# LLMs Enable Large Scale Design of Nanobodies[1]

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## Abstract

In the coming decades, AI will be one major contributor to the offense-defense balance. If we want to steer the future towards a high-robustness state, it is important to develop in advance a portfolio of defensive technologies that directly benefit from economic growth and technological progress.
What would a general defensive technology against biological threats look like? As a motivating example, we investigate whether present-day LLMs are capable of autonomous nanobody design.
Using computational tools [2] as a harness for protein design, we enable a generalist LLM to design and test nanobodies. Examination of performance trends across LLMs and reasoning efforts reveals performance improvements in the designed antibodies, demonstrating a scaling trend relevant for safety.
We argue that theoretical and empirical facts about LLMs make them exceptionally well suited for this type of hyperparameter search task [8][9]. Moreover, this type of evaluation enables both a new paradigm for capabilities assessment and potential for scaling defensive technologies.

*Keywords: AIxBio, LLM Search, Evaluations*

[1] Research conducted at the def_acc hackathon 2025

# 1. Introduction

We want to build technology that protects us from the biggest threats we will face as a society in the coming decades. To achieve this with high robustness it is important to maintain a balanced portfolio of defensive technologies that both leverage scaling factors like compute, power, and industrial capacity, while maintaining uncorrelated components that function independently of those general improvements.

Resilience against threats of biological origin is especially relevant due to direct impact on public health. This has been made apparent with the recent concerns about AI-enabled bio-threats [6][7] . But, what if we could use the power of AI for the benefit of defense?

To investigate this question, we focus on potential application of AI for Bio Defense, the automated design of pharmacological compounds. Concretely we focus on a type of protein: the nanobodies. Nanobodies (also known as Single Domain Antibodies) are a class of proteins with the ability to bind to specific antigens, much like antibodies, but substantially smaller and simpler.

Nanobodies offer potential advantages that are highly relevant for situations in which a fast reaction is necessary (like a natural or man-made pandemic). For example, nanobodies have very short development times and don't require specialized equipment to be developed, this is specially relevant when dealing with fastly evolving strains. They also have many drawbacks, which would make mass deployment very challenging.

There is growing interest in using nanobodies for pharmaceutical applications [5][10][11].

In recent years, the tools available to protein engineers have been dramatically expanded by ML-based biological models [12][13]. This is also true for nanobody design [2]. However despite the ease of use of these tools, many aspects of protein design are still poorly understood and rely on diffuse and tacit knowledge that only researchers have.

This prompts our central question: "**Can we leverage the biological knowledge present in state-of-the-art LLMs to automate the design of nanobodies?**"

To answer this question we evaluate several LLMs on the autonomous design of nanobodies for Nipah virus using RFantibody as a harness. Several in-silico metrics [4] will be used to assess the quality of the designed nanobodies.

## 2. Methods

To operationalize the Nb design task, we provide to the Agent, a specification shit with information about the Nipah virus, and the G protein (PDB ID 2VSM) (responsible for the binding to Ephrin B2, and the start of the infectious process), and request values for hyper-parameters related to the design, like the Length of the Complementarity Determining Regions or the Hotspots.

The design experiments were performed on different models under different harnesses.

**Tools:**

- No tools: The agent had access to the internet and terminal but no specific tooling for Protein Design was provided.
- Documentation Tool: The model was additionally provided with documentation about the RFantibody harness.
- Few-shot Tool: The model was provided with n-examples of previous designs and the corresponding metrics for those designs.

We will mainly report the performance of the models under each condition based on the **ipSAE** metric . This metric does not fully capture the quality of a nanobody, but has the benefit of being comparable with a human baseline of expert protein designs [1].

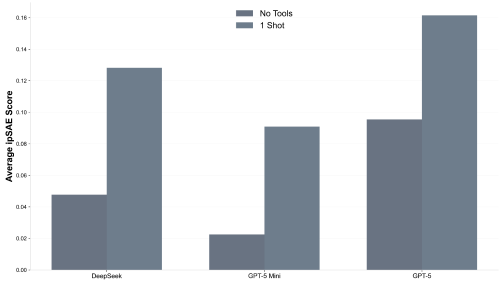


*Figure 1 – Comparison of ipSAE across models with and without the Documentation Tool*

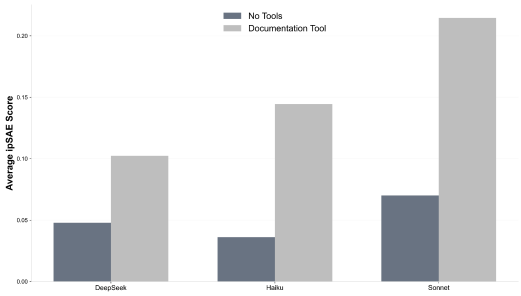


*Figure 2 – Comparison of ipSAE across models with and without the 1-Shot Tool*

## 3. Results

Showcase and explain your results here. This is where you include the graphs, screenshots, visualizations, and statistical results from your research.

*Figure 1 – Representation of benchmarking Number Comprehension Conflation*

## 4. Discussion and Conclusion

## 5. References


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## 6. Appendix

**Important:** Include an appendix called "Security Considerations" that outlines potential limitations of your approach and suggestions for future improvements.