Towards a computational QSP platform to support ADC design in cancer

Théo Galland[1], Claire Couty[1*], Brian Topp[2], Jim Bosley[1], Simon Arsène[1], Azher Hussain[2], Lara Bruezière[1]

[1] Nova In Silico, Lyon, France; [2] Merck & Co., Inc., Rahway, NJ, USA; * Presenting author

BACKGROUND

Antibody-drug conjugates (ADCs) are innovative therapies designed to selectively target and deliver cytotoxic drugs to cancer cells. However, their development is often hampered by the intricate interplay between the antibody, linker, and payload components that significantly influence the distribution, potency, and overall efficacy of ADCs. To streamline the development process and enhance the prediction of therapeutic outcomes, we propose leveraging data from both approved and under investigation ADCs to build a QSP platform that can support drug development. In this context, we present our initial progress in developing such a platform, using PADCEV as a case study. PADCEV is a Nectin-4 targeting ADC with Monomethyl auristatin E (MMAE) as cytotoxic payload. By using PADCEV as an example, we demonstrate how our QSP platform can help in optimizing trial design.

A QSP platform to **optimize the drug development process** of antibody-drug conjugates (ADCs)

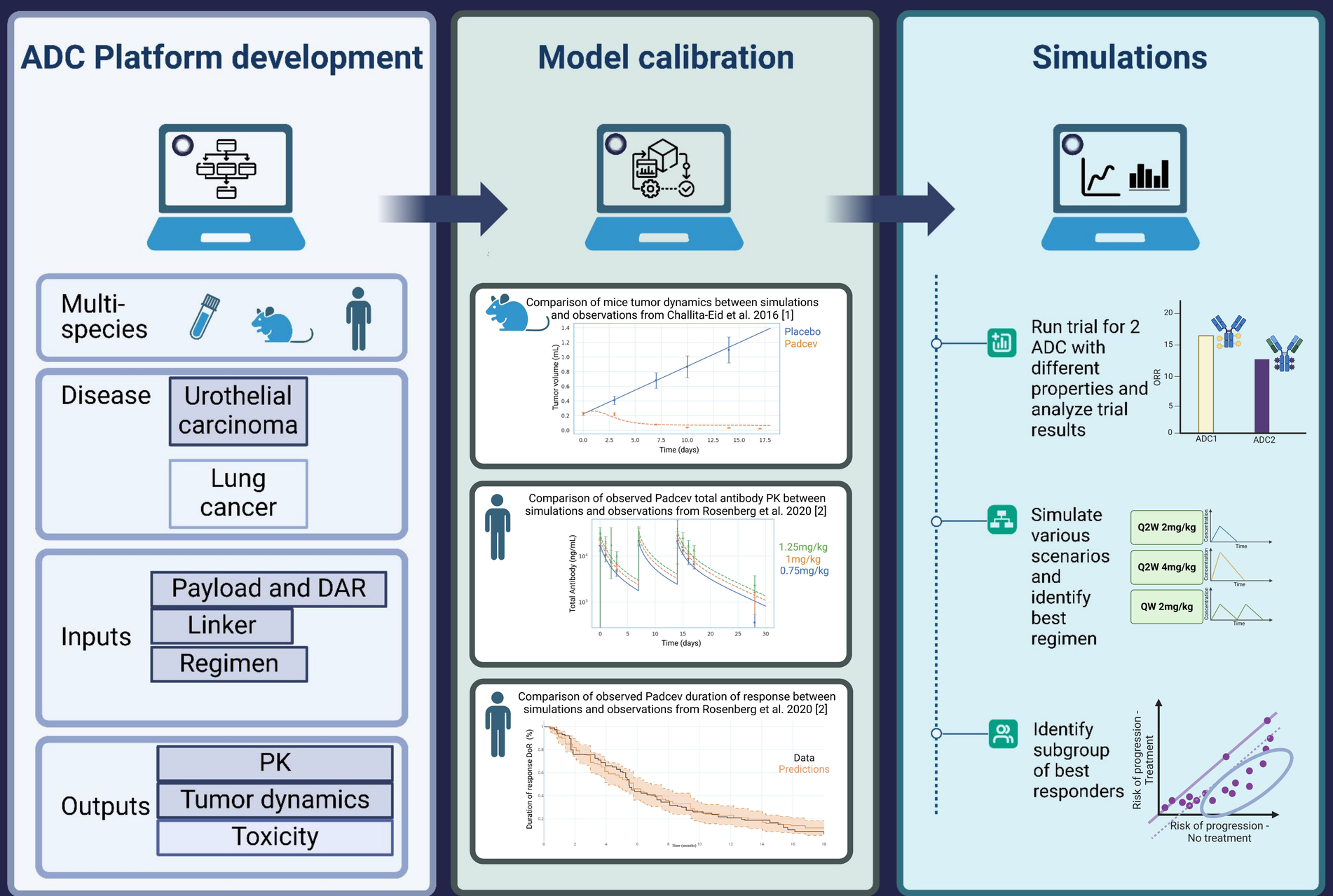

Figure 1: ADC platform development process from model development to model calibration to finally investigate and explore research questions

METHODS

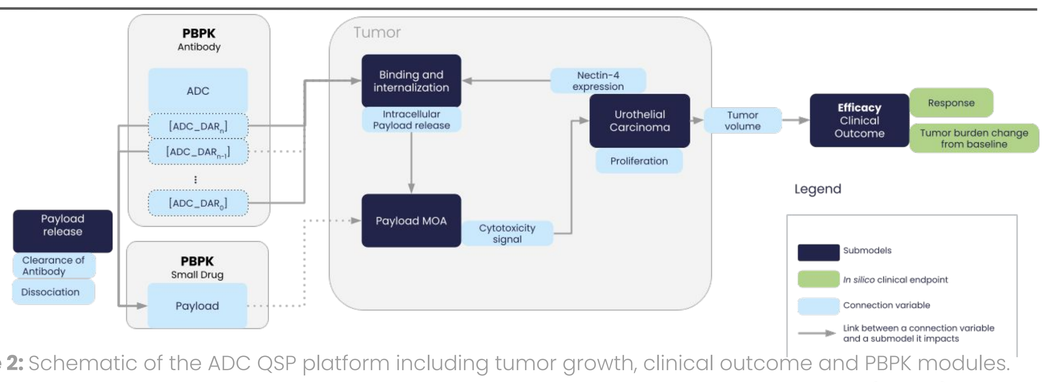

Figure 2: Schematic of the ADC QSP platform including tumor growth, clinical outcome and PBPK modules.

We developed a multi-species physiologically-based pharmacokinetic (PBPK) model to simulate the distribution of ADCs and free payloads. A DAR-based clearance and dissociation were added, higher DAR increasing non-specific clearance [3], and leading to more dissociation [4][5]. This model, trained with literature pharmacokinetic data from mouse studies (free MMAE) and human data (PADCEV), incorporates payload release via on-target binding or non-specific clearance and integrates ADC binding and internalization. Due to the lack of specific in vitro data for PADCEV, we used data from Brentuximab Vedotin (BV), which shares the same linker and payload, to inform our model. We then connected this to a Simeoni tumor growth model (Figure 2) to replicate preclinical bladder cancer tumor profiles. Finally, we trained the model with PADCEV efficacy literature data from both mice experiments [1] and a Phase 1 study [2], using a realistic virtual population to match Phase 1 outcomes.

RESULTS

Informed by PADCEV pharmacokinetics (PK) data and supported by in vitro data from Brentuximab Vedotin (BV), the platform accurately captures the PK of PADCEV, including the free payload, total antibody, and ADC, and replicates efficacy outcomes from a preclinical experiment [1] and a Phase I study [2] (Figure 1).

Simulations: impact of regimen on progression free survival (PFS)

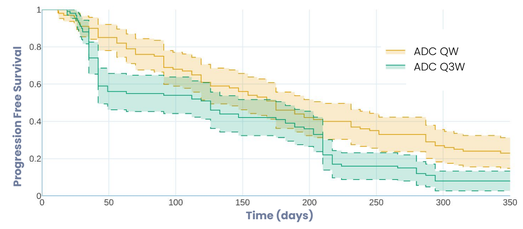

Figure 3: Time to progression and 95% confidence intervals estimated using the Kaplan-Meier estimator

We used the Jinkō platform to investigate the impact of administration regimen on time to progression. We ran an exploratory 2-arm in silico trial on a virtual population of 100 patients with the previously calibrated ADC model:

- Arm A with QW 1 mg/kg regimen
- Arm B with Q3W 3 mg/kg regimen.

We chose the total dose administered during a cycle to be similar between both arms so that the exposure is the same in the two scenarios.

Patients receiving more frequent treatment showed a prolonged duration of response, suggesting a slower rate of disease progression, as illustrated in Figure 3. Less frequent administration with higher doses leads indeed to higher peak-to-trough ratio and decreases the time spent above critical efficacy threshold, resulting in more rapid disease progression.

CONCLUSION

Our study introduces a QSP platform designed for ADCs, demonstrated through its application to PADCEV. This platform effectively models ADC PK and efficacy, addressing key development challenges. As a proof of concept, we show the potential for optimizing ADC design by evaluating factors such as linker stability and minimizing off-target effects. Enhanced by data from similar ADCs such as Brentuximab Vedotin (BV), the platform hold promises to reduce development time and costs through more efficient trial design and outcome prediction. Future expansions could include additional ADCs, adverse effect analysis, and adaptation for various cancer types.

REFERENCES

[1] Challita-Eid et al. (2016); [2] Rosenberg et al. (2020). [3] Hamblett et al. (2004) [4] Sanderson et al. (2005) [5] Bender et al (2005). Detailed references available upon request.