Assignment Cover Page

BCH 3125 – Protein Structure and Function

Student Name:	Corrie daCosta
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PDB ID:	2BG9, chain A
Protein:	Alpha subunit of the nicotinic acetylcholine receptor
Organism:	*Torpedo marmorata*
Oligomeric protein:	Yes. Heteropentamer with four unique subunits.
Structure completeness:	66 residues missing in the cytoplasmic domain.
Structural method:	ELECTRON MICROSCOPY
Resolution:	4 Å

Alpha subunit of the nicotinic acetylcholine receptor (PDB ID: 2BG9)

Nicotinic acetylcholine receptors are pentameric ligand-gated ion channels, formed from five homologous subunits arranged pseudosymmetrically around a central ion-conducting pore (Fig.1). These integral membrane proteins convert the binding of small chemical ligands into electrical impulses, and are essential for electrical communication in the nervous system.

In terms of primary structure, the α-subunit of the nicotinic acetylcholine receptor from *Torpedo marmorata* shares 79% sequence identity with its human counterpart (Fig.2). The overall fold of the five acetylcholine receptor subunits from *Torpedo marmorata* is similar, with each subunit having an all α helical transmembrane domain, and a predominantly β sheet extracellular ligand binding domain (Fig.3). Each subunit contains a sequence motif, known as the "Cys-loop", which comprises 13 highly conserved amino acids bracketed by a Cystine disulfide bond (Figs.2,3). The structure of the *Torpedo* acetylcholine receptor is not complete, with the largest missing component of the 2BG9 structure being a stretch of 66 amino acids, which corresponds to a large fraction of the intracellular/cytoplasmic domain (Fig.3).

To perform its function, the acetylcholine receptor has to specifically recognize and bind the neurotransmitter acetylcholine. Acetylcholine binding occurs at the interface between two subunits in the extracellular ligand-binding domain, with the α-subunit contributing a number of loops and residues to the binding pocket (Fig. 3), including: W149, Y189, Y198, and pair of Cysteines that form a vicinal disulfide bond found in a hairpin like structure at the end of a long two-strand antiparallel β sheet known as loop C (Fig.3). Binding of acetylcholine in this region triggers a conformational change opening a transmembrane pore that is formed from α helices of adjacent subunits. These amphipathic helices converge upon a central hydrophobic constriction that forms the ion channel gate (Fig.3).

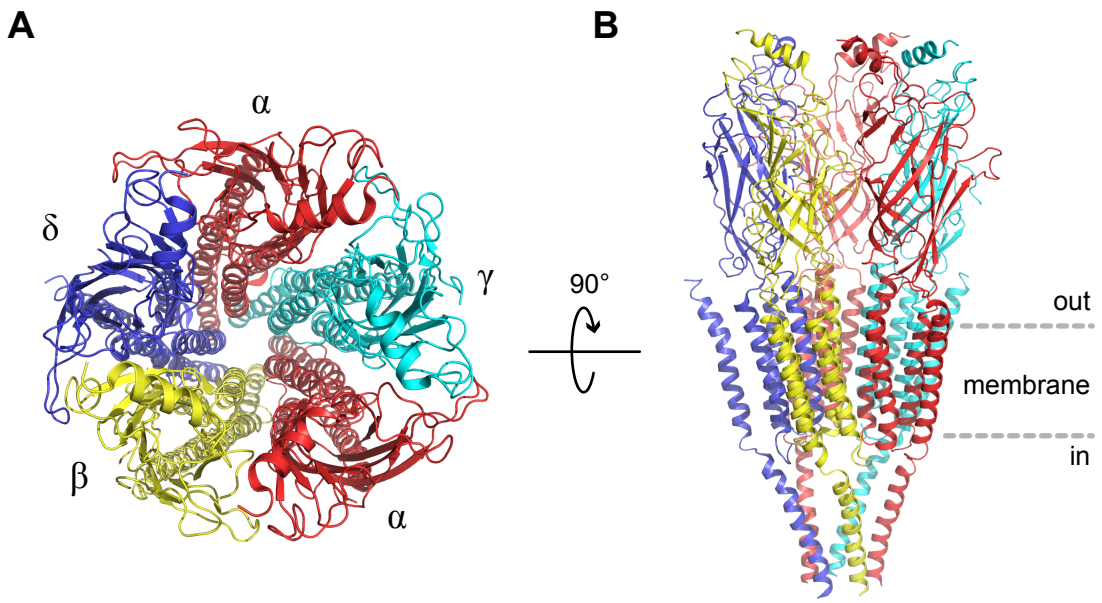

Figure 1: (A) Overall architecture of the nicotinic acetylcholine receptor from *Torpedo marmorata* (PDB ID: 2BG9).View is looking down the central pore axis. Note the pseudosymmetric pentameric assemly is composed of 5 homologous subunits ((2α)γδβ). (B) Side view showing the limits of the membrane. The α-subunits (assigned protein) are shown red.

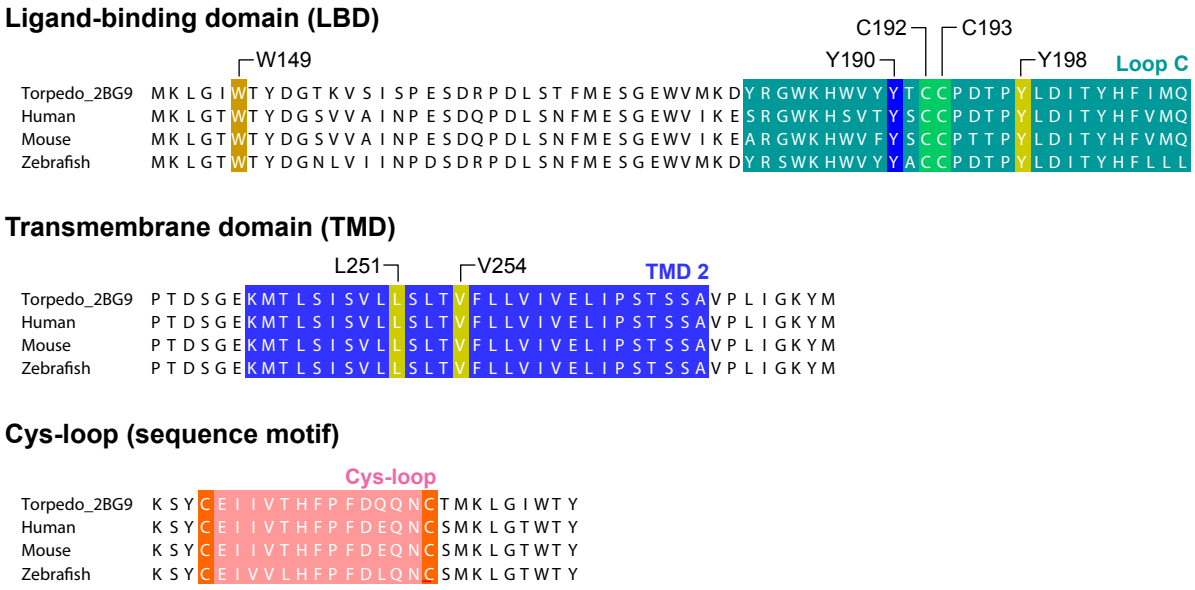

Figure 2: Amino acid sequence alignments showing selected regions of the *Torpedo*, human, mouse and zebrafish α-subunit ligand-binding, transmembrane, and Cys-loop (a sequence motif). Selected regions (Loop C, TMD 2) and residues have been highlighted and coloured as in Figure 3.

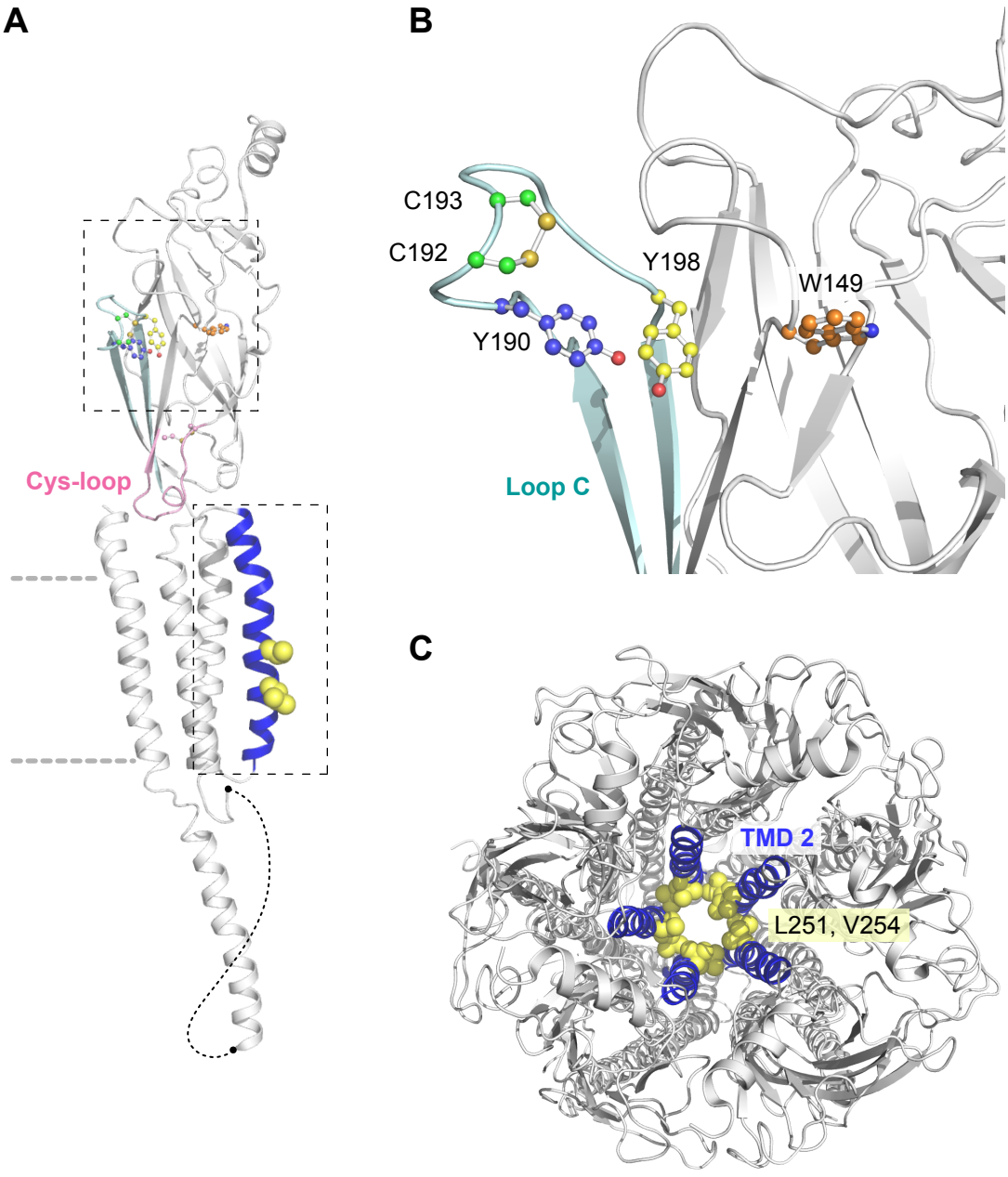

Figure 3: (A) Structure of the acetylcholine receptor α-subunit with functionally relevant structures (cyan: Loop C; pink: Cys-loop motif; blue: pore-lining TMD 2) and residues highlighted. Note also that the 66 amino acids missing in the cytoplasmic domain are depicted as a dotted line. Boxes denote the functionally important regions expanded in panels B and C. (B) Close up view of the α-subunit side of the ligand-binding site, with side chains of residues known to be important for binding shown in ball and stick representations. (C) View of the entire acetylcholine receptor pentamer where the second transmembrane domain (TMD 2) of each subunit has been coloured blue. Van der Waals spheres of hydrophobic residues that form the ion channel gate are shown in yellow.