VERISIMLife

Case Study

Predicting Translatable Drug Combinations for ADCs -A Pharma Partner Case study

Introduction

- Among blood cancers, acute myeloid leukemia (AML) and diffuse large B-cell lymphoma (DLBCL) are the most rapidly progressing tumors, with malignant cells interfering with the production of normal white blood cells, red blood cells, and platelets. Current chemotherapy regimens cure only a minority of patients with AML and DLBCL.
- One of the promising approaches to AML and DLBCL therapies includes the administration of antibody-drug conjugates (ADC) delivering highly toxic antitumor agent payloads linked to highly specific antibodies.
- Unlike conventional systemic distributed chemotherapy, this approach that we implemented for our partner targeted specific cancer cells, reducing the toxic side effects patients otherwise endure during treatment.



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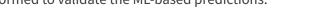
How VeriSIM Life Helped

- VeriSIM Life investigated for our client **Debiopharm** a novel drug combination strategy that combines ADCs with current therapies to enhance their effectiveness in reducing tumor burden.
 - their effectiveness in reducing tumor burden. VeriSIM Life's hybrid AI computational platform, BIOiSIM[®], ranked the predicted optimal combinations with regard to efficacy based on our multi-dimensional Translational Index[™] technology.

Learn more about the BIOiSIM drug decision engine.

Challenges and Approach

- Predictions of combinatorial drug efficacy are extremely difficult for antitumor agents, especially those in different modalities. Numerous targets and pathways affected by the drugs produce multiple choices of therapy efficiencies. VeriSIM Life addressed this complexity by using digital biological models driven by artificial intelligence (AI) and machine learning (ML) to simulate the combined potency and the efficacy of ADCs and other modalities.
- This approach was especially useful because experimental efficacy data is typically sparse or non-existent for novel therapeutic agent combinations.
- The application of ML also helped predict synergy or inhibition induced by individual small molecules or an ADC-linked payload inside cancer tumor cells. The proliferation rate of the therapeutic agents in tumor cells can be simulated to predict potency in vitro and in vivo across multiple animal models. More specifically, confirming experiments can then be performed to validate the ML-based predictions.



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• The complexity of the therapy with regard to toxicity potential was also taken into account. The project synthesized the existing predictive capabilities of the BIOiSIM platform with project-specific data and models to ultimately rank investigative anticancer combinatorial therapies.

Solution

- PKPD monotherapy digital models were designed to evaluate the efficacy of a monotherapy at an arbitrary dosing regimen.
- Tumor-specific ML models were then trained to provide concentration-dependent predictions of synergy or inhibition between two therapeutic agents.
- A matrix of dosing regimens was created for each combinatorial therapy to evaluate the predicted combinatorial efficacy at different dosing regimens.



- Finally, a combinatorial therapy's dosing matrix was then analyzed to establish the following metrics:
 - Maximum and average inhibition predicted across a dosing matrix.
 - Average potency predicted across a dosing matrix.
 - Average predicted synergy of therapeutic agents inside tumor cells.
 - Therapy count: In general, combinations with fewer therapies were preferred, as there is a lower chance of negative interactions between the compounds or toxicity concerns.
- Each metric above was a component of the project-specific Translational Index. VeriSIM Life worked with the team at Debiopharm to establish relative weights of importance for each of absolute inhibition, potency, synergy of compounds, and complexity of therapy. A multidimensional Translational Index score was generated for each combinatorial therapy, the end result being a ranking of Debiopharm's combinatorial therapies from most promising to least promising.

Results

Translational index values served as a ranking tool indicating the most and less efficacious combination of drugs regardless of their modalities (see Table). *In vivo* studies confirmed the predicted efficacy and other dimensions of the various modules used to synthesize the Translational Index score.

Drug combination	Translational Index [™]
Chemo combination W	6.00
Chemo combination X	5.65
Chemo combination Y	4.85
Chemo combination Z	4.66

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Conclusion

The multidimensional Translational Index is a customizable, transparent, and objective summary of a therapy's experimental and predicted outcomes. It enables an investigator to make informed decisions on which compounds progress to the next stage of development and its potential likelihood of success towards the clinic.

The AI-driven predictions of the ADC and therapeutic agents combinations evaluated in this project suggested the most efficacious combination. Guided by these predictions, Debiopharm was able to reduce the total volume of studies, focusing only on the highest probability candidates.

"Our mission at Debiopharm is to develop tomorrow's standard of care for cancer and improve patient quality of life. Accelerating the translation of our research to clinical success is a priority, and our work with VeriSIM Life is focused on this critical objective. With insights from the BIOiSIM platform, we believe our innovative therapies will rapidly move closer to addressing the unmet needs of cancer patients worldwide."

- Dr. Valerie Nicolas, Deputy to the Head of Translational Medicine at Debiopharm

About VeriSIM Life

VeriSIM Life, founded in 2017, brings together a team of world-class scientists, machine learning engineers, and in silico simulation experts to optimize drug development discovery and research using computational approaches to reduce trial, error and animal testing. The company partners with notable clients including Mayo Clinic, Daiichi-Sankyo and Locus Biosciences, and has garnered grants, funding and recognition from leaders across industry and the public sector.

Learn More

<u>Contact us</u> today to see how VeriSIM Life can transform your asset program. **Explore our online** <u>resources</u> and <u>publications</u>