Accelerating and de-risking late pre-clinical drug development with the Zebrafish Tumor Xenograft (ZTX®) Platform

Gabriela Vazquez Rodriguez [1], Zaheer Ali [1], Decky Tandiono [1], Michael Jury [1], Sujit S. Nair [2], Dimple Chakravarty [2], Ashutosh K. Tewari [2], Randi Altschul [3], Neil Theise [4], Przemyslaw Pilaszek [5], Melissa Barr [6], Amelia Hatfield [6], Gareth Griffiths [6], Mark Eccleston [6], Anna Fahlgren [7], Lasse Jensen [1,7].

1- BioReperia AB, Linköping, Sweden; 2- Icahn School of Medicine at Mount Sinai, New York, USA; 3- Pop Test & Palisades Therapeutics, USA; 4- NYU Langone Medical Center, New York, USA; 5- FiLeClo, Łódź, Poland; 6- Inaphaea Biolabs, Nottingham, UK; 7- Linköping University, Linköping, Sweden

Introduction

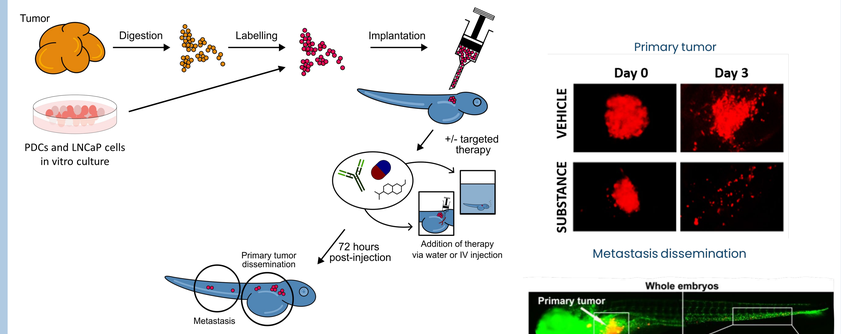
Nearly 95% of oncology drug candidates fail during clinical development, primarily due to heterogeneous patient responses. Personalized pre-clinical testing is essential to improve translational success. Traditional mouse PDX or organoid models are limited by low engraftment rates, high cost, and long timelines. The Zebrafish Tumor Xenograft (ZTX®) model provides a rapid, cost-effective alternative, enabling individualized drug-response profiling within five days, at sensitivity and specificity comparable to mouse PDXs and at a fraction of the cost [1, 2].

Aim

This study aimed to evaluate the anti-tumor efficacy of novel drug candidates, alone or in combination with other oncological therapies, on xenografts generated from established cell lines, patient-derived cell lines, and primary clinical tumor samples using the ZTX® platform, demonstrating the benefit of using ZTX® models during late pre-clinical drug development.

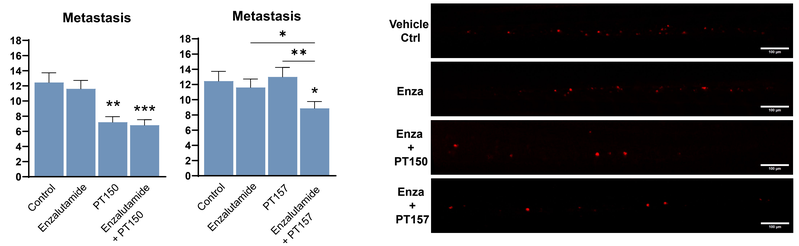
Methods

Cancer cells from cell lines, patient-derived cells, and primary biopsies were labeled with a red fluorescent dye and implanted into zebrafish embryos (48 hours post fertilization, n=20/group). Implanted embryos were incubated with test compounds at 35.5°C. Drug efficacy was measured by tumor burden and metastatic dissemination to the caudal venous plexus (CVP) were quantified after three days using fluorescence imaging.



Results

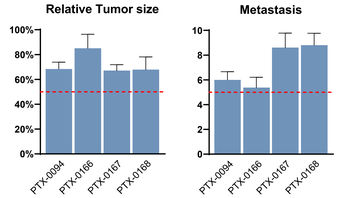
Identifying superior anti-metastasis treatment for AR/GR driven prostate cancer



- ✓ PT150 alone showed a significant reduction in metastatic dissemination of LNCaP prostate cancer cells, indicating potent anti-metastatic efficacy.
- ✓ The combination of PT150 and Enzalutamide resulted in metastatic dissemination comparable to PT150 alone, confirming PT150's significant contribution to the anti-metastatic effect.
- ✓ Results also showed that PT157, a dimer of PT150, demonstrated a strong, synergistic reduction in metastatic spread when combined with enzalutamide, a standard androgen receptor antagonist. This supports the rationale for combination therapies, especially where conventional agents fail to impact metastatic progression
- ✓ The rapid, robust anti-metastatic effects observed with PT150, and the synergistic activity of PT157 plus Enzalutamide, position these compounds as promising candidates for future prostate cancer therapies. Their ability to override established metastasis highlights a novel opportunity for drug development aimed at reducing metastatic dissemination in prostate cancer.

Superior engraftment and rapid metastatic data for glioblastoma indication with low take rates in mouse PDX models

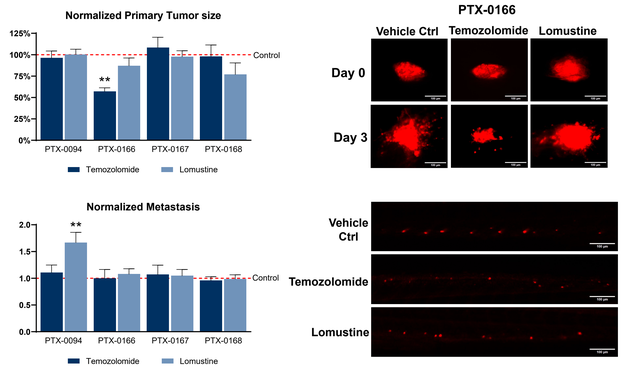
100% take rate and high metastatic dissemination



- ✓ All glioblastoma models successfully engrafted and disseminated in the zebrafish embryos.

Results

Identify responders and non-responders to standard of care treatments



- ✓ After 3 days evaluation time, the ZTX® model could identify the PTX-0166 model as the only model sensitive to temozolomide
- ✓ Treatment with TMZ or Lomustine did not affect the metastatic dissemination of PTX-0166, PTX-0094, PTX-0167, and PTX-0168 cells to the CVP compared to the control group after 3 days of treatment.

Conclusions

- ✓ The ZTX® platform enables rapid (5-day) predictive evaluation of drug efficacy and metastatic potential across diverse tumor types.
- ✓ High engraftment rates, including in difficult indications such as glioblastoma, demonstrate robust feasibility compared to mouse PDX models.
- ✓ By identifying responders and non-responders within days, it supports precision oncology, biomarker discovery, and rational clinical trial design.
- ✓ The robust anti-metastatic activity of PT150 and the synergistic performance of PT157 with enzalutamide underscore the translational value of this approach for AR/GR-driven prostate cancer.

The platform's speed and predictive power highlight its potential role as a companion tool in precision oncology.

References

[1] Ali, Z., et al. Zebrafish patient-derived xenograft models predict lymph node involvement and treatment outcome in non-small cell lung cancer. J Exp Clin Cancer Res 41, 58 (2022).
[2] Lindahl G, et. al. Zebrafish tumour xenograft models: a prognostic approach to epithelial ovarian cancer. NPJ Precis Oncol. 2024 Feb 27;8(1):53