Discovery and development of novel CNS-penetrating PARP1-selective inhibitors

Sarah Truong[1,2,3], Fuqiang Ban[1,3], Jason Smith[1,3], Mohit Pandey[1,3,4], Ekaterina Manskaia[1,3,4], Beibei Zhai[1,2,3], Louise Ramos[1,2,3], Mona Marzban[1,2,3], Fariba Ghaidi[1,2,3], Kally Singh[2], Hans Adomat[1,3], Xiaoqi Chen[2], John Langlands[2], Dennis Brown[2], Jeffrey Bacha[2], Colin Collins[1,3,4], Artem Cherkasov[1,3,4] & Mads Daugaard[1,2,3,4]

[1]*Vancouver Prostate Centre, Vancouver, BC, Canada*
[2]*Rakovina Therapeutics, Vancouver, BC, Canada*
[3]*M. H. Mohseni Institute of Urologic Sciences, Vancouver, BC, Canada*
[4]*Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada*

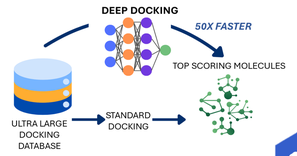
Introduction

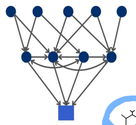
- Brain tumors, including primary brain tumors and central nervous system (CNS) metastases, remain among the most challenging malignancies to treat, with therapeutic options often limited by the inability of drugs to penetrate the blood-brain barrier[1,2].
- Breast and ovarian cancers with BRCA1 alterations exhibit higher risk of brain metastases[3,4].
- Poly(ADP-ribose) polymerase (PARP) is a key enzyme in DNA repair, and inhibition of PARP1 drives synthetic lethality in BRCA-mutated disease[5,6].
- First generation PARP inhibitors have dramatically improved patient outcomes in BRCA-mutated cancers, but are limited in their utility to treat brain malignancies as they cannot readily pass through the blood-brain barrier. Additionally, they have adverse side effects, possibly driven by the collateral inhibition of PARP2[6,7].
- Development of a PARP1-selective, CNS penetrant inhibitor could reduce toxicity, while providing a new therapeutic option for brain tumors[7].
- Traditional drug discovery methods are time-consuming and costly, necessitating innovative approaches. Artificial intelligence (AI) models enable deep and rapid exploration of chemical space, accelerating the drug discovery process.

Here, we describe the use of AI methods for the discovery and development of a novel, PARP1-selective and CNS-penetrating inhibitor.

Deep Docking™/Generative AI Modeling Processes

Using a Deep Docking algorithm, we were able to analyze billions of compounds against the target.

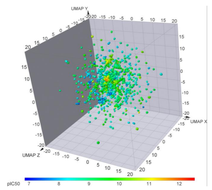




State-of-the-art artificial intelligence models empower researchers to rapidly generate novel molecular structures and evaluate multiple ADMET endpoints, including cell permeability, off-target effects, and metabolism. The seamless integration of AI accelerates the drug discovery process, enabling more efficient optimization.



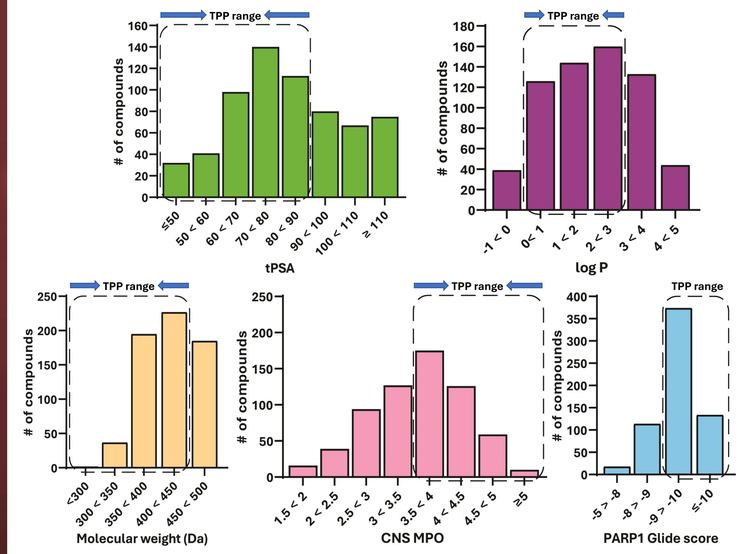
A multi-disciplinary team of biologists, chemists, computer scientists and intellectual property experts work closely to feed our proprietary state-of-the-art Generative Medchem machine with exhaustively curated data to pioneer transformative advancements in cancer therapeutics.



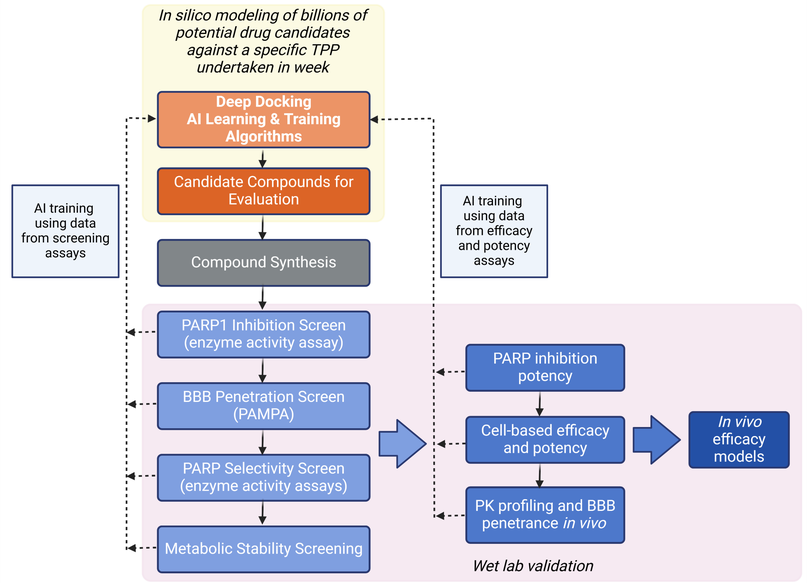
A near-spherical UMAP visualization highlights our capability to explore vast and diverse chemical spaces effectively. The dense concentration of predicted high-affinity PARP1 compounds (depicted in red) at the center underscores our precision and efficiency in identifying promising candidates.

Compound Summary

In silico screening of billions of compounds resulted in a shortlist of compounds predicted to have PARP1 selective inhibition and CNS penetrance.

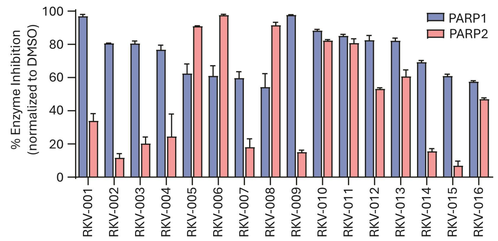


Drug Development Process



Inhibition of PARP1 and PARP2

- Activity of 389 compounds functionally assessed against PARP1 and PARP2 enzymes
  - 16 example compounds shown
- Relative selectivity based on activity against each enzyme
- **Inhibitory activity, potency of all selective and non-selective compounds from the first round are used for AI training and refining additional compound lists**



Example *In Vitro* and *In Vivo* ADME Profiling

- Compounds were evaluated for metabolic stability using human liver microsomes
- Relative metabolic stability:
  - RKV-009 = RKV-001 ≈ AZD9574 > RKV-010 > olaparib

	Slope	T ½ (min)	Cl (µl/min/mg)
RKV-001	0.0007	990	1
RKV-009	0.0003	2310	1
RKV-010	0.0023	301	8
AZD9574	0.0012	578	2
olaparib	0.0044	158	7

	T ½ (min)	C_{max}	AUC(0-∞)
RKV-001	60	3456	563364
RKV-009	132	2402	317295
RKV-010	252	14687	5128622
AZD9574	104	7367	645467
olaparib	32	2269	152617
Corrected for dose; Cmax/D = nM/(mg/kg)); AUC(0-∞)/dose= ((nM*min)/(mg/kg))			

- For selected compounds, PK profiles have been determined after a single dose administration (ip) to mice
- Relative plasma exposure:
  - RKV-010 > RKV-001 = AZD9574 > RKV-009 > olaparib

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Conclusions and Future Directions

- AI-driven drug discovery has the potential to streamline the identification of new best-in-class drug candidates for the treatment of many diseases, including cancer.
- Through Deep Docking and Generative AI, we have virtually screened billions of drug candidates to generate a curated list of small-molecule drug candidates meeting a specific target-product-profile *in silico*, specifically, novel PARP1-selective inhibitors which are brain penetrating.
- Select compounds from the first round of *in silico* screening have been synthesized and are being evaluated.
- Through the first round of screening evaluation, we have identified compounds exhibiting selectivity towards PARP1 and desirable drug-like properties.
- PARP activity and ADME data from the first round of compounds will be used to further train the AI model for refinement and lead candidate selection.

RAKOVINA THERAPEUTICS INC.
VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence
M.H. Mohseni Institute of Urologic Sciences
THE UNIVERSITY OF BRITISH COLUMBIA