A translational QSP model to characterize the preclinical pharmacodynamics of combining a KRAS G12C inhibitor with a SHP2 inhibitor

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Background

- Divarasib, a covalent inhibitor targeting the Kirsten rat sarcoma virus oncogene homologue glycine-to-cysteine mutation at position 12 (KRAS G12C), is currently in clinical development for Non Small Cell Lung Cancer (NSCLC) treatment, with various combination partners, such as the Src homology region 2 domain-containing phosphatase-2 (SHP2) inhibitor migoprotafib.
- A quantitative systems pharmacology (QSP) model is essential to quantitatively assess the single-agent and combination pharmacodynamic (PD) effects observed in the preclinical setting to reveal the potential mechanisms of enhanced PD in the combination setting and enable translation of clinical dosing regimen.

Methods

- Extensive single-agent and combination experiments to evaluate the PD effects of divarasib and migoprotafib were performed with H2122, a NSCLC cell line harboring the KRAS G12C mutation, both in an in vitro setting and in a mouse xenograft model (Fig 1).
- These studies quantitatively assessed the concentration-response relationship with the following key PD endpoints: i) target occupancy by KRAS G12C alkylation, ii) mitogen-activated protein kinase (MAPK) pathway inhibition by the changes of phosphorylated extracellular signal-regulated kinase (pERK) in vitro, and the negative feedback regulation by transcript levels of dual-specificity phosphatase (DUSP6) and Sprouty (SPRY4) in mice tumor.
- A QSP model was adapted from literature (Sayama et al) to include the following components: in vitro media free concentrations or mouse plasma free drug pharmacokinetics, covalent binding of divarasib to KRAS G12C in its inactive state, reversible binding of migoprotafib to SHP2 protein, and MAPK pathway signaling components including pERK, DUSP6 and SPRY4. The PD effect of drug combination was implicitly inferred by the interactions of these signaling molecules (Fig 2).

Results

- The QSP model structure is shown in Fig 3. A total of 31 QSP model parameters were calibrated to simultaneously fit for both the in vitro and mouse PD data.
- The model adequately described the in vitro shift in divarasib concentration - response curves by the combination of migoprotafib, quantifying the enhanced KRAS G12C alkylation and pERK inhibition (Fig 4 & 5).
- The model also quantified the mice PD data, including a deeper KRAS G12C alkylation, DUSP6 inhibition & SPRY4 inhibition (data not shown), longer duration of response and slower rebound to the baseline by combination, compared to single-agent divarasib in H2122 xenograft tumor model (Fig 6 & 7).
- The model fitting results suggested that the model's assumption of the mechanism of migoprotafib on enhancing divarasib PD mainly through increasing KRAS G12C alkylation adequately described experimental data.

Conclusions

- A translational QSP model was established to characterize the preclinical PD of the combination of divarasib and migoprotafib.
- The model can be readily adapted as a platform model to quantify the combination PD of divarasib / migoprotafib with other MAPK pathway inhibitors, and the PD of new molecular entities in development, such as other KRAS inhibitors.

References

1. Sayama H, et al., Virtual clinical trial simulations for a novel KRASG12C inhibitor (ASP2453) in non-small cell lung cancer. CPT-PSP Vol 10, 864-877, 2021

Acknowledgements

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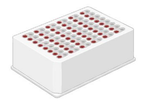
Experimental data: in vivo & in vitro

Mouse PK/PD study (H2122 tumor)

- Divarasib and migoprotafib: single-agent and combination at various dose levels
- Alkylation%: derived from %unalkylated KRAS G12C by LC-MS/MS
- DUSP6, SPRY4: gene expression (mRNA) by high throughout Fluidigm RT-PCR technology



In vitro study (H2122 cell line)

- Divarasib and migoprotafib: single-agent and combination at various concentrations
- Alkylation%: measured by immunofluorescence assay (2D assay) using conformation-locking antibodies for molecular probes (CLAMPs)
- Phospho-ERK: immunofluorescence assay (2D assay) using pERK specific antibody

Fig 1. Experimental data from in vitro and preclinical for model calibration

Translational QSP modeling workflow

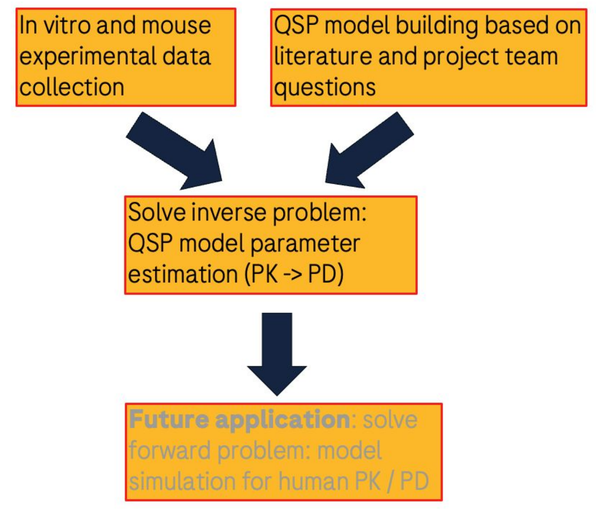


Fig 2 Translational QSP modeling workflow

QSP model structure

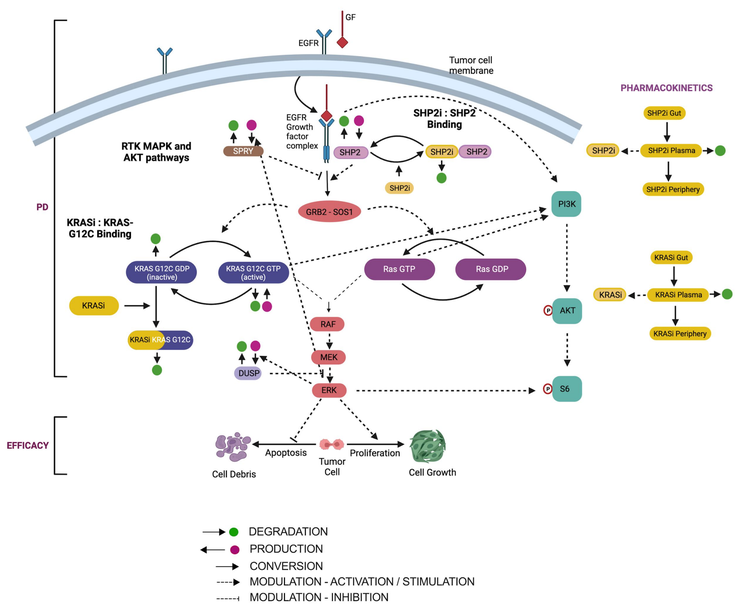


Fig 3. QSP model structure to describe EGFR-MAPK pathway and drug pharmacology (generated from Biorender)

$$\text{Alkylation \%} = \frac{\text{KRASi-KRAS-G12C}}{\text{KRASi-KRAS-G12C} + \text{KRAS G12C GDP} + \text{KRAS G12C GTP}} \times 100\%$$

$$\frac{d(\text{DUSP})}{dt} = \left(\text{DUSP\_prod\_rate\_k} \times \frac{\text{ERK}}{\text{ERK\_DUSP\_prod\_rate\_EC50} + \text{ERK}}\right) - (\text{DUSP\_clearance\_rate\_k} \times \text{DUSP})$$

$$\frac{d(\text{SPRY})}{dt} = \left(\text{SPRY\_prod\_rate\_k} \times \frac{\text{ERK}}{\text{ERK\_SPRY\_prod\_rate\_EC50} + \text{ERK}}\right) - (\text{SPRY\_clearance\_rate\_k} \times \text{SPRY})$$

- Model is composed of ordinary differential equations (ODEs) and initial / repeated assignment rules; 31 model parameters estimated by global search
- Key PD endpoints: alkylation% of KRAS G12C, DUSP6, SPRY4, pERK change from baseline

QSP model fitting to in vitro H2122 cell line PD data

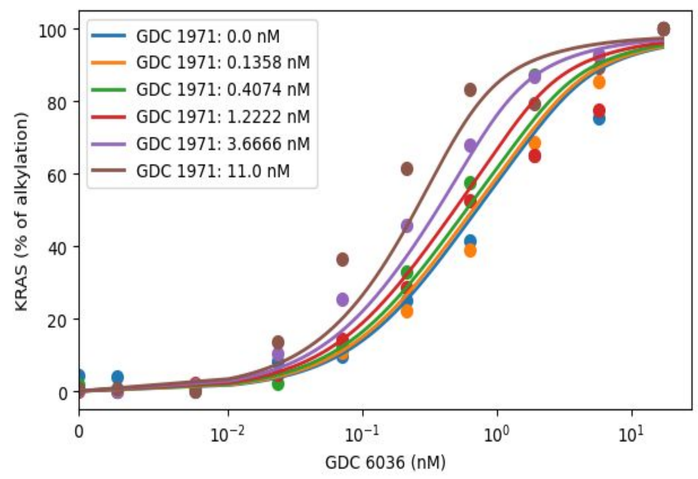


Fig 4. QSP model fit to in vitro alkylation% in H2122 cell line at 24 hour time point, given various drug concentrations (free in cell culture media is presented)

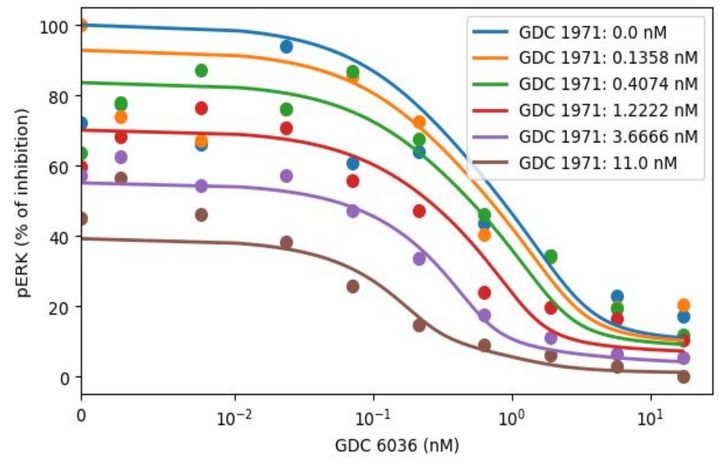
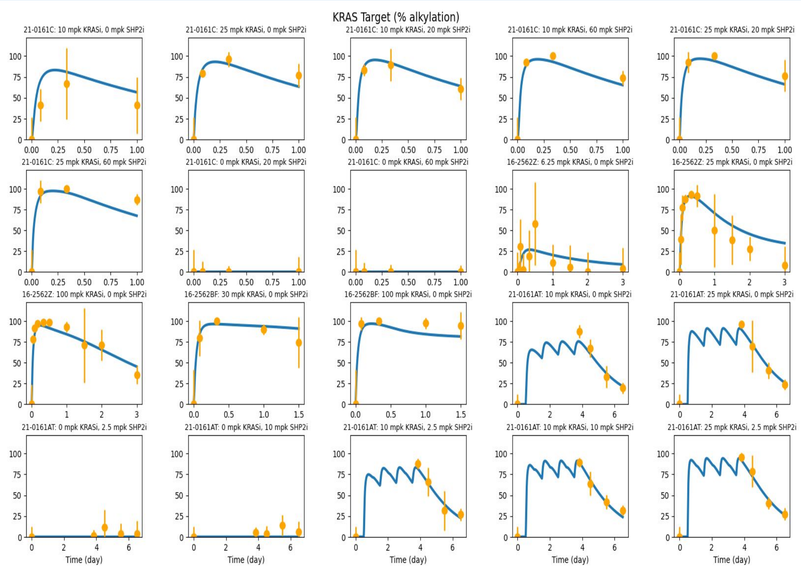


Fig 5. QSP model fit to in vitro pERK (% of baseline) in H2122 cell line at 24 hour time point, given various drug concentrations (free in cell culture media is presented)

- Model adequately described alkylation and MAPK pathway inhibition across a range of concentrations of divarasib and migoprotafib, and their combinations in vitro

QSP model fitting to PD data in mouse with H2122 xenograft tumor



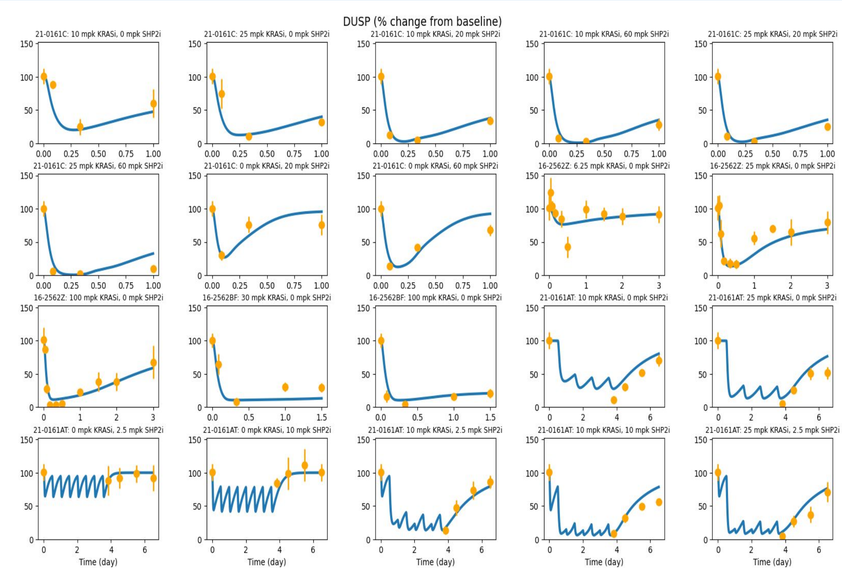


Fig 6. QSP model fit to KRAS G12C alkylation% for divarasib / migoprotafib single-agent and their combination. Blue solid line: model fit; orange dots with bars: observed mean +/- SD data

Fig 7. QSP model fit to DUSP6 inhibition (% of baseline) for divarasib / migoprotafib single-agent and their combination. Blue solid line: model fit; orange dots with bars: observed mean +/- SD data

- Model adequately described alkylation and MAPK pathway inhibition across a range of doses of divarasib and migoprotafib, and their combinations given to mice
- As in vitro and in vivo data can be described by a same set of model PD parameters, the calibrated model has a great potential for human PD translation.

Discussions & future work

- As a platform QSP model, the model has a great potential to be readily applied to the following aspects
  - Use human PK to simulate human PD and explore various clinical dosing regimen for single agent divarasib and combination with migoprotafib
  - Explain human PD differences in different indications (e.g., lung cancer vs. colorectal cancer)
  - Quantify the combination PD of new molecular entities and approved drugs to identify optimal combination partner with divarasib
  - Compare human PD across molecules with similar MOA (e.g., KRAS G12C inhibitors) based on their human PK and binding affinity to target
  - The model can be easily adapted to drugs with other MOAs targeting MAPK pathway (e.g., other KRAS inhibitors) to describe preclinical PD data and inform clinical translation