Using A.I. to generate peptide therapeutics against the VWF-GP1bα interaction

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Introduction: Platelet glycoprotein-1b alpha (GP1bα) is a surface glycoprotein that is functionally defective in platelet-type von Willebrand disease (PT-VWD), which is characterized by gain-of-function mutations within the β-sheet thereby converting GP1bα to an open conformation. This results in the excessive association of GP1bα with its receptor von Willebrand clotting factor (VWF), counterintuitively leading to a bleeding phenotype in PT-VWD patients. The β-sheet mutations (clustered within the Trp230 - Met239 window) therefore represent an attractive site to develop peptide therapeutics. Recently, we developed the *In-Silico Protein Synthesizer* (InSiPS), which is a computational tool that intelligently designs small peptides to interfere with important protein-protein interactions (PPIs). Thus, we used InSiPS to generate small peptides against the GP1bα-VWF interaction.

Methods: We first used InSiPS to generate a peptide candidate list specific to GP1bα. InSiPS is a genetic algorithm developed around co-occurring protein motifs that mediate PPIs. It is a closed system that generates small peptides with a given interaction profile. The resulting peptides can bind to specific regions of a target protein while also avoiding interactions with a set of predefined, non-target proteins. These peptides are constantly improved through a cycle of evaluating and mutating an initial pool of sequences. After generating a ranked-list of peptide candidates that specifically target GP1bα, we took the top five-scoring peptides and performed a combination of in-silico docking experiments and in-vitro binding assays.

Results: We have generated five peptides that are specific to GP1bα. The interaction between some of these peptides and GP1bα were further confirmed in-silico using AlphaFold2. Our preliminary in-vitro data confirms the interaction between some of these peptides and GP1bα. We will further evaluate the ability of these peptides to interfere with the interaction between GP1bα and VWF.

Conclusions: We conclude that InSiPS is a suitable tool to develop small peptides against pharmaceutically important targets, such as GP1bα. Future work will focus on testing the efficacy of these peptides against GP1bα in a mammalian system.