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# Engineering the Tumor Surface: Synthetic Nutrient Mimicry Peptides as Stable Extracellular Anchors for Precision Cancer Therapy

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## ABSTRACT

This project introduces a conceptual framework for a proposed modular synthetic biology platform based on synthetic nutrient mimicry peptides (SNMPs). These lipid-anchored molecules are designed to preferentially insert into tumor cell membranes by exploiting differences in metabolism and membrane biophysics between malignant and normal tissue. Once anchored, SNMPs may serve as extracellular docking sites for engineered, non-replicative bacteriophages or virus-like particles (VLPs) carrying therapeutic payloads. The present study is explicitly scoped to the initial membrane anchoring mechanism as a necessary first step in establishing targeting specificity. All conclusions are limited to initial positional feasibility as assessed through static membrane packing analysis; no dynamic simulations or experimental validation were performed. Using CHARMM-GUI Membrane Builder, four SNMP constructs—three lipidated variants and one non-lipidated control—were positioned in a tumor-mimetic POPC/POPS/Cholesterol bilayer at pH 6.5. Static packing output was analyzed for palmitoyl chain depth relative to the bilayer midplane, peptide orientation, and conformation type. SNMP A demonstrated the deepest initial insertion (palmitoyl terminal carbons at approximately −12 to −14 Å relative to the midplane), SNMP C showed partial and angled positioning (−5 to −8 Å), SNMP B remained solvent-exposed despite lipidation, and the non-lipidated control showed no membrane association. These findings provide a plausible structural basis for selective SNMP insertion and motivate future molecular dynamics simulations and experimental validation.

## 1. INTRODUCTION

Cancer treatments routinely encounter a fundamental tension between efficacy and toxicity. Most chemotherapeutic agents are systemic cytotoxic agents that kill cells indiscriminately, directing destructive action toward tumor cells while causing considerable collateral harm to healthy tissue. Although many targeted therapies are under development, the majority lack adequate tumor specificity or

sufficient tissue penetrance to demonstrate reliable efficacy at therapeutic concentrations. A critical unresolved challenge is the delivery of therapies to tumors via a stable extracellular targeting interface capable of discriminating between malignant and normal cells while remaining biochemically compatible with delivery vectors.

The Synthetic Nutrient Mimicry Peptide (SNMP) offers a mechanistic approach to this problem grounded in tumor metabolism. Cancer cells, frequently driven by the Warburg effect, exhibit upregulated expression of nutrient transporters such as GLUT1 and ASCT2, and display altered lipid raft composition, creating physicochemical membrane signatures distinct from those of normal tissue [1, 2]. Lipid-modified peptides designed to structurally or electrostatically mimic nutrient substrates may preferentially partition into these tumor-associated membrane microdomains, forming stable extracellular anchors that can serve as docking interfaces for engineered phages or VLPs.

This study focuses exclusively on the first step of this platform: establishing a computationally plausible model for SNMP membrane insertion. We present a theoretical, early-stage analysis using static membrane packing simulations and make no claims regarding dynamic stability, membrane residency time, or therapeutic efficacy. These remain subjects for future molecular dynamics simulations and experimental validation.

## 2. BACKGROUND RESEARCH

### 2.1 Tumor Metabolism and the Warburg Effect

Otto Warburg's characterization of aerobic glycolysis in cancer cells established the conceptual basis for metabolic targeting [2]. This metabolic reprogramming enables sustained glucose and amino acid uptake, increased lactate secretion, and altered lipid raft composition in malignant membranes. The Warburg effect, combined with specialized expression of nutrient transporters such as GLUT1 and ASCT2, produces membrane microdomain properties not observed in healthy tissue [1]. These biochemical signatures can in principle be exploited by SNMPs designed to mimic nutritional substrates structurally or electrostatically.

### 2.2 Lipid-Based Peptide Modifications and Membrane Anchoring

Lipid modification—including palmitoylation and myristoylation—enables peptide integration into lipid bilayers via hydrophobic interactions [3]. Retention depends on acyl chain length, degree of saturation, and local membrane charge. Palmitoylated proteins have longer residency times in cholesterol-enriched lipid raft microdomains, which are overrepresented in tumor membranes [4]. This behavior is consistent with the broader literature on lipid-anchored peptides: Peitzsch and McLaughlin demonstrated that acylation substantially increases membrane affinity, and Resh has reviewed how the geometry and number of acyl chains influence insertion depth and lateral mobility [1, 3]. On this basis, a dual-palmitoyl

SNMP design was hypothesized to favor deeper and more stable initial positioning compared to mono- or non-lipidated variants.

### 2.3 Membrane-Targeting Strategies and the SNMP Modular Interface

Existing tumor-targeting strategies include antibody-drug conjugates (ADCs), lipid nanoparticles, and viral vectors, each with distinct trade-offs in specificity, payload capacity, and manufacturability [5, 6]. The SNMP platform is designed to decouple the targeting interface from the delivery vehicle—SNMPs anchor to the tumor membrane extracellularly and present a recognition domain for separately engineered phage or VLP vectors. This modular design addresses a key limitation of ADC and nanoparticle systems, namely the structural coupling of targeting and payload that complicates optimization of either component independently [5]. Prior work on lipid-anchored membrane-targeting peptides and proximity-labeling systems supports the feasibility of extracellular lipid anchoring as a general strategy [3, 8].

## 3. METHODS

### 3.1 Membrane Model Construction

Tumor-mimetic lipid bilayers were constructed using the CHARMM-GUI Membrane Builder interface [version accessed December 2025]. Each bilayer consisted of 170 lipids per leaflet composed of POPC, POPS, and cholesterol in a ratio chosen to reflect the elevated anionic lipid content and cholesterol enrichment characteristic of malignant cell membranes [4]. The bilayer was solvated with explicit water and ionic strength was set to 0.15 M NaCl to replicate physiological conditions. No membrane-associated proteins or potassium ion components were included, in order to isolate peptide–lipid interactions. The pH was set to 6.5 to reflect the acidic tumor microenvironment [1].

### 3.2 Peptide Design and Sequences

Four SNMP constructs were modeled: three lipidated variants (SNMP A, B, C) and one non-lipidated control. All constructs are based on short cationic sequences designed to remain solvent-exposed after anchoring, consistent with a functional extracellular docking domain. N-terminal cysteine residues were substituted with palmitic acid using the built-in CHARMM-GUI palmitoylation residue to introduce dual-palmitoyl (di-C16) anchors. This substitution rendered the constructs fully lipidated within the CHARMM-GUI parameter set, without requiring custom force-field parameters. The sequences and key structural properties of each construct are as follows:

**SNMP A:** Pal-Pal-KKAAAKK (di-palmitoylated N-terminus; compact conformation; X = 19.5 Å, Y = 5.8 Å). Rationale: short cationic sequence designed to minimize steric bulk and maximize hydrophobic tail insertion.

**SNMP B:** Pal-Pal-RRGSSGSSGRRK (di-palmitoylated N-terminus; extended conformation; X ≈ 40 Å). Rationale: longer flexible linker sequence intended to increase extracellular reach; tested as a structural contrast to SNMP A.

**SNMP C:** Pal-Pal-KRGDKK (di-palmitoylated N-terminus; intermediate conformation; X = 34.8 Å, Y = 9.8 Å). Rationale: RGD-containing sequence intended to explore integrin-proximal membrane anchoring.

**Non-lipidated control:** KKAAAKK (identical backbone to SNMP A without palmitoyl modification). Serves as a negative control to confirm that membrane association in lipidated constructs is attributable to lipid anchoring rather than peptide backbone chemistry.

### 3.3 Static Packing Analysis

Each construct was introduced into the tumor-mimetic bilayer using CHARMM-GUI's membrane insertion and static packing functions. Molecular dynamics (MD) simulations were not performed; all analysis is based on the initial packing geometry output. The primary metrics extracted were: (1) depth of palmitoyl chain terminal carbons relative to the bilayer midplane (defined as 0 Å), with negative values indicating penetration into the hydrophobic core; (2) peptide backbone orientation relative to the bilayer normal (vertical, angled, or solvent-exposed); and (3) overall peptide conformation (compact vs. extended), assessed from coordinate file dimensions in the X and Y axes.

A construct was classified as 'inserted' when terminal carbons fell between 0 Å and −15 Å relative to the bilayer midplane. Constructs with terminal carbons above 0 Å were classified as 'solvent-exposed.' Partial insertion was designated when terminal carbons fell between 0 Å and −8 Å with a non-vertical orientation angle. These classifications reflect initial positional geometry only and do not imply dynamic stability or thermodynamic favorability.

## 4. RESULTS

CHARMM-GUI Membrane Builder generated a single tumor-mimetic bilayer system (170 lipids per leaflet: POPC, POPS, and cholesterol) into which all four SNMP constructs were independently positioned for direct comparison. Despite identical membrane composition across all four systems, the initial placement depth and orientation of each construct differed substantially, indicating that both lipidation and peptide sequence geometry influence initial membrane positioning.

### 4.1 Non-Lipidated Control

The non-lipidated control peptide was positioned entirely above the membrane surface in all packing outputs, with no penetration of the palmitoyl tail region and no contact between the peptide backbone and the acyl chain region of the bilayer. Terminal residues were located at approximately +8 to +12 Å relative to the bilayer midplane, fully within the aqueous phase. This result confirms that peptide backbone

chemistry alone does not drive spontaneous membrane association under these static packing conditions, and serves as the baseline against which lipidated constructs are interpreted.

### 4.2 SNMP A

SNMP A produced the deepest initial insertion among all constructs. Palmitoyl terminal carbons were positioned at approximately −12 to −14 Å relative to the bilayer midplane, within the hydrophobic core of the POPC/POPS bilayer. The peptide backbone remained above the membrane surface (approximately +4 to +6 Å), with a predominantly vertical acyl chain orientation. The compact conformation of SNMP A (X = 19.5 Å, Y = 5.8 Å) minimized steric interference with adjacent lipid tails. No steric clashes or lipid ring penetration artifacts were identified in the CHARMM coordinate output. This initial geometry is consistent with the known behavior of di-palmitoylated peptides in cholesterol-rich membranes and identifies SNMP A as the most promising candidate for further MD simulation.

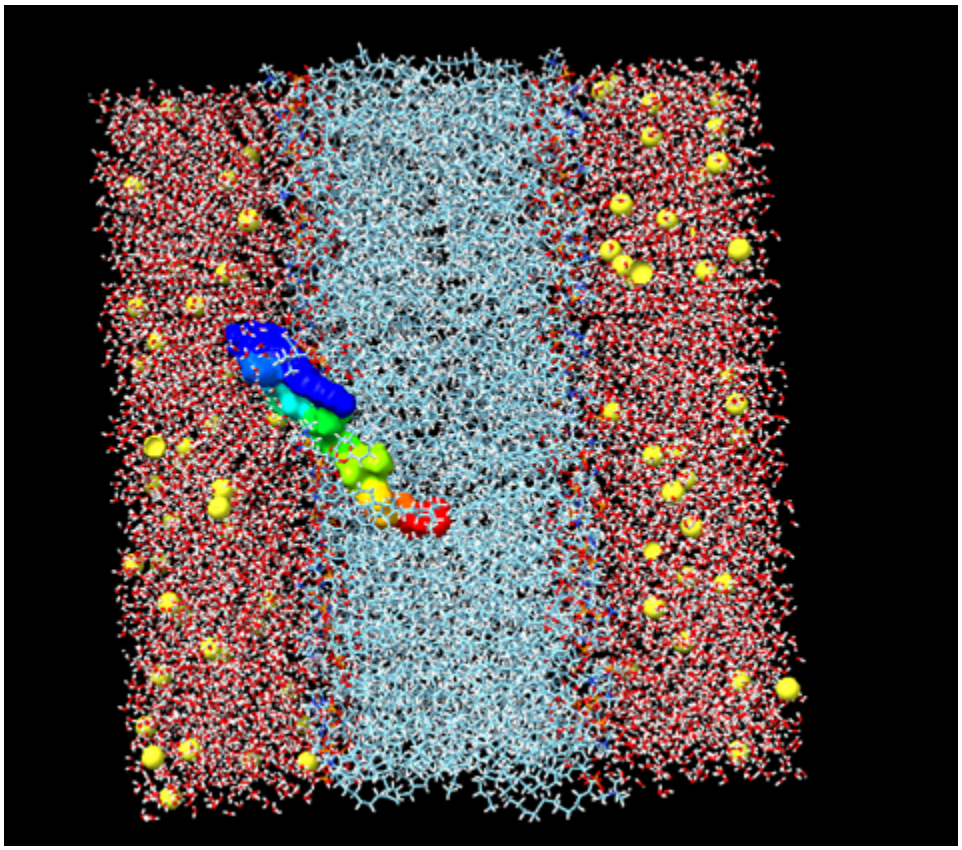

*Figure 1. SNMP A anchored in the tumor-mimetic bilayer. The di-palmitoyl lipid tail (deepest colored region) is buried in the hydrophobic core at approximately −12 to −14 Å relative to the bilayer midplane, while the cationic peptide backbone remains solvent-exposed. No steric clashes were detected in the CHARMM static packing output.*

### 4.3 SNMP C

SNMP C showed intermediate initial positioning. Palmitoyl terminal carbons were located at approximately −5 to −8 Å relative to the midplane in the most favorable packing outputs, with a non-vertical (angled) orientation relative to the bilayer normal. In some coordinate outputs, the acyl chains appeared to traverse the interfacial region diagonally rather than inserting vertically into the hydrophobic core. The larger overall dimensions of SNMP C (X = 34.8 Å, Y = 9.8 Å) likely contributed to this behavior by increasing steric bulk at the lipid–water interface. Partial insertion suggests some affinity for membrane association, though full anchoring comparable to SNMP A was not achieved in the static packing geometry. Whether environmental factors such as elevated cholesterol density or reduced pH would favor deeper insertion cannot be determined from static analysis alone.

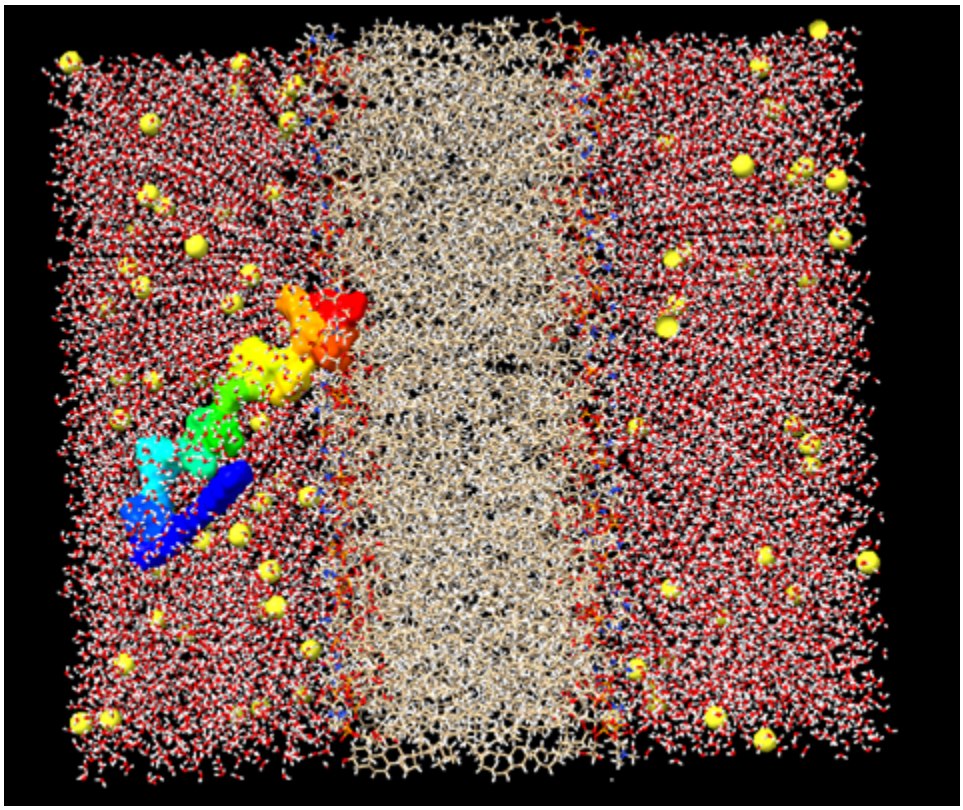

*Figure 2. SNMP C (left) and the non-lipidated control (right) in the tumor-mimetic bilayer. SNMP C shows a shallow, angled orientation at the lipid–water interface (approximately −5 to −8 Å), indicating partial insertion. The non-lipidated control is fully solvent-exposed with no penetration into the acyl chain region.*

### 4.4 SNMP B

SNMP B showed the least favorable initial positioning of the lipidated constructs. Despite carrying the same di-palmitoyl modification as SNMP A and C, the palmitoyl tails remained proximal to the aqueous

face of the bilayer, with terminal carbons located at approximately +1 to +3 Å—above the midplane and outside the hydrophobic core. The extended conformation of SNMP B (X ≈ 40 Å) appeared to prevent the packing algorithm from accommodating acyl tails into the bilayer interior without generating steric conflicts. The peptide backbone was predominantly solvent-exposed in both leaflet orientations tested. These observations suggest that the sequence-dependent extended geometry of SNMP B prevents productive initial insertion under these modeling conditions, irrespective of lipidation.

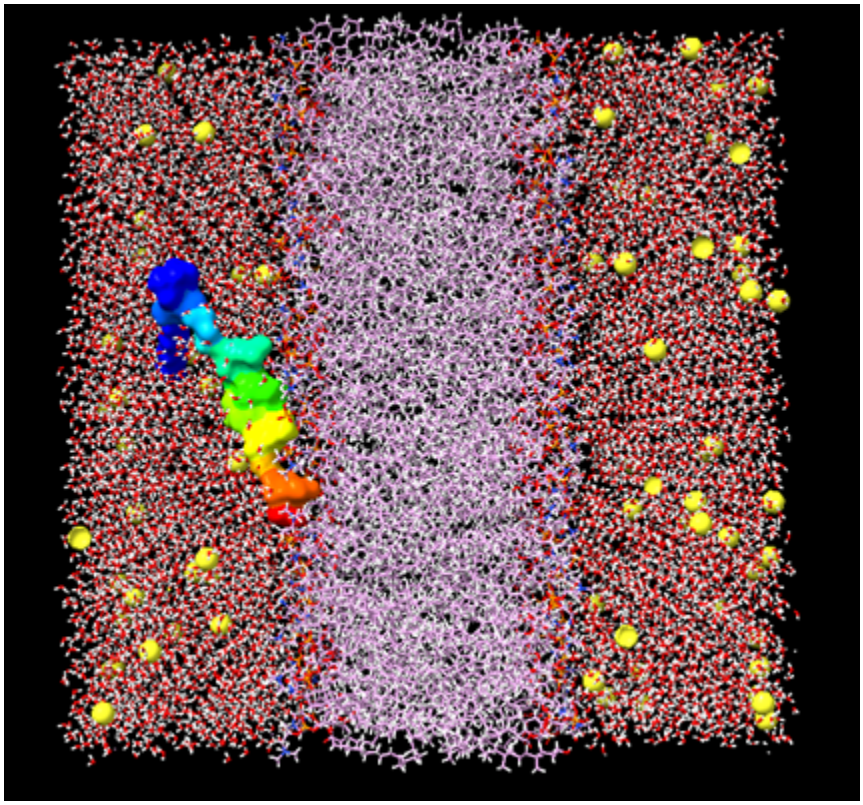

*Figure 3. SNMP B in the tumor-mimetic bilayer. Despite di-palmitoyl modification, the peptide remains entirely solvent-exposed (terminal carbons at +1 to +3 Å). The extended conformation (~40 Å in X) prevents accommodation of the acyl tails into the hydrophobic bilayer core under CHARMM static packing conditions.*

### 4.5 Summary of Quantitative Comparisons

Table 1 summarizes the key structural metrics for each construct. The ranking by initial insertion depth is: SNMP A > SNMP C > SNMP B ≈ Control (non-lipidated). All depth values reflect initial static packing geometry and should not be interpreted as equilibrium insertion depths or thermodynamic stability measurements.

**Table 1. Summary of SNMP Construct Structural Properties and Initial Insertion Metrics**

Construct | Lipidation | X Dim | Y Dim | Terminal Carbon Depth | Orientation | Classification

SNMP A | Di-palmitoyl | 19.5 Å | 5.8 Å | −12 to −14 Å | Vertical | Inserted
SNMP C | Di-palmitoyl | 34.8 Å | 9.8 Å | −5 to −8 Å | Angled | Partially inserted
SNMP B | Di-palmitoyl | ~40 Å | N/A | +1 to +3 Å | Extended/solvent | Not inserted
Control | None | ~19 Å | ~5 Å | +8 to +12 Å | Solvent-exposed | Not inserted

## 5. DISCUSSION

### 5.1 SNMP A as the Leading Candidate for Further Validation

The static packing results indicate that SNMP A achieved the deepest initial positioning of all constructs, with palmitoyl terminal carbons reaching approximately −12 to −14 Å relative to the bilayer midplane—consistent with the expected insertion depth of di-palmitoylated peptides in PC/PS bilayers as characterized by Peitzsch and McLaughlin [1] and reviewed by Resh [3]. The vertical orientation of the acyl chains and the solvent exposure of the cationic backbone are geometrically consistent with the functional requirement of the SNMP platform: the peptide must remain accessible extracellularly to serve as a docking interface for phage or VLP vectors. These findings support SNMP A as the most promising candidate for future molecular dynamics simulation and experimental insertion assays. It is important to note, however, that static packing geometry does not predict thermodynamic stability, equilibrium insertion depth, or membrane residency time; these parameters require MD simulations and, ultimately, biophysical experiments such as fluorescence depth quenching or surface plasmon resonance.

### 5.2 Structural Determinants of Insertion: Lessons from SNMP C and B

The intermediate behavior of SNMP C and the failure of SNMP B to insert despite identical lipidation patterns demonstrate that the presence of palmitoyl chains is necessary but not sufficient for productive membrane insertion. The extended conformation of SNMP B (~40 Å in X) appeared to constrain the acyl tails in orientations incompatible with hydrophobic core accommodation under CHARMM's packing algorithm. This is consistent with the concept that membrane anchoring is a property of the entire lipid–peptide entity, not of the lipid modification alone—a principle supported by studies of GPI-anchored proteins and other membrane-tethered peptides, in which backbone geometry influences lateral organization and insertion depth [4, 9].

SNMP C's partial insertion and potential environmental sensitivity raise the possibility of a tunable, conditionally inserting variant. Tumor microenvironments are typically more acidic (pH 6.2–6.8) and cholesterol-enriched than normal tissue [1, 4], conditions that may favor deeper insertion of SNMP C through electrostatic and packing effects. Whether this represents a therapeutically exploitable selectivity mechanism cannot be determined from static analysis and would require pH-titration MD simulations to evaluate.

### 5.3 Comparison with Prior Membrane-Targeting Approaches

The SNMP approach shares conceptual features with lipid-anchored membrane-targeting strategies used in proximity-labeling and cell-surface engineering [3, 8], but differs in its explicit exploitation of tumor metabolic and biophysical signatures for selective insertion. Unlike ADCs, which require direct antibody–antigen binding for targeting, the SNMP platform leverages physicochemical membrane selectivity—a potentially more robust mechanism in heterogeneous tumors with variable antigen expression [5]. Compared to lipid nanoparticle delivery systems, SNMPs offer a smaller molecular footprint and the possibility of extracellular docking without endocytosis, though payload capacity depends on the engineering of the docking vectors rather than the anchor itself [6, 11].

### 5.4 Limitations

This study has several important limitations. First, all analysis is based on static membrane packing geometry and does not capture molecular dynamics, thermal fluctuations, or equilibrium behavior. Insertion depths and orientations reported here reflect initial placement geometry only. Second, the peptide sequences used are theoretical constructs; no synthesis, experimental characterization, or cell-based validation has been performed. Third, the tumor-mimetic bilayer is a simplified model (POPC/POPS/Cholesterol) that does not capture the full complexity of tumor cell membranes, including glycolipids, membrane proteins, and asymmetric leaflet composition. Fourth, the depth values extracted are estimates from coordinate file inspection rather than rigorously computed free-energy profiles. These limitations mean that the present findings should be interpreted as a plausibility assessment and hypothesis-generation exercise, not as evidence of validated biological behavior.

## 6. CONCLUSION

This study presents a theoretical, early-stage computational assessment of membrane insertion feasibility for a family of synthetic nutrient mimicry peptide constructs. Static packing analysis in a tumor-mimetic POPC/POPS/Cholesterol bilayer demonstrated that dual-palmitoylation significantly promotes initial membrane positioning, but that successful insertion also depends critically on peptide sequence and conformation. SNMP A, with its compact geometry, achieved the deepest initial anchoring configuration (palmitoyl terminal carbons at approximately −12 to −14 Å) and is the most promising candidate for subsequent investigation. SNMP C showed partial and potentially environment-dependent insertion, suggesting tunability. SNMP B failed to insert despite lipidation, illustrating that acyl chain geometry must be compatible with overall peptide conformation to enable membrane accommodation.

These findings establish a plausible structural basis for SNMP membrane anchoring and identify SNMP A as a priority candidate for molecular dynamics validation. Future work should include all-atom MD simulations to assess insertion thermodynamics and membrane residency, experimental validation using fluorescence-based membrane insertion assays and liposome co-sedimentation, and extension of the membrane model to include additional tumor-relevant lipid species. Clinical or therapeutic relevance

cannot be claimed on the basis of the present analysis and awaits the results of this future experimental program.

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