Finding Calcitonin Gene-Related Protein (CGRP) Receptor Antagonists

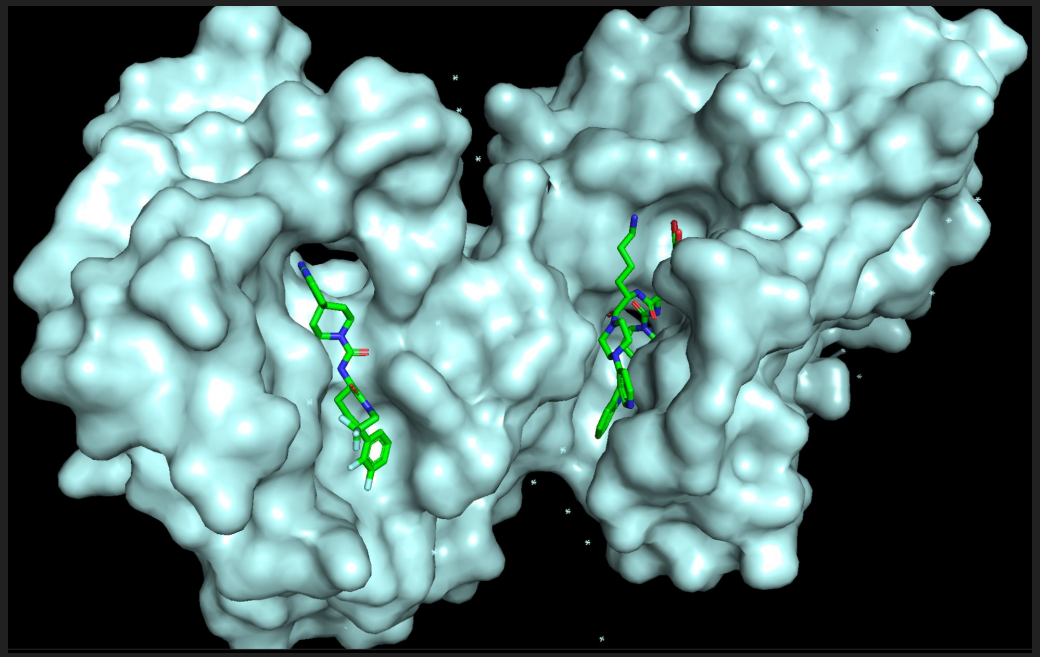


Figure 1. Molecular visualization of binding Olcegepant and Telcagepant at the CGRP receptor, generated using PyMOL (version 2.5.5, Schrödinger, LLC).

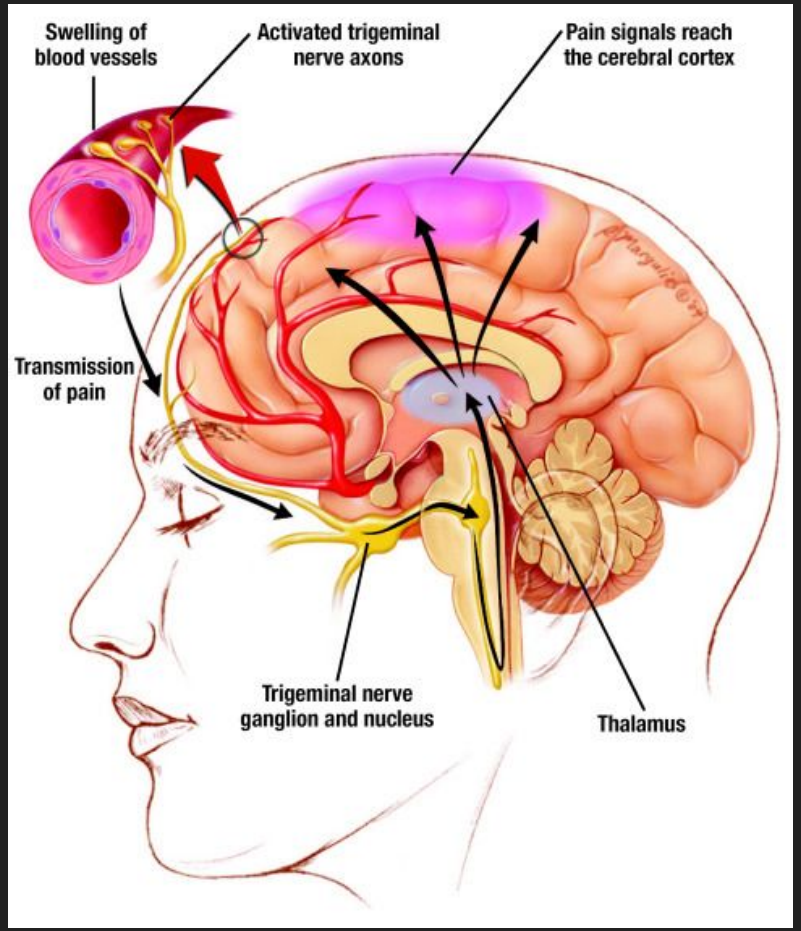


Figure 2. Vasodilation in *Migraine*.
From "Novel migraine therapy with calcitonin gene-related peptide receptor antagonists," by L. Edvinsson, 2004, *Current Opinion in Investigational Drugs*, 5(6), p. 673.

The CGRP Receptor in Migraines

Calcitonin Gene-Related Peptide (CGRP)

- Neurotransmitter (causes vasodilation)
- Interest in CGRP receptors located in Trigeminal (Cranial Nerve V)
- Immune system activation leads to neuroinflammation (Edvinsson, 2004)

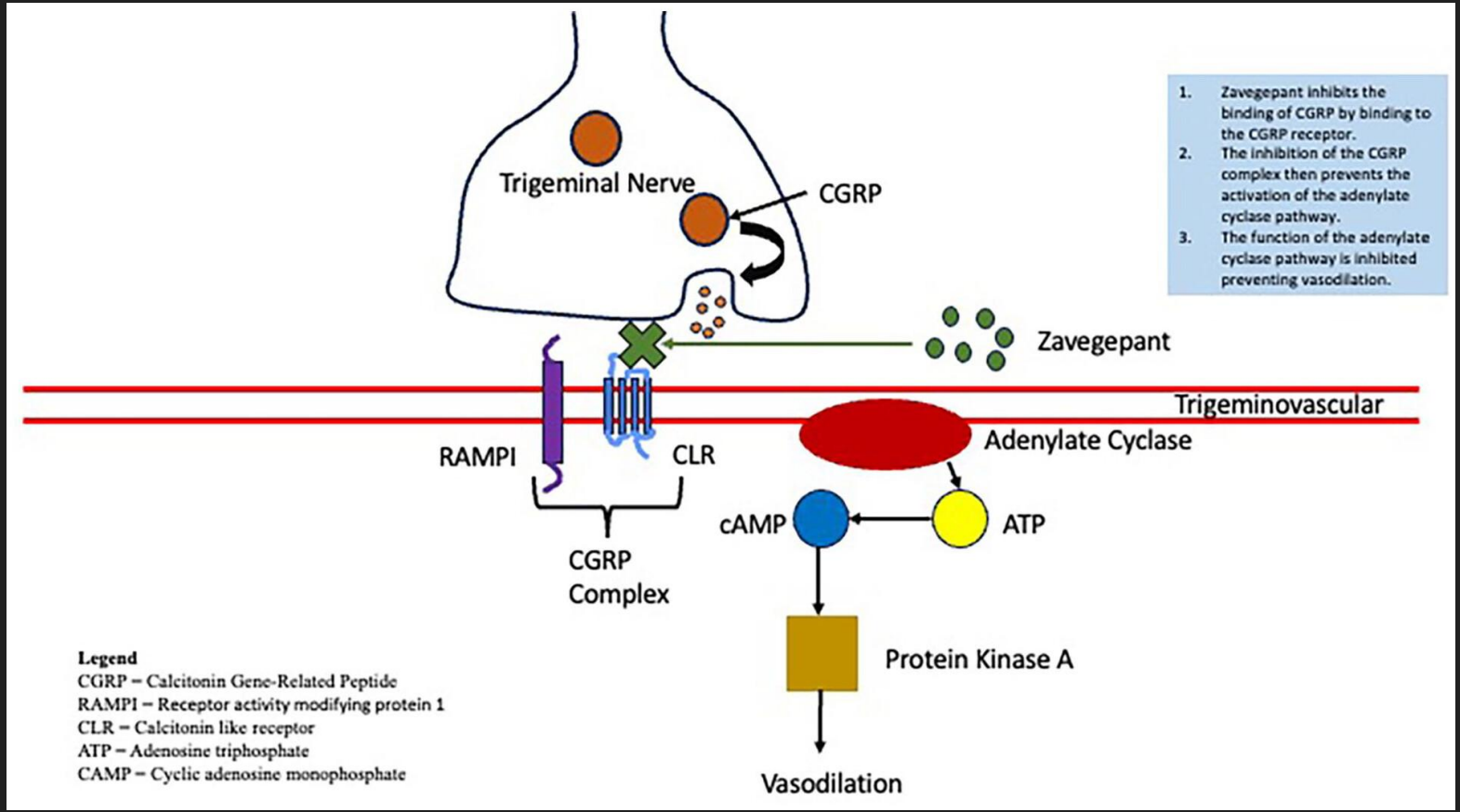


Figure 3. *Drug Mechanism*.
Adapted from "Zavegepant Intranasal Spray for Migraines," by Martirosov, A. L., Giuliano, C., Shupp, M., Channey, S., & Kale-Pradhan, P. B., 2024, *Annals of Pharmacotherapy, 58(8)*, p. 829. https://doi.org/10.1177/10600280231209439.

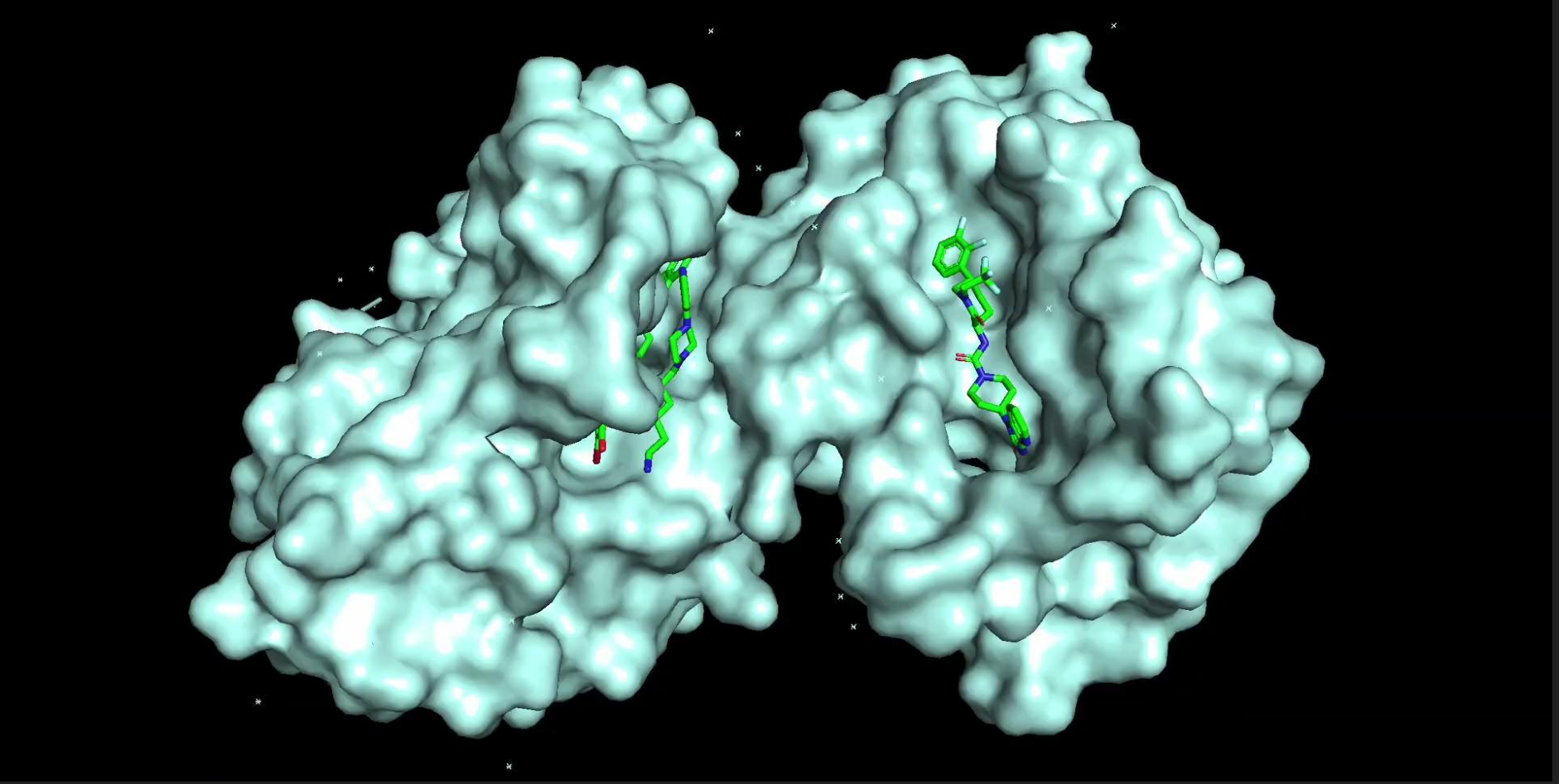


Figure 2. Molecular visualization of binding Olcegepant and Telcagepant at the CGRP receptor, generated using PyMOL (version 2.5.5, Schrödinger, LLC). Video created by Jessica Geiger, recorded on Feb 18, 2025.

Promising, but not quite there….

- Currently, there are seven FDA-approved drugs for migraines. Four of these are monoclonal antibodies, and three are small molecules known as gepants (Premera Blue Cross, 2024).
- The monoclonal antibodies are effective for only 50% of migraine sufferers (Muddam et al., 2023).
- Current FDA-approved gepants, have mild side effects (Zhou et al., 2019).
- About 40% of migraine sufferers continue to live with disabling conditions and often over-rely on barbiturates (Premera Blue Cross, 2024).

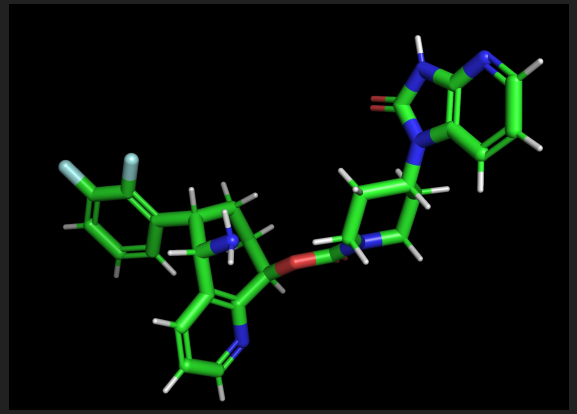
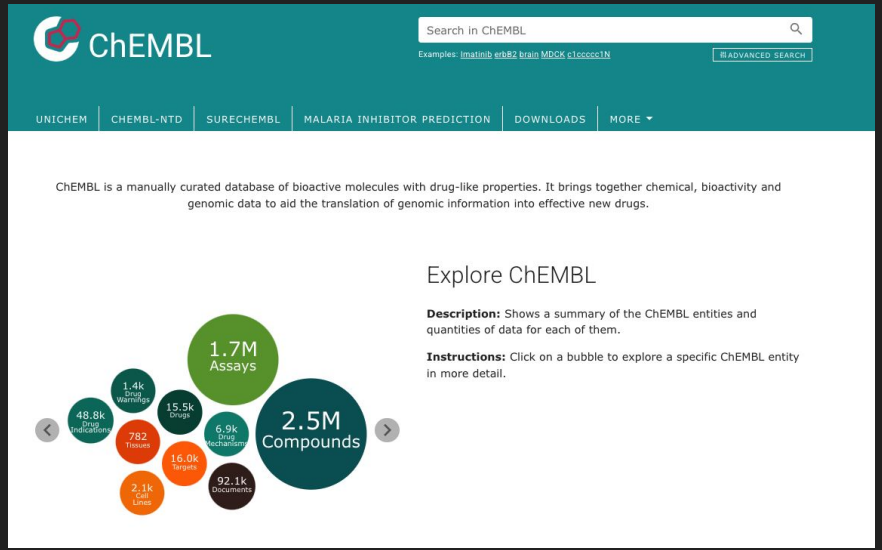


Figure 4. Molecular visualization of rimegepant, generated using PyMOL (version 2.5.5, Schrödinger, LLC).

- ChEMBL is a chemical database curated by the European Bioinformatics Institute, of the European Molecular Biology Laboratory (EMBL) on bioactive drugs.
- It's purpose is to provide open-source data to any one contributing to drug discovery.
- It contains data on over 2.5 Million Compounds
- Based near Cambridge, United Kingdom.



Target and Features

Target: IC50 standard values

- IC50: the concentration of a drug (in nanomolar) needed to displace the CGRP from its molecule.
- Technically we will be using the negative logarithm of the IC50 value in Molar units to create a uniform distribution.

Features: pubchem fingerprints

- Binary (1 for yes, and 0 for no)
- 880 fingerprints
- derived from molecular formulas (canonical SMILES)

Expected Outcome:

This project aims to develop a system where users can input canonical SMILES representations of molecules, and the model will predict the potency of the compound as a CGRP receptor antagonist (inhibitor) with reasonable accuracy.

To achieve this, the SMILES input will:

1. Be processed using PaDELpy to generate PubChem fingerprints.
2. Be evaluated by a fine-tuned machine learning model trained on known inhibitors.
3. Output a predicted IC_{50} value (in nanomolar), indicating the molecule's inhibitory potency

Ultimately, this high-throughput system would generate
new candidates for further lab and clinical research.

Limitations to this Project

- **Small dataset** after filtering and cleaning.
- **PubChem fingerprints** only capture sequence of atoms, **not molecular folding**
- **Different chemical groups** can perform the **same function** (e.g., binding the same receptor site).
- **Group arrangement is not recorded**, meaning similar groups may be **close together or far apart** in a molecule.

References

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