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Sticky Illusions: The Case of SGVYKVAYDWQH and the Polystyrene Trap

Ralf Weiskirchen[1,*]

[1]*Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry (IFMPEGKC), RWTH University Hospital Aachen, Germany*

Abstract: SGVYKVAYDWQH consistently emerges from phage-display screens not as a genuine multitarget ligand but as a target-unrelated peptide with high affinity for polystyrene. AlphaFold predicts a compact, amphipathic α-helix that is ideal for hydrophobic surfaces, while BLASTp shows only weak, short homologies, ruling out evolutionary conservation. Reported protein or cell affinities (in the low-μM range) seldom replicate, indicating nonspecific hydrophobic binding. Therefore, plastic-free assays, hydrophobic-site mutagenesis, and solution-phase kinetics are essential to confirm any real high-affinity partners and to either utilize or avoid this peptide's stickiness in therapeutic or materials applications.

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1. Main Text

Abagna and colleagues present a timely and thought-provoking reassessment of the peptide SGVYKVAYDWQH, a 12-mer that has been notably common in phage-display campaigns over the past two decades [1]. By compiling 22 peer-reviewed studies, 16 patents, and the latest entries in the Biopanning Data Bank, the authors illustrate that this specific sequence has been shown to bind to a diverse range of 26 biological and non-biological targets. These targets include the blood-brain barrier (BBB) endothelium, breast cancer cells, the cancer stem cell marker CD133, amyloid-β42, anti-HIV antibodies, printer toner, and parabens. Initially, it was believed that SGVYKVAYDWQH could function as a broadly applicable mimotope, mimicking various epitopes on different templates.

However, the meta-analysis presented in the review prompts a more skeptical perspective. By utilizing the SAROTUP suite of tools, the authors discovered that while TUPScan did not detect any classical target-unrelated motifs, PSBinder indicates a 0.91 probability that the peptide might actually be a polystyrene-surface-binding peptide. This suggests that the enrichment of the peptide during screening could be due to its affinity for plastic, such as the polystyrene material commonly found in ELISA wells, cell culture dishes, and panning plates, rather than its intended biological target. This theory is supported by the fact that SGVYKVAYDWQH is retrieved at a similar rate from negative-control plates and that many research groups eventually discarded the sequence after discovering weak or non-reproducible binding to the supposed target.

Plastic affinity explains most enrichment, yet some studies hint at genuine bioactivity. SGVYKVAYDWQH promotes clathrin-mediated transcytosis across an in vitro BBB [2], binds MCF-7 breast cancer cells to enhance doxorubicin uptake [3], and as a free peptide, recognizes Aβ42 with tenfold higher affinity than earlier motifs [4]. It has also been selected by an anti-*Mycobacterium tuberculosis* LAM antibody [5] and binds strongly to *E. coli* O157:H7 biofilms [6]. These findings suggest the 12-mer, or a sub-motif, can engage biological targets in solution or on cell surfaces. Clarifying true versus plastic-driven interactions will require polystyrene-free measurements (SPR, BLI, ITC, NMR) and mutational trimming of the hydrophobic Val-Tyr-Val-Ala core. PS-silent variants might serve as BBB shuttles for biologics or imaging agents, and validating nanomolar Aβ42 binding could revive the sequence as a scaffold for Alzheimer diagnostics or therapy.

Re-analysis of the "exception cases" shows a spectrum from likely receptor-mediated to fully explainable by hydrophobic stickiness. In the BBB work, Díaz-Perlas et al. used a Ph.D-12™ library, repeated panning three times, and found the sequence in 2 of 31 clones; the peptide was nontoxic, permeated bEnd.3 and HeLa cells, and doubled GFP uptake [2]. Zhang et al. likewise panned the same library on MCF-7 cells, retrieving the peptide six times; flow cytometry showed only moderate but above-control affinity versus a random sequence AGPMLARRQPHG [3]. Kim et al. obtained the peptide after four rounds and reported strong binding to Aβ aggregates, capturing oligomers from aged Alzheimer mice [4]. Shin et al. selected it with an anti-LAM monoclonal antibody, noting high in vitro affinity but no anti-LAM response in mice when the peptide was coupled to KLH or baculovirus, leaving specificity unresolved [5]. Finally, Sun et al. chose the peptide for an

***Corresponding author:** Ralf Weiskirchen, Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry, RWTH University Hospital Aachen, Germany. Email: rweiskirchen@ukaachen.de

antibacterial biosurfactant; with a Lys_3 tail, it formed micelles and bound *E. coli* O157:H7 biofilms, although tests were still conducted on polystyrene plates [6].

Only the BBB transcytosis and Aβ42 studies suggest activity beyond hydrophobic stickiness; cancer cell, antibody, and biofilm claims still need plastic-free confirmation. Rigorous tests should include alanine or scrambled-sequence competitors and solution assays, SPR, BLI, ITC, and NMR in detergent buffers. The fact that the same 12-mer reportedly binds brain endothelium, Aβ42 oligomers, breast cancer membranes, anti-LAM antibodies, and bacterial biofilms is unlikely if interactions were truly sequence-specific. A simpler explanation is that labs using the same Ph.D-12™ library and standard plasticware enriched clones that stick to polystyrene first and to immobilized targets second. SGVYKVAYDWQH's recurrence thus reflects a library-intrinsic plastic-binding bias, underscoring the need for plastic-free validation.

The review also highlights a broader methodological lesson for the phage-display field: recurrent sequences are not necessarily privileged binders; they may instead be artifacts of the screening process. Rigorous counter-selections on blank plastic, tighter washing conditions, and early adoption of deep-sequencing to monitor clonal convergence should become standard practice to eliminate such target-unrelated peptides before costly follow-up studies begin. In the longer term, understanding why SGVYKVAYDWQH so effectively "cheats" the system may even be advantageous. Its robust adhesion to hydrophobic polymers could be deliberately exploited as a universal anchoring tag for immobilizing enzymes, antibodies, or nanoparticles on plastic medical devices, microfluidic chips, or point-of-care diagnostics where covalent coupling is impractical.

AlphaFold structure prediction [7] indicates that SGVYKVAYDWQH adopts a completely α-helical conformation (Figure 1). This peptide is predicted to form a compact, amphipathic α-helix with a hydrophobic face dominated by Val3, Tyr4, Val7, Ala8, Tyr9, and Trp10, while its polar/charged side is contributed by Ser1, Lys6, Asp10, Gln11, and His12. As a result, the peptide can interact with hydrophobic substrates through van-der-Waals and π-stacking contacts, showing apparent affinity in the low- to sub-micromolar range, as seen with printer toner, parabens, and polystyrene. However, achieving nanomolar affinities for protein targets is rare unless there is a fortuitous shape complementarity such as with Aβ42 and CD133 to a lesser extent. Consequently, most protein-binding claims that pass secondary screening fall within the single- to double-digit micromolar Kd range, while sequences discarded after ELISA typically bind more weakly (>10–30 μM). This underscores a general pattern of moderate, hydrophobically driven adhesion rather than high-specificity, high-affinity recognition.

A BLASTp search of SGVYKVAYDWQH against the NCBI nr database yielded several short, high-identity hits, confirming the motif is not unique to phage-display libraries (Suppl. Table 1). The best match (80% identity over 10 residues, $E = 5.8$) appears in uncharacterized red and black abalone proteins. Additional hits include a *Paenibacillus* tail-fiber domain (83%, $E = 11$), an InlB B-repeat from *Ruminococcus* (73%, $E = 33$), a *Shewanella* TraF protein (75%, $E = 66$), and hypothetical *Gordonia* proteins (≈ 73%, $E = 66$). Although limited to short segments and not indicating full-length homology, these alignments show that SGVYKVAYDWQH-like motifs naturally recur in diverse proteins, likely as generic surface-interaction elements.

Nevertheless, the *E*-values were rather low (the best alignment reached only 5.8), indicating weak statistical significance for these short-sequence matches. However, because the query consists of just 12 residues, even near-perfect identity can yield *E*-values

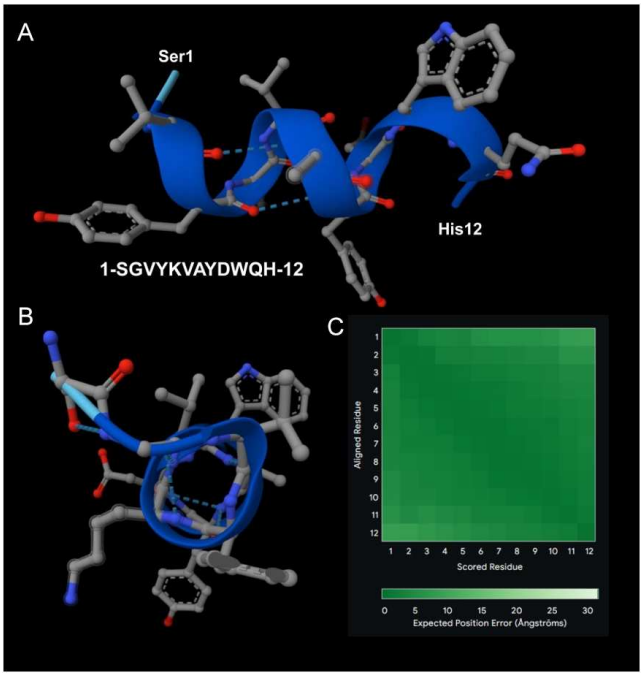

Figure 1 AlphaFold3 (default settings) predicts SGVYKVAYDWQH as a continuous right-handed α-helix. (A) Side view. (B) End-on view reveals an amphipathic pattern: hydrophobic Val3, Tyr4, Val7, Ala8, Tyr9, and Trp10 on one face and polar/charged Ser1, Gly2, Lys6, Asp11, and His12 on the other. (C)PAE heatmap shows minimal error. Predicted IDDT scores exceed 70 for residues 1–3 and 90 for residues 4–12, indicating high reliability despite AlphaFold's protein-focused design [7].

above conventional significance thresholds. Values in the 5.8–66 range suggest that the observed 72–83% identities may just as easily arise by chance. Consequently, the similarities do not by themselves establish evolutionary or functional relatedness but instead likely reflect convergent, surface-exposed motifs whose relevance must be verified by additional structural or biochemical studies. In this context, it should be noted that short alignments tend to have relatively high *E*-values because the calculation takes into account the length of the query sequence, which in this case is only 12 amino acids for the peptide. As a result, it is not an effective way to describe biological significance and is possibly not useful for drawing conclusions.

In summary, Abagna and colleagues transformed SGVYKVAYDWQH from an enigmatic multitarget mimotope into a cautionary exemplar of selection-related bias. They left the door open for genuine biomedical applications once its promiscuity is tamed. Their work reminds us that specificity cannot be inferred from frequency alone and provides a clear roadmap for validating, or refuting, peptide binders in future therapeutic discovery efforts.

2. Conclusion

Phage display is valued for its speed, low cost, and simplicity. Genotype and phenotype are linked; libraries can be stored as DNA, and binders are selected entirely in vitro without animal immunization. Filamentous phages reach high titers without lysing their hosts, enabling rapid amplification under varied panning conditions. However, there are key limitations to consider [8]. Large or highly hydrophobic inserts can destabilize virions and reduce

infectivity, limiting library diversity. Proteins that misfold, aggregate, or require eukaryotic disulfide bonds may become inactivated during periplasmic secretion. cDNA fragments with internal stop codons or very long sequences may not propagate well, and passage through bacterial membranes can exclude certain clones, introducing bias. Artifactual binders may also emerge when unintended factors, such as polystyrene affinity, masquerade as true target interactions. Abagna et al. reframe a 12-mer from a putative multitarget mimotope into a cautionary tale of selection bias, but note that once its promiscuity is controlled, it could still serve real biomedical roles. Their analysis reminds us that clone frequency alone does not prove specificity and provides a roadmap for rigorously validating or repurposing peptide binders in future discovery efforts.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The author declares that he has no conflicts of interest to this work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

Ralf Weiskirchen: Conceptualization, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

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