

Investigating and Modeling the Binding Mechanism between VK4-40 and D3 Receptor

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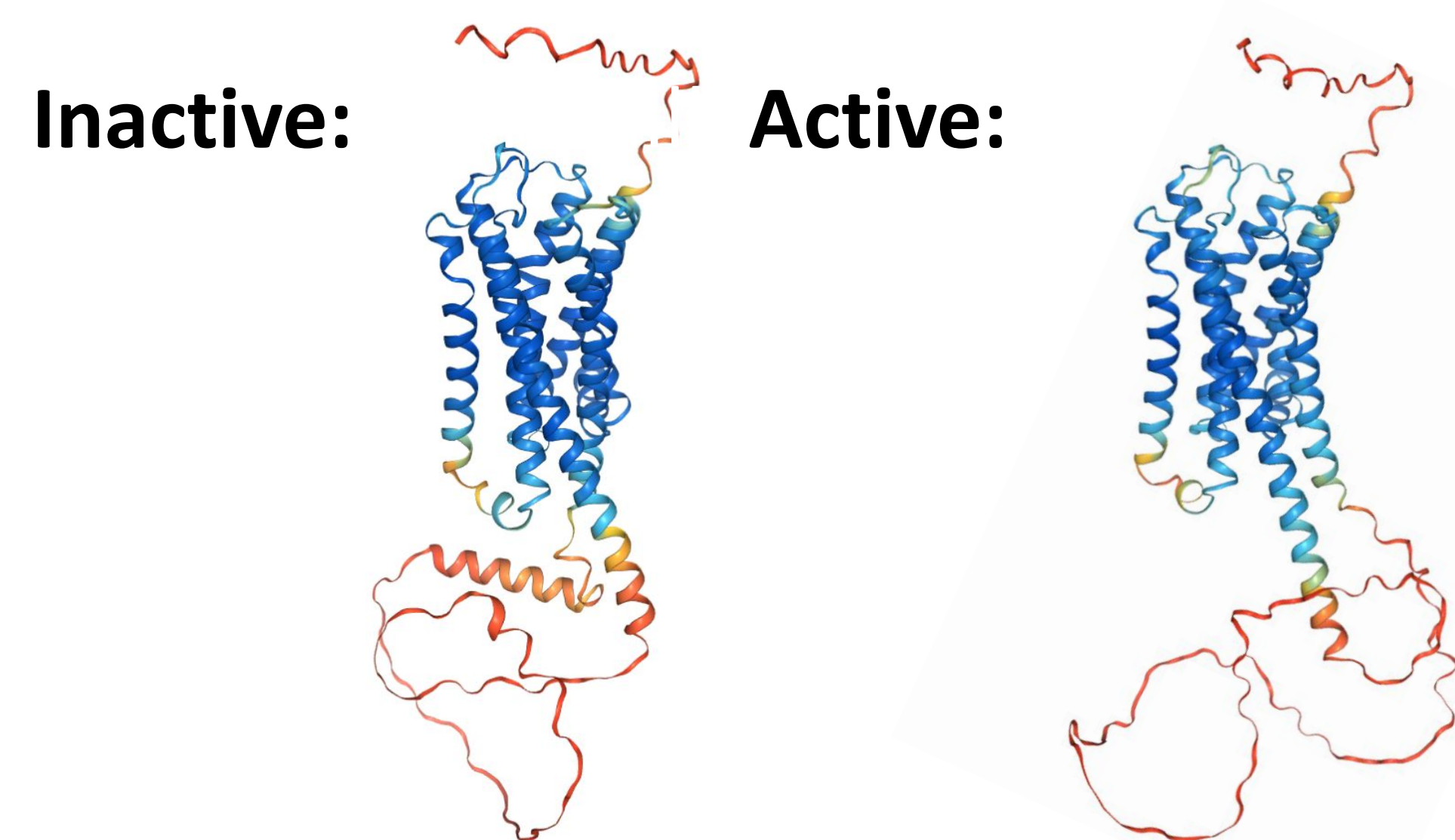
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Background

- The drug VK4-40 is a partial agonist for the dopamine 3 receptor (D₃R).¹
- VK4-40 mimics the binding mechanism of cocaine
 - This allows us to further understand cocaine use disorder (CUD) for which there are no approved treatments.¹
- VK4-40 is a novel target for CUD treatment
 - It has been shown to dose-dependently reduce cocaine intake in previous studies.¹
- By elucidating the structure of VK4-40 and its binding mechanism with D₃R, we aim to provide a model to educate stakeholders.



Methods

- From research, most prominent conformational change was inward rotation of Helix 6. Model was printed on Ultimaker 3D printer and is co-polyester material
- Discussion of how model should look
 - Design sketches of prototype
 - Prototype 3D printed from TinkerCAD
 - Model assembled and shown to group...cycle repeats!

Design Process

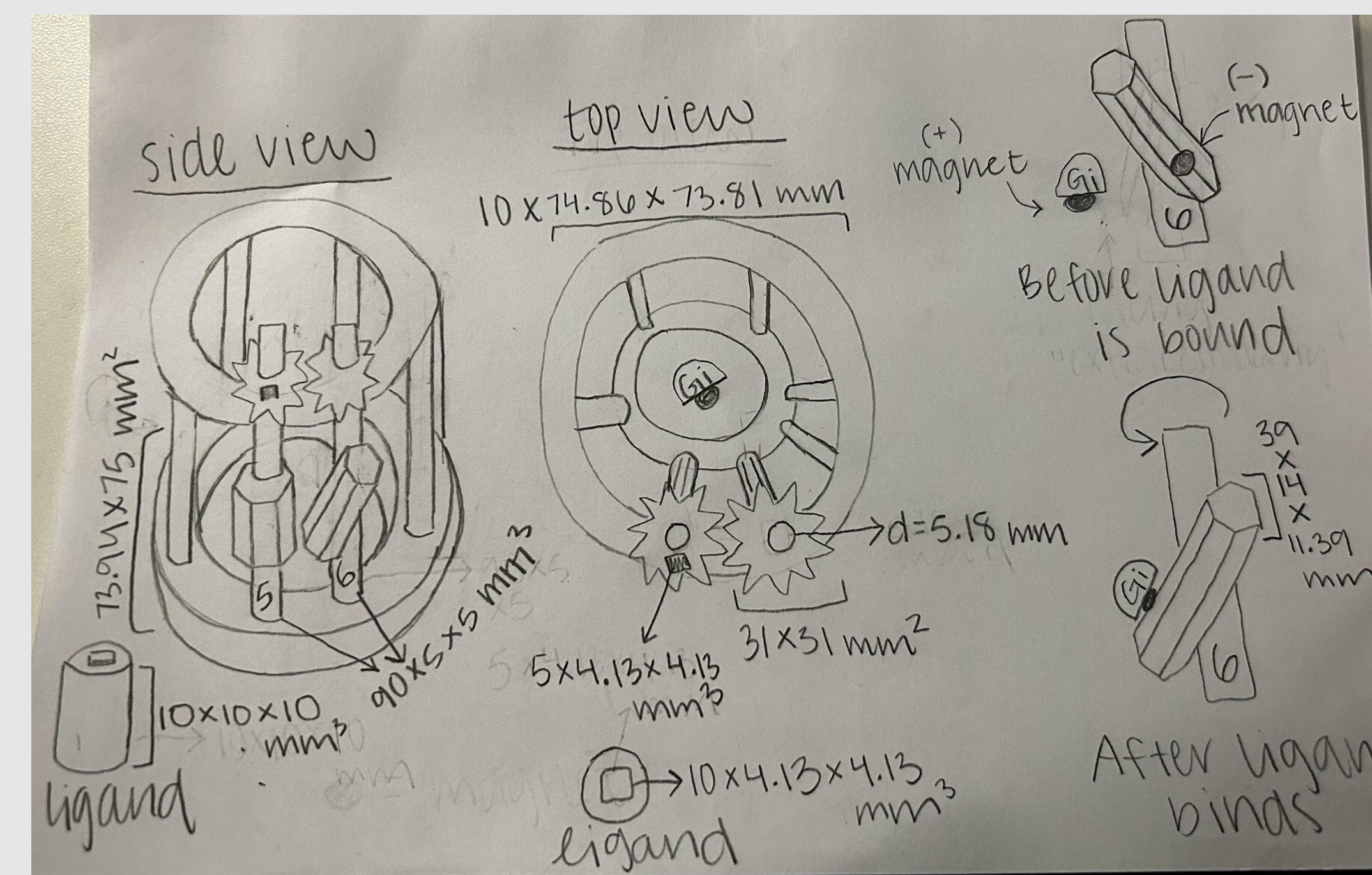
Low Fidelity Prototyping



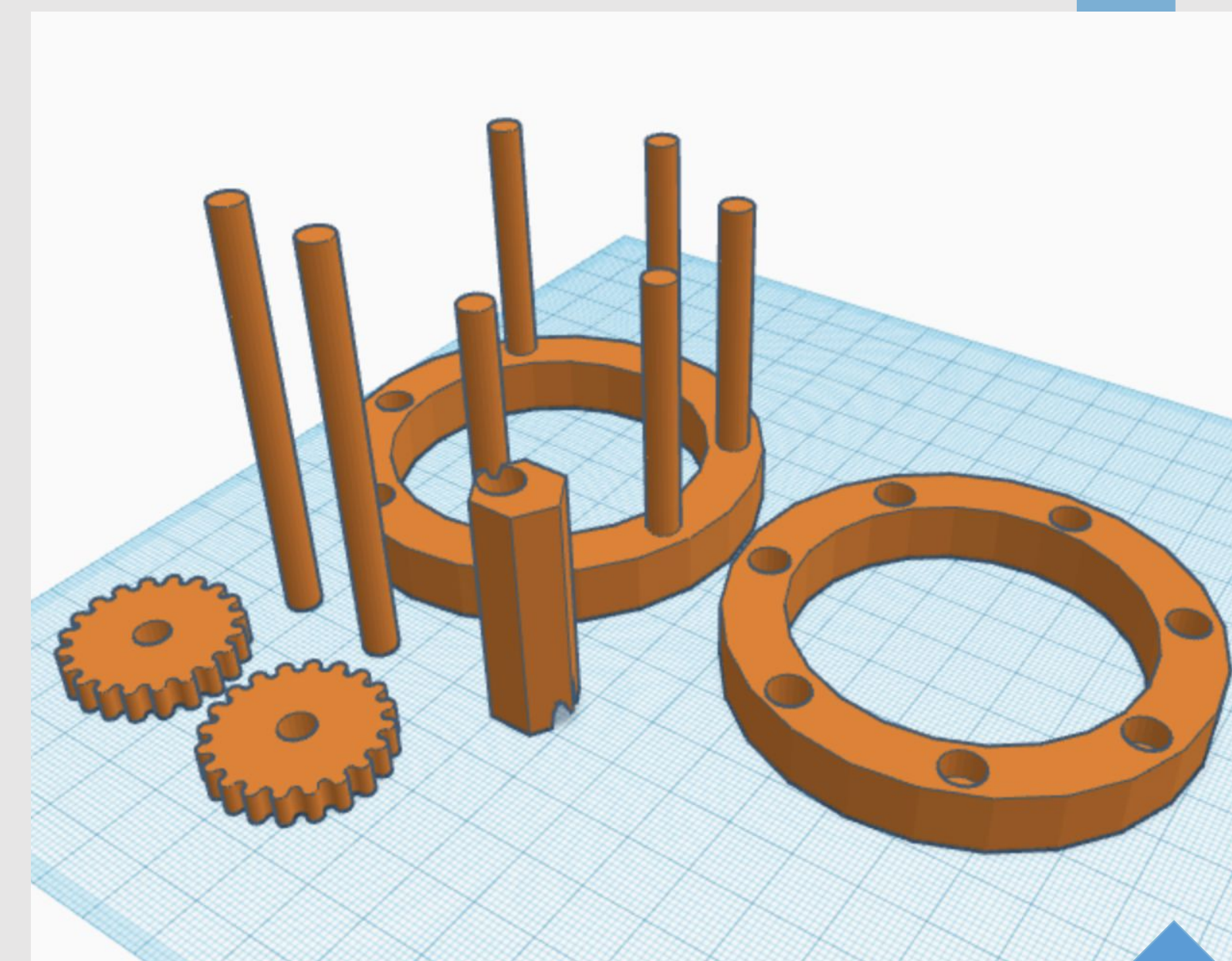
- Explore different mediums
- Generate abstract shape of D3 receptor
- Establish relationship of helices

Design Sketching

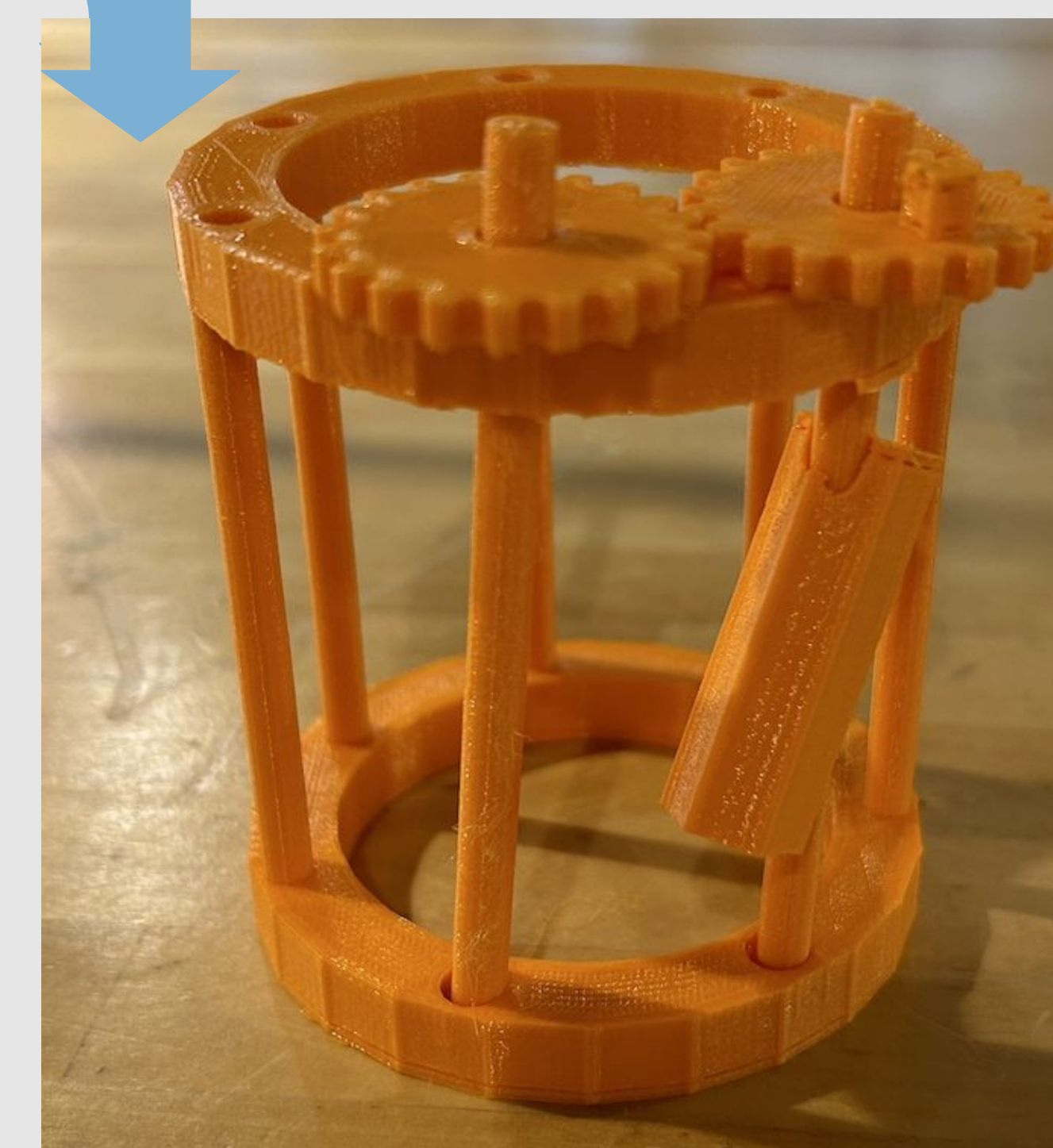
- Determined model measurements
- Visualize movement mechanism
- Clarify feasibility of model



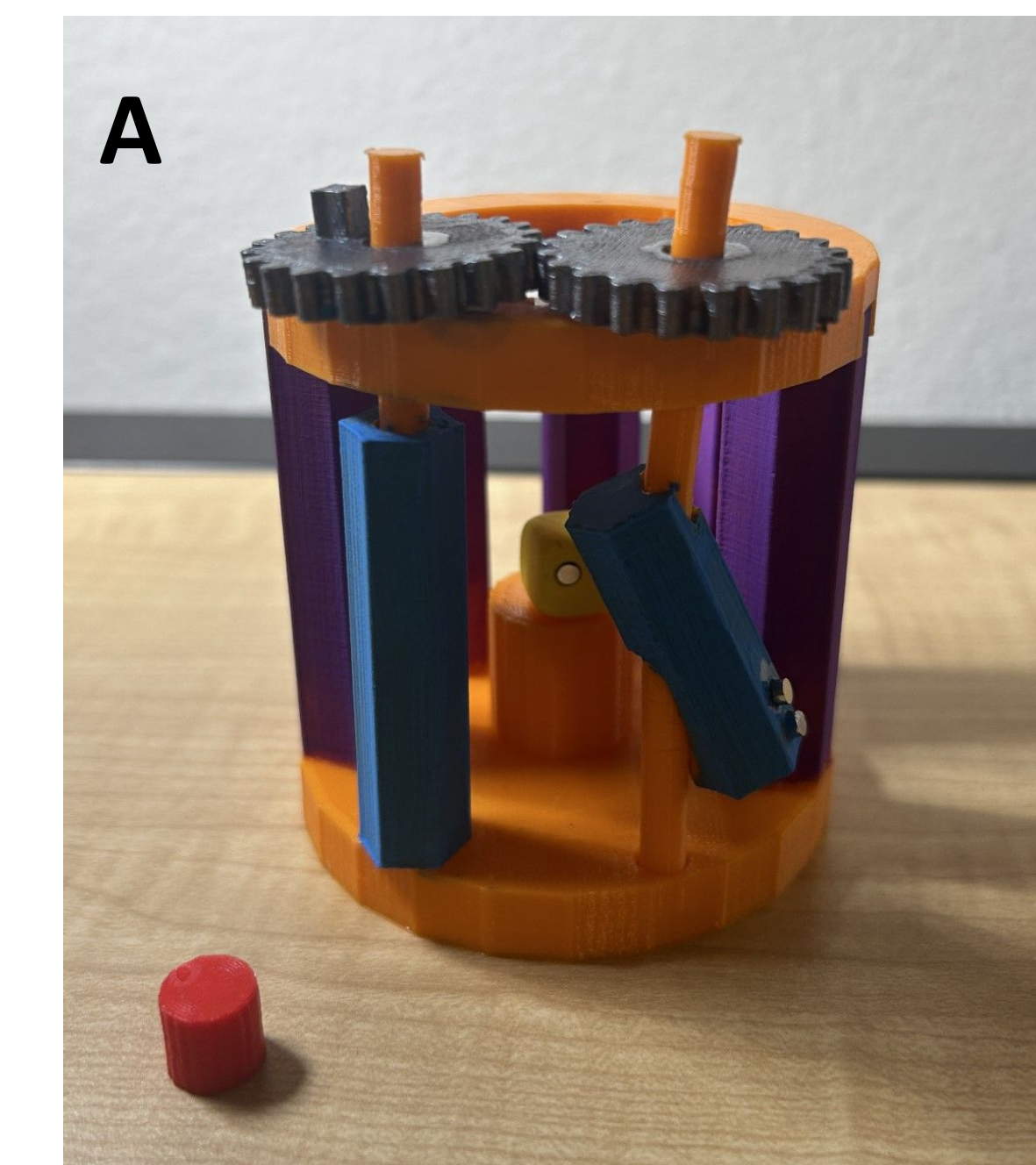
Build, Revise, Repeat



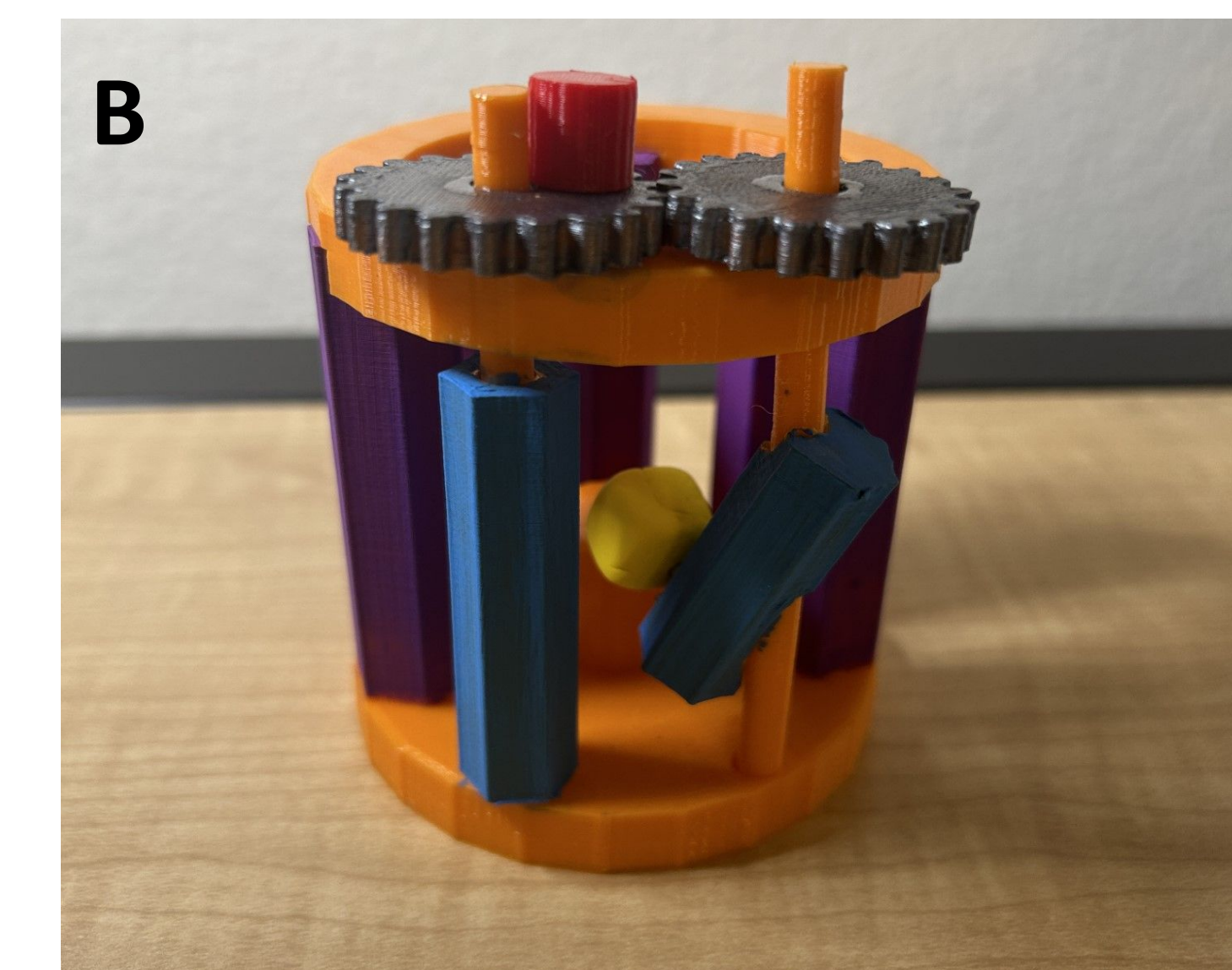
- Optimize fit of gears, rods, and lid
- Address limitations of 3D printing



Results



- A. Ligand unbound to receptor
B. Ligand bound to receptor, Helix 6 turned, and Gi protein is attached to Helix 6



QR code to see model in action

Limitations:

- Model only depicts change caused by Helix 6
- Binding site and ligand were simplified due to 3D printing constraints

Future Direction:

- Understanding structure will help researchers and physicians understand CUD and its possible treatments
- Clinical trials should be conducted to see how VK4-40 affects those with CUD and if it can be used with another drug for treatment.

References, Contributions

