HARP-pSAR: A pLM-based Framework for Protein Fitness Landscapes in Practical Drug Discovery

Poster D-008

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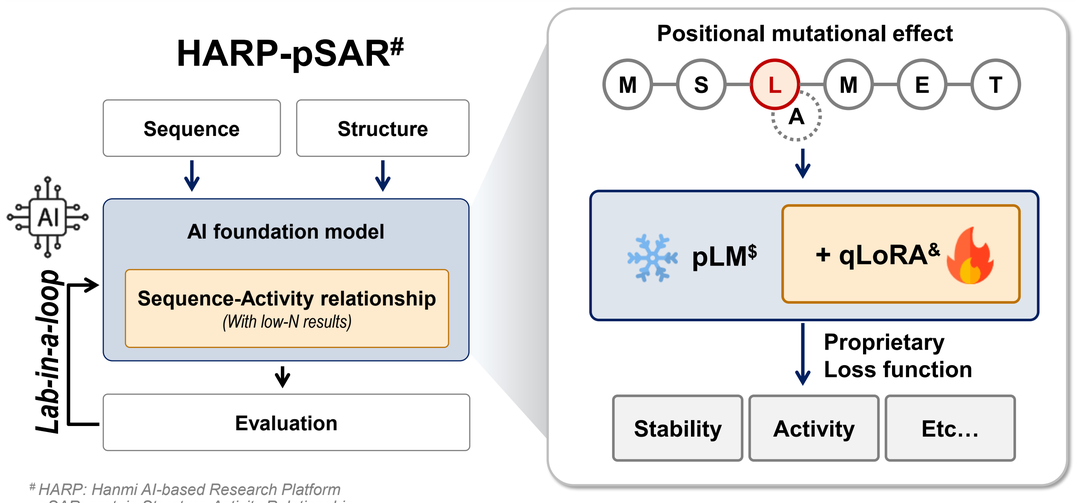
Introduction

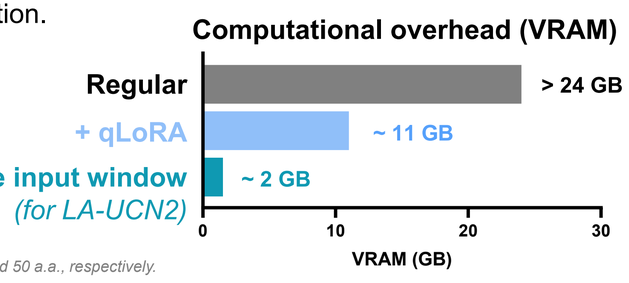
Artificial Intelligence (AI) accelerates drug discovery, but moving beyond AlphaFold's structural data to accurately predict protein fitness, such as distinguishing on-target and off-target effects, is essential for rapid candidate evaluation. BERT-based Protein Language Models (pLMs) address this by extracting intrinsic information directly from sequence data. However, acquiring experimental fitness labels is expensive and time-consuming, making reliable fitness landscape construction with 'low-N' data a major technical hurdle. To address this challenge, we introduce HARP-pSAR (Hanmi AI-driven Research Platform-Protein Sequence-Activity Relationship), one of Hanmi's AI research platform tools which is a pLM-based platform designed for fitness landscape learning under severe low-N data constraints. By applying LoRA (Low-Rank Adaptation) quantization for efficient fine-tuning, the platform significantly reduces computational overhead, allowing it to be operated directly on local PCs.

HARP-pSAR: Fitness prediction with low-N experiment data



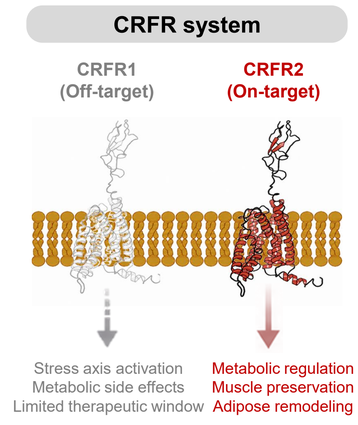
HARP: Hanmi AI-based Research Platform
pSAR: protein Structure-Activity Relationship
$ pLM: Protein Language Model
& qLoRA: Quantized Low-Rank Adaption

- **AI-based SAR for peptide/protein.**
- **Work with low-N results.** (30+ results)
- **Enhanced with lab-in-a-loop method.**
  1) Feasible candidate generation.
  2) Evaluation.
  3) Re-training AI model.
  → Generation again.

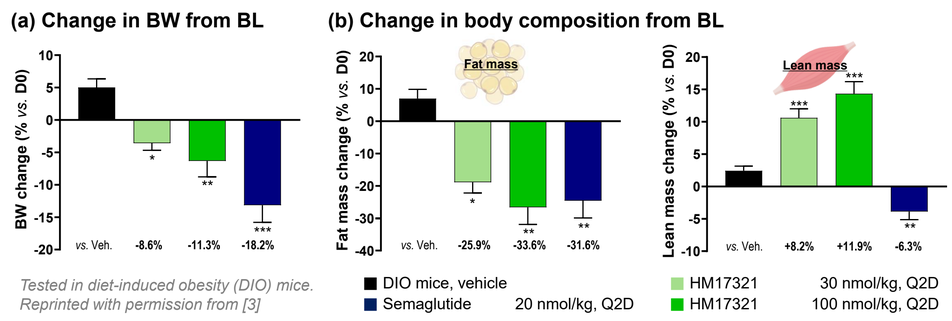


ESM-2 650M used as a foundation model.
Regular and LA-UCN2 input window is set to 200 a.a. and 50 a.a., respectively.

Case Study: LA-UCN2 (Long-acting Urocortin 2 analog)



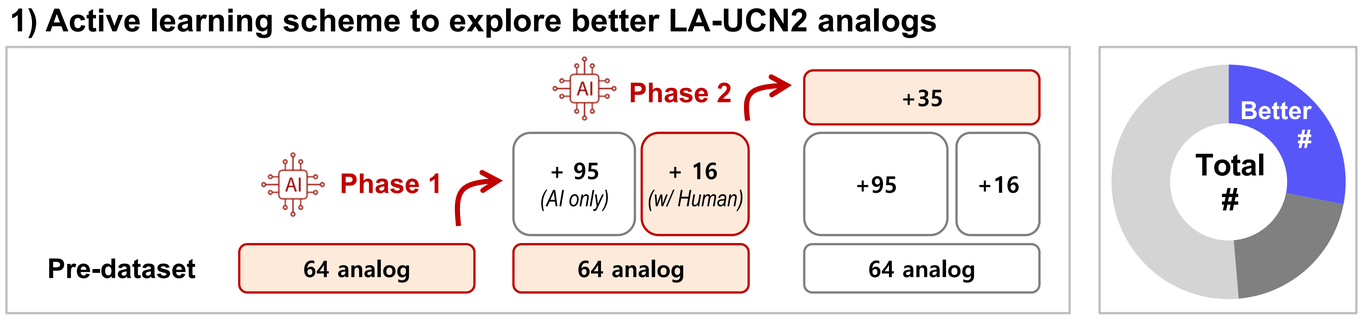
HM17321 is designed for obesity medication with lean mass maintenance.
Hanmi's LA-UCN2 (a novel long-acting CRFR2-selective UCN2 analog)



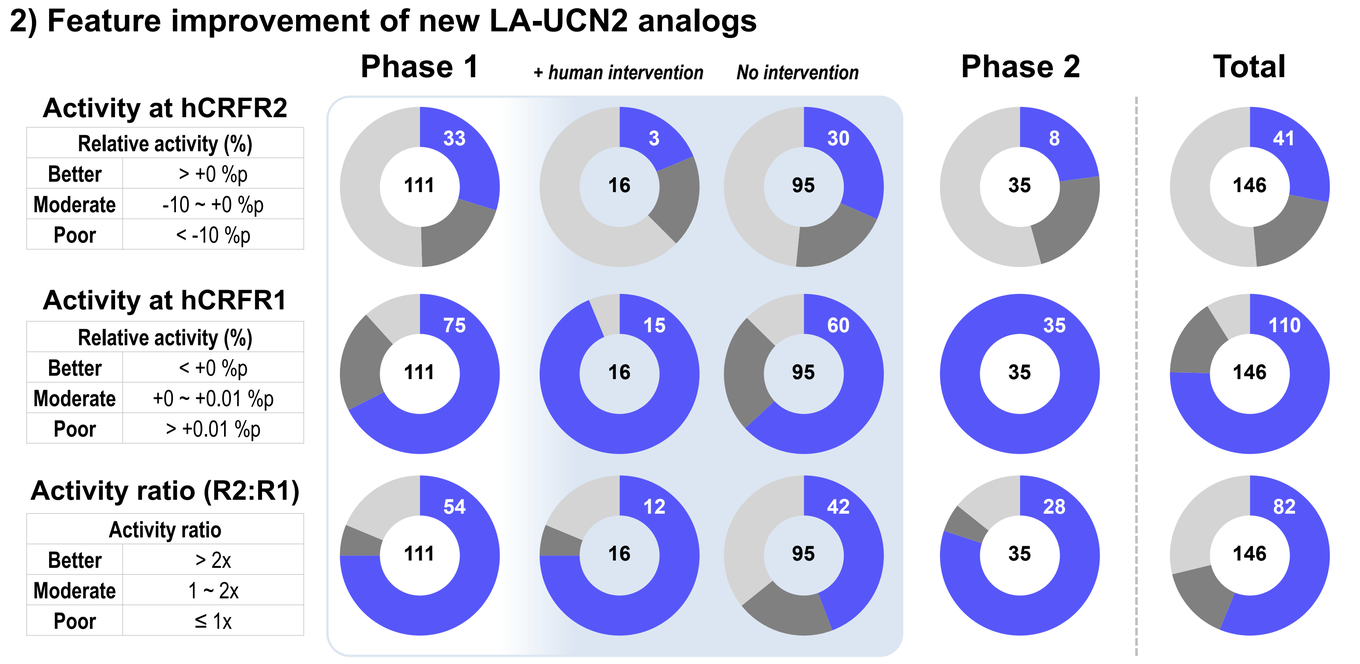
Tested in diet-induced obesity (DIO) mice.
Reprinted with permission from [3]

LA-UCN2: Active learning toward out-of-distribution (OOD) landscape

1) Active learning scheme to explore better LA-UCN2 analogs



2) Feature improvement of new LA-UCN2 analogs



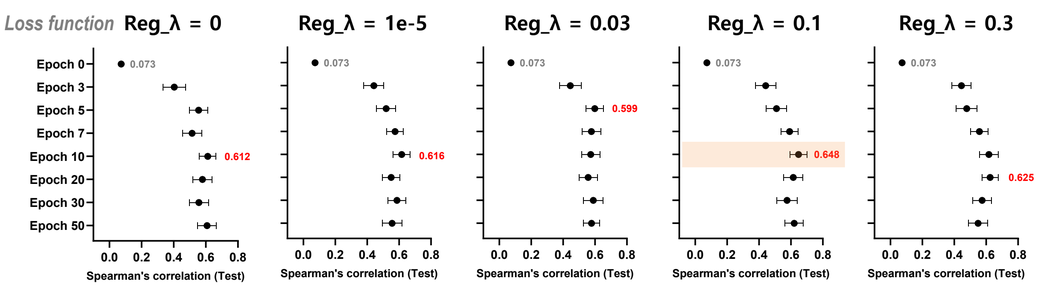
vs. Hanmi's LA-UCN2 representative analog

Framework Configuration for the case study

Feature example: CRFR1-mediated cAMP activity of LA-UCN2s

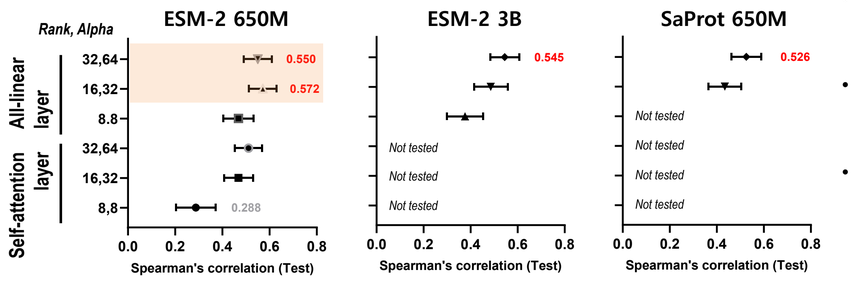
1) Training hyperparameters

Mean w/ S.E.M. (n = 30)



Partial dataset used (28 for training, 10 for test). 100-runs with distinct sampling seed.
ESM-2 650M used as a foundation model. qLoRA (4-bit quantization) was applied with r = 16 and alpha = 32 to all-linear layers.

2) Foundation model & LoRA hyperparameters

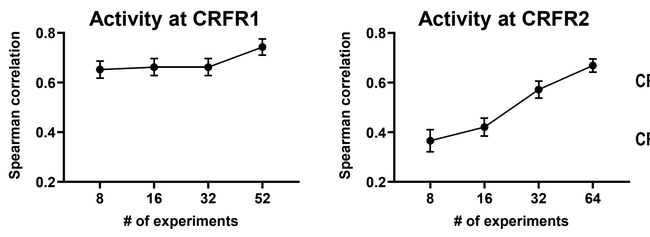


- **ESM-2 650M** *Sequence-based, developed by Meta*
- **ESM-2 3B** *Sequence-based, developed by Meta*
- **SaProt 650M** *Structure-aware, developed by Westlake University*

Partial dataset used (28 for training, 10 for test). 100-runs with distinct sampling seed.
Training epoch and loss function regularization lambda were set to 10 and 0.1, respectively.

Mean ± 95% CI (n = 100)

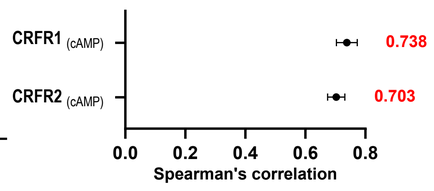
'Lab-in-a-loop' effect



Mean ± 95% CI (n = 100)

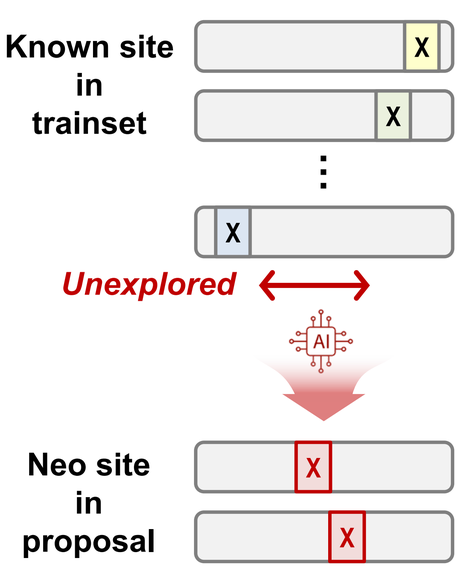
Model performance (Configured)

ESM-2 650M, the optimized hyperparameters.
52-shots (CRFR1) and 64-shots (CRFR2)



Mean ± 95% CI (n = 100)

LA-UCN2: Neo site proposal by HARP-pSAR



Activity at hCRFR2

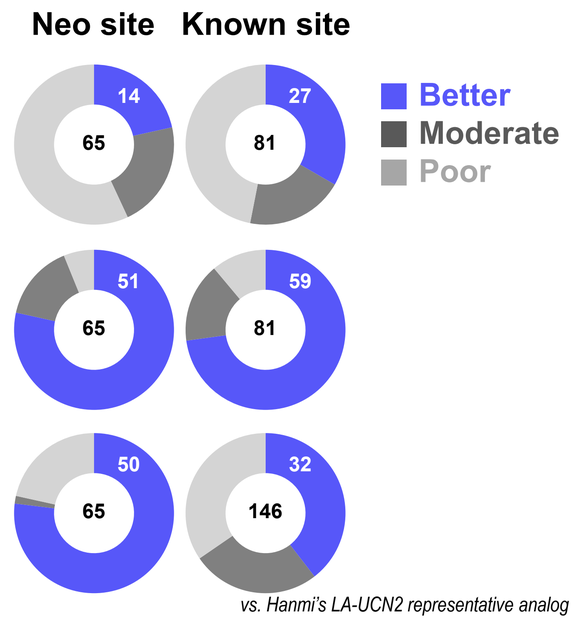
Relative activity (%)	
Better	> +0 %p
Moderate	-10 ~ +0 %p
Poor	< -10 %p

Activity at hCRFR1

Relative activity (%)	
Better	< +0 %p
Moderate	+0 ~ +0.01 %p
Poor	> +0.01 %p

Activity ratio (R2:R1)

Activity ratio	
Better	> 2x
Moderate	1 ~ 2x
Poor	≤ 1x



vs. Hanmi's LA-UCN2 representative analog

References

1. Lin et al., *Science*. 2023 Mar 17;379(6637):1123-1130.
2. Su et al., *bioRxiv*. 2024, doi: 10.1101/2023.10.01.560349.
3. Lee et al., ObesityWeek 2024 poster-504.

Concluding Remarks

- **HARP-pSAR is a pLM platform designed for low-N fitness landscape learning. LoRA quantization minimizes computational overhead, enabling high-performance AI drug discovery directly on local PCs.**
- **In study case of CRFR2-selective UCN2 analogs, HARP-pSAR demonstrated strong OOD generalization, identifying a novel, experimentally validated neo-residue site.**
- **This validates HARP-pSAR as a cost-effective, deployment-ready tool. We will extend this framework to additional pipeline assets to accelerate Hanmi's therapeutic development strategies.**