Validation of *TFX1*, a first-in-class target for cancer metastasis

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Background

- Most of the drugs approved for metastatic epithelial carcinomas treat the proliferation of the tumor and not the biology of metastasis
- Over the last decade, the average overall survival of patients treated with all FDA-approved drugs for solid tumors is 2.8 months, ranging from 1.97 – 4.6 months. Similarly, the average progression-free survival of patients treated with these drugs is only 3.3 months, ranging from 1.5 to 5.8 months[1].
- A candid appraisal of FDA approvals for adult solid tumors from 2017–2021 indicated a low level of clinical benefit for a substantial proportion (~20%) of the new indications, with most (~44%) providing intermediate benefit[2].

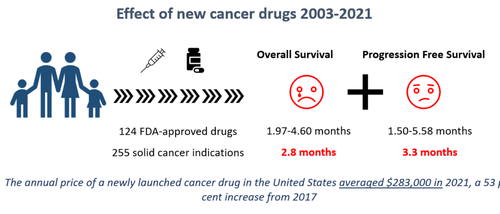


Fig. 1

Methods

- Creation of the METAssay® platform, consisting of 30 cellular assay and characterization steps, dissecting the complete metastasis biology[3,4].
- Analysis of patient tumor derived purified colon tumor cells on the platform (primary tumor of any grade & node status, but M0) and subsequent follow up for metastasis.

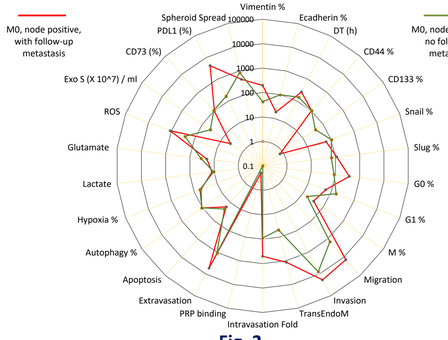


Fig. 2

Results — Machine Learning

- Characterization of 25 patient samples and incorporation of METAssay® data.
- Supervised learning with METAssay® data as input and follow-up clinical metastasis data as output (SVM and random forest regressor/classifier used, two cut-offs of 0.05 and 0.08)[5].
- Identified 8 weighted steps critical for metastasis (quality check with Precision-Recall and ROC curve).
- Four first-in-class targets were identified; one is presented below, a transcription factor (*TFX1)*.

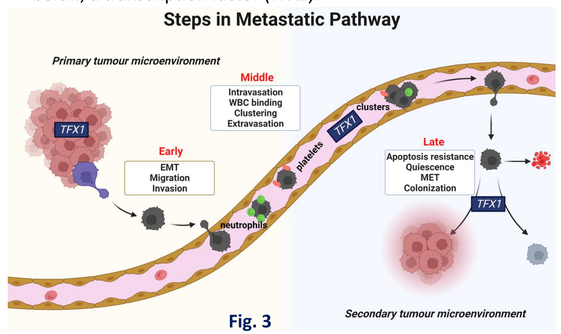
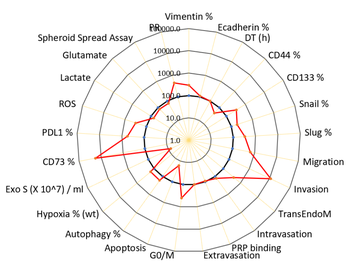


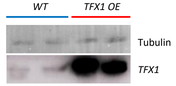
Fig. 3

Results — *TFX1 (Genetic PoC)*

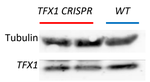


Similar PoC in TNBC, work in progress in H&N

Overexpression of *TFX1* in CRC (HT29)



CRISPR CAS of *TFX1* in CRC (HCT116)



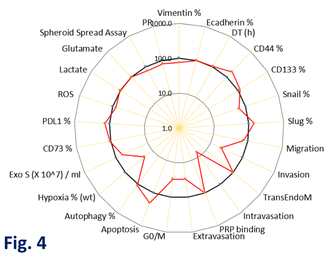
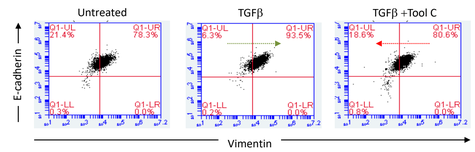


Fig. 4

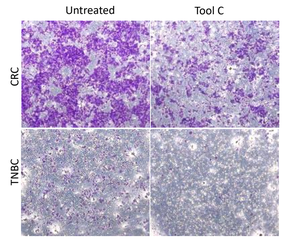
Results — *TFX1* tool compound inhibits *'EARLY'*

- A tool compound was used for pharmacological PoC across early steps (Fig. 3) of metastatic pathway (data from cell lines).

Inhibition of EMT in CRC (HT29)

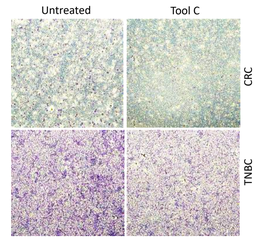


Inhibition of Migration



CRC: HCT116, TNBC: MDAMB 468

Inhibition of Invasion



CRC: Colo205, TNBC: MDAMB 231

Fig. 5

Results — *TFX1* tool compound inhibits *'LATE'*

- The tool compound shifted cells from the quiescent mesenchymal axis towards the epithelial axis.

Promotion of MET (HT29 inducible clone 12BC6)

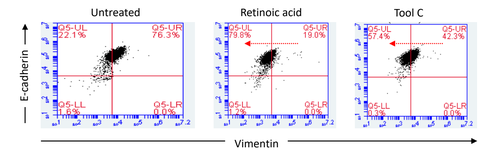


Fig. 7

Results — Purification of *TFX1*

Overexpression and Purification

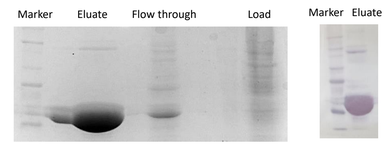
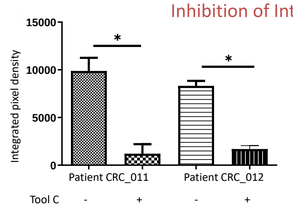


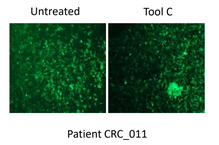
Fig. 8

Results — *TFX1* tool compound inhibits *'MIDDLE'*

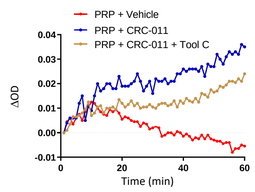
- The tool compound was used for pharmacological PoC across middle steps (Fig. 3) of metastatic pathway (data from patient samples).

Inhibition of Intravasation





Inhibition of Platelet Binding



Inhibition of Extravasation

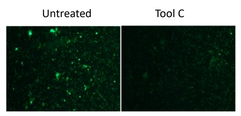


Fig. 6

Results — Biochemical assay of *TFX1*

Isothermal Calorimetry with Tool C

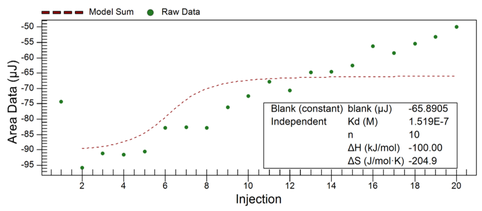


Fig. 9

Conclusion

Inhibition of *TFX1* alters multiple steps in the metastatic cascade, in both cell lines and patient-derived tumor cells, highlighting its potential as a novel drug target.

References

1. J Clin Oncol. 2022 Dec 10; 40(35):4095-4106
2. Nature Clin Oncol., 2022, 19, 486-492
3. Cancer Res 2021;81(13_Suppl):Abstract nr 2868
4. Cancer Res (2021) 81 (13_Supplement): 2841.
5. Metastasis Research Society Biennial Congress, 2022, Buenos Aires, 13-16 November