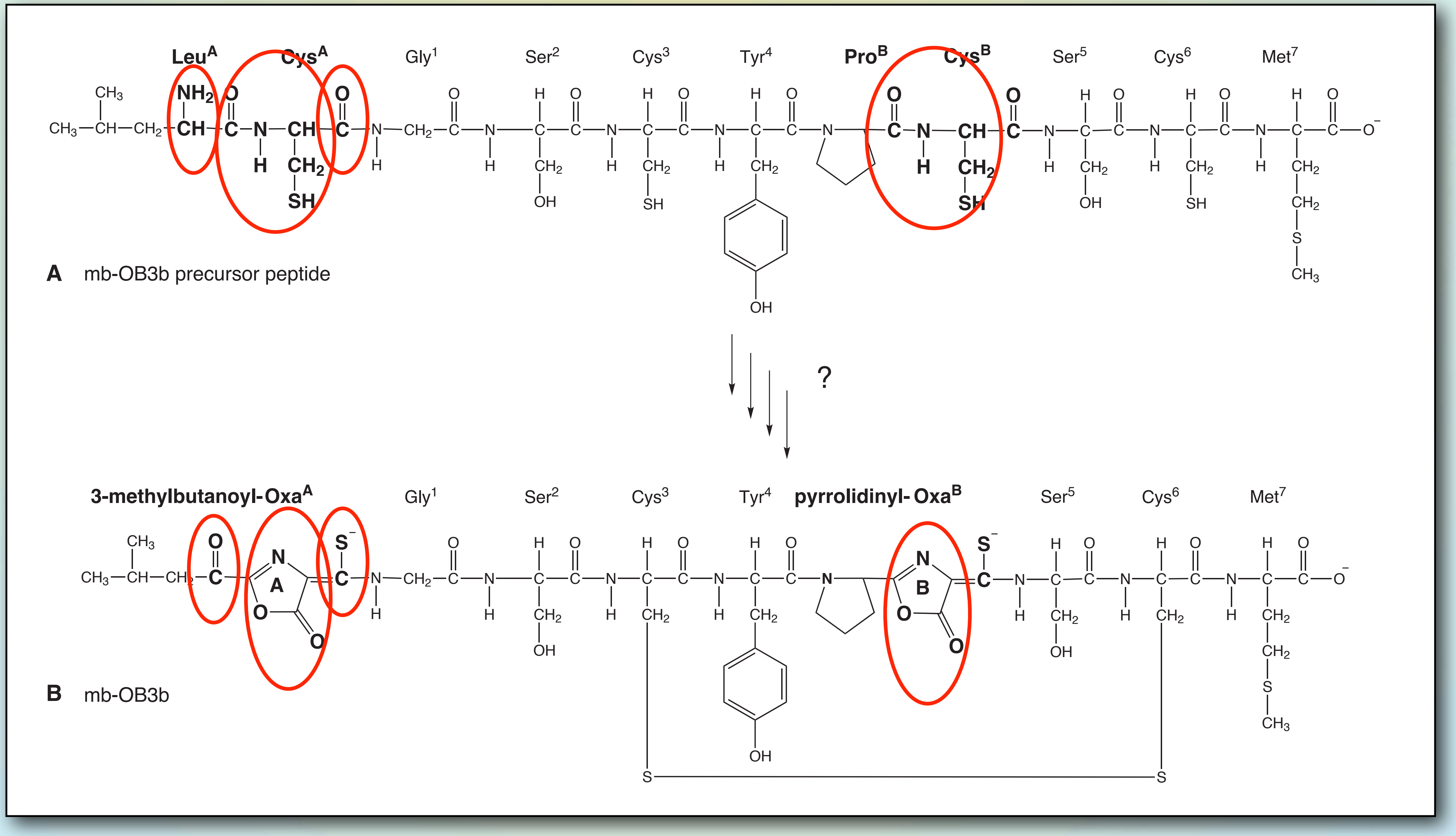

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B mb-OB3b

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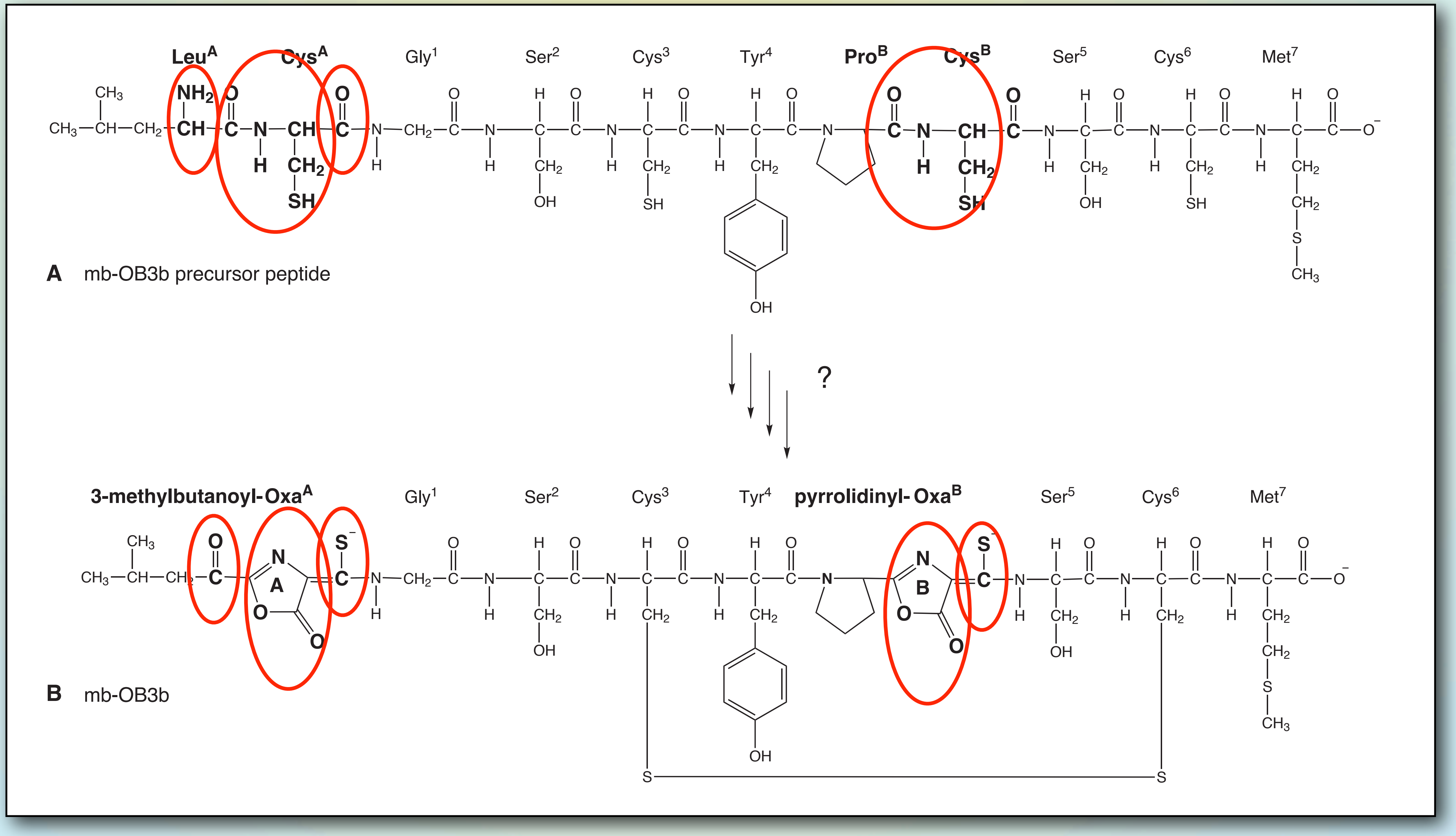

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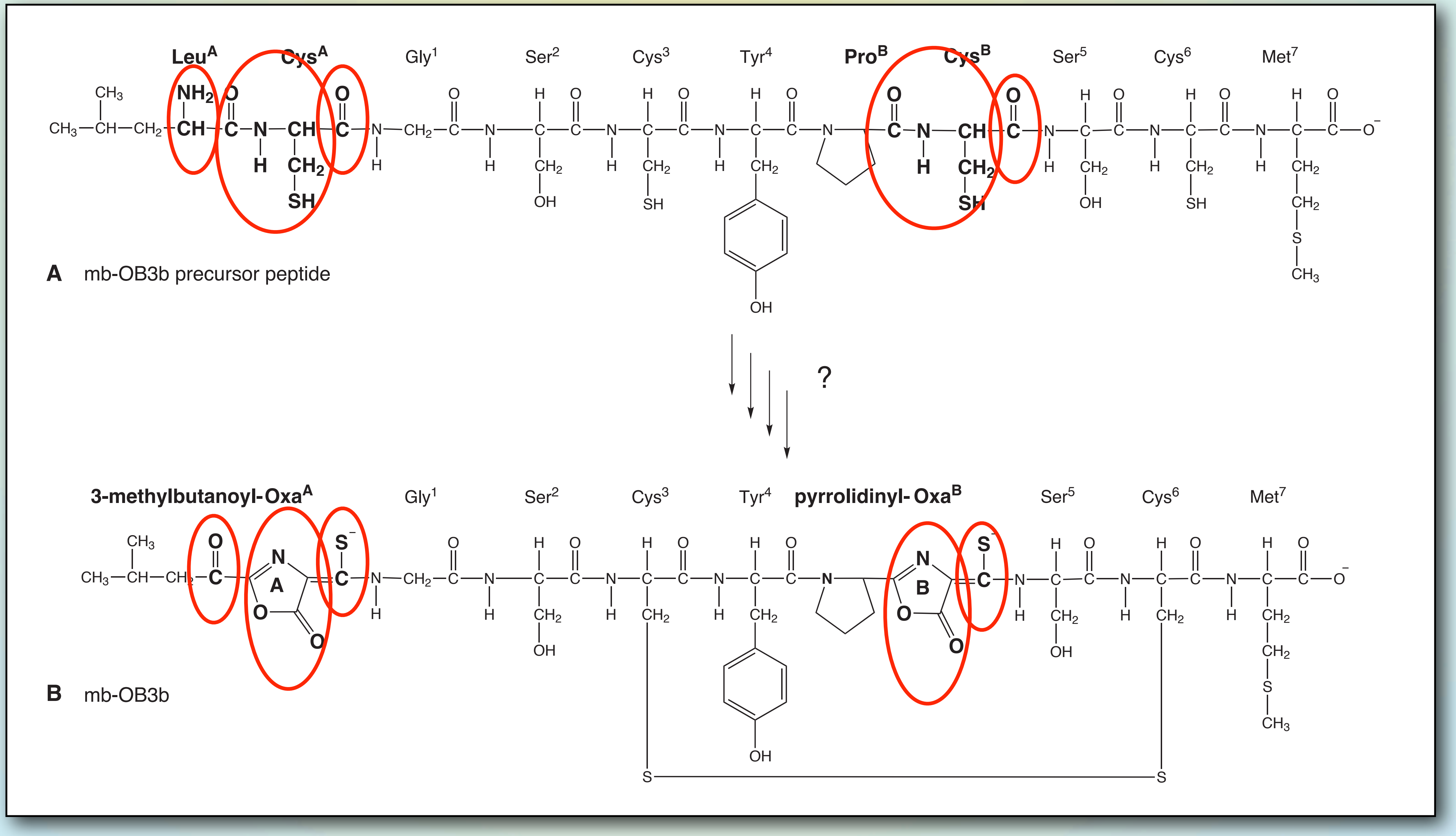

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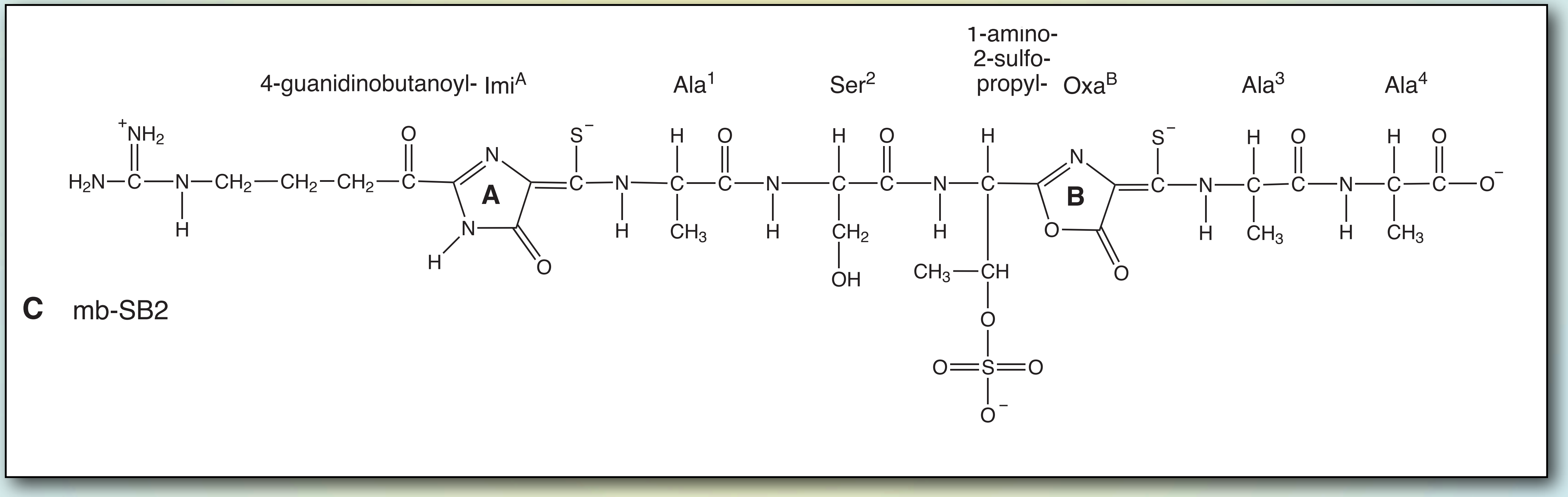

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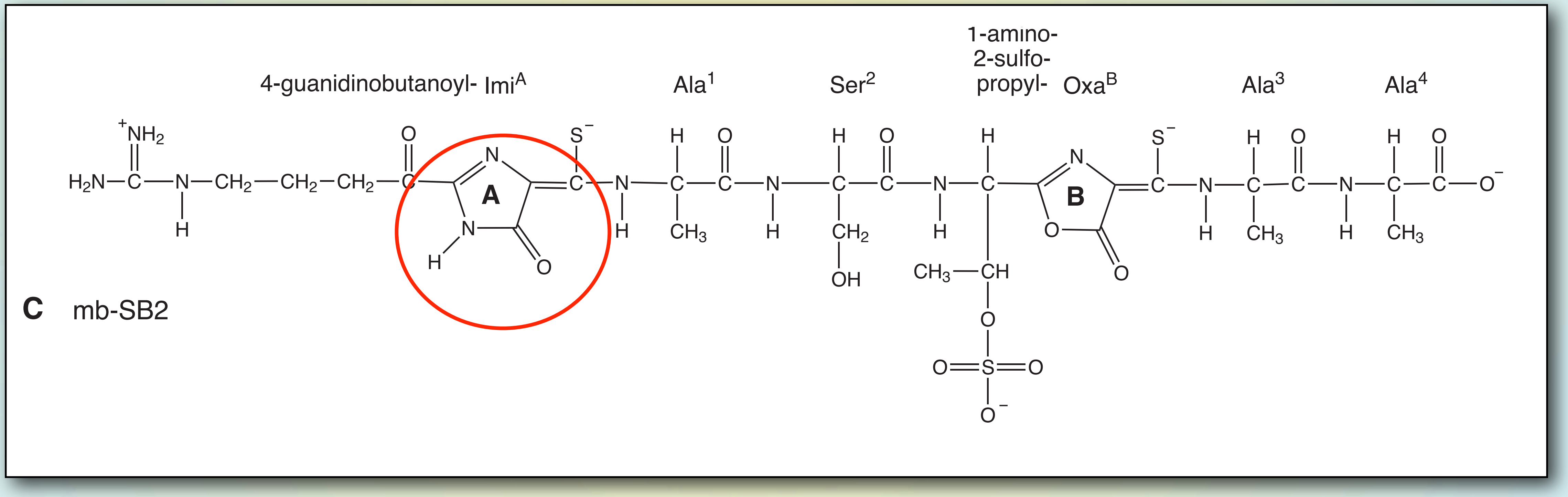

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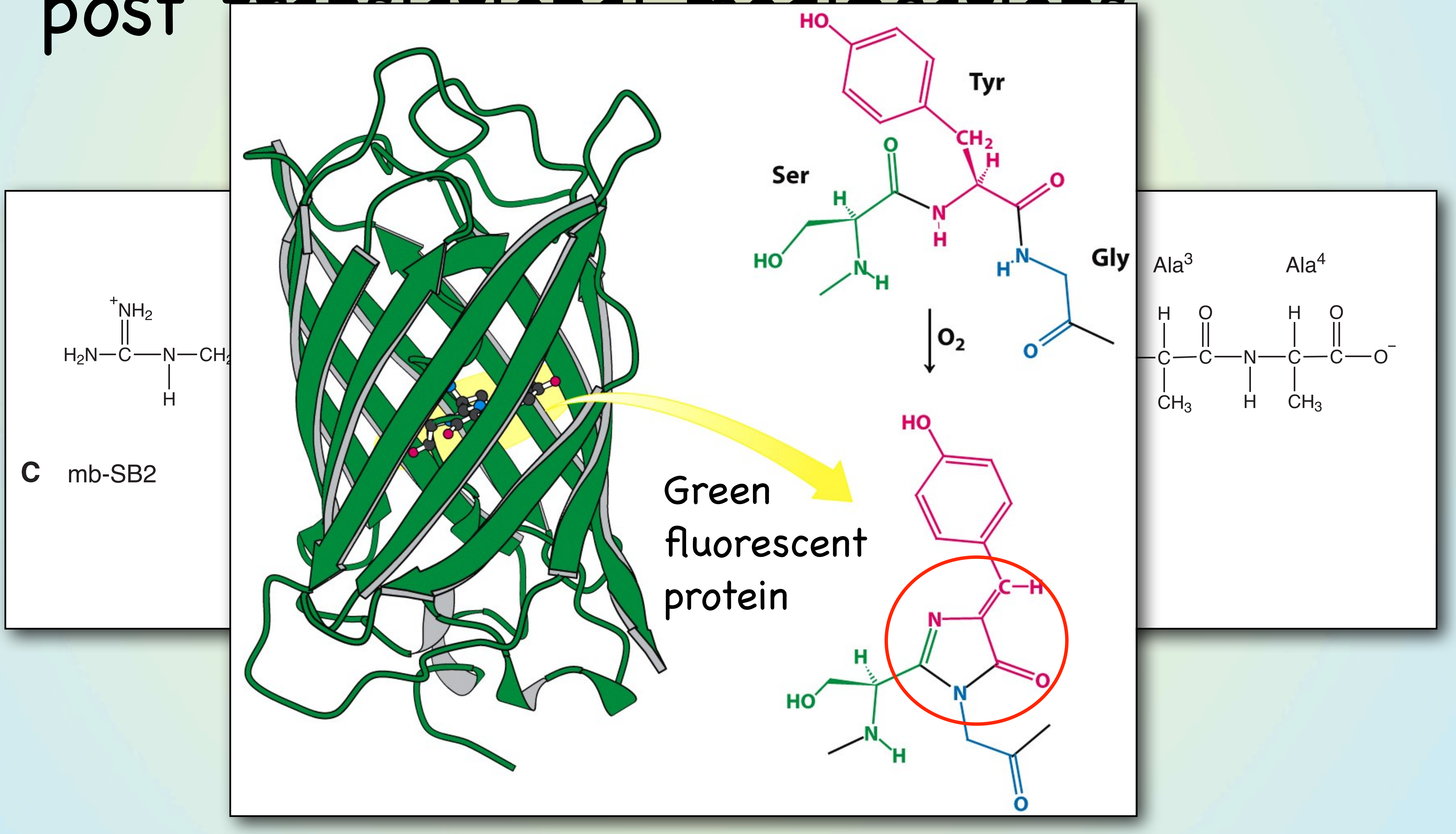

Green fluorescent protein

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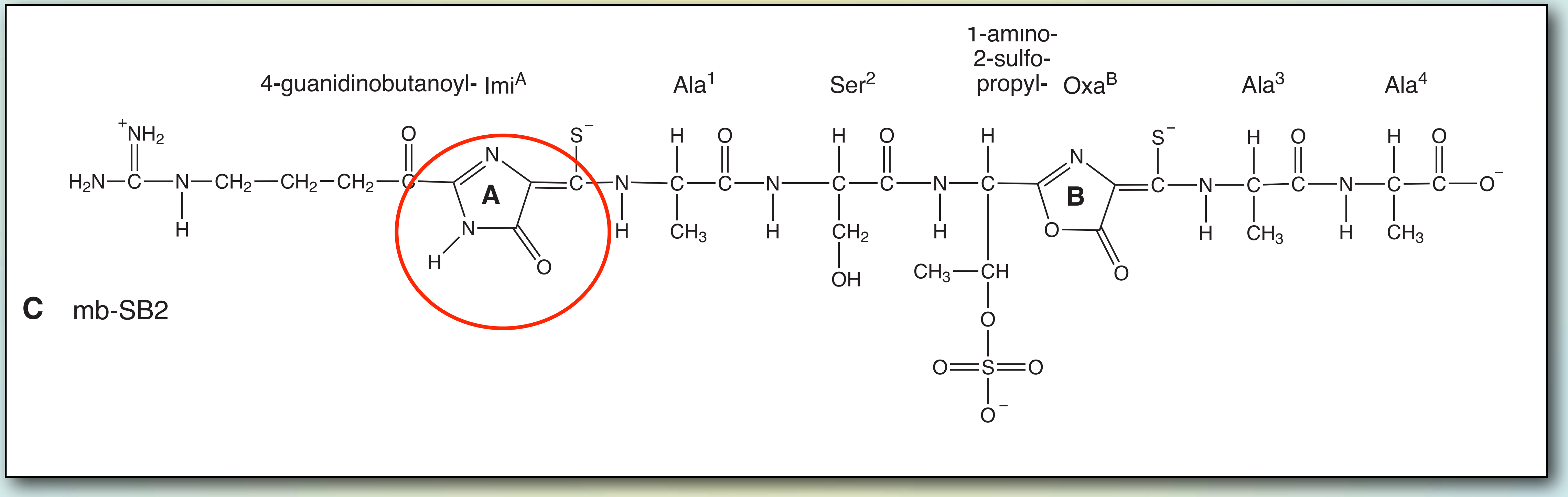

C mb-SB2

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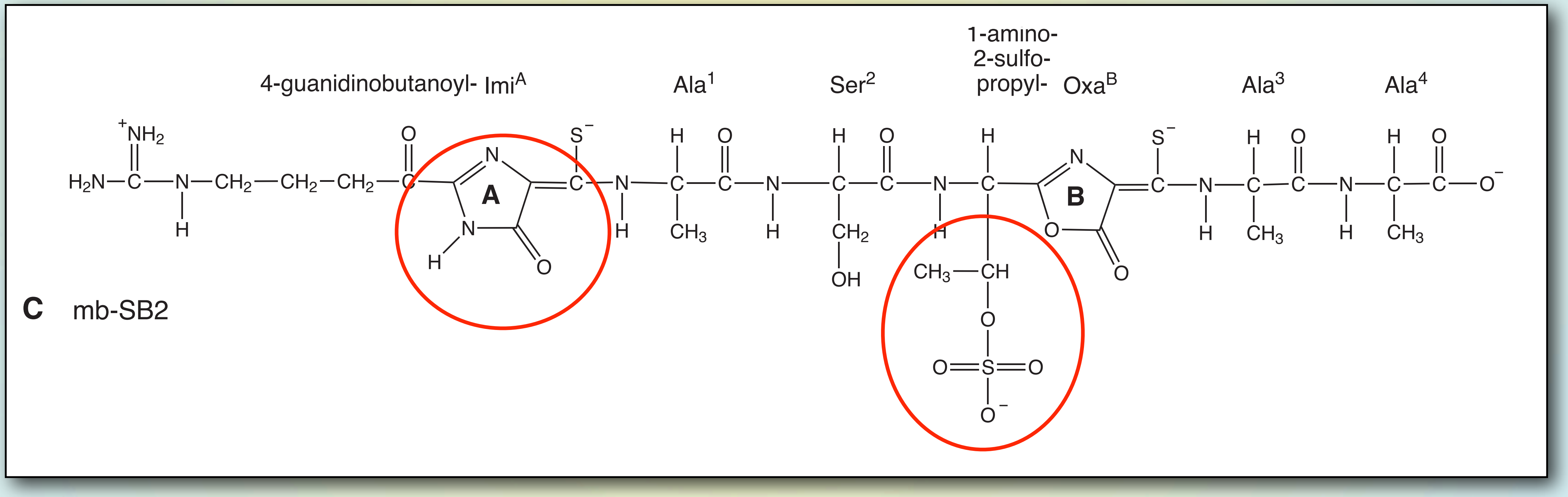

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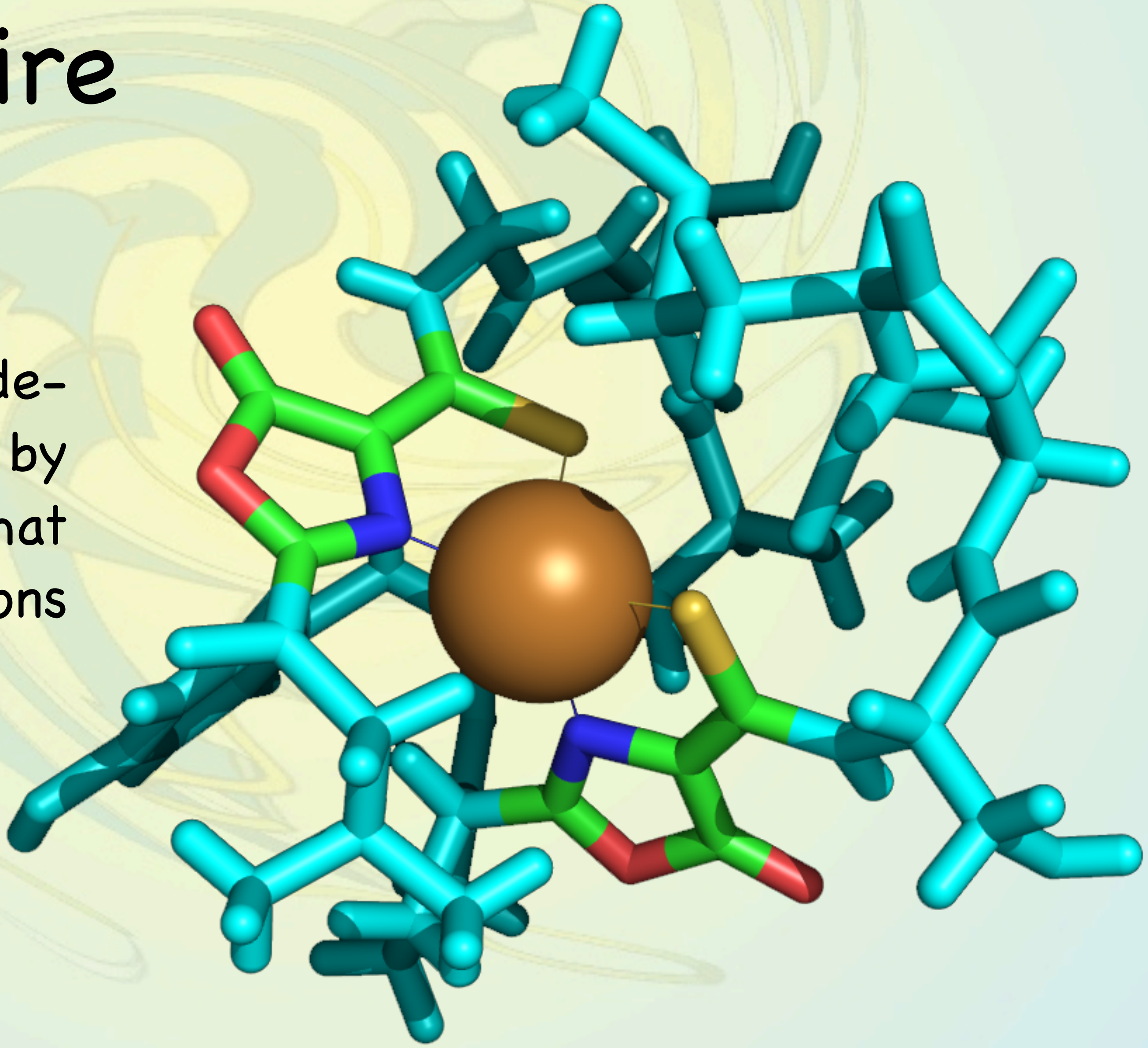

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Next up

- Hemoglobin and Myoglobin.