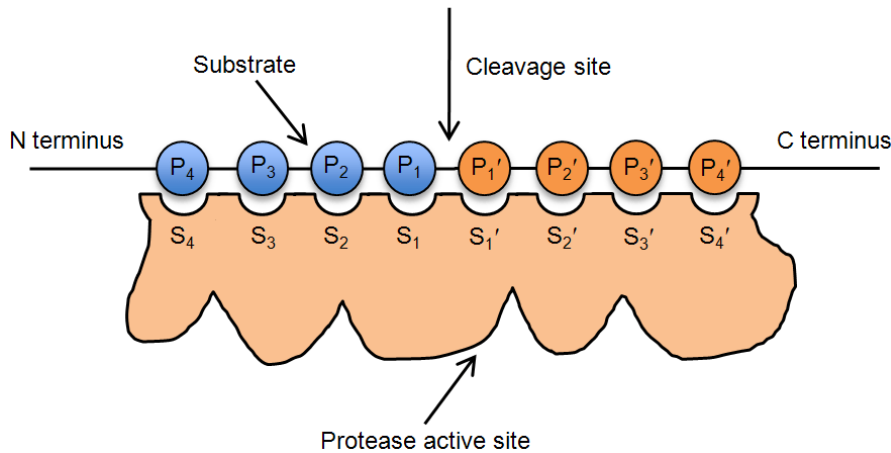


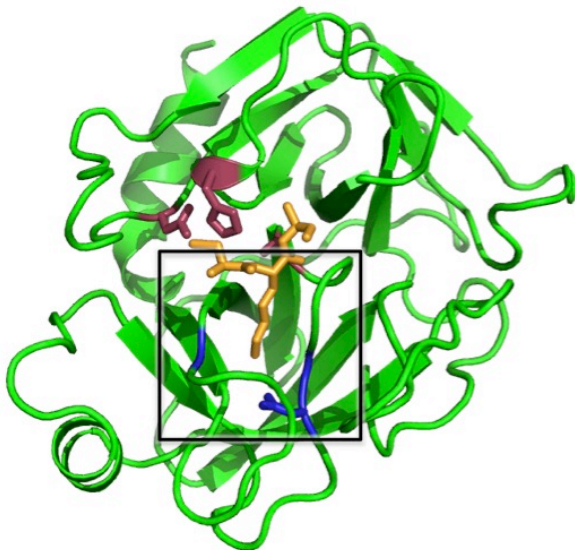
## Serine Proteases Substrate Specificity

Proteases preferentially hydrolyze the peptide bonds of polypeptide substrates depending on the amino acids preceding and/or following the cleavage site. This specificity for the substrate is due to the favorable binding interaction of the substrate amino acid side chain with residues that form the binding site of the serine protease. The protease binding sites (labeled  $S_1$ ,  $S_1'$ , etc) are chemical and spatial complements of the substrate amino acid (labeled  $P_1$ ,  $P_1'$ , etc).



from <https://prosper.erc.monash.edu.au/methodology.html>

The substrate residue N-terminal to the cleavage site ( $P_1$ ) largely determines the specificity of serine proteases.  $P_1$  binds  $S_1$ , which is called the specificity pocket; its interactions were found early on to be a major determinant of the substrate specificity for trypsin, chymotrypsin and elastase.  $S_1$  is near the catalytic triad (the region boxed below) and is made of protease residues that interact with the  $P_1$  residue. The ribbon diagram below is for trypsin, which is structurally very similar to chymotrypsin discussed in lecture. The view is slightly rotated from that shown in lecture for chymotrypsin. The catalytic triad is red and residues of  $S_1$  are blue. The  $P_1$  residue side chain and only part of the main chain of a substrate is shown in gold.



Additional information on serine protease specificity, including an interactive structure viewer, appears on the proteopedia website: [http://www.proteopedia.org/wiki/index.php/Serine\\_Proteases](http://www.proteopedia.org/wiki/index.php/Serine_Proteases)

Below are two schematics to illustrate serine protease specificity and the S<sub>1</sub> pocket for chymotrypsin, trypsin and elastase.

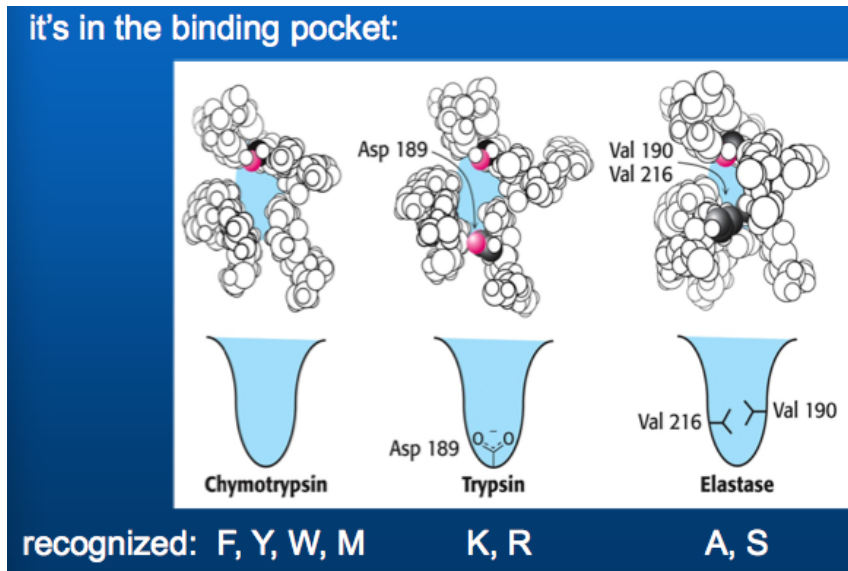
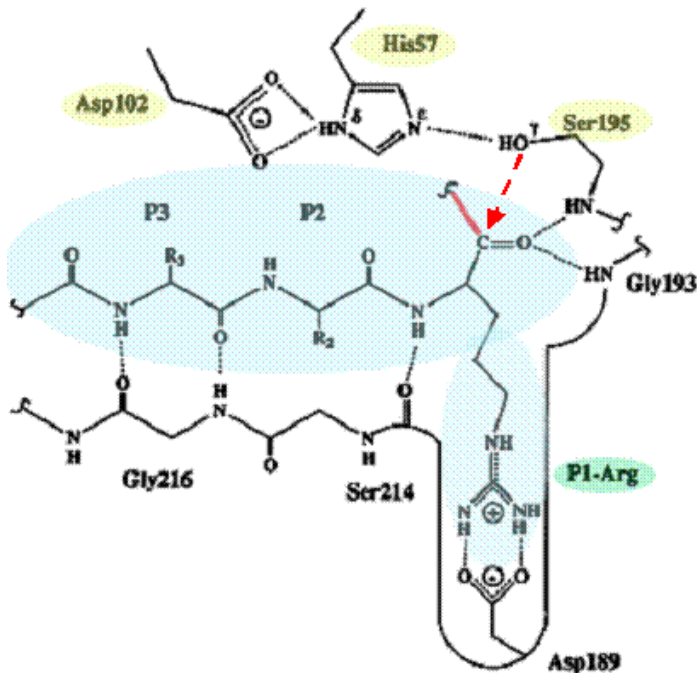


Figure 9.13

Biochemistry, Seventh Edition, 2012, W. H. Freeman and Company.

*Explain based on this figure the specificity of the recognized P<sub>1</sub> residues (bottom line) given the S<sub>1</sub> residues in the binding pocket.*



Adapted from Perona and Craik, Prot Sci 1995 4:337-360. The red arrow points to the carbonyl at the cleavage site.

*Which serine protease is described by this figure?*