Zebrafish patient tumor-derived xenograft models used for pre-clinical evaluation of CAN04 for lung and pancreatic cancer

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Introduction

Lung and pancreatic cancer are among the deadliest malignant diseases accounting for 24% of all cancer deaths or 80% mortality within 1-year respectively. One reason for this high mortality is extensive patient heterogeneity and generally poor efficacy of current treatments, leading to an urgent need for new and more effective drugs.

Understanding the individual variability in the efficacy of new treatment candidates, delineating whether they should be combined with existing chemotherapeutics, and to what extent they affect metastatic dissemination of the tumor cells, are key preclinical indicators needed to increase the chance of success in clinical trials. Developing such data, however, requires animal models that recapitulate individual differences of different lung and pancreatic cancer patients, include insights into metastatic activity and allow analysis of a large amounts of treatment combinations for each patient model.

As such, an in vivo screening system which has higher throughput than mouse models and at the same time allows analysis of metastatic activity would be very valuable in mimicking human disease.

Aims

To evaluate a zebrafish tumor xenograft model (ZTX) as screening system to address individual differences in drug sensitivity on both primary tumor and metastasis on patient derived xenograft models.

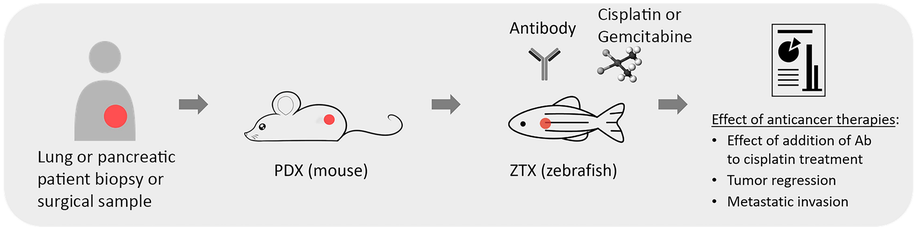
Methods

Here we conducted zebrafish patient tumor derived xenograft (PDX)-studies based on lung and pancreatic cancer PDX material, to test the efficacy of a a novel antibody, CAN04 (3F8), under development for this indication.

Zebrafish PDX studies are useful for understanding intrinsic resistance and early metastatic dissemination, whereas mouse PDX models provide insights into adaptive resistance and late-stage (metastatic) regrowth in target organs. These models may therefore synergize during drug development.

CAN04 targets Interleukin-1 Accessory Protein (IL1RAP) and has shown synergistic effects with cisplatin in murine models of cancer. CAN04 is currently in phase II development in combination with chemotherapy in lung cancer and pancreatic cancer. CAN04 was given either alone or with cisplatin or gemcitabine for lung and pancreatic cancer respectively, and the effects on primary tumor growth and metastasis three days after tumor implantation was evaluated.

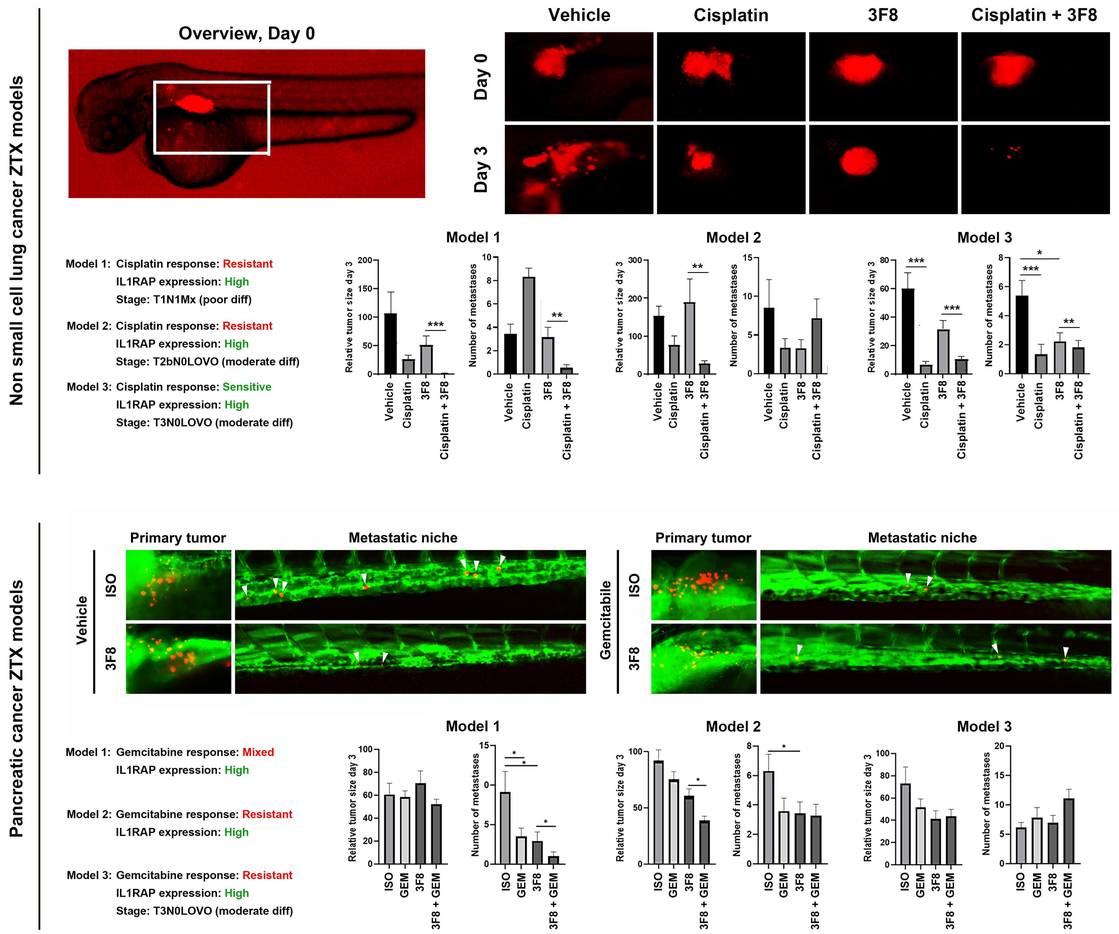
Lung- and pancreatic PDX models was chosen from Charles River Laboratories´ PDX library based on the sensitivity towards the standard of care (cisplatin or gemcitabine respectively).



Tumor tissue was digested and dyed with a red fluorescent dye and implanted into the perivitelline space in zebrafish embryos aged 48 hours post fertilization (hpf, n=20 per group). CAN04 and control antibody (ISO) was co-injected with the tumor cells and embryos were placed in separate wells in multi-well plates in PTU water, with or without cisplatin (lung cancer PDX) or gemcitabine (pancreatic cancer PDX). The effects on primary tumor growth and metastasis three days after tumor implantation was evaluated by fluorescent imaging.

Results

Zebrafish Tumor Xenograft (ZTX) models for pre-clinical evaluation of tumor growth and dissemination/metastasis



- CAN04 (3F8) synergize with 10 mg/kg cisplatin to cause tumor regression in two of four NSCLC ZTX models. In one of these (Model 2), the combination caused near-complete tumor regression. The effects were concentration-dependent (not shown).
- In model 2, the antibody and cisplatin co-treatment led to robust inhibition of metastatic dissemination, which was not seen in either group alone. This substantiates the beneficial therapeutic efficacy of combining CAN04 to cisplatin treatment in lung cancer.
- CAN04 (3F8) induced robust, synergistic tumor regression when combined with 37.5 mg/kg Gemcitabine in a pancreatic ZTX model (Model 3), that was otherwise Gemcitabine resistant. The effect was concentration dependent (not shown)
- CAN04 alone or CAN04 in combination with Gemcitabine inhibited pancreatic tumor dissemination and metastasis in two of four ZTX models tested.

Conclusions

- Zebrafish-PDX (ZTX) models are powerful tools for evaluating individual differences of PDX-models in terms of drug sensitivity on both primary tumor growth and metastasis.
- ZTX models are suitable for screening various drug concentrations and/or –combinations, in multiple PDX-models, to identify drug candidates, concentrations and combinations with the highest potential. Results are furthermore generated within one or a few weeks.
- CAN04 is inducing cisplatin and gemcitabine sensitivity in a NSCLC and Pancreatic cancer, in a model-dependent manner.
- ZTX models provide insights that synergistically complement those gained from mouse-PDX studies