# SMART Teams 2013-2014
# Research and Design Phase


## Kettle Moraine High School SMART Team

Jon Doenier, Jerad Grewe, Matt Griesbach, Mahi Gokuli, Emily Hinds,
Lili Kim, Madison King, Anna Schwarzkopf, Allie Smith

Teacher: Melissa Kirby
Mentor: Michelle Myleiff, Ph.D., Marquette University, Department of Biological Sciences

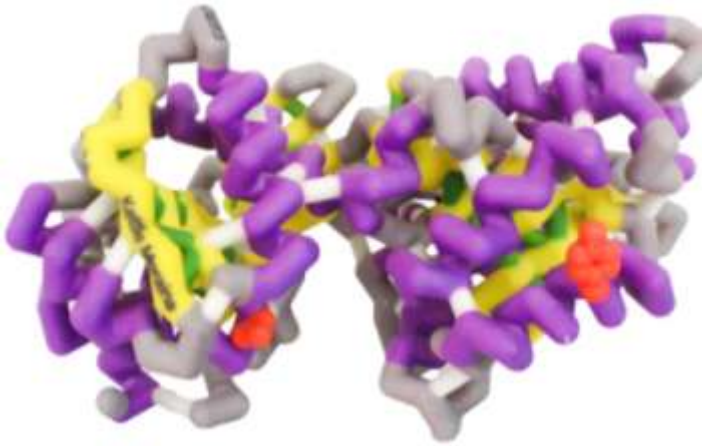

## The Function and Structure of the Metabotropic Gamma-aminobutyric Acid Receptor

**PDB**: 4F12

**Primary Citation:** Geng, Y., Xiong, D., Mosyak, L., Malito, D.L., Kniazeff, J., Chen, Y., Burmakina, S., Quick, M., Bush, M., Javitch, J.A., Pin, J.P., Fan, Q.R. (2012).Crystal structure of the extracellular domain of human GABA(B) receptor GBR2. *Nat. Neurosci.* 15: 970-978

**Format:** Alpha carbon backbone

**RP:** Zcorp with plaster



**Description:**
In the mammalian central nervous system, gamma-aminobutyric acid (GABA) is the primary inhibitory signaling molecule. One receptor for this molecule, $GABA_B$, has been linked to feelings of calmness, as well as mental disorders such as alcoholism and depression. Pharmaceutical compounds that bind the $GABA_B$ receptor are currently used to treat muscle spasticity and various types of addiction. However, excessive activation of this receptor can hinder muscle function. Activation of the metabotropic $GABA_B$ receptor by GABA influences neuronal activity by coupling with G proteins to activate a signaling cascade that leads to downstream effects including the modulation of various ion channels. The $GABA_B$ receptor is a dimer composed of two different subunits (GBR1 and GBR2), each with 7 helices within the membrane and an extracellular domain that binds GABA. Only the GBR1 subunit directly binds the GABA molecule and other ligands with a similar structure. However, recent studies have shown that GBR2 can affect the efficiency of GABA binding to GBR1. In addition, the GBR2 subunit activates the G protein after GABA binds, leading to various downstream effects. One well known effect is the opening of potassium channels, hyperpolarizing the cell, preventing action potentials from firing, and ultimately stopping neurotransmitter release. Using 3D printing technology, the Kettle Moraine SMART (Students Modeling A Research Topic) Team has modeled the $GABA_B$ receptor to study its structure to determine therapeutic possibilities. $GABA_B$ receptors' widespread importance in the nervous system may lead to new uses in the neurological and medical fields.

**Specific Model Information:**

- The alpha carbon backbone is colored grey.
- Alpha helices are highlighted purple.
- Beta sheets are highlighted yellow.
- The amino acids Tyr118 and Asp256 are displayed in ball and stick and colored red. A mutation at the Tyr118 site decreases GABA's control of potassium ion channels and activation of G proteins. Amino acid Asp256 is only important when mutated into Asn256. When GBR2 has the Asn256 mutation, the IC-50 of the GABA-B receptor is increased during a competition binding assay, meaning that the binding strength of the GBR1 subunit is higher.
- Hydrogen bonds in the beta sheets are colored green.
- Structural supports to stabilize the model are colored white.

http://cbm.msoe.edu/smartTeams/

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