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.

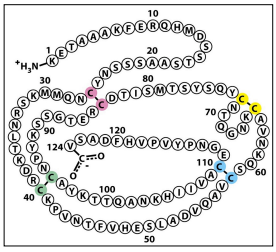
Protein Folding

- 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

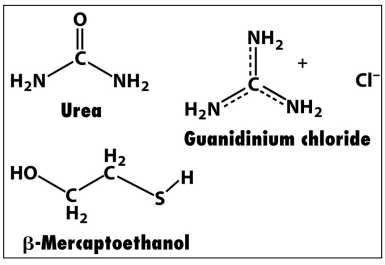
- Anfinsen's Experiment



Bovine Ribonuclease A

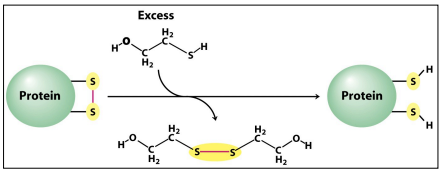
Protein Folding

- Anfinsen's Experiment



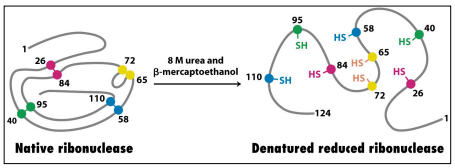
Protein Folding

- Anfinsen's Experiment



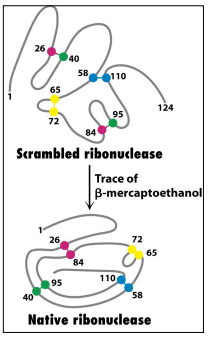
Protein Folding

- Anfinsen's Experiment



Protein Folding

- Anfinsen's Experiment



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

...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. ...

Christian Anfinsen
1972 Nobel Prize in Chemistry

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
ze in Chemistry

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. ...

Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein Folding

- The primary structure determines the other levels of structure.

... 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

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

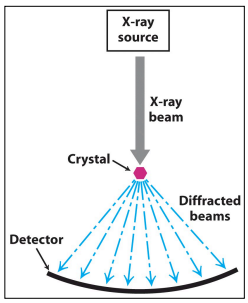
Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein 3-Dimensional Structures

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

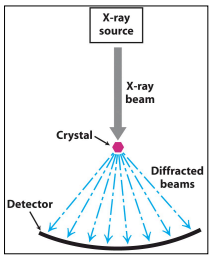
Protein 3-Dimensional Structures

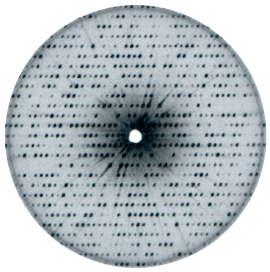
- X-ray crystallography (Section 3.6)



Protein 3-Dimensional Structures

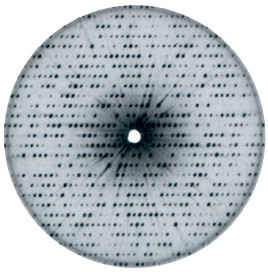
- X-ray crystallography (Section 3.6)

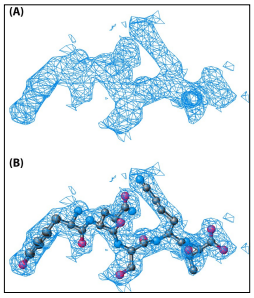




Protein 3-Dimensional Structures

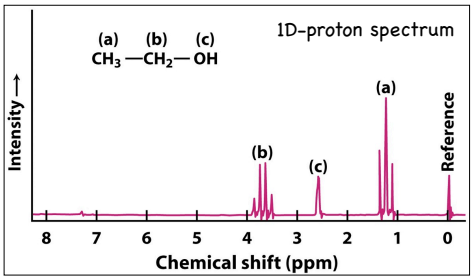
- X-ray crystallography (Section 3.6)





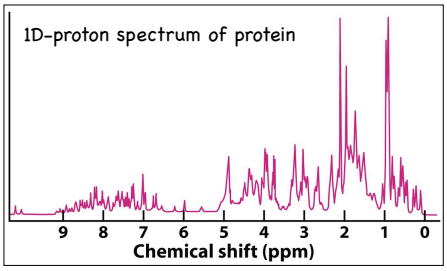
Protein 3-Dimensional Structures

- NMR Spectroscopy (Section 3.6)



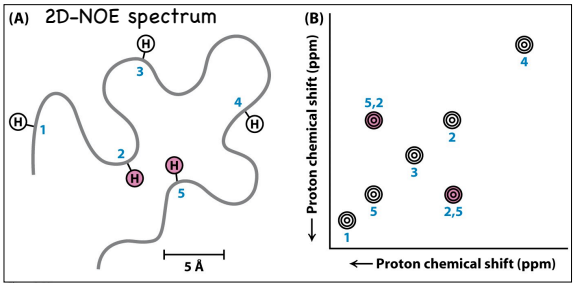
Protein 3-Dimensional Structures

- NMR Spectroscopy (Section 3.6)



Protein 3-Dimensional Structures

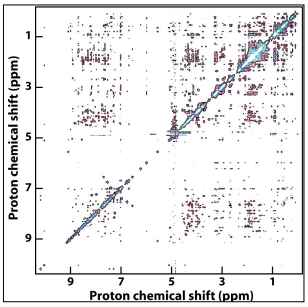
- NMR Spectroscopy (Section 3.6)



Protein 3-Dimensional Structures

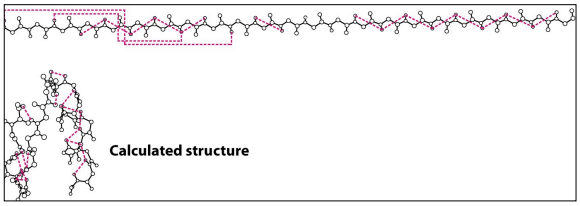
- NMR Spectroscopy (Section 3.6)

2D-NOE spectrum



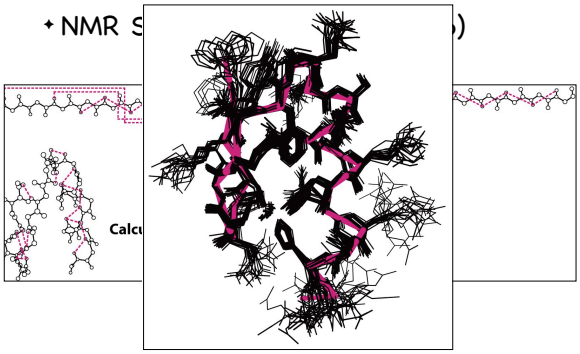
Protein 3-Dimensional Structures

- 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).

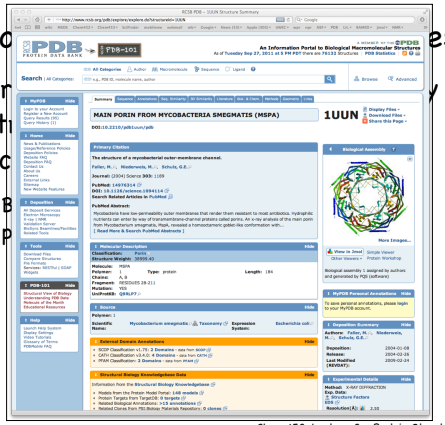
SOURCE: T. E. Creighton, *Proteins: Structures and Molecular Properties,* 2d ed. (W. H. Freeman and Company, 1992), p. 256.

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.

Pro...es

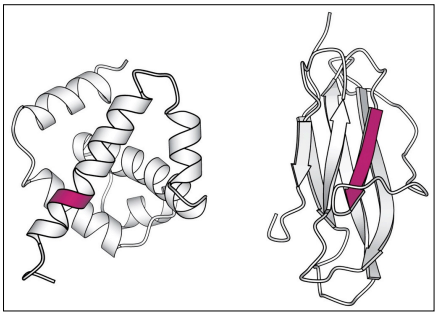
- Pr...
  - st...
  - ac...
  - B...
    p...



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.

Protein 3-Dimensional Structures



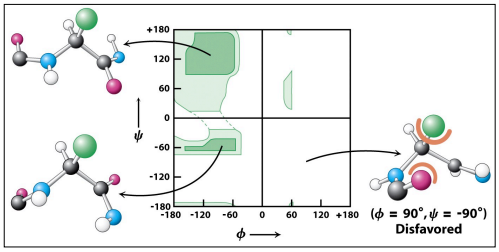
The sequence VDLLKN

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

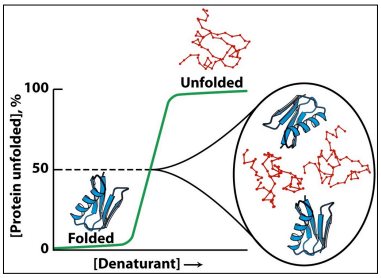
Protein 3-Dimensional Structures

- The Levinthal Paradox



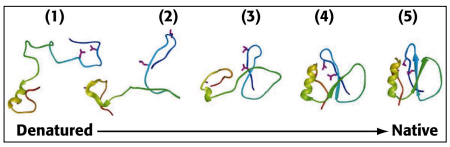
Protein Folding

- Proteins folding is highly cooperative



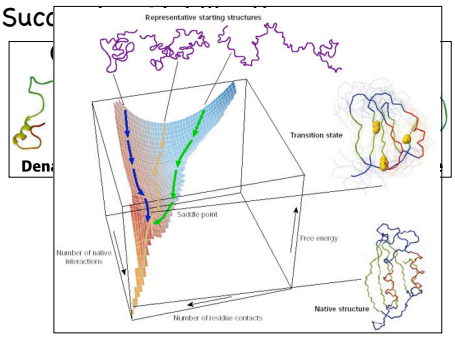
Protein 3-Dimensional Structures

- Successive Stabilization



Protein 3-Dimensional Structures

- Succ



Chem 452, Lecture 2 - Protein Structure 25

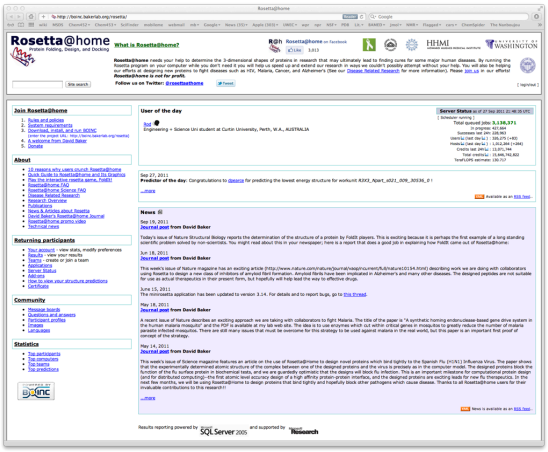
Protein 3-Dimensional Structures

- 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

- Predicting a 3-D structure (tertiary structure) by analyzing the amino aci
  - By
    pr
  - By
    lo
    -

Chem 452, Lecture 2 - Protein Structure 26



Protein 3-Dimensional Structures

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

Protein 3-Dimensional Structures

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

Pr res

- P

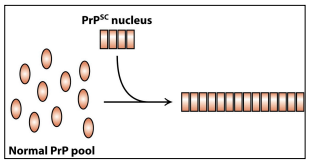
Structure 28

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

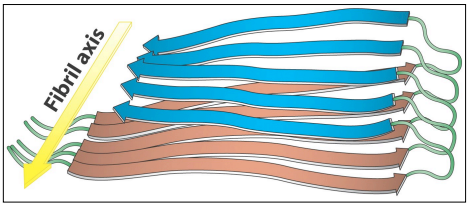
- Prions



Stanley Prusiner
1997 Nobel Prize in Medicine

Protein Misfolding

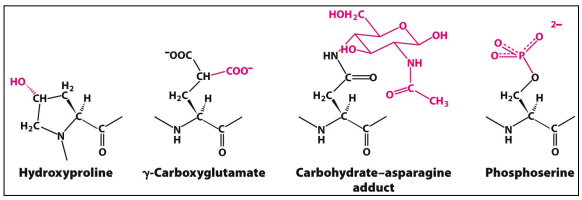
- Alzheimer's Disease



Amyloid β-fibrils

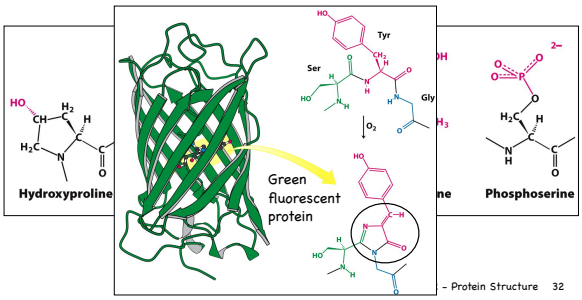
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



Modifications to the Primary Structure

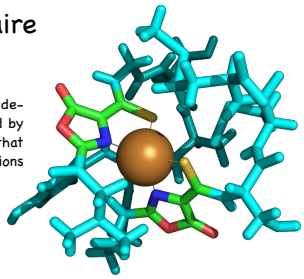
- Many proteins and peptides undergo post translational modifications



Modifications to the Primary

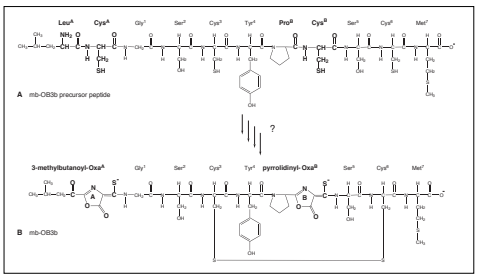
- Some post translational modifications that we have discovered here at UW-Eau Claire

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



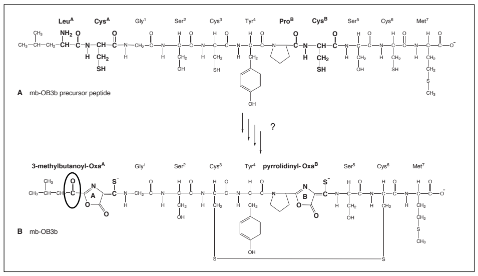
Modifications to the Primary Structure

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



Modifications to the Primary Structure

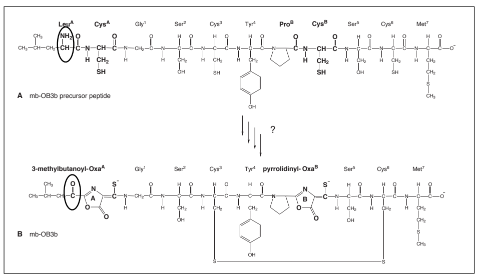
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

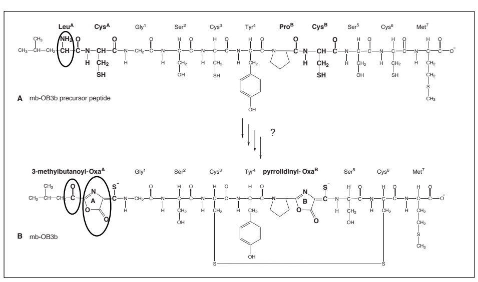
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

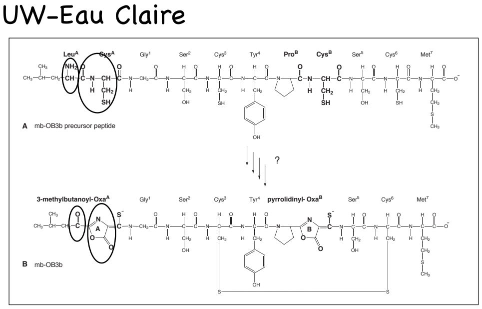
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

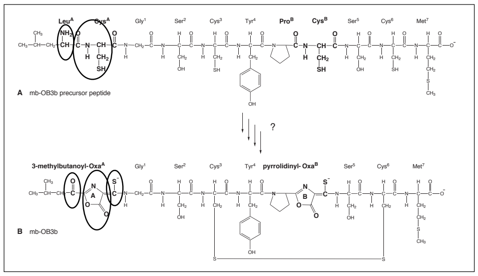
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

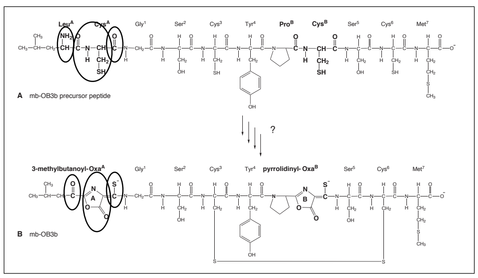
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

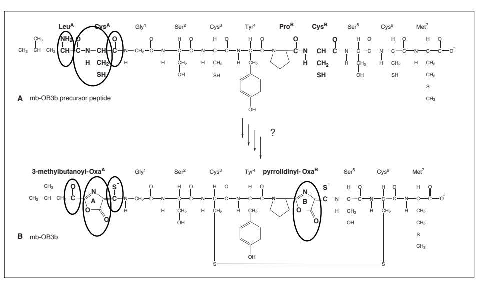
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

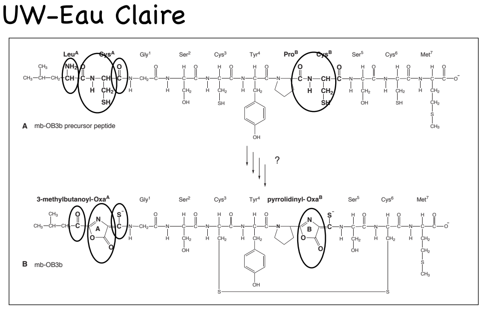
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

Modifications to the Primary Structure

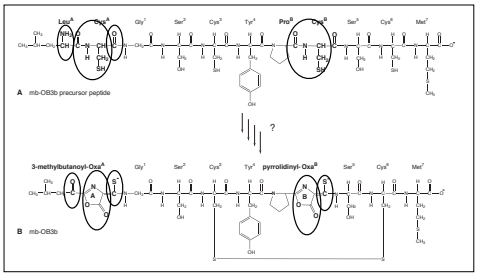
- Some post translational modifications that we have discovered here at UW-Eau Claire



34

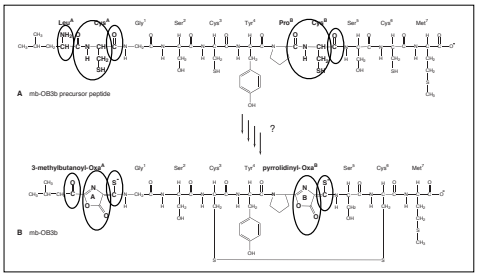
Modifications to the Primary Structure

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



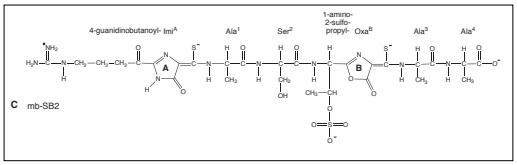
Modifications to the Primary Structure

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



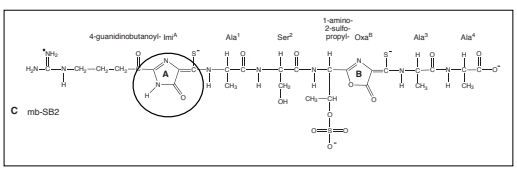
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



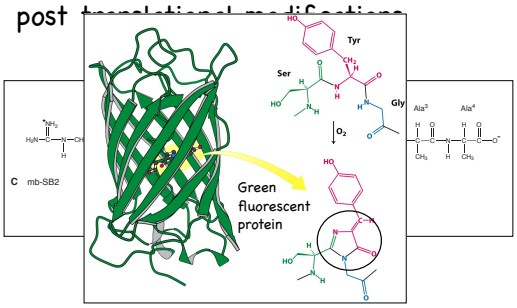
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



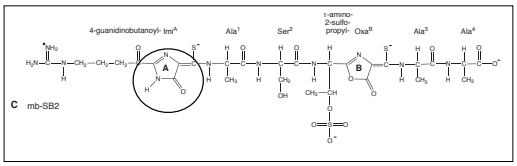
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



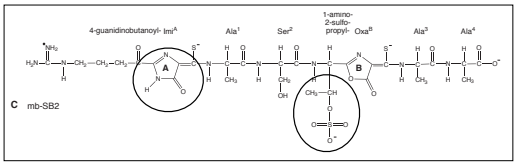
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



Modifications to the Primary Structure

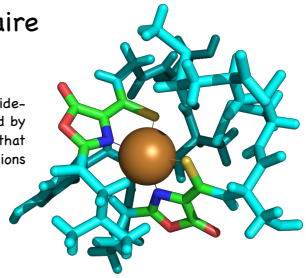
- Many proteins and peptides undergo post translational modifications



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



Next up

- Hemoglobin and Myoglobin.