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Targeting Allosteric Sites in Drug Discovery through the Magellan™ 3.0 Physics-AI Platform

GAIN THERAPEUTICS

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Elena Cubero,[1] Ana María García-Collazo,[1] Joanne Taylor,[2] Simon Bray,[2] and Rinaldo W. Montalvao[1]

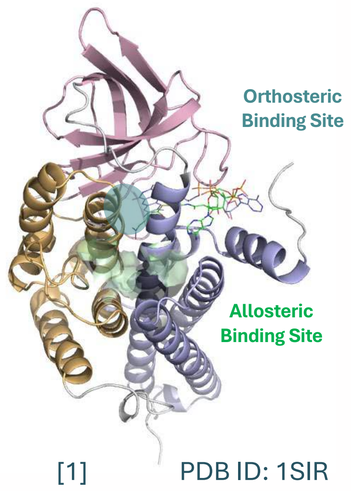
[1] Gain Therapeutics Sucursal en España, Barcelona, Spain; [2] Gain Therapeutics Inc., Bethesda, MD, USA

Introduction

Allosteric modulation unlocks precise and selective control over protein function. Unlike orthosteric ligands, allosteric modulators fine-tune activity without competing with the natural ligand - resulting in greater specificity and fewer side effects. This selectivity opens opportunities in oncology, rare diseases, and drug resistance.

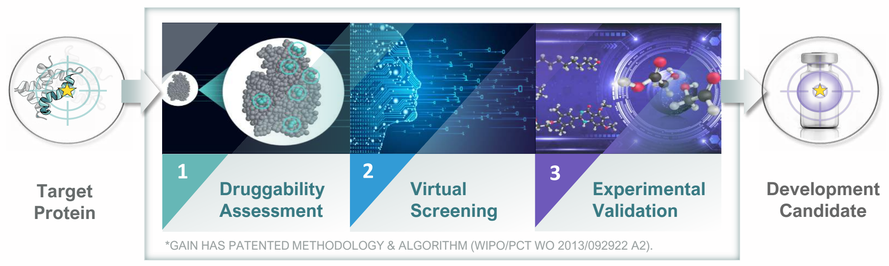
At Gain Therapeutics, we leverage our proprietary Magellan™ 3.0 physics-AI platform for advanced structure-based drug design. Magellan rapidly identifies allosteric binding pockets and screens vast chemical libraries enabling efficient discovery of novel modulators.

Although designed for allosteric site identification, Magellan is equally capable of screening any protein binding pocket (including orthosteric/ active sites), making it a versatile engine for innovative small molecule discovery.



[1] PDB ID: 1SIR

Methods – Magellan 3.0 Workflow



. **Target Protein:** Selection of disease-related proteins using available 3D structures (from experiments like X-Ray, cryo-EM, NMR, or reliable predictions such as homology modelling and AlphaFold)

. **Druggability Assessment:** Finding allosteric sites and important hotspots with molecular dynamics simulations using different solvents (MDmix)

. **Virtual Screening:** Searching huge libraries of compounds and applying advanced filtering (hotspot-guided docking, DUck scoring with AI) to select the most promising hit compounds.

. **Experimental Validation:** Confirming the effect of selected hits in the lab, then refining and advancing the best candidates.

Magellan 3.0 integrates physics-based modelling, artificial intelligence, and active learning to predict and optimize protein-ligand interactions, screening over 4.4 trillion compounds. Benchmarking against DUDE-Z and PDBBind datasets validated the performance of the platform in enriching hit compounds.

Results & Discussion – Magellan 3.0 Benchmarks

Magellan™ 3.0 incorporates a unique rapid AI-based scoring method that assesses the chemical environment and biophysical interactions of each docking pose. This AI-based scoring component has been benchmarked on ultra-large virtual screening tasks and ligand prediction, using gold-standard datasets:

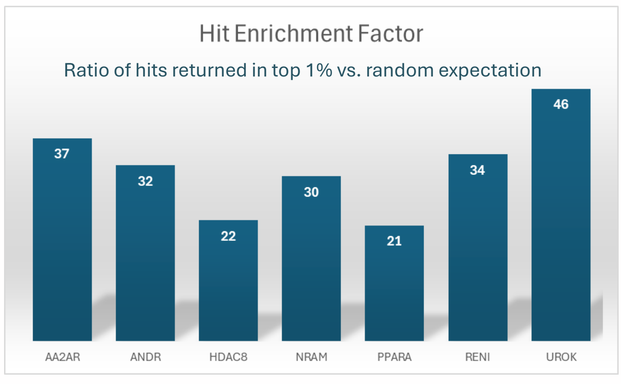
A. Virtual Screening Enrichment

- Screened over 350 million compounds across seven DUDE-Z [2] disease targets: AA2AR, ANDR, HDAC8, NRAM, PPARA, RENI, UROK
- Identified top candidates up to 46× more efficiently than random selection (minimum 21×), accelerating drug discovery

Virtual Screening Top 1% Results

Target	Actives	Decoys	Total	Selected 1%	True Positives	False Positives	Hit Enrichment Factor
AA2AR	87	4400	4487	45	19	26	37
ANDR	32	2038	2070	21	7	14	32
HDAC8	75	4035	4110	41	12	29	22
NRAM	81	5339	5420	54	17	37	30
PPARA	28	579	607	6	3	3	21
RENI	78	3189	3267	33	15	18	34
UROK	72	4326	4398	44	19	25	46

+Zinc22 ligands database (over 350 million) [3]

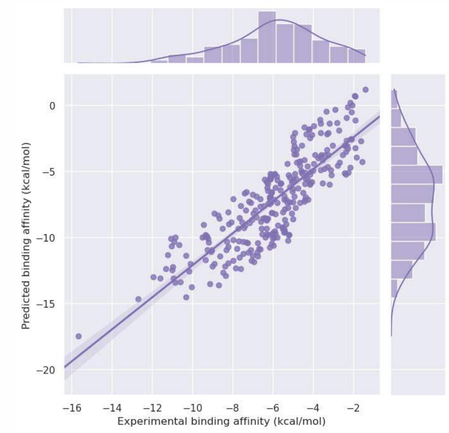


B. Quantum Mechanics Binding Prediction

Correlation between experimental and predicted drug-target binding affinities using the Victoria neural network model.

The diagonal indicates perfect agreement. Marginal histograms show the distribution of experimental (x-axis) and predicted affinities (y-axis). Pearson correlation and RMSE are reported for model accuracy.

Number of complexes: 4,057
Training dataset: 3,767
Test datasets: 290



- Ranked in the top 0.5% of published computational methods for protein-ligand prediction (PDBBind 2016 benchmark) [4]
- Results closely reflected real experimental data (Pearson Rp = 0.859; RMSE = 1.922 kcal/mol)

Comparison Table – Traditional Docking vs. Magellan 3.0

Magellan 3.0 demonstrates improvements in speed, accuracy, scalability, and allosteric detection compared to traditional docking methods, as shown in benchmark evaluations.

	Traditional Docking	Magellan 3.0
Speed	Moderate	Very High
Accuracy	Medium	Top 0.5%
Scalability	Up to 10^9	> 4 x 10^{12}
Allosteric Detection	Limited	Advanced

Conclusions

Magellan™ 3.0 integrates physics-based modelling and AI learning to improve the accuracy and scalability of virtual screening. Experimental benchmarking supports its computational robustness, and the use of generative AI may help accelerate ligand discovery cycles. These features contribute to bridging computational predictions with experimental data in drug discovery.

References:

1. Magellan, formerly named SEE-Tx; DOI: 10.1021/acs.jmedchem.4c00292
2. DUDE-Z Benchmark; DOI: 10.1021/acs.jcim.0c00598
3. ZINC20 database; DOI: 10.1021/acs.jcim.0c00675
4. PDBBind 2016 dataset; DOI: 10.57702/lqg6lwtn

Platform available for collaboration and partnership - contact details below:

ecubero@gaintherapeutics.com