Response to Checkpoint Inhibition by GEMM Breast Cancer Allograft

Poster: 382

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Abstract

Background. Response to immunotherapy (I/O, *e.g.* to checkpoint inhibitors) in cancer patients, differs greatly, likely due to their genetic composition (e.g. neo-mutation) or to the immunological profile of their tumors. Experimental models may facilitate the identification of responders or of the approach to enhance response. Syngeneic mouse tumor models have been widely used as experimental model for testing surrogate immunotherapy, but their application is restricted by the limited number of available models and their inconsistent response to current checkpoint inhibitors. Allografts of mouse spontaneous tumors (MuPrime™) may be used as new model for I/O thanks to: 1) their primary natures with "stem cell diseases" and relevant tumor microenvironment as seen in PDX[1-5]; 2) the availability of diverse cancer types, deriving from a wide range of spontaneous mouse tumors.

Methods. We created the MuPrime mBR6004 model, by allografting the breast adenocarcinoma derived from MMTV-PyVT transgenic mice[1]. We then characterized this model by examining its subcutaneous and orthotopic growth, and its ability to metastasize. We also transcriptome-sequenced and immune-profiled the tumor, and assessed its response to different treatments, including I/O therapy.

Results. mBR6004 was found to overexpress Erbb2, but not ER and PR. It maintains its original primary tumor histopathology, grows robustly, and is confirmed to express its original transgene. It is also resistant to docetaxel. The orthotopic implantation resulted in lung metastasis. We detected and quantitatively confirmed the presence of tumor-infiltrating immune cells, *e.g.* TIL, CTL, Treg, immune-suppressive macrophages, NK, etc. We confirmed, per flow analysis, that the tumor cells express relatively low but inducible levels of PD-L1. Our preliminary data indicate that the model partially responds to anti-mouse PD1 and anti-mouse CTLA-4 antibodies when mice are preconditioned. These responses are associated with increased CD8+ TIL in tumors. We are currently investigating whether combinatory therapies can enhance antitumor responses synergistically.

Conclusions. Our data suggest that the MuPrime platform can be used as an alternative to common syngeneic cell line-derived models.

References

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2. Guy, C.T., *et al.* Expression of the *neu* protooncogene in the mammary epithelium of transgenic mice induces metastatic disease. Proc Natl Acad Sci USA 89, 10578-10582 (1992).

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Results

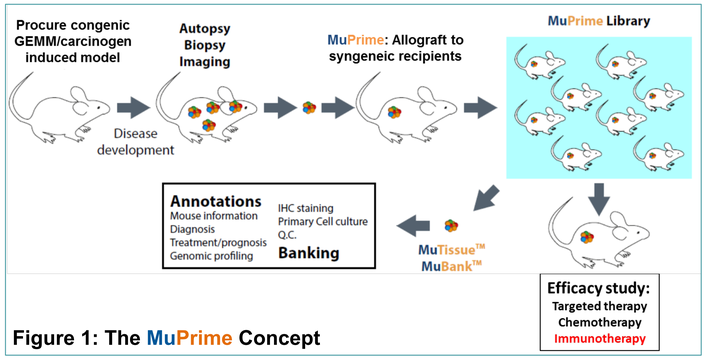


Figure 1: The MuPrime Concept

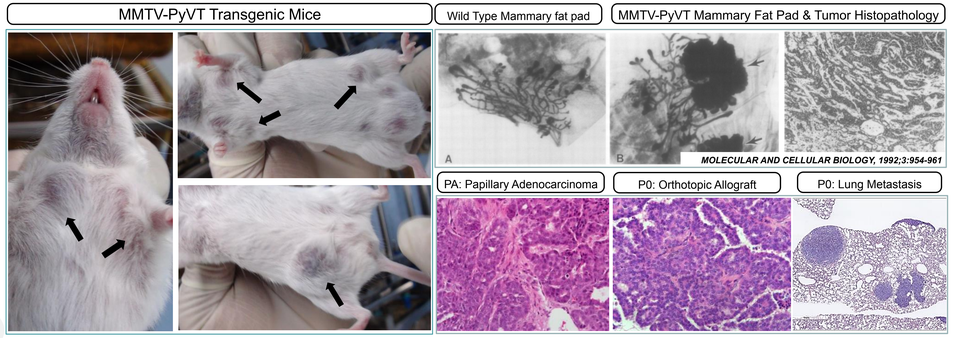
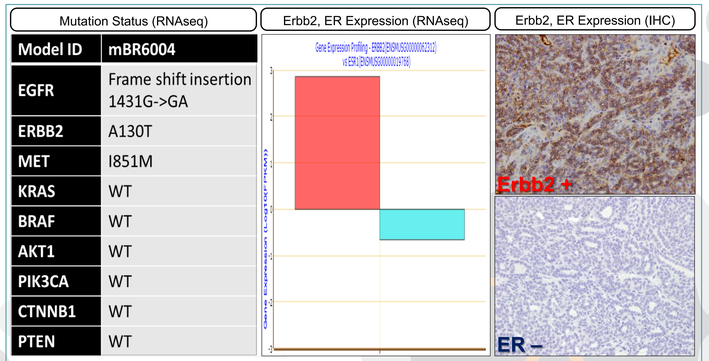


Figure 2: Gross Pathology & Histopathology



Model ID	mBR6004
EGFR	Frame shift insertion 1431G->GA
ERBB2	A130T
MET	I851M
KRAS	WT
BRAF	WT
AKT1	WT
PIK3CA	WT
CTNNB1	WT
PTEN	WT

Figure 3: Molecular Pathology. mBR6004 is Erbb2 positive, ER & PR negative.

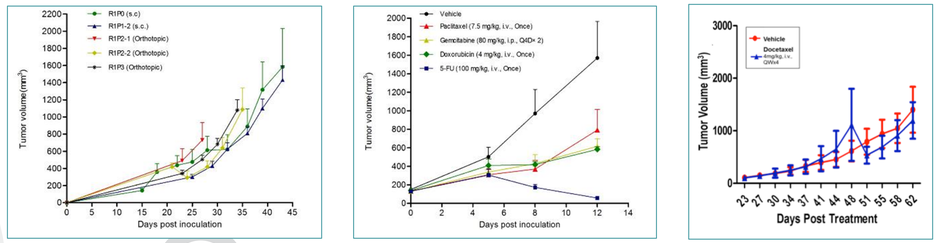
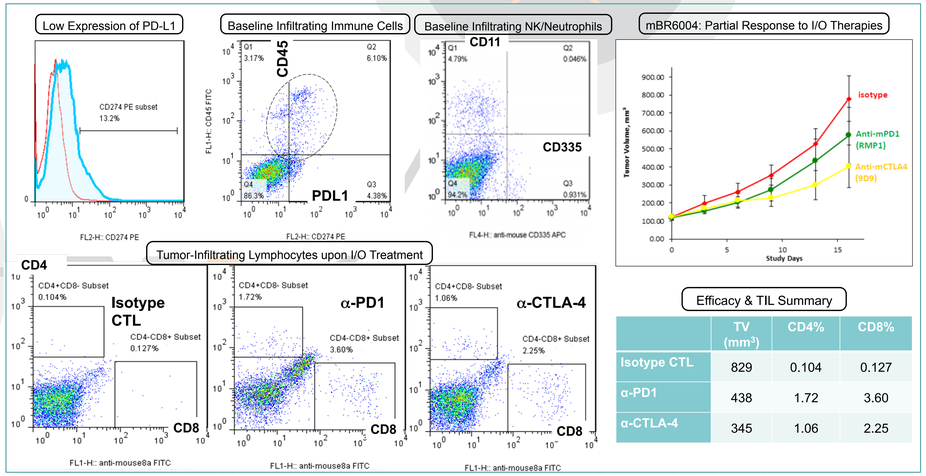


Figure 4: mBR6004 Growth Curve & SoC. The mBR6004 model is Resistant to Docetaxel.



Efficacy & TIL Summary

	TV (mm^3)	CD4%	CD8%
Isotype CTL	829	0.104	0.127
α-PD1	438	1.72	3.60
α-CTLA-4	345	1.06	2.25

Figure 5: Immune Profile of mBR6004 and its Response to α-PD1, α-CTLA4 mAbs

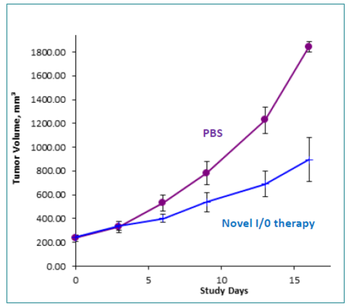


Figure 6: Partial Response to a Novel I/O Agent

Conclusions

We successfully demonstrated the establishment of a MuPrime allograft model for immuno-oncology research using spontaneous mouse tumors derived from genetically engineered mice.

- The mBR6004 model is derived from MMTV-PyVT transgenic mice with FVB/N background.
- mBR6004 responds to both anti-mPD1 and anti-mCTLA4 antibodies
- These responses correlate with increased TIL.
- More MuPrime models are currently being built and validated.

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