Oncopig Hepatocellular Carcinoma Cell Lines Recapitulate Human Liver Cancer Chemotherapy Responses

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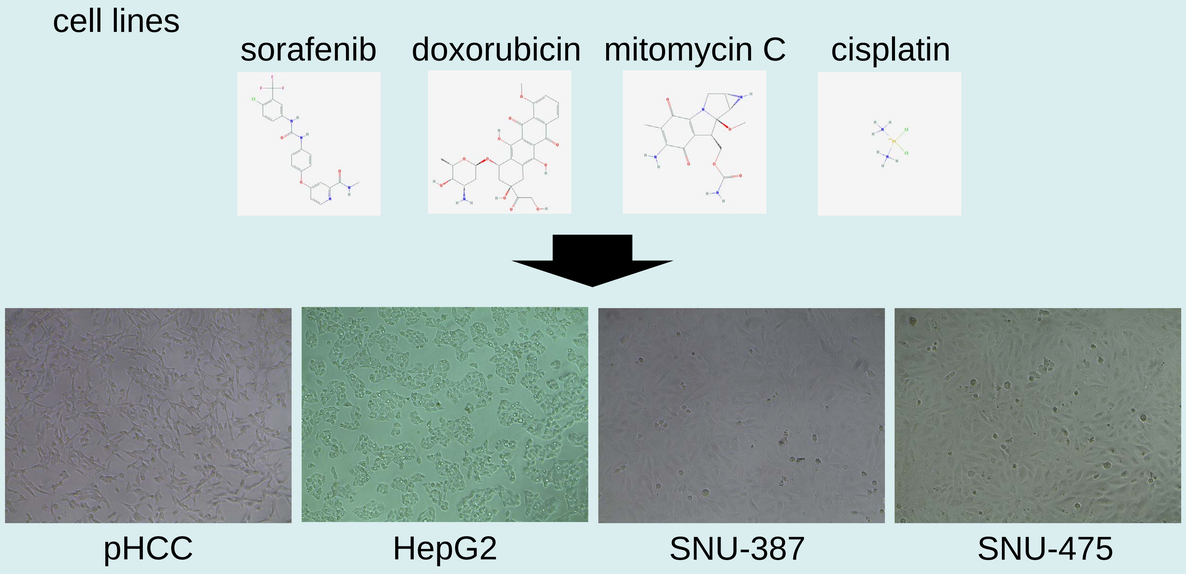
Introduction

- Many therapeutics showing promise in mouse studies fail to translate into successful human clinical trials
- Pigs share many genetic, physiological, and metabolic characteristics with humans
- The Oncopig Cancer Model (OCM) is a novel, inducible large animal model to study human cancer and bridge the pre-clinical gap
- The OCM has Cre-inducible porcine transgenes encoding *KRAS*^{G12D} and *TP53*^{R167H}, which represent a commonly mutated oncogene and tumor suppressor in human cancers, respectively.

Do porcine HCC (pHCC) and human HCC cell lines share similar drug responses to commonly used chemotherapy agents?

Methods

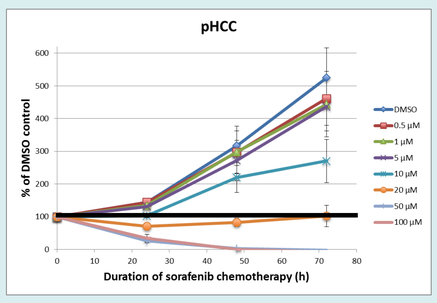
- pHCC cell line produced from pig liver resection, hepatocyte isolation and AdCre transformation
- Commonly used chemotherapy agents added to pHCC and human HCC cell lines

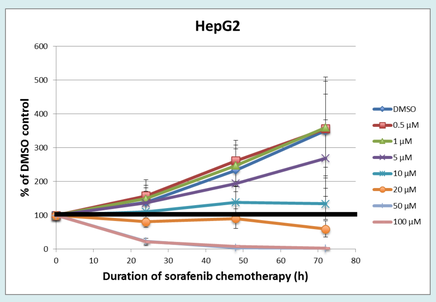


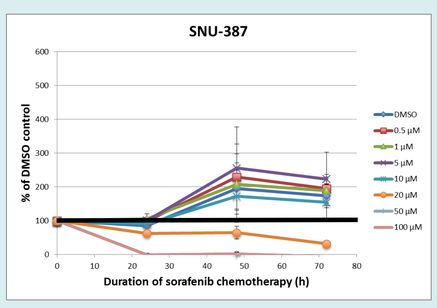
- MTT assay, which assesses oxidoreductase enzymatic activity, and reflects the number of viable cells, performed at 0, 24, 48, 72h

Add MTT to cells → MTT converted to insoluble Formazan in live cells → Solubilizing agent allows for absorbance readout at 570 nm

Sorafenib is cytostatic at clinically relevant concentrations







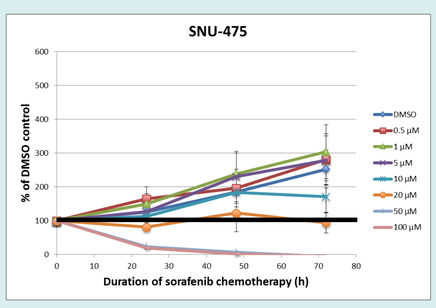
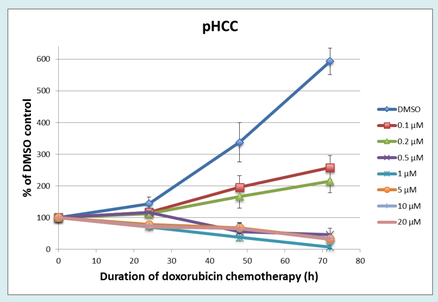
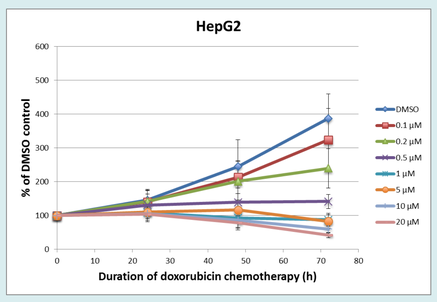
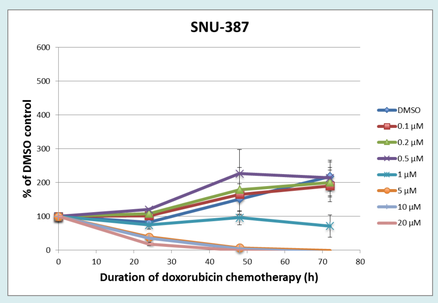


Figure 1 – Cell growth in the presence of increasing concentrations of sorafenib, when compared to number of cells seeded at time 0h (100%), after 24, 48 and 72h, as determined by an MTT assay. Negative control was 1% DMSO. n = 3; error bars are S.E.

Doxorubicin leads to comparable IC_{50} in pHCC, HepG2 and SNU-387







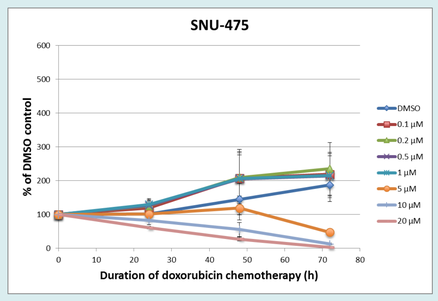


Figure 2 – Cell growth in the presence of increasing concentrations of doxorubicin, when compared to number of cells seeded at time 0h (100%), after 24, 48 and 72h, as determined by an MTT assay. Negative control was 1% DMSO. n = 3; error bars are S.E.

Table 1 – Half maximal inhibitory concentration (IC_{50}) after 72h exposure to doxorubicin. MTT assay results at 72h were normalized to DMSO only control (100%); a trend line was fitted to the results and line equations determined; IC_{50} corresponds to 50% growth. n = 3

Cell Line	IC_{50} Dox (µM)
pHCC	0.19
HepG2	0.45
SNU-387	0.94
SNU-475	3.31

Mitomycin C has similar IC_{50} in all tested lines

Effect of Cisplatin in pHCC and HepG2 is similar

Table 2 – Half maximal inhibitory concentration (IC_{50}) after 72h exposure to mitomycin C or cisplatin. MTT assay results at 72h were normalized to DMSO (MMC) or media (cis-Pt) only control (100%); a trend line was fitted to the results and line equations determined; IC_{50} corresponds to 50% growth. n = 3

Cell Line	IC_{50} MMC (µM)	IC_{50} cis-Pt (µM)
pHCC	1.77	7.54
HepG2	1.73	8.34
SNU-387	7.91	25.89
SNU-475	2.93	16.57

Conclusions / Future Work

- pHCC and human HCC lines display comparable responses to the tested chemotherapy agents
- pHCC responses are most similar to HepG2
- Differences observed might be explained by different mechanisms of action across compounds and genetic differences among human cell lines
- **The OCM can be used to screen promising chemotherapy agents**

- Test drug response of different pHCC lines
  → If different, these lines might have genetic differences
- Test mouse lines to study if OCM could be used to better predict clinical trial success
  → Determine if compounds that are cytotoxic to mouse but not human cancer have higher IC_{50} in pig cancer cell lines

Acknowledgements

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