AI-Assisted Combinational Targeted Drug Discovery in Ovarian Cancer

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PATTERN™

MOTIVATION

- Combinational targeted therapy is a promising strategy that has revolutionized the landscape of cancer treatment; this approach can enhance efficacy, reduce drug resistance, and decrease the chances of tumor growth and metastasis compared to single-agents thus, yielding clinical benefit.[1]
- Given the limited resources and factorial number of combinations that can be envisioned, strategies to reduce the search space and the number of experiments are needed.
- Pattern™ has developed a unique, proprietary, and innovative computational platform, 'Pattern Discovery Engine™(PDE)' that can extract patterns of relevance (genes and gene associations) within high-dimensional genomics data; these patterns can be translated into testable hypothesis (combination/ repurposed drugs).

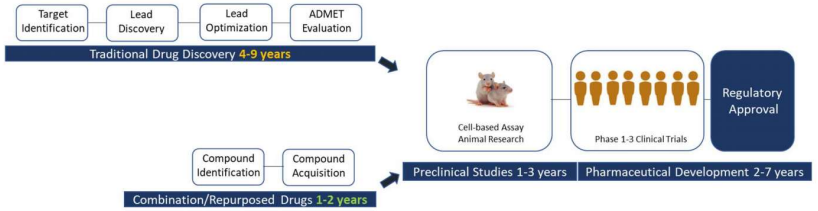

Figure 1. Pattern's AI-Assisted Drug Discovery - making the process faster, cheaper & with lower failure rates.

- This study highlights ongoing work in indications of high unmet need such as High-grade Serous Ovarian Cancer (HGSOC)[2] where using our drug discovery platform we were able to uncover unique synergistic drug pairs with distinct underlying joint mechanisms of action that elicit anti-proliferative activity against ovarian cancer growth *in vitro*.
- Given that cocktails of well-known drugs in clinics were established through a lengthy, empirical, trial and error process, our approach of identifying 'combinations by design' can:
  - **Fast-track** the unbiased **discovery of novel drug combinations**
  - **Rank-order** the most effective **drug combination for biological evaluation**
  - **Streamline** the process of **translational science *via* drug repurposing**

METHODS

- **Data-driven & hypotheses-free**. We analyze high-dimensional data with no preconceived notions. This shift elevates the data to a primary function of revealing complex structures to yield novel and often surprising correlations.
- **Drug Discovery with faster, cheaper, and with lower failure rates.** PDE can predict, within weeks, gene association networks relevant to a disease, allowing identification of actionable higher-order gene interactions. This enables us to pursue a commercial pathway from discovery to clinical trials within 12-24 months when focusing on repurposed or combination therapies.
- **Flexible.** Our discovery platform can be easily integrated into a comprehensive and flexible framework for data mining & actionable knowledge discovery allowing it to operate equally successfully in non-biomedical domains.

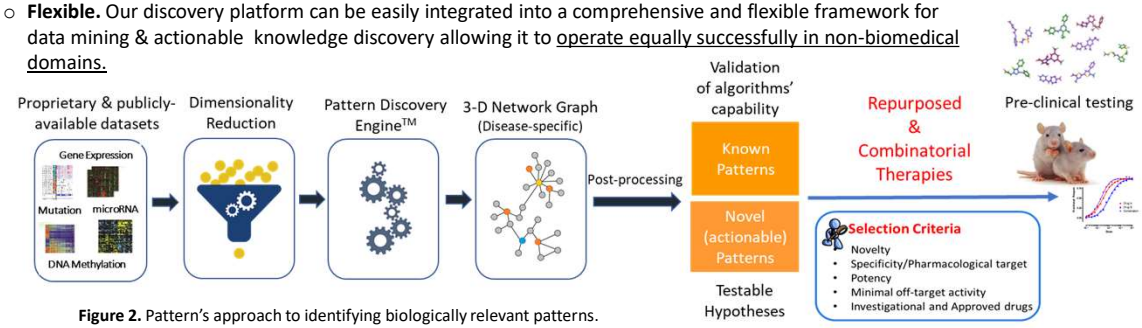

Figure 2. Pattern's approach to identifying biologically relevant patterns.

RESULTS

Table 1. The 5 potentially synergistic drug combinations against HGSOC identified using PDE. Synergy scores are generated utilizing the Bliss model contained in the SynergyFinder web-based tool.

Drug Combination	Synergy Score	Maximum Inhibition (%)	Most Synergistic Area Score
PCI-150302	15.55	91.26	38.00
PCI-150303	14.26	97.17	24.72
PCI-150304	14.08	97.55	24.16
PCI-150301	13.64	95.08	23.33
PCI-150305	15.80	80.99	31.06

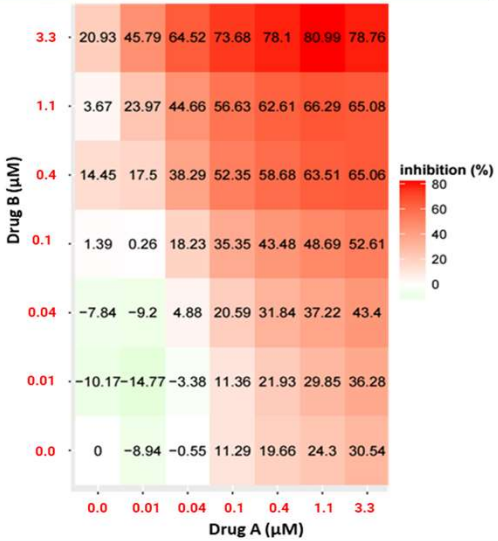

Figure 3. PCI-150305: Dose-response matrix (inhibition), left. *Redacted drugs represent proprietary Pattern™ content.

- Using PDE and publicly available HGSOC gene expression data, we identified several potentially synergistic combination drugs (*in silico* discoveries).
- The combination candidates were subjected to *in vitro* cell viability assay to determine the combination interaction of submitted compounds in a custom panel of 3 human ovarian tumor cell lines - OV90, OVCAR3 and CaoV3.
- Among the limited number of potential candidates submitted, five combinations demonstrated significant synergy in killing cancer growth, Table 1.
- A representative dose response matrix for one of the successful combinations is shown (right)
- Further validation through targeted *in vivo* studies is currently underway.

CONCLUSIONS

- Using Pattern's drug discovery platform, in combination with genomics dataset, we identified and validated 5 novel potentially synergistic combination therapies against one of the most prevalent and lethal form of Ovarian cancer.
- The systematic and computationally exhaustive search for repurposed/combination drug discovery that our engine achieves may overcome the many challenges in identifying novel, effective drug combination therapies and getting approval for their clinical usage.
- Our platform tools can be easily directed toward drug discovery efforts in the search for equally promising treatment candidates for other complex and intractable disease types.

REFERENCES

1. Jin H, Wang L, Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nat Rev Drug Discov.* 2023 Mar;22(3):213-234.
2. Dion L., Carton I., Jaillard S., *et al.* (2020). The landscape and therapeutic implications of molecular profiles in epithelial ovarian cancer. *J. Clin. Med.* 9 (7), 2239.