Establishment of a Mouse Breast Cancer Allograft Model for In Vivo Pharmacological Analysis of Immunotherapy

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Introduction

The recent clinical success of novel therapeutics blocking the immune checkpoints cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) has fueled an intense interest in immunoncology. However, the lack of relevant animal models is a major bottleneck for understanding the mechanism of action and evaluating the efficacy of such therapeutics. Syngeneic mouse tumor models, despite being widely used as experimental models for efficacy studies, are limited by the fact that only a restricted number of models is available and their response to the current checkpoint inhibitors is partial. Genetically engineered mouse models (GEMMs) are effective tools for mechanistic analysis, but not suitable for efficacy studies due to unsynchronized tumor progression. Allografts of spontaneous mouse tumors derived from GEMMs (MuPrime®) may be used as a new model for immunoncology with the following advantages: 1) their primary nature of “stem cell disease” and relevant tumor microenvironment as seen in patient-derived xenograft (PDX) models; 2) the availability of various cancer types and oncogenic drivers deriving from a wide range of available GEMMs.

Abstract

We created the MuPrime model, mBR6004, by engrafting the breast adenocarcinoma derived from MMTV-PyV/T transgenic mice3 to the syngeneic FVB/N mice. The allografted tumor maintains histopathological features similar to the primary tumor and grows robustly when implanted subcutaneously or orthotopically. Interestingly, we found orthotopic implantation consistently results in lung metastasis. Transcriptome sequencing revealed high levels of HER2 expression in tumor cells, which are negative for ER and PR. When we assessed the responsiveness of the tumor to various treatment, we found it was resistant to Docetaxel. Immune-profiling of the tumor by FACS quantitatively confirmed the presence of tumor-infiltrating immune cells, e.g. TIL, CTL, Treg, immune-suppressive macrophages, NK, etc. We have also confirmed that PD-L1 is expressed at relatively low levels in the tumor cell in an inducible manner. Our preliminary data indicated that mBR6004 partially responds to anti-mouse PD-1 and anti-mouse CTLA-4 antibodies when mice are preconditioned. Currently, we are investigating whether these responses are associated with a reduced level of Treg and increased presence of CD8+ TIL in the tumor, and whether combination therapy results in synergistic enhancement of antitumor activity. Together, our data suggest that we have established an allograft model suitable for in vivo efficacy analysis of immunotherapy using surrogate anti-mouse antibodies.

References


Results

Figure 1: Overview of the MuPrime™ Concept

Figure 2: Gross Pathology & Histopathology

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

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

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

Figure 7: mSK6005 Skin Squamous Carcinoma MuPrime Model

Conclusions

We successfully established a MuPrime allograft models for immunoncology research using spontaneous murine tumors derived from a genetically engineered model.

- The mBR6004 model is derived from MMTV-PyV/T transgenic mice with FVB/N background.
- The mBR6004 model responds to both anti-mPD1 and anti-mCTLA-4 antibodies
- These responses correlate with increased TIL.
- More MuPrime models are currently being built and validated (e.g. mSK6005).

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