A novel, orthotopic spontaneous metastasis animal model for drug discovery that works in only six weeks

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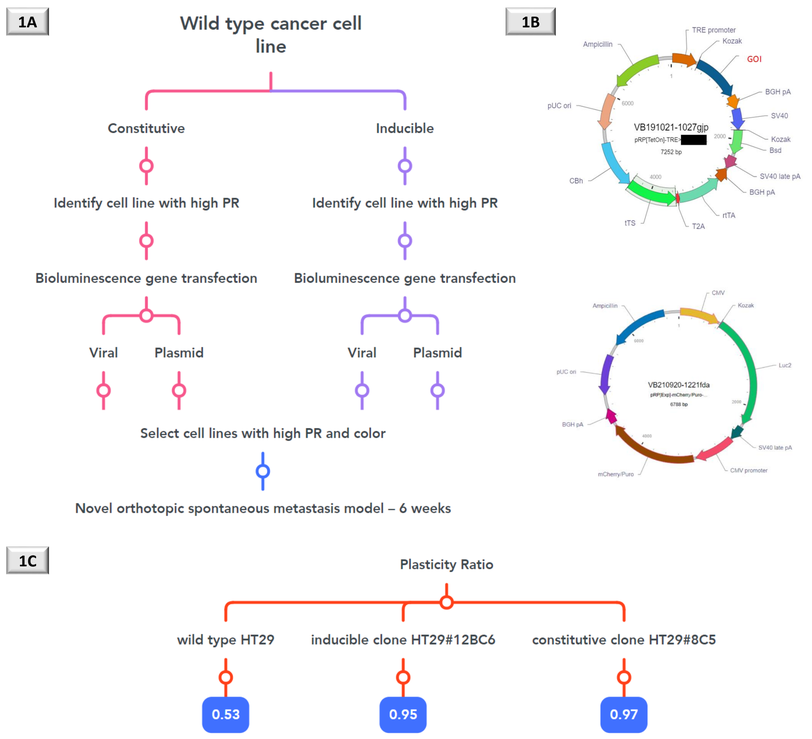
Background

1. Drug discovery efforts around metastasis, have been de-prioritized for the lack of both translatable *in vitro* and *in vivo* platforms[1,2].
2. We have previously described our *in vitro* platform METAssay™ that duplicates complete metastasis biology on bench[3-5].
3. Here we describe our *in vivo* platform METVivo™, a spontaneous and orthotopic metastasis model, which works in only 6 weeks.
4. The current model is established in colorectal cancer, to monitor liver metastasis but in future will be expanded to other solid carcinomas, e.g., breast tumor metastasising to lungs.

Method

1. Wild type colon cancer cell line HT29 was genetically engineered by transforming with pro-metastatic transcription factors to give metastatic HT29; either HT29#12BC6 (inducible under tet promoter) or HT29#8C5 (constitutive expression).
2. We have previously shown in our METAssay™ platform that engineered HT29 (both constitutive and inducible) had a higher plasticity ratio (PR; a ratio of mesenchymal to epithelial nature of a cell) that promotes less tumorigenesis but more metastasis *in vitro*.
3. Both wild type and engineered cells lines were transplanted either subcutaneously in the right flank of NOD-SCID mice (for tumorigenesis study) or ceco-colic junction of the cecum of NOD-SCID mice by laparotomy (for metastasis study).

Fig. 1 (A) Workflow (B) representative plasmid vectors (C) plasticity ratio (PR)



Results

Fig. 2: High PR show less tumorigenesis in heterotopic model (A) only txn Factor (B) txn factor + luciferase

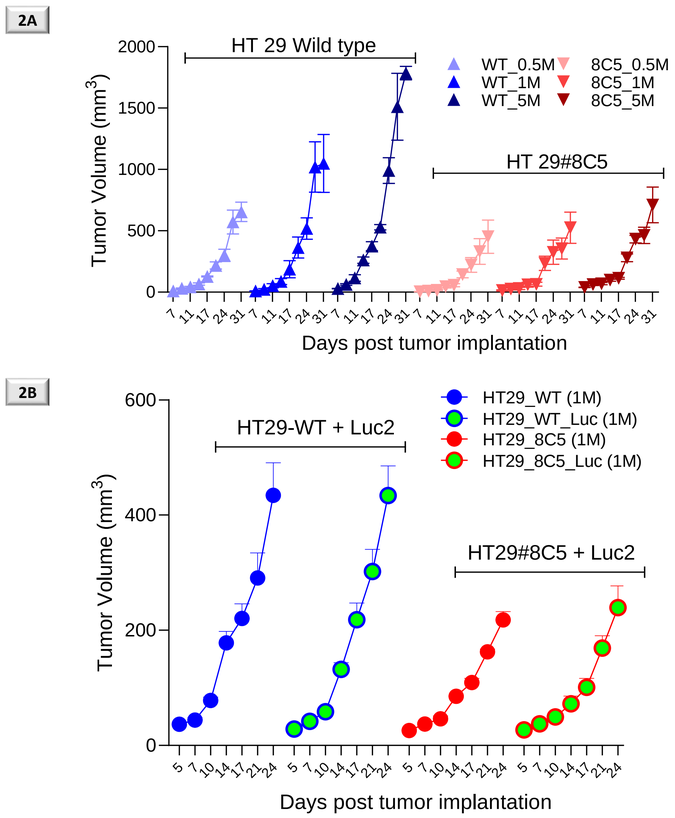


Fig. 3: Metastasis with Inducible clone HT29#12BC6 containing Luc2 in the orthotopic model

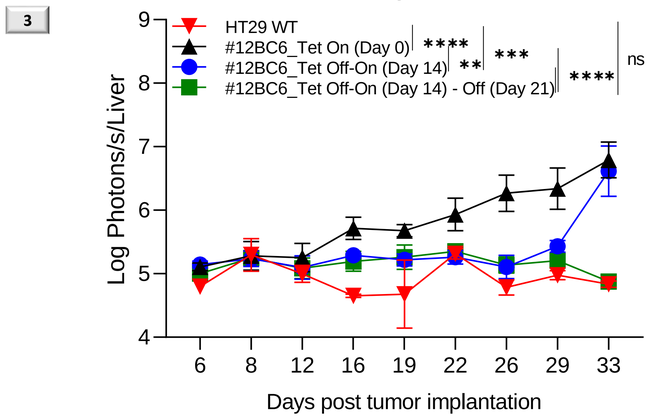


Fig. 4: Endpoint organ analysis for metastasis - #12BC6 orthotopic model (A) Comparative chart (B) Representative pictures of metastasis

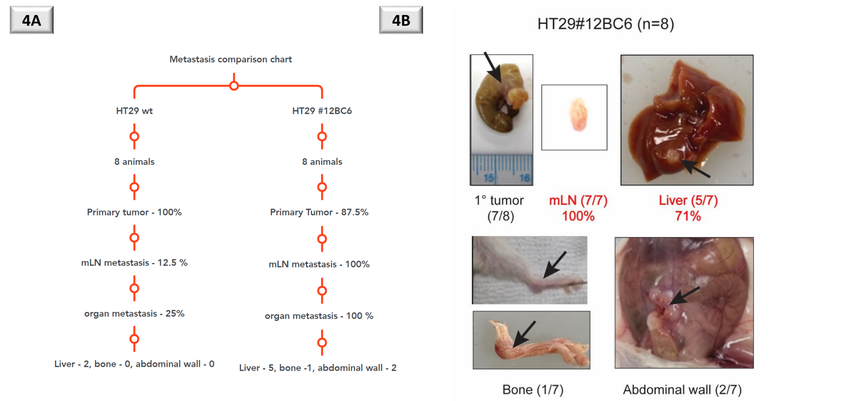
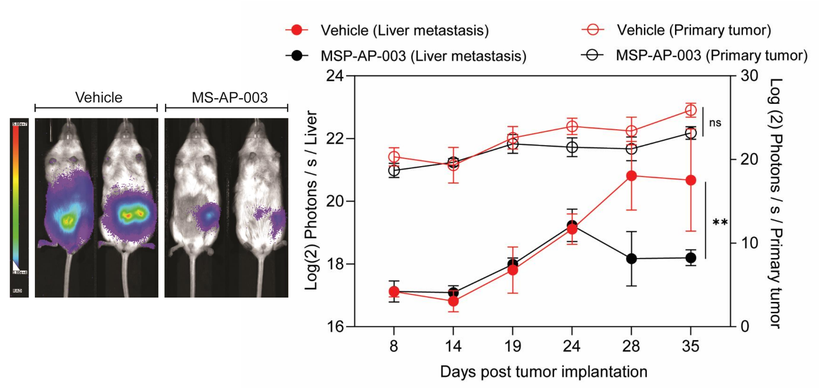


Fig. 5: Effect of repurposed compound (MS-AP-003) on liver metastasis with HT29#12BC6



Summary

Mestastop has standardized a biologically relevant metastasis model with the following advantages

- ✓ 90 – 100 % metastasis take rate compared to 20-30%
- ✓ Time and cost-effective: 6 weeks compared to 6 months
- ✓ Statistically more robust

References

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