Identification of predictive biomarkers of response to ADCs by HTS of highly molecularly characterized panels of patient-derived organoids (PDOs)

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INTRODUCTION

Antibody-drug conjugates (ADCs) such as the NECTIN-4 targeting agent enfortumab vedotin, the HER2-targeting agent trastuzumab deruxtecan, and the TROP-2 targeting agent sacituzumab govitecan, have resulted in increased clinical response rates in previously difficult to treat solid tumor indications, but only a minority of patients exhibit such responses. Increased understanding of the molecular underpinnings of sensitivity and resistance to ADCs beyond membranous target expression is needed. To that end, we developed a cohesive systems biology platform that pairs functional screening of extensive panels of multimodal characterized patient-derived organoids (PDOs) and anchoring findings in real world data (RWD). Here, we report on a screening panel of 65 PDOs representing 10 solid tumor indications and focus on response to the NECTIN-4 targeting ADC, enfortumab vedotin.

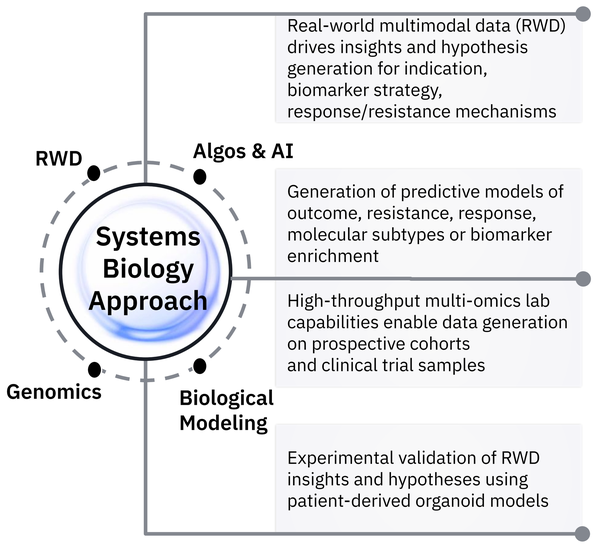


Figure 1. Tempus provides tumor platforms that balance disease relevance and scale, and combine with real-world data (RWD) to uncover meaningful drug response insights to rapidly advance client programs/pipelines.

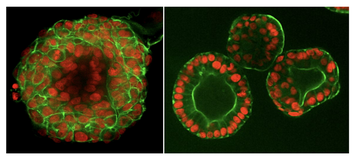
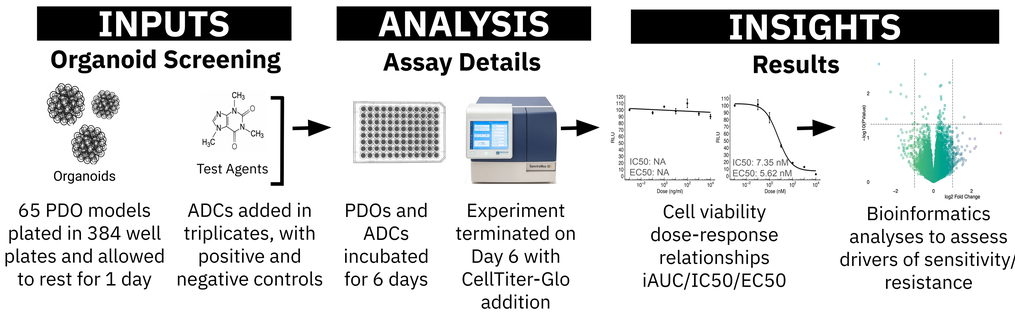


Figure 2. PDOs more accurately recapitulate the tumor microenvironment compared to traditional 2D cell line cultures.

METHODS



- Drug response was quantified using a normalized inverse area under the curve metric (iAUC), where higher values indicate a larger reduction in viability.
- Full transcriptome RNA-seq data from xR (Tempus real world data platform) was initially quantified with our standard pipeline (Kallisto, hg19)
- Genes were selected that had a mean expression >1 TPM log2+1 and had a variance across PDOs >1 (n=4,695)
- A final gene list was selected using an elastic net regression and genes were selected utilizing bootstrapping, within 1 standard error of the min lambda and were included in at least 50 of 100 bootstraps.

RESULTS

Heatmap of ADC and payload efficacy across PDOs

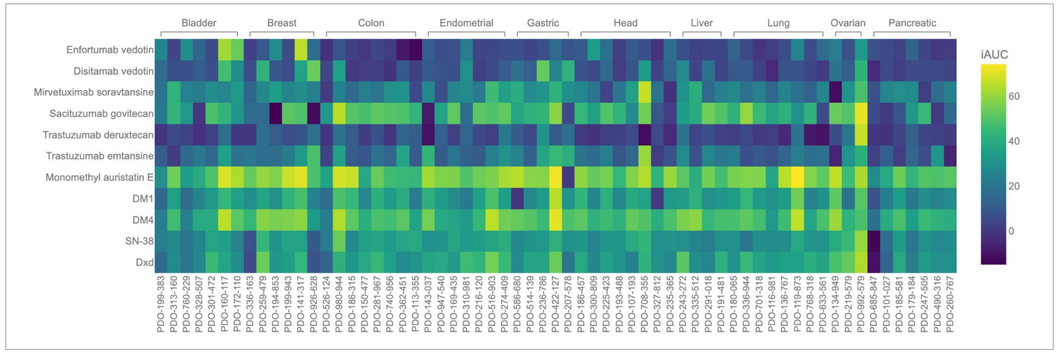


Figure 3. Heatmap of the inverse area under the curve (iAUC) for PDOs across 10 cancer types. The X-axis represents individual PDO models, while the Y-axis displays the screened antibody-drug conjugates (ADCs) and their payloads.

PDO sensitivity to enfortumab vedotin is correlated with NECTIN-4 expression

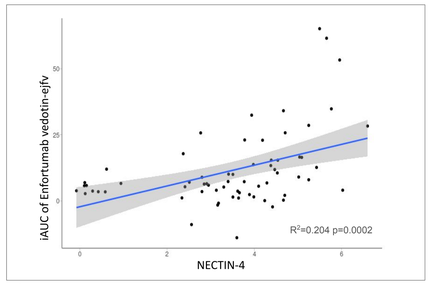


Figure 4. Comparison of PDO response to enfortumab vedotin (measured as iAUC) and NECTIN-4 expression (Log2(TPM+1)).

PDO sensitivity to enfortumab vedotin exhibits a strong correlation with the enfortumab vedotin sensitivity signature (EVSS) score

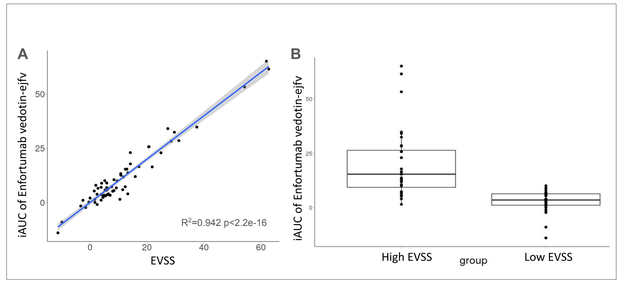


Figure 5. Narrowing down the EVSS from the whole transcriptome including NECTIN-4 without informed or forced selection. (A) Correlation between PDO enfortumab vedotin (EV) dose-response iAUC and EVSS. (B) Box plots depicting the correlation between EVSS and iAUC of EV dose response.

Patients with high enfortumab vedotin sensitivity signature had significantly prolonged progression-free survival specifically in urinary tract malignancies treated with enfortumab vedotin

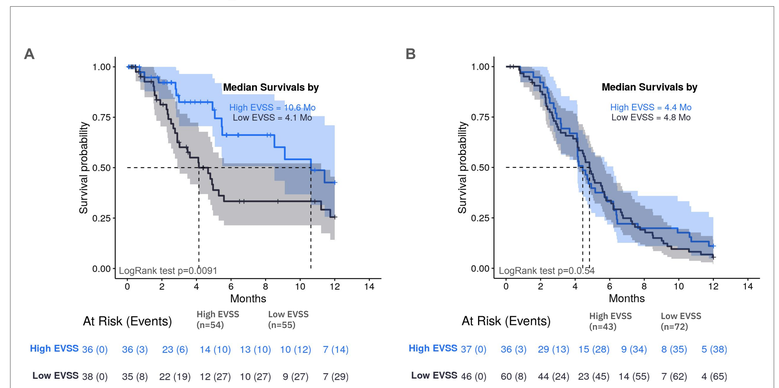


Figure 6. Real-world data on clinical outcomes in urinary tract patients with NECTIN-4 gene alterations. The Kaplan-Meier curves illustrate progression-free survival (PFS) stratified by high and low EVSS:
(A) Patients with pre-treatment biopsies who received EV.
(B) Patients with pre-treatment biopsies who did not receive EV.

SUMMARY

- Our results demonstrate that screening pan-indication panels of PDOs can reveal ADC specific differences in efficacy which are rooted in molecular factors that include, but are not limited to target expression.
- Further analysis is ongoing, including establishing the prevalence of non-ADC target biomarkers in real-world patient populations via projection of our screen-derived data onto Tempus RWD.

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