**Department of Chemistry Honors Thesis Proposal**

Author: Student’s Name

Supervisor: Supervisor's Name

Date: Submission Date

**Title:** A concise statement reflecting the essence of the research.

**Introduction:** *Provide a brief overview of the research topic, including background information and the significance of the study. Highlight key studies and theoretical frameworks relevant to your topic and the gap in current knowledge that your research aims to fill.*

**Hypothesis:** *Clearly state the hypothesis or hypotheses that your research will test, grounded in the context of existing theories and research.*

**Objectives:** *List the primary objectives of your research. Clearly define the questions you aim to answer or the hypotheses you propose to test.*

**Methodology:** *Outline the research methods you will use to achieve your objectives. Include information on the study design, data collection techniques, and analysis plan. Specify any tools, software, or equipment you will use.*

**Expected Outcomes:** *Discuss the potential findings and their implications. Explain how your research will contribute to the field of study and what new knowledge or insights it might produce.*

**Reflection:** *Reflect on how the process of working on this project might contribute to your personal and professional growth. Consider the challenges you anticipate and how you plan to address them. Also, mention what you hope to learn from this research experience.*

**References**: *Provide a very selective list of the most critical references that support your research proposal. [This section is optional and does not count towards the two-page limit and is optional]*

**Formatting:** Arial 11 pt, 1.5-line spacing, 2-page maximum

**[Example] Department of Chemistry Honors Thesis Proposal**

**Author:** Alex Meyer

**Supervisor:** Damien Thévenin

**Date:** April 16, 2024

**Title:** A Multivariable Approach for the Rational Design of pH-sensitive Transmembrane Peptides

**Introduction:** Membrane-active peptides capable of forming pH-inducible transmembrane domains represent a significant advancement in targeted cancer therapeutics. These peptides, such as the pH(Low) Insertion Peptides (pHLIPs), are designed to exploit the acidic microenvironments of solid tumors to deliver drugs selectively. Their activity and specificity depend on the pH at which they insert in lipid bilayers (pH50). Current literature, including key studies on pHLIPs, highlights the potential of these peptides but also underscores the challenges in precisely tuning their pH50. This proposal addresses the gap in efficient, rational design methodologies for these peptides.

**Hypothesis:** Based on prior studies, the empirical tuning of pH50 for therapeutic peptides has proven challenging. Our hypothesis stems from the premise that a more structured approach using Partial Least Squares Regression (PLSR) can enhance the predictability and effectiveness of peptide design. This hypothesis builds on preliminary findings suggesting that PLSR can effectively handle the multidimensional, collinear data typical of sequence-based peptide properties. We propose that successfully implementing this methodology will enable more precise targeting of cancer cells, reducing off-target effects and improving therapeutic outcomes.

**Objectives: (1)** Develop a predictive model for the pH50 values of membrane-active peptides using PLSR, leveraging biophysical insights from existing research. **(2)** Validate the model with experimental data from pHLIP peptides and peptide agonists of receptor protein tyrosine phosphatases. **(3)** Refine the model based on experimental outcomes to increase its predictive accuracy.

**Methodology:** Our study will employ PLSR to create a predictive model for pH50 values based on peptide sequences. We will collect data on sequence properties and known pH50 values from existing literature and experimental validations. The study design will include (i) Data compilation of known peptide sequences and their pH50 values. (ii) Application of PLSR to develop the predictive model. (ii) Experimental verification and model refinement using synthetically derived peptides, assessing their insertion behavior in lipid bilayers at varying pH levels.

**Expected Outcomes:** We anticipate that the predictive model will accurately determine the pH50 values of new peptides, thereby facilitating their design for specific therapeutic contexts. This research is expected to contribute significantly to the field of targeted cancer therapy by providing a reliable tool for designing membrane-active peptides with high specificity. Moreover, the insights gained could lead to broader applications in drug delivery systems.

**Reflection**: This research will allow me to engage with a topic that may contribute to future innovations in cancer treatment, which is a driving force behind my career choice. It will also enhance my analytical skills through mastering advanced statistical methods and experimental research, which will be helpful in graduate school. Anticipated challenges include managing the high dimensionality of the data involved, which I plan to address by collaborating with biostatisticians on campus and our collaborators at UVA. This collaborative environment will provide technical solutions and expand my professional network and interpersonal skills.