Ex vivo 3D drug response profiling of XPDX-derived tumor cells for acceleration of preclinical drug development

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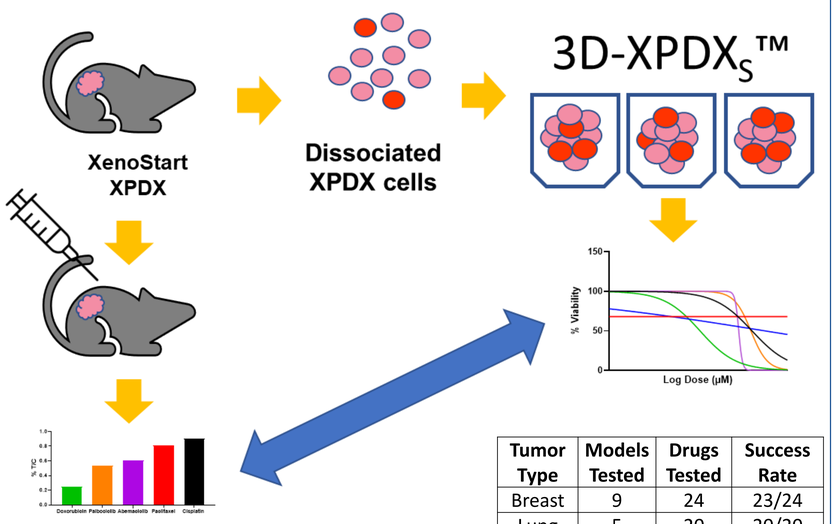
Abstract

Patient-Derived Xenografts (PDX) represent a versatile tool for preclinical drug development because they recapitulate many key features of the parent tumors, including molecular and histopathological profiles, tumor microenvironment, and tumor heterogeneity. The clinical relevance of PDX thus offer several advantages over other commonly used tools such as cell lines and genetically modified mice. Many large collections of PDX have been developed across a wide range of tumor types that profile the genetic diversity of each disease and the ability to bank PDX material allows repeated generation of mice for *in vivo* drug screens. As a result, PDX are used in several parts of the drug development pipeline, including early cancer biology studies, biomarker development, evaluation of therapeutic efficacy, and assessing/overcoming drug resistance. However, there remain drawbacks to this approach, most notably the large number of mice required for comprehensive drug screens and the associated time and costs. One approach to streamline PDX model selection and *in vivo* study execution would be to predict *in vivo* drug responses by assessing responses to the same drugs in an *ex vivo* platform utilizing PDX-derived dissociated tumor cells. KIYATEC's KIYA-PREDICT™ PDX assay is a 3D spheroid-based *ex vivo* platform that has been used to screen a wide range of drugs and tumor types to predict drug responses in primary patient-derived tumors and PDX-derived tumors, including several PDX from XenoSTART's extensive library of XPDX models. Here, we dissociated XPDX-derived tumors from a panel of 20 breast, ovarian, and lung cancer models provided by XenoSTART and evaluated their *ex vivo* responses to a panel of chemotherapy agents in our 3D KIYA-PREDICT™ assay. After exposure to drugs for 3-7 days, viability was assessed and both IC50s and percent survival values were calculated. The percent survival was then compared to *in vivo* drug response data provided by XenoSTART, and correlations between *in vivo* and *ex vivo* data were assessed. Drug responses were highly correlative between *ex vivo* and *in vivo* models, including the ability to recapitulate palbociclib resistance and platinum and taxane response. These results indicate that the KIYA-PREDICT™ PDX assay is a valuable tool to incorporate into drug development pipelines to accelerate the screening of new drug compounds on a wide range of clinically relevant samples and to guide selection of PDX models for *in vivo* studies.

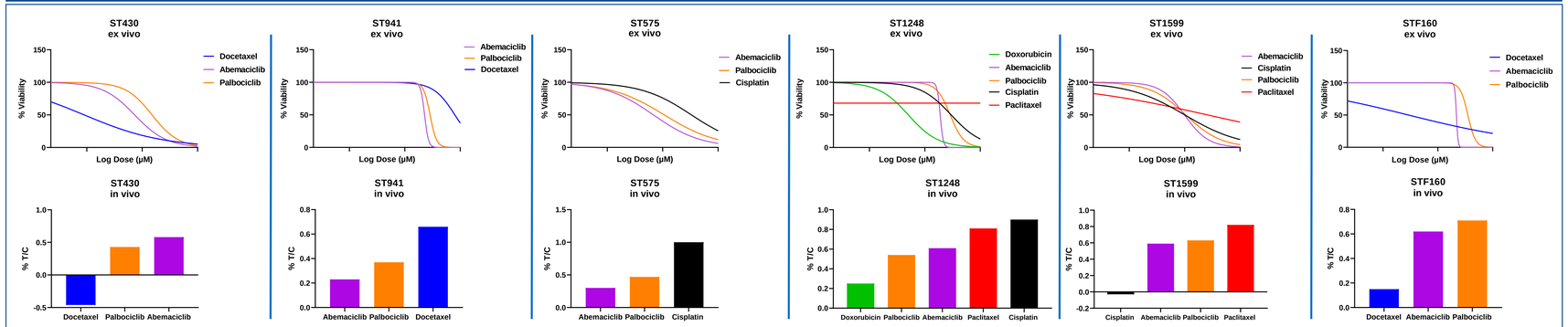
Methods



Tumor Type	Models Tested	Drugs Tested	Success Rate
Breast	9	24	23/24
Lung	5	20	20/28
Ovarian	7	28	24/28

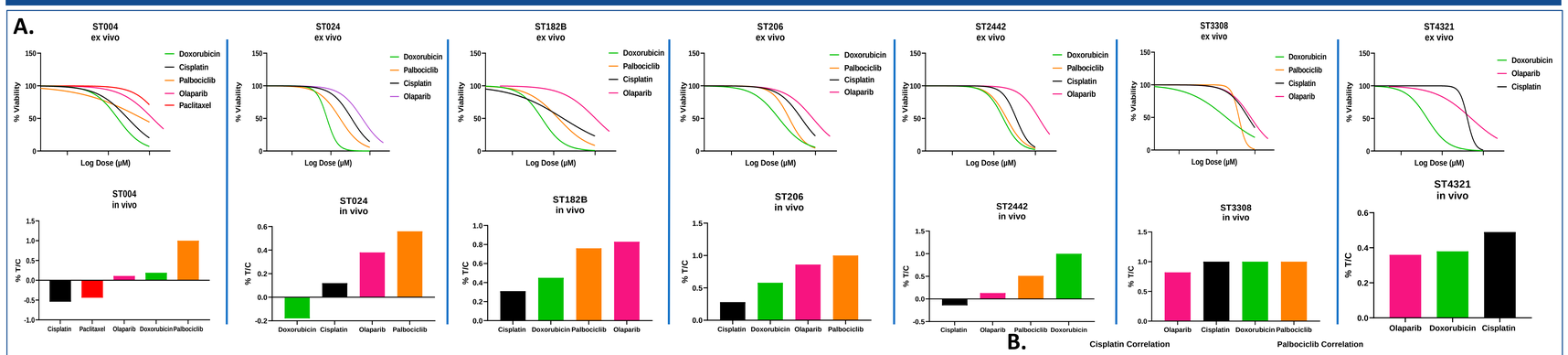
Patient-derived tumor samples were grafted into mice to form PDX tumors, which were subsequently propagated and passaged as the tumors grew to specified sizes. After several passages, tumors were excised and cryopreserved prior to being thawed and dissociated to single cells for drug response profiling in the KIYA-PREDICT™ assay. Following dissociation, XPDX cells were plated in multiwell plates as 3D spheroids and cultured prior to drug dosing. Spheroids were then treated with a panel of drugs specific to each tumor type. Viability was assessed by CellTiter-Glo® 3D. IC50's and % survival (area under curve) were calculated and compared to the % treatment/control (%T/C) for in vivo drug dosing studies performed with the same XPDX models.

Breast Cancer



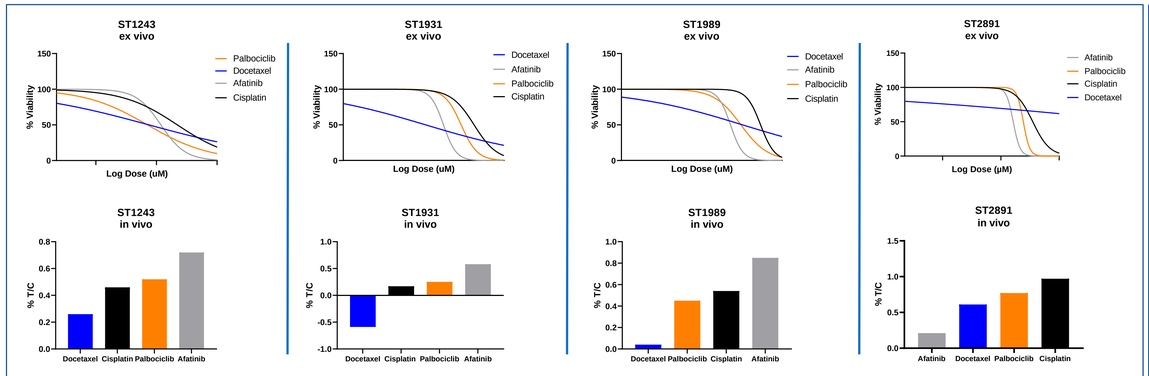
Breast XPDX models were treated *in vivo* with cisplatin, paclitaxel or docetaxel, abemaciclib, and palbociclib to evaluate tumor responses. Excised tumors from the same XPDX models were dissociated to single cells, plated as 3D spheroids, and treated with the same drugs. Calculated IC_{50} and % survival values in the ex vivo models were predictive of *in vivo* response when assessed by rank order for 6/7 tissues (86%). Response / non-response to docetaxel was replicated in 3 models, in the in vivo models, abemaciclib performed similarly and this was replicated in the ex vivo platform as was cisplatin resistance.

Ovarian Cancer



Ovarian XPDX models were treated in vivo with cisplatin, palbociclib, doxorubicin, paclitaxel, and olaparib to evaluate tumor responses. Excised tumors from the same XPDX models were dissociated to single cells, plated as 3D spheroids, and treated with the same drugs. Calculated IC_{50} and drug response categories in the ex vivo models were predictive of in vivo response when assessed as responders versus non-responders for palbociclib (R^2 = 0.8670) and cisplatin (R^2 = 0.5176).

Lung Cancer



Lung XPDX models were treated in vivo with cisplatin, palbociclib, docetaxel, and afatinib to evaluate tumor responses. Excised tumors from the same XPDX models were dissociated to single cells, plated as 3D spheroids, and treated with the same drugs. Calculated IC_{50} and rank order in the ex vivo models were predictive of in vivo response to docetaxel.

Applications

KIYATEC provides ex vivo screening of XPDX models generated by XenoSTART. The benefits of ex vivo screening include:

- High-throughput drug screening in less than 10 days of >40 compounds and combinations
- Large number of models screened in a short period of time
- Identification of models with a higher probability of response/non-response in vivo
- Reduction in the number of models tested in vivo
- Combination ex vivo / in vivo studies providing
- Screening I/O compounds and cellular therapies