

# Protein Tyrosine Phosphatase 1B (PTP1B)

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# Introduction

- ◆ PTP1B is a therapeutic target for type 2 diabetes
  - Inhibition of PTP1B can lead to a possible treatment for a diabetes type II
- ◆ PTP1B is a negative regulator of the tyrosine phosphorylation cascade of the insulin signaling pathway

# Background

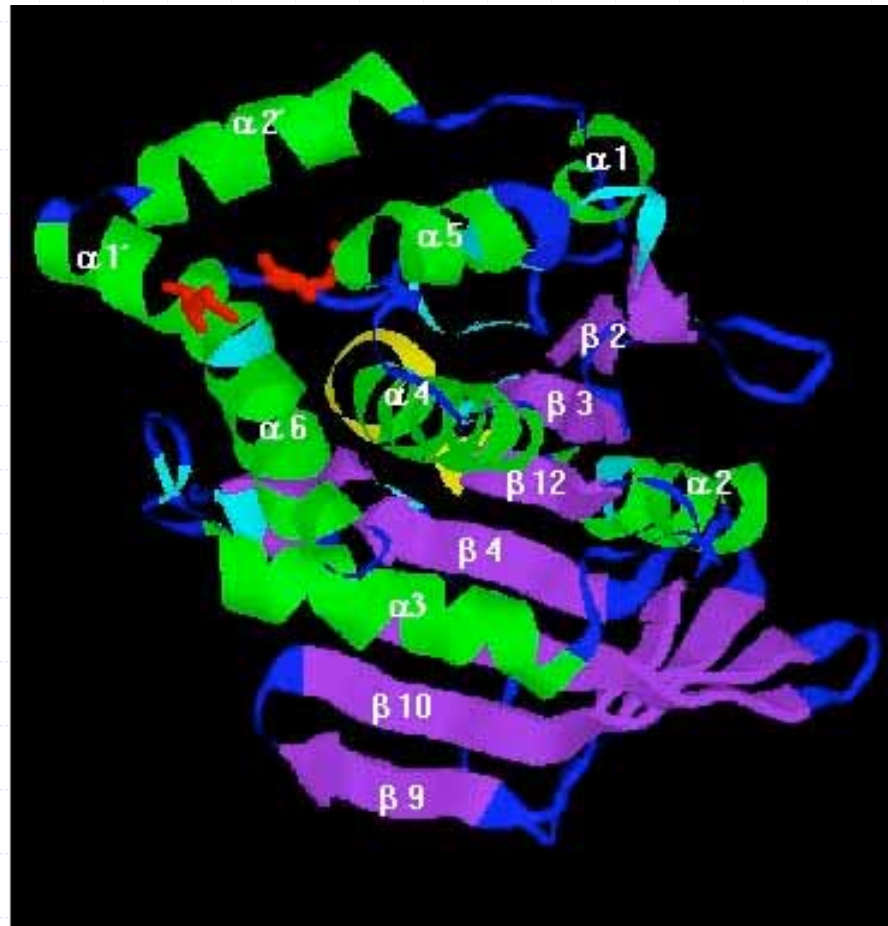
- ◆ PTP family are receptor-like and signal transducing enzymes
  - Catalyzes the dephosphorylation of phosphotyrosine residues
  - Characterized by homologous catalytic domains
- ◆ Large diverse family (>40 members)
  - PTPases signature sequence motif
    - ◆ (I/V)HCXAGXGR(S/T)G

# PTP1B (1SUG)

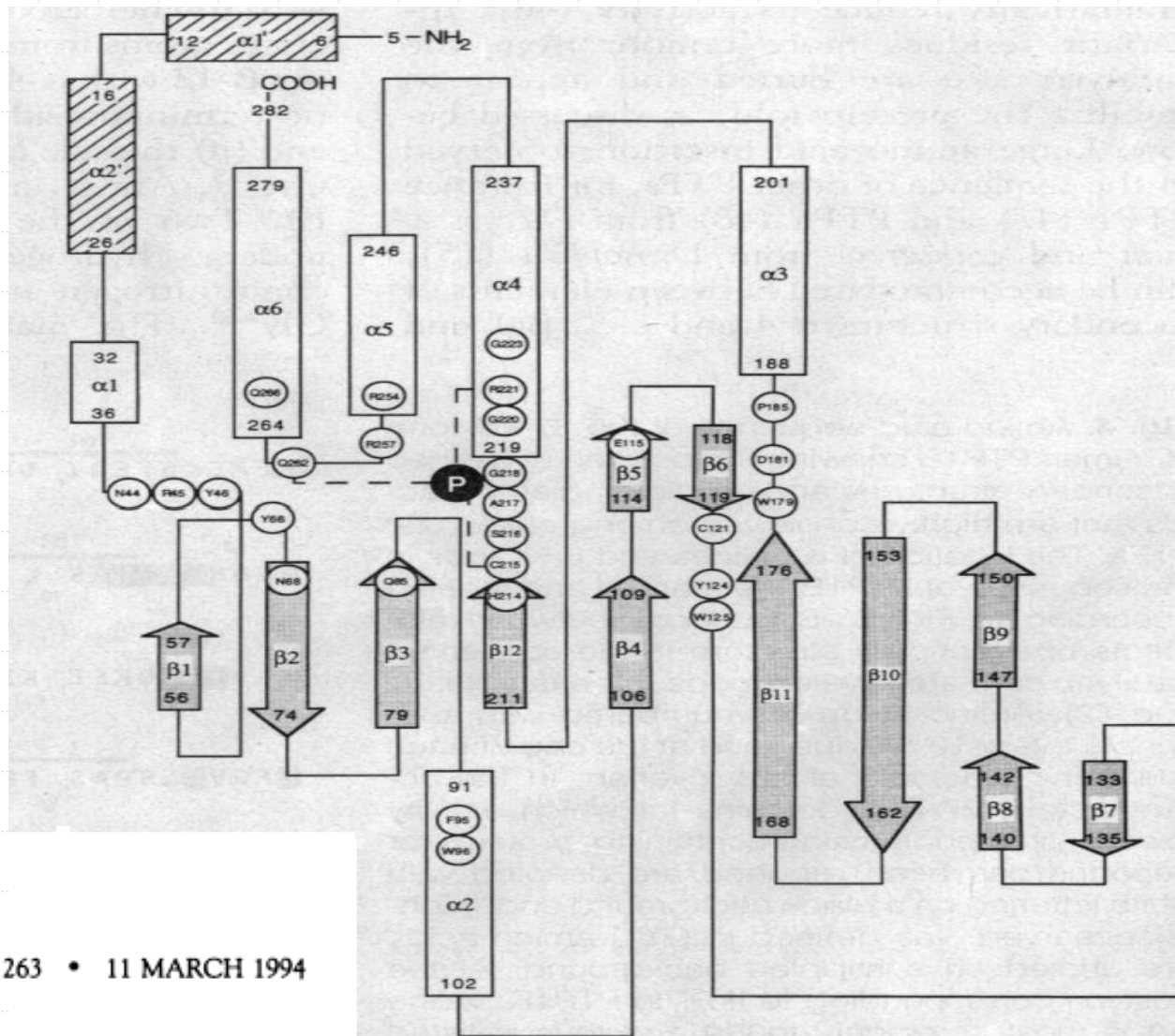
- ◆ 1.95 angstroms
- ◆ 321 residues
- ◆ 0.188 R-factor
- ◆ 0.203 R-free
- ◆ 251 water molecules
- ◆ Occupancy of 1.00

# Structure of PTP1B

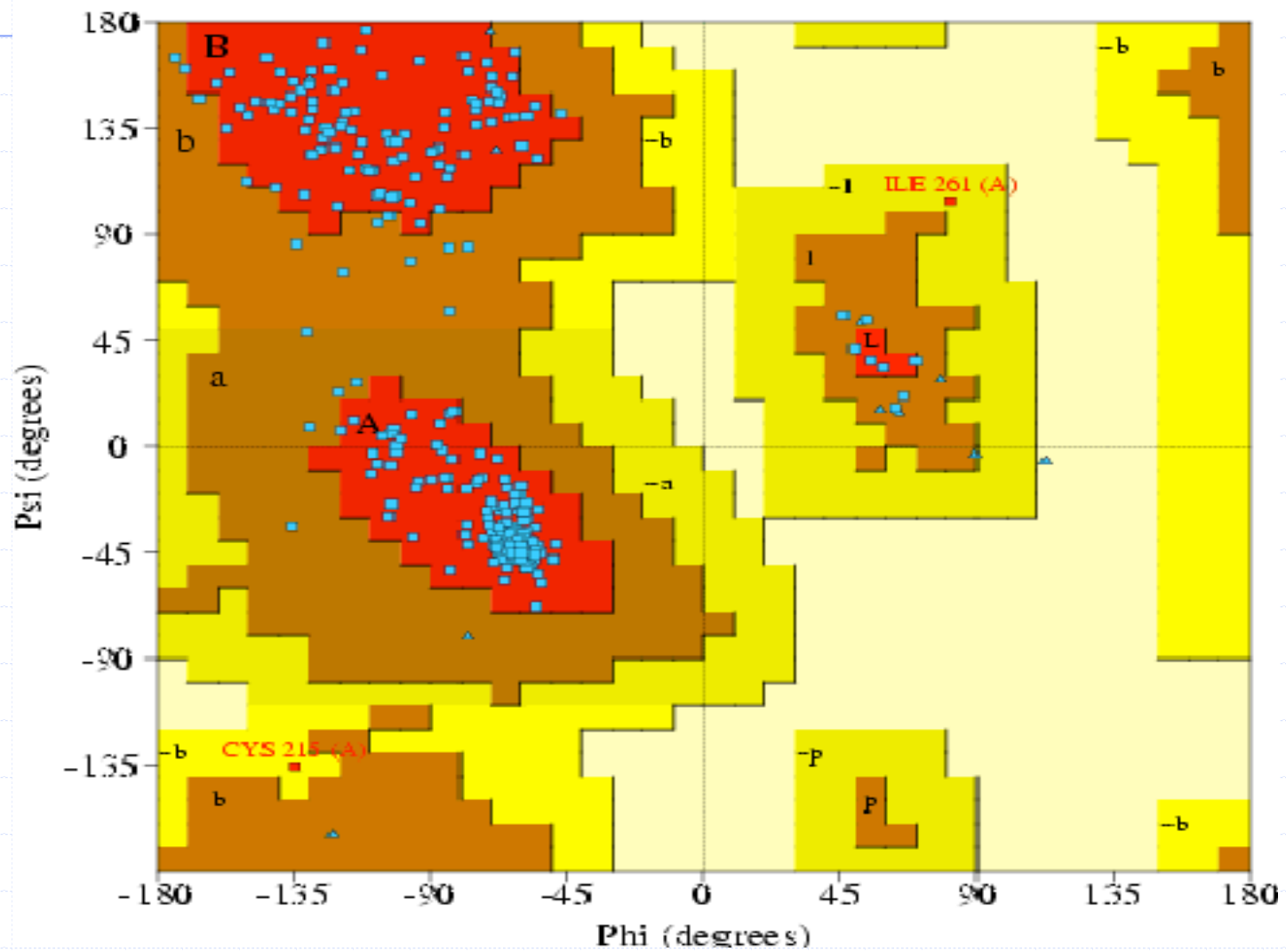
- ◆ 37 kD protein
- ◆ 8 alpha helices, 12 beta sheets
- ◆ 10 strand mixed beta sheet



# Topology Diagram of PTP1B

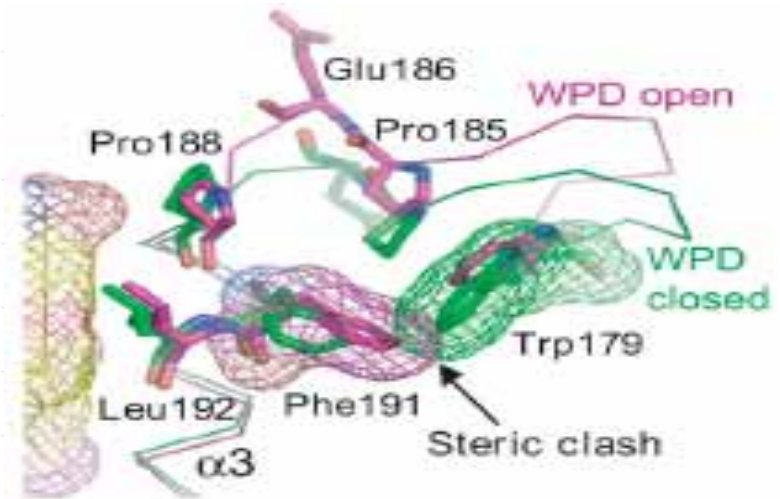
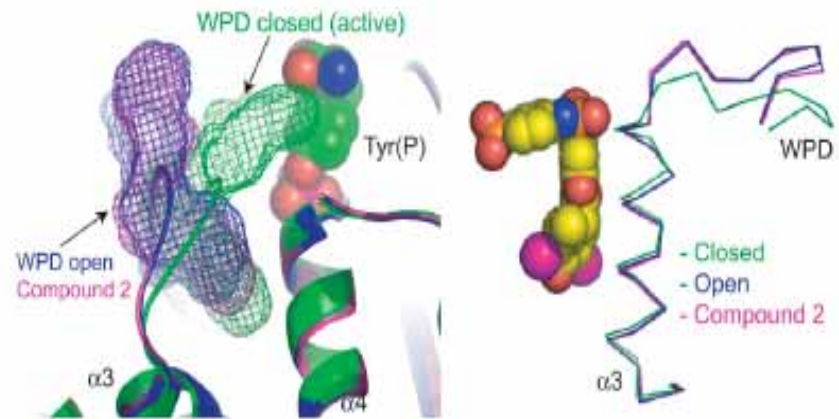


# Ramachandran Plot



# WPD loop (Trp179,Pro180,Asp181)

- ◆ PTP1B exists in open and closed conformations
- ◆ Open
  - Binding accessible to substrate
- ◆ Closed
  - Closed in presence of active site ligand/substrate

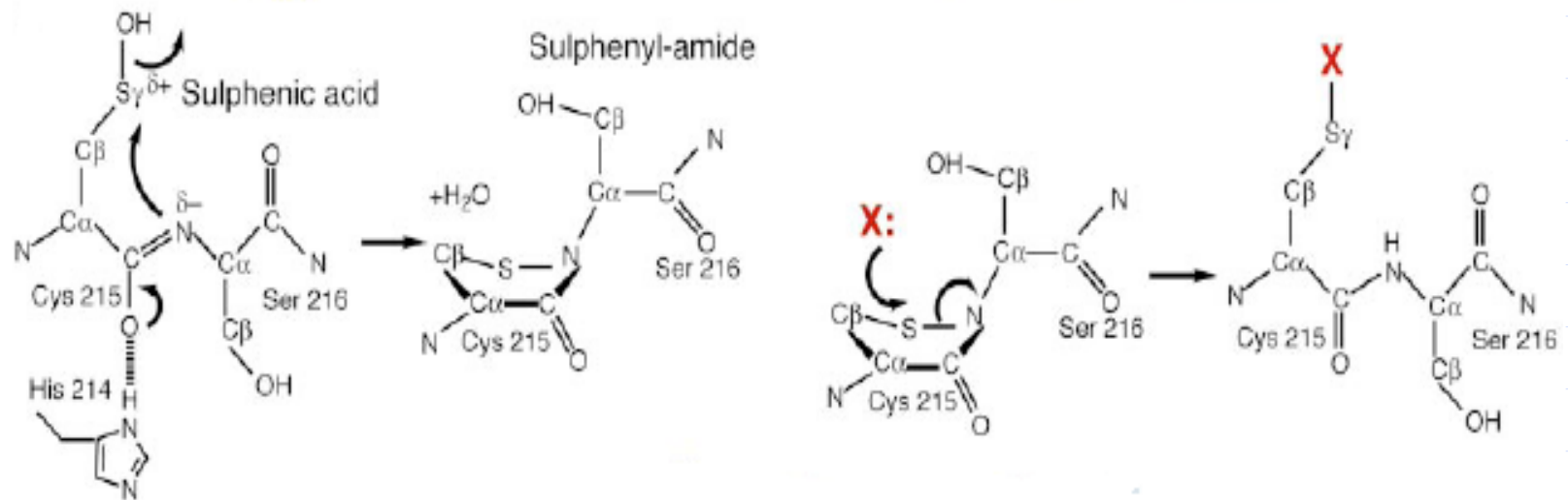




# Sulphenyl-amide Intermediate

- ◆ Sulphenic acid intermediate produced in response to PTP1B oxidation
- ◆ The sulfur atom of the catalytic Cys is covalently linked to the main chain N of an adjacent residue
- ◆ Conformational changes in the catalytic site
  - Inhibits substrate binding
    - ◆ Protects the active site Cys residue from irreversible oxidation to sulphonic acid
    - ◆ Permits redox regulation of the enzyme by promoting its reversible reduction by thiols

# Mechanism for generating the sulphenyl-amide bond



- ◆ Oxidation of Cys215 to sulphenic acid
- ◆ Nucleophilic attack of the backbone nitrogen of Ser216

# Oxidative States of catalytic Cys

