Original Work Part 3

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Independent Study and Mentorship

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Wang, Qinghua et al. “Application progress of RVG peptides to facilitate the delivery of therapeutic agents into the central nervous system.” *RSC advances* vol. 11,15 8505-8515. 24 Feb. 2021, doi:10.1039/d1ra00550b

Research Assessment

The reviewed article provides a comprehensive overview of rabies virus glycoprotein (RVG) peptides as emerging tools for transporting therapeutic agents across the blood–brain barrier (BBB). From this work, I learned that RVG-derived peptides, particularly the RVG29 segment and the sequences spanning residues 189–214 and 330–357, bind primarily to neuronal nicotinic acetylcholine receptors (nAChR) and, to a lesser extent, GABA receptors. These interactions facilitate receptor-mediated endocytosis and subsequent transcytosis into the central nervous system. I also learned that RVG can traverse neuronal pathways, including the olfactory and trigeminal systems, enabling non-invasive CNS access. The article outlines how RVG-modified carriers (liposomes, dendrimers, polymers, exosomes, and micelles) can efficiently encapsulate and deliver diverse therapeutic cargos, including siRNA, proteins, DNA, and small molecules. Additionally, it distinguishes between covalent and electrostatic linking strategies used to functionalize nanocarriers with RVG peptides. Overall, the article illustrates the biological mechanisms and engineering principles underlying RVG-mediated CNS delivery.

The information presented is directly relevant to my ISM project, RVG-Xplorer 2.0, which aims to computationally engineer enhanced RVG variants for the delivery of Alzheimer's disease drugs. Understanding the natural biology of RVG provides essential context for my AI-driven design process. The article reinforces the rationale behind using RVG as the foundational scaffold because of its inherent neurotropism, BBB permeability, and compatibility with multiple therapeutic formats. It also validates my project's focus on receptor interactions by emphasizing the central role of nAChR and GABA receptors in RVG entry. This connection strengthens the justification for expanding receptor targeting to include LRP1 and p75NTR, which my project explores computationally. Furthermore, the article's discussion of nanocarrier systems helps me anticipate how engineered RVG variants might eventually be applied in real-world therapeutic formulations. This review consolidates the importance of RVG in CNS translational research and aligns closely with my long-term goals of developing AI-optimized delivery molecules for neurodegenerative disease treatment.

The article's core components can be classified into four primary categories: (1) the structural domains of RVG and their receptor-binding significance; (2) the mechanisms by which RVG peptides traverse the BBB; (3) the engineering strategies used to attach RVG to various nanocarriers; and (4) specific therapeutic applications demonstrated in preclinical models. Compared to my prior knowledge, which was heavily computationalfocusing on protein language models, docking, and molecular dynamicsthis article enhanced my biological understanding of RVG's native function. It clarified which residue segments must remain structurally conserved and which regions may tolerate mutations. This new information modifies my previous approach by encouraging a more biologically informed constraint system during

sequence generation. It also highlights the importance of receptor specificity and the implications of altering peptide charge, hydrophobicity, or glycosylation patterns.

Integrating the insights from this article with my existing knowledge enables me to explore several new directions for my project. First, I can incorporate domain-preservation rules into my transformer fine-tuning process to avoid disrupting crucial receptor-binding motifs identified in the literature. Second, the article's emphasis on carrier compatibility suggests that future versions of RVG-Xplorer might include optimization not only for receptor affinity but also for compatibility with liposomal or polymeric delivery systems. Third, the evidence describing RVG's long-range neuronal transport aligns well with my idea of integrating HSV glycoprotein motifs to enhance neuronal specificity further. This raises new questions about how multi-receptor binding might influence trafficking dynamics or immune recognition. These possibilities expand the creative potential of my project while keeping it grounded in experimentally supported biology.

The information from this article was highly effective in advancing my project. It strengthened my scientific foundation, validated the relevance of my research direction, and provided reassurance that RVG engineering is meaningful yet still underexplored in the literature, especially from an AI-based perspective. It was motivating to see that while RVG-based delivery systems are widely studied, no existing work attempts systematic computational protein design or multi-receptor optimization, confirming the novelty of RVG-Xplorer 2.0. The article also helped me refine the potential limitations and biological risks associated with modifying viral glycoproteins. Overall, this knowledge was both supportive and thought-provoking, enhancing my confidence in the scientific contribution my project aims to make.