Towards a QSP platform to support drug development in hematological cancers

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Our QSP platform enables the exploration **of drug regimen** for hematological diseases, improving trial design and success.

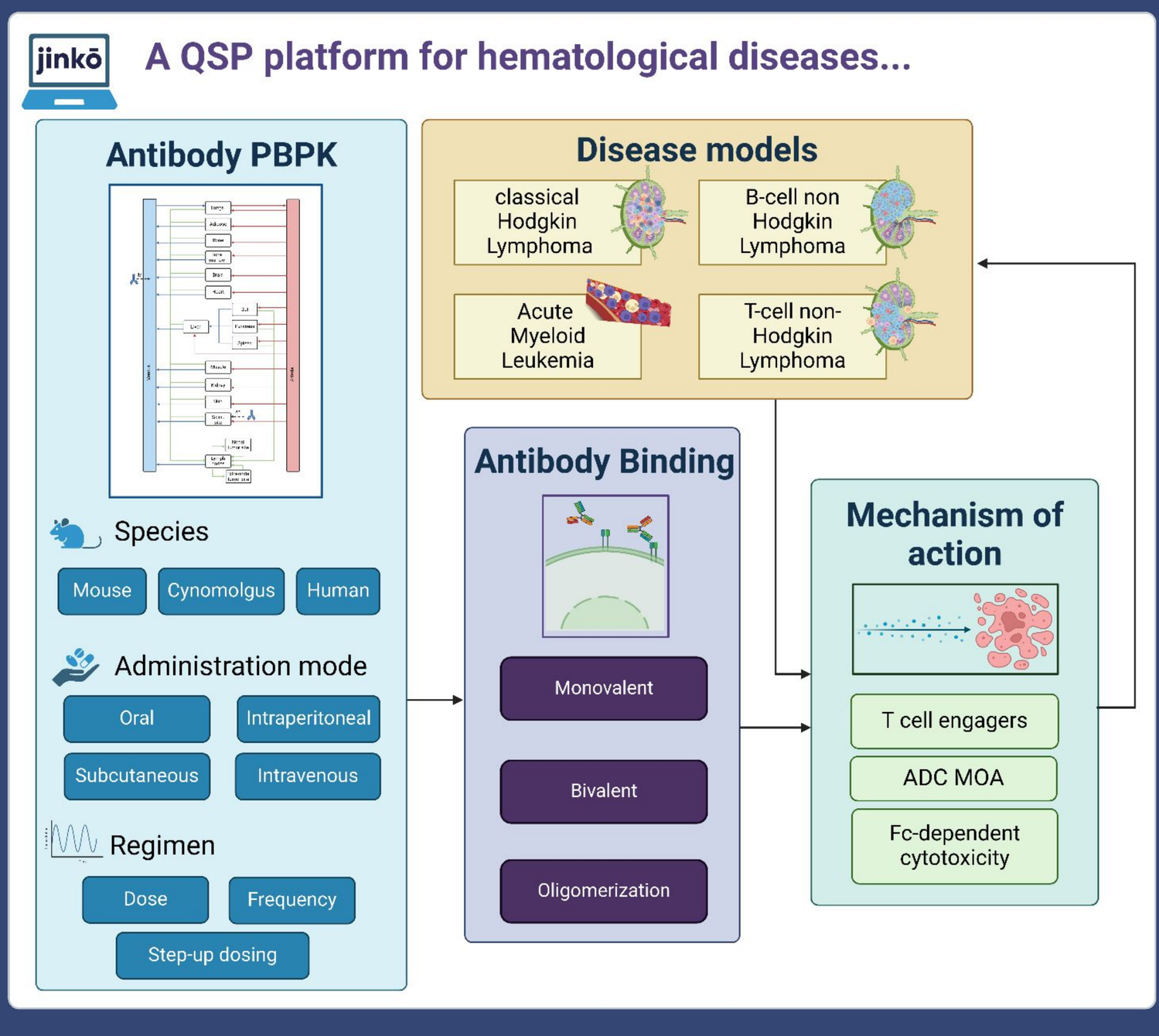

Figure 1: Overview of the QSP platform and its submodules and how the platform allows to answer various research questions

BACKGROUND

The development of new treatments for hematological cancers, such as classical Hodgkin lymphoma (cHL) and T-cell or B-cell non-Hodgkin lymphomas (TCL or B-NHL), faces significant challenges due to the heterogeneous nature of these diseases. Each type of lymphoid malignancy exhibits distinct biological behaviors concerning tumor proliferation, immune response, and resistance to treatment. Choosing the optimal drug regimen is crucial. A Quantitative Systems Pharmacology (QSP) platform offers a promising solution by allowing researchers to explore various treatment scenarios virtually and identify the treatment maximizing efficacy. This innovative approach provides valuable insights into clinical research by simulating in silico trials and optimizing therapeutic strategies.

METHODS

The QSP platform was built using a modular approach, employing ordinary differential equations (ODEs) to capture the complex dynamics of hematological cancers and drug interactions. We suggest to focus here on a model developed for an Antibody Drug Conjugate (ADC) treatment. This model was calibrated using in vitro data, human pharmacokinetic (PK) data, as shown in Figure 2, and human PD data for cHL, as shown in Figure 3, and TCL diseases (not shown). Simulations were conducted on the Jinkō platform [1] to explore different treatment regimens for a virtual population of classical Hodgkin Lymphoma patients.

RESULTS

➢ The QSP platform incorporates several key components:
- A mechanistic **cancer** submodel for each specific disease —cHL, TCL, and B-nHL— that details the proliferation of malignant cells, the tumor microenvironment, as well as the tumor heterogeneity.
- A **full body PBPK** submodel designed to predict the concentration and distribution of antibodies in the different organs.
- A **treatment** submodel that simulates the mechanism of action of the ADC, including its binding to the target cells, internalization, and the subsequent release and impact of the therapeutic payload.

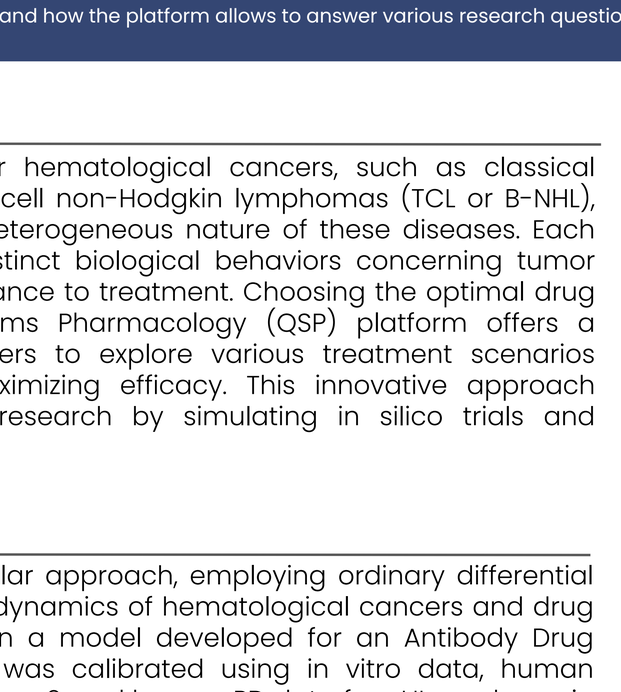

Figure 2: Calibration of the plasma total ADC and payload concentration for different regimen

➢ The model accurately replicates the observed in vitro cytotoxicity, PK dynamics, and human clinical responses to treatment and the validation of the plasma PK proved successful.

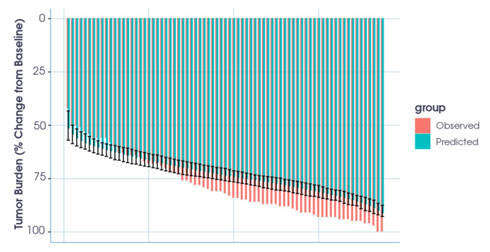

Figure 3: Best tumor change from baseline. Comparison between observed and bootstrapped percentile prediction interval for 200 virtual patients

Use case

As a use case, a multi-arm in silico trial comparing different doses and two administration modes was launched on the classical Hodgkin lymphoma calibrated virtual population to investigate the impact of both dose and administration frequency. Figure 4 shows that the time to response seems to be a function of both the dose and the frequency. Higher doses lead to shorter time to response while higher frequency increases the response variability, especially for smaller doses. In order to achieve optimal efficacy, a lower frequency seems particularly beneficial at lower doses.

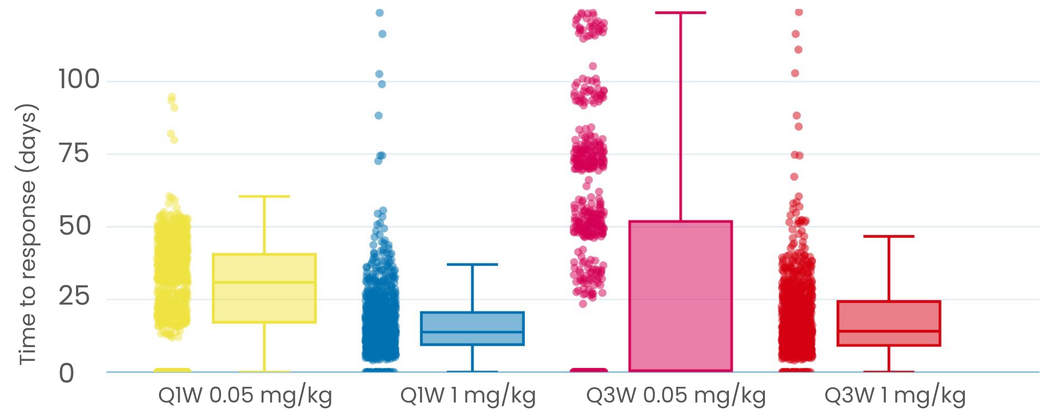

Figure 4: Distribution of the time to response in the virtual population for each arm of the trial.

Conclusions

This work paves the way for a transformative QSP platform that can significantly impact drug development for blood cancers. By integrating a wide range of data and insights from various diseases and treatments, this platform can help optimizing trial design, identifying optimal drug regimens, and predicting efficacy across multiple indications. Prospective validation is essential for its adoption in drug development pipelines.

REFERENCES

[1] https://www.jinko.ai/