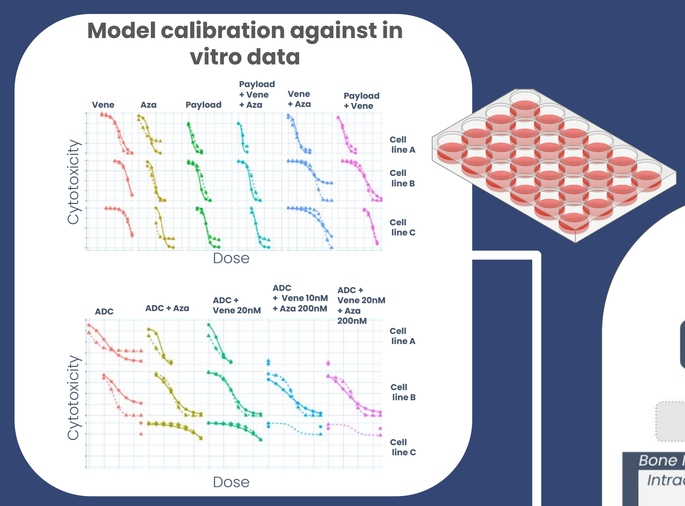
From rich preclinical datasets to virtual patients: a QSP framework to support the development of an ADC in AML

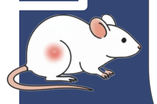
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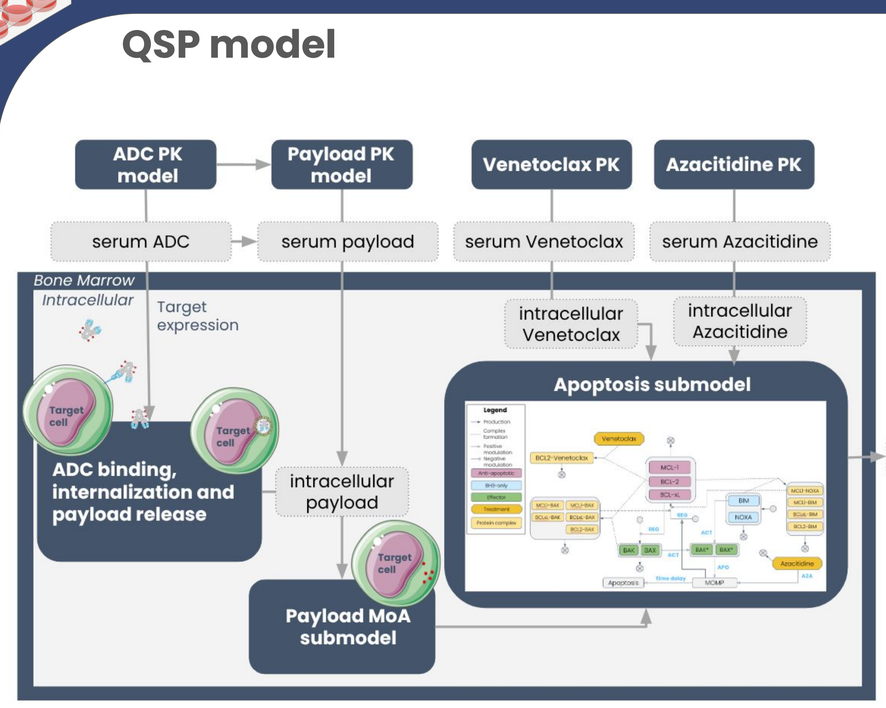
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Integration of **complex preclinical signals** into a QSP model ...

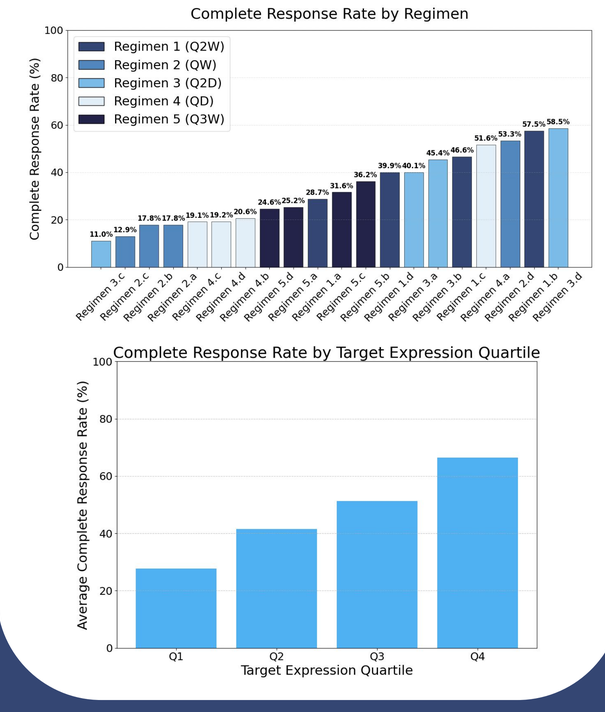
...to provide **clinical insights** allowing for systematic exploration of dosing schedules.











BACKGROUND

Acute myeloid leukemia (AML) is associated with poor long-term outcomes, even after adoption of venetoclax plus azacitidine for patients unfit for intensive chemotherapy [1]. Antibody–drug conjugates (ADCs) deliver potent cytotoxics selectively but exhibit complex, often non-linear exposure–response relationships.

Combining ADCs with standard of care seems a key strategy to overcome resistance [2]. We developed a QSP model integrating the mechanisms of a novel ADC with venetoclax and azacitidine. This model combines extensive preclinical datasets with AML knowledge to explore dose and schedule options before first-in-human studies.

METHODS

A mechanistic apoptosis module tailored to the available dataset was developed to capture BCL-2 pathway and its modulation by Venetoclax and Azacitidine. This core module was integrated with ADC-specific processes: target binding, internalization, and payload release, linking cytotoxic signaling to the apoptotic cascade. We integrated these into an in vitro AML model and calibrated against cytotoxicity and apoptosis biomarkers.

In vitro assays	Cell lines	Doses
Internalization and binding	2	2
Relative values of 5 apoptosis cascade proteins under ADC and payload	2	Baseline values
Growth inhibition under ADC and payload	2	10
Relative values of MC1-BIM and BCL2-BIM complexes under ADC, payload and Venetoclax	1	10
Growth inhibition under ADC, payload and Venetoclax	2	6
Growth inhibition (%) under Azacitidine as single agent or in combination	3	7
Total = 258 experimental conditions and 381 data points		

The framework was then translated to mouse and cynomolgus monkey by adding species-specific PK and target-mediated drug disposition (TMDD). These in vivo models were calibrated against PK data and leukemic-burden trajectories across Cell Derived Xenograft (CDX) and Patient Derived Xenograft (PDX) data.

To bridge preclinical findings to the clinic, a translational framework was developed linking clinical PK (scaled allometrically from cynomolgus for the ADC) with a PDX-mirrored AML PD model. A Virtual Population (VPOP) was built, inheriting PD parameters from seven mouse PDX-derived profiles, supplemented with variability in target concentration and clonal heterogeneity.

RESULTS

The calibrated models demonstrated robust alignment with an extensive preclinical dataset. In vitro, the framework successfully captured payload-release kinetics, biomarker modulation, and growth inhibition across more than 250 experimental conditions.

In vivo, the model accurately captured the PK profiles of the ADC, payload, venetoclax, and azacitidine, while replicating the diverse tumor-response dynamics observed across CDX/PDX models and over 80 dosing regimens.

This framework was used to explore alternative translational hypotheses across more than 100 ADC + Venetoclax dosing schedules spanning seven trial-design dimensions. Although several dose-schedule combinations led to enhanced leukemic burden reduction, the predicted benefit of sequencing strategies varied across translational assumptions. The simulations did not allow to identify one single optimal combination but highlighted key biological drivers—such as clonal heterogeneity and target availability—as primary determinants of dosing schedule sensitivity.

CONCLUSION

- ➔ This work shows a mechanistic QSP framework that reconciles extensive in vitro and in vivo datasets through a multi-stage calibration process. By integrating payload kinetics, biomarker modulation, and tumor-burden trajectories across CDX and PDX models, we established a robust foundation for human translation.
- ➔ Simulations identified promising candidate regimens and highlighted key efficacy drivers, providing a quantitative basis for trial design and for advancing more effective AML therapies.

REFERENCES

[1] Jiménez-Vicente. et al. (2025); [2] Inase et al. (2026); Detailed references available upon request.