QSP modeling of OPB-171775, a phosphodiesterase 3A–Schlafen 12 molecular glue, to predict clinical responses in patients with gastrointestinal stromal tumors

Tomohiro Sasaki[1], Christina Friedrich[2], Krishnakant Dasika[2], Vincent Hurez[2], Renee Myers[2], Lesley Benyon[2], Miyuki Yuasa[3], Emiri O Takaki[4], Kazuhide Nakamura[4], Yosuke Kawai[1]

[1]Office of Clinical Pharmacology, Department of Biometrics, Headquarters of Clinical Development, Otsuka Pharmaceutical Co., Ltd., Osaka, Japan; [2]Rosa & Co, LLC, San Carlos, California, USA; [3]Department of Clinical Science 2 Group 1, Headquarters of Clinical Development, Otsuka Pharmaceutical Co., Ltd., Osaka, Japan; [4]Osaka Research Center for Drug Discovery, Otsuka Pharmaceutical Co., Ltd., Minoh, Japan

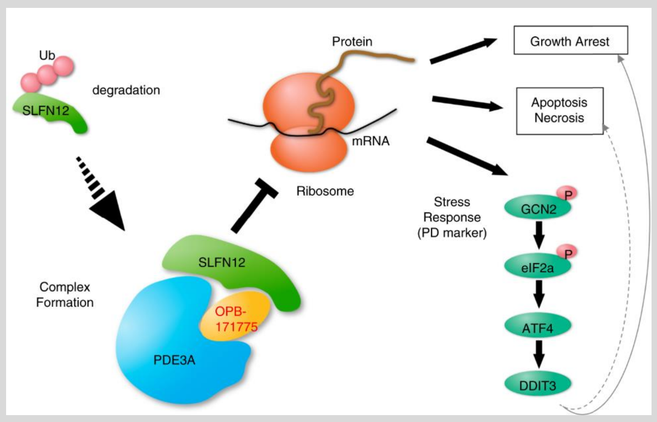
Background/Objectives

Explore MoA and efficacy for GIST

- Gastrointestinal stromal tumor (GIST), is typically treated with tyrosine kinase inhibitors (TKIs), such as imatinib [1]. However, in advanced GISTs, resistance to TKIs due to secondary mutations is common [2].
- OPB-171775 (OPB or OPC-320) is a first-in-class anti-tumor agent that selectively kills phosphodiesterase 3A (PDE3A)/Schlafen 12 (SLFN12) double-positive cancer cells [3] by inducing PDE3A–SLFN12 complex formation, leading to the downregulation of anti-apoptotic proteins and increased cancer cell death.
  - ✓ GIST cells co-express PDE3A and SLFN12, making them particularly sensitive to OPB-induced tumor growth inhibition.
- Here, quantitative systems pharmacology (QSP) modeling characterized OPB's anti-tumor effects on GISTs and predicted its clinical efficacy to aid in OPB's therapeutic development.

Figure 1: Proposed mode of action (MoA) for the anticancer mechanism of OPB-171775.

Adapted from article [3].
Ub = ubiquitin
GCN2 = general control non-derepressible 2
eIF2a = α subunit of eukaryotic translation initiation factor 2
ATF4 = activating Transcription Factor 4
DDIT3 = DNA damage-inducible transcript 3



Methods

QSP model to characterize MoA of OPB, clinical response and predictive biomarker

- The QSP model (**Figure 2**) was developed to characterize the anti-tumor effect of OPB.
- GIST virtual patients (VPs) were created to represent in vivo tumor growth in GIST and a range of clinical response to imatinib calibrated to match literature data [4].
- A simulation was conducted to explore the clinical efficacy of OPB with a different doses/dosages of OPB.
- To test the impact of target expression, PDE3A and SLFN12 expression were varied between 0.1x and 10x of reference VP values and examined the impact on the OPB efficacy.

QSP Model

GIST PhysioPD Platform with OPB and imatinib

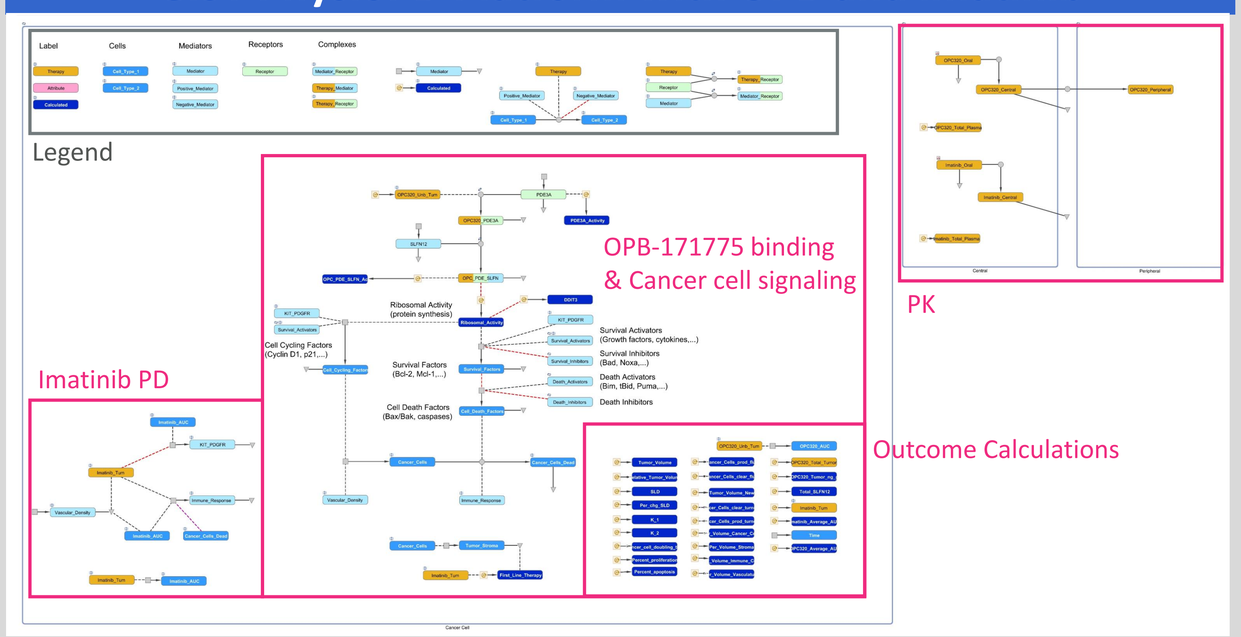


Figure 2: Graphical representation of the model, implemented in MATLAB® SimBiology®.

- The model includes intracellular binding of OPB to PDE3A and the consequent recruitment of the SLFN12 protein to form a PDE3A:SLFN12 complex that affects ribosomal activity and relevant cell death and cell cycling pathways.
  - ✓ The parameters on each pathway were calibrated using internal and publicly available data from in vitro experiments.
  - ✓ The model was tested to produce the expected cell-level behaviors in response to various doses of OPB.
  - ✓ In vivo response was calibrated by using data from patient-derived xenograft.
- The model was expanded to address clinical research questions in GIST patients. This model includes calculations of tumor size and volume, OPB and imatinib PK and PD effects estimated for GIST patients.
  - ✓ In order to reproduce the slow reduction in imatinib efficacy over time in "imatinib-resistant" GIST patients, an alternative VP was created with a progressive increase in the imatinib IC50 for the KIT-dependent tumor growth inhibition effects.

Conclusions

OPB is predicted to be efficacious in GIST

- OPB is predicted to be efficacious in GIST patients with or without imatinib resistance.
- Under reasonable assumptions, a range of clinical dosing protocols ranging from 0.1 mg QD to 2 mg Q2W of OPB are expected to achieve at least partial response.
- PDE3A and SLFN12 expression are predictive of OPB response.

Results

Responses in reference VP are predicted with various regimen

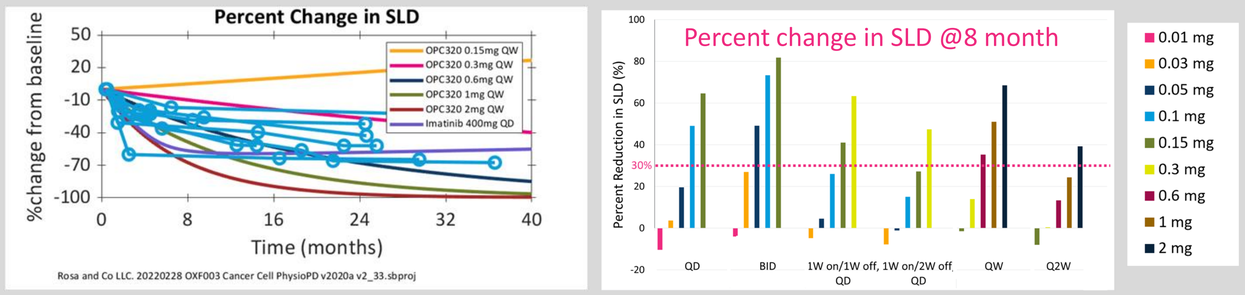


Figure 3: Percent Change in SLD in treatment-naïve VP (left) and imatinib-resistant VP (right).

-O- GIST patient's data for imatinib responders treated with 400 mg QD treatment [4]
SLD = sum of the longest diameters. OPC-320 = OPB-171775.

Percent change in SLD with OPB treatment is compared with Imatinib treatment and data for Imatinib 400mg QD [4] is overlayed (**Figure 3 left**). A range of OPB dosing were simulated in the reference GIST VP (**Figure 3 right**).

Model reproduced the variability in the disease progression

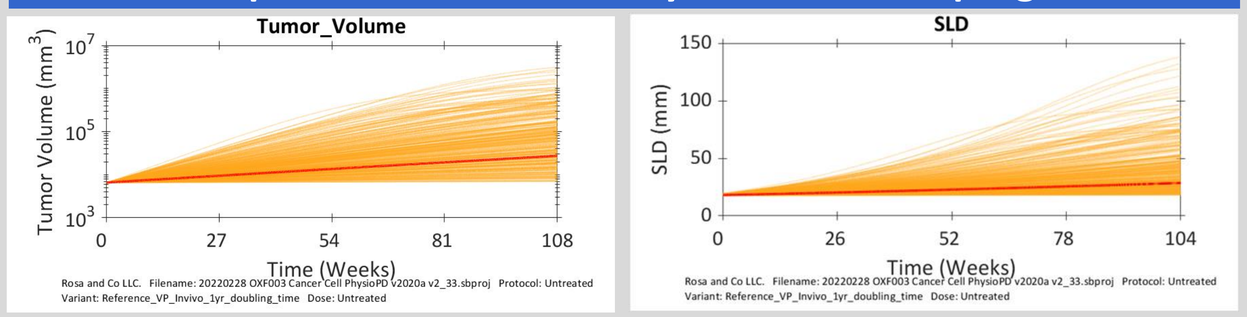


Figure 4: Simulated untreated tumor size and SLD distribution VPs.

Tumor sizes and progression rates are consistent with data from publications [5, 6] (**Figure 4**). The reference GIST VPs achieve RECIST 1.1 partial response (>30% reduction in SLD) under several of the protocols of interest (**Table 1**).

Table 1: Simulated responder rate with OPB-treatment for imatinib-resistant VPs.

	0.1 mg QD	0.3 mg QD 1W on, 2W off	0.6 mg QW	2 mg Q2W
Partial + Complete Responders (>30% reduction in SLD)	101 (34%)	138 (46%)	99 (33%)	111 (37%)
Stable Disease (30% reduction in SLD – 20% increase in SLD)	97 (32%)	90 (30%)	96 (32%)	94 (31%)
Progressive Disease (>20% increase in SLD)	101 (34%)	71 (24%)	104 (35%)	94 (31%)

Simulation identified predictive biomarkers of response

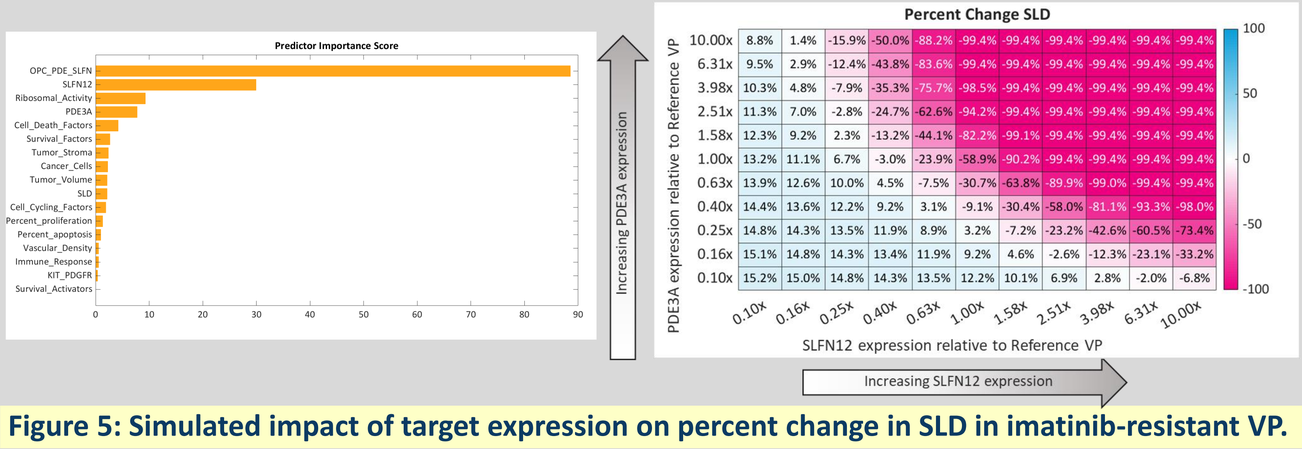


Figure 5: Simulated impact of target expression on percent change in SLD in imatinib-resistant VP.

Sensitivity analysis identified target expression (SLFN12, PDE3A) and Ribosomal Activity as top three biomarkers for classification of VPs as OPB responders/non-responders (**Figure 5**).

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