# Advancing Peptide Therapeutics: A Generative AI-Driven Approach

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by

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# CERTIFICATE

It is certified that the work contained in this thesis, titled **"Advancing Peptide Therapeutics: A Generative AI-Driven Approach"** by **Vishva Saravanan Ramasubramanian**, has been carried out under my supervision and is not submitted elsewhere for a degree.

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Date Adviser: Dr. Bhaswar Ghosh

To my family and friends.

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# Abstract

The field of therapeutic peptide design is ripe for transformation, fueled by the convergence of biotechnology and artificial intelligence. Peptides, short chains of amino acids, offer a promising avenue for targeted drug therapies due to their inherent advantages over small molecules, including specificity and reduced side effects. However, the development of peptide therapeutics has been hindered by their limited oral bioavailability and susceptibility to enzymatic degradation. Recent advancements in deep learning techniques have opened new possibilities for addressing these challenges through innovative peptide design strategies.

This thesis explores the development of a novel hybrid deep learning framework for de novo peptide design. By harnessing the power of diffusion models, known for their ability to learn complex data distributions, and integrating them with binding affinity maximization algorithms, we have created a system capable of generating peptide sequences optimized for specific target receptors. To demonstrate the applicability of this framework, we focus on designing therapeutic peptides targeting proteins expressed by Plasmodium falciparum Erythrocyte Membrane Protein 1 (PfEMP1) genes, key contributors to malaria pathogenesis.

Our results highlight the potential of this hybrid deep learning approach to revolutionize peptide drug discovery. By generating peptide candidates conditioned on the binding sites of target receptors, we offer a promising avenue for developing effective therapies for malaria and other diseases. This research underscores the transformative power of AI in peptide therapeutics, paving the way for a new era of precision medicine with enhanced efficacy and reduced toxicity.

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*Chapter 1*

# Introduction

## 1.1 Computational Drug Design

The landscape of drug discovery is being reshaped by computational drug design, an interdisciplinary field that harnesses computational models, simulations, and data analysis to streamline the identification and development of novel therapeutics. [17]. Computational Drug Design encompasses a spectrum of techniques, from structure-based methods like molecular docking [11] and virtual screening [18] to ligand-based approaches like quantitative structure-activity relationship (QSAR) modeling [3] and machine learning algorithms [7].

Recent advances in artificial intelligence, particularly deep learning, have propelled computational drug design into a new era. Deep learning models, trained on massive datasets of molecular structures and bioactivity data, can predict molecular properties, binding affinities, and even generate novel drug-like molecules [21] These AI-powered tools are not only accelerating the traditionally time-consuming and costly drug discovery process but also expanding the druggable chemical space and enabling the design of personalized medicines [7]

## 1.2 Peptide Therapeutics

Peptide therapeutics have garnered significant attention due to their unique advantages over small-molecule drugs. Peptides, composed of short chains of amino acids, exhibit high target specificity, minimal off-target effects, and reduced immunogenicity [20]. Their inherent biocompatibility and the ease of chemical modifications make them versatile tools for therapeutic interventions. Peptides often contain a mix of hydrophilic and hydrophobic amino acids, which can affect their solubility and interaction with cell membranes [14]. This can impact their ability to pass through cell membranes and work effectively inside cells. Peptides with a slightly higher percentage of hydrophobic residues may have increased cell permeability [14] and be more effective at interacting with cell membranes, as hydrophobic residues can interact very well with the hydrophobic regions of lipid bi-layers, enhancing the transit of

the peptide across cell membranes [14].

Peptide-based drugs have already made a substantial impact in the treatment of various diseases. For instance, insulin, a peptide hormone, has transformed diabetes management while peptide-based antibiotics have effectively treated bacterial infections [2]. The development of peptide-based vaccines against infectious diseases and cancer is another exciting frontier in peptide therapeutics [16].

Despite their promise, peptide therapeutics face challenges like limited oral bioavailability and susceptibility to proteolytic degradation [15]. However, recent advances in peptide engineering, such as cyclization [9], incorporation of non-natural amino acids [13], and the development of novel delivery systems, are addressing these limitations and expanding the therapeutic potential of peptides.

## 1.3 Malaria

Malaria, predominantly transmitted through bites of infected female Anopheles mosquitoes, remains a significant global health burden, particularly in tropical and subtropical regions [5, 8]. Its severity is underscored by its lethality, especially in young children and pregnant women. In 2019, the World Health Organization (WHO) reported an estimated 229 million malaria cases and 409,000 deaths, highlighting the urgent need for effective treatment alternatives [10]. Around 6.3 million cases were reported from the Southeast Asia region, majority of cases were present in India [4].

The *Plasmodium falciparum* parasite, the most lethal species causing malaria, has developed resistance to multiple antimalarial drugs, highlighting the urgent need for novel therapeutic strategies [6]. This resistance hampers treatment efficacy, potentially leading to prolonged illness, increased healthcare costs, and elevated mortality risks. Beyond immediate mortality, malaria can have lasting detrimental effects on individuals, even in non-fatal cases. Recurrent infections can contribute to anemia, cognitive decline (particularly in children), and other complications, ultimately diminishing quality of life and economic productivity [19].

Peptide therapeutics offer a promising avenue for combating malaria. Peptides can target specific parasite proteins essential for survival and replication, potentially overcoming drug resistance mechanisms [12]. Additionally, the lower likelihood of resistance development against peptides compared to small molecules makes them attractive candidates for antimalarial drug development. Recent efforts have focused on designing peptide inhibitors against key parasite proteins like *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PfEMP1), which plays a crucial role in parasite sequestration and immune evasion [1]. Computational methods, particularly generative AI approaches, have proven invaluable in accelerating the discovery of novel peptide-based antimalarials by efficiently exploring the

vast peptide sequence space and identifying promising candidates with high affinity and specificity for critical parasite targets [**?**].

*Chapter 2*

# Methods

Chapter 2 goes here ...

*Chapter 3*

# Experiments

Chapter 3 goes here ...

*Chapter 4*

# Data

Chapter 4 goes here ...

*Chapter 5*

# Results and Discussion

Chapter 5 goes here ...

*Chapter 6*

# Conclusions

Conclusion goes here ....

# Related Publications

*Vishva Saravanan R, Soham Choudhuri, and Bhaswar Ghosh.* **A Hybrid Diffusion Model for Stable, Affinity-Driven, Receptor-Aware Peptide Generation**. Journal of Chemical Information and Modeling, Manuscript ID: ci-2024-010205. Submitted on 28 Apr 2024, under review.

# Bibliography


[1] Y. A. Anja Ramstedt Jensen and L. Hviid. Cerebral plasmodium falciparum malaria: The role of pfemp1 in its pathogenesis and immunity, and pfemp1-based vaccines to prevent it. *Immunol Rev*, 293:230–252, 2020.

[2] A. Cesaro, S. Lin, N. Pardi, and C. de la Fuente-Nunez. Advanced delivery systems for peptide antibiotics. *Advanced Drug Delivery Reviews*, 196:114733, 2023.

[3] L. Chang, A. Mondal, and A. Perez. Towards rational computational peptide design. *Frontiers in Bioinformatics*, 2, 2022.

[4] A. e. a. Cherkasov. Qsar modeling: where have you been? where are you going to? *Journal of medicinal chemistry*, 57:4977–5010, 2014.

[5] J. C.-F. Deisy Cristina Restrepo-Posada and J. A. Cardona-Arias. Systematic review of microeconomic analysis of pregnancy-associated malaria. *Heliyon*, 6, 2020.

[6] T. e. a. Duguma. Prevalence of malaria and associated risk factors among the community of mizan-aman town and its catchment area in southwest ethiopia. *Journal of parasitology research*, 2022, 2022.

[7] R. M. e. a. Fairhurst. Artemisinin-resistant malaria: research challenges, opportunities, and public health implications. *The American journal of tropical medicine and hygiene*, 87, 2012.

[8] E. e. a. Gawehn. Deep learning in drug discovery. *Molecular informatics*, 35:3–14, 2016.

[9] C. S. Ghosh, B. Drug design for malaria with artificial intelligence (ai). *IntechOpen*, 2021, 2021.

[10] Y.-H. T. Heather C. Hayes, Louis Y. P. Luk. Approaches for peptide and protein cyclisation. *Org Biomol Chem*, 19:3983–4001, 2021.

[11] K. e. a. Jain. Prevalence of pregnancy associated malaria in india. *Frontiers in global women's health*, 3, 2022.

[12] F. J. B. J. Kitchen DB, Decornez H. Docking and scoring in virtual screening for drug discovery: methods and applications. *Nat Rev Drug Discov*, 3:935–49, 2004.

[13] X. Li, H. Chen, N. Bahamontes-Rosa, J. F. Kun, B. Traore, P. D. Crompton, and A. H. Chishti. Plasmodium falciparum signal peptide peptidase is a promising drug target against blood stage malaria. *Biochemical and Biophysical Research Communications*, 380(3):454–459, 2009.

[14] D. P. A. Li. Yiwen. Engineering of enzymes using non-natural amino acids. *Biosci Rep*, 42, 2022.

[15] F. e. a. Madani. Mechanisms of cellular uptake of cell-penetrating peptides. *Journal of biophysics*, 2011, 2011.

[16] M. e. a. Muttenthaler. Trends in peptide drug discovery. *Nat Rev Drug Discov*, 20:309–325, 2021.

[17] A. W. e. a. Purcell. More than one reason to rethink the use of peptides in vaccine design. *Nat Rev Drug Discov*, 6:404–14, 2007.

[18] W. W. P. A. e. a. Schneider, P. Rethinking drug design in the artificial intelligence era. *Nat Rev Drug Discov*, 19:353–364, 2020.

[19] B. K. Shoichet. Virtual screening of chemical libraries. *Nature*, 432:862–5, 2004.

[20] G. P. I. Swarnim Shukla, Soham Choudhuri and B. Ghosh. Supervised learning of plasmodium falciparum life cycle stages using single-cell transcriptomes identifies crucial proteins. *Journal of Bioinformatics and Systems Biology*, 6, 2023.

[21] W. N. Z. W. Wang, L. Therapeutic peptides: current applications and future directions. *Sig Transduct Target Ther*, 7, 2022.

[22] X. Zeng, F. Wang, Y. Luo, S. gu Kang, J. Tang, F. C. Lightstone, E. F. Fang, W. Cornell, R. Nussinov, and F. Cheng. Deep generative molecular design reshapes drug discovery. *Cell Reports Medicine*, 3:100794, 2022.