Systemically administered chemotherapeutic agents typically have low access

- Systemic toxicity typically precludes efficacy on HCC – many trial failures
- Not a good alternative as neoadjuvant to curative treatment

Topographic invasive methods only prove way to hit therapeutic window (TACE)

- Transtumoral administration of doxorubicin, oxaliplatin or radiation
  - Scafellia in presence or absence of concomitant embolization
- Costly and risky as well as tech demanding
- Limited by AV-shunt, portal vein tumor thrombosis, arteritis
- Not suitable as neoadjuvant to curative treatment

Soralen, an oral tyrosine kinase inhibitor with proven efficacy in HCC

- Primarily hepatic pharmacokinetics, with oral dosing - 51% parent eliminated in bile
- This "passive" liver targeting potentially contributes to the efficacy of soralen in this indication

Prodrugs of troxacitabine

Many prodrugs have significantly increased potency compared to troxacitabine. Similar data obtained for HuH7 and HepG2 (not shown)

Prodrug combinations with soralen are synergistic

- New therapy will need to be considered in a combination with soralen
- Prodrugs of troxacitabine including 944 show synergy with soralen in Hep3B cells

Low toxicity in human primary hepatocytes suggests potential tumour selectivity

- Prodrugs show high selectivity for HCC cell lines relative to primary human hepatocytes compared to soralen in viability assays

Conclusions

- Phosphoramidate prodrugs of troxacitabine have been identified that show greatly improved in vitro properties compared to the parent nucleoside, including
- Potent inhibition of HCC cell line growth and selective induction of DNA damage relative to primary human hepatocytes
- Increased formation of the active metabolite, troxacitabine triphosphate
- A number of these compounds have properties that enable them to be orally bioavailable and targeted for metabolism and activation in the liver
- These compounds are synergistic with soralen, suggesting that they might prove efficacious in combination treatment
- Further preclinical profiling of the best compounds is ongoing. GLP safety studies are expected to be started later this year with the intention to develop this class of compounds for the treatment of HCC and other liver cancers