Building Mouse Tumor Derived allografts for Immune-Oncology Research

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Introduction

Immuno-oncology is an area under intensive investigation, however, many questions remain to be answered due to lack of sufficient number of adequate experimental models: 1) why only subsets of patients respond? 2) who will respond? 3) what can we do to make more patients to respond? Patient derived xenograft (PDX or HuPrime®) mirrors patients' histopathological/genetic profiles, considered more predictive than traditional human cell line derived xenograft (CDX) and also syngenic mouse cell derived models, due to the primary natures of PDX. On the other hand, both xenografts (PDX/CDX) grow in absence of immunity, thus unsuitable for immune oncology research. Limited types/numbers of available syngenic cells also restrict its application. Genetically engineered mutant mouse cancer model (GEMM) are diverse, grow in immune environment, and are primary tumors. However, GEMM has logistic limitation for pharmacology research for high cost and high variations in tumor development (spontaneous) in type/time.

Abstract

We set out to create a library of primary mouse tumor allografts (MuPrime™) as standard experimental models, aiming at overcoming these limitations. We established a number of such allografts and are profiling them for growth, histopathology, genomic (RNAseq), and standard of care (SOC). We are also charactering their immune oncology properties: tumor infiltrating immune cells, including different subtypes of Tcells (CTL,T-reg), as well as their functional activation/suppression and tumor responses to immune modulating agents. We are currently characterizing its histopathology and other property.

In general, these allografts keep the original primary tumor histopathology, but distinct from conventional syngenic cell line derived tumors, a contrast seen between PDX vs. CDX. The models grow robustly after engraftment, thus ideal for pharmacology evaluation. Our ongoing studies will provide a useful platform with normal immunity for drug evaluation, particularly for immune oncology agents.

Method

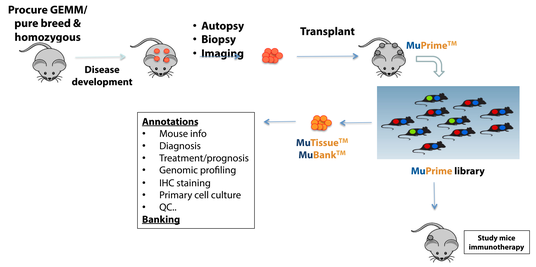

Figure 1: Model establishment flow chat

Results

ID	Types	Status	Origin	Background Strain
6003	Prostatic	Establish	C57BL/6-Tg(TRAMP)824Ng/Jnju	C57BL/6
6004	Breast cancer	Establish	FVB/N-Tg (MMTV-PyTV)634Mul/Jnju	FVB/N
6005	squamous cell carcinoma	Establish	C57BL/6J-ApcMin/Jnju	C57BL/6J
6011	unidentified	Establish	Balb/C	Balb/C
6012	Brain	Establish	Ptch1tm1Mps/Jnju	C57BL/6
6014	Lymphoma (B)	Establish	Spontaneous tumor from NCG	NOD
6013	intestinal adenoma(under conformation by pathology)	Under development	C57BL/6J-ApcMin/JNju	C57BL/6J
6002	(principally lymphomas and sarcomas	Under development	B6.129S2-Trp53tm1Tyj/JNju	C57BL/6J
6006	intestine and lung adenomas	Under development	B6.129S4-Cdkn1btm1Mlf/JNju	B6
6007	Lung	Under development	A/JNju	BALB/cBy
6008	reticular neoplasms, primary lung tumors, and renal tumors.	Under development	BALB/C ByJNju	BALB/C
6010	hepatomas	Under development	C3H/HeJNju	C3H/HeJNju

Table 1: List of MuPrime™ models.

Analysis

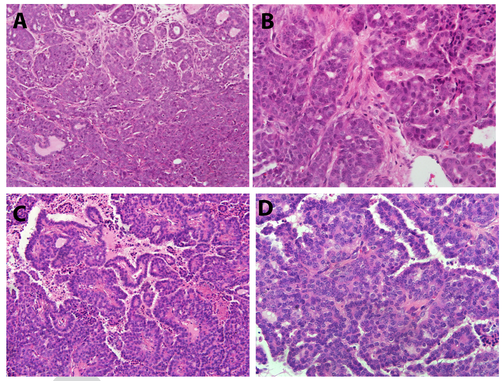

Figure 3: A. Passage: PA, 20X10; B: Passage: PA, 40X10; C: Passage: P0, 20X10; D: Passage: P0, 40X10.

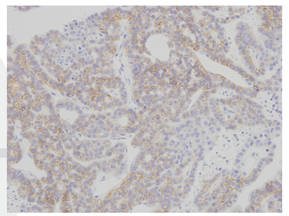

Figure 4: HER2 expression by IHC staining for MBR 6004

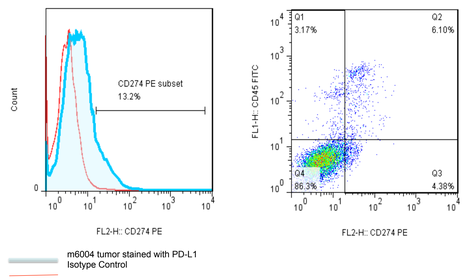

Figure 5: PD-L1 expression exad by FACS

Analysis

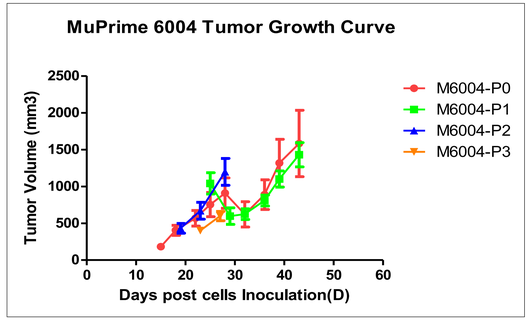

Figure 1: Tumor Growth Curve.

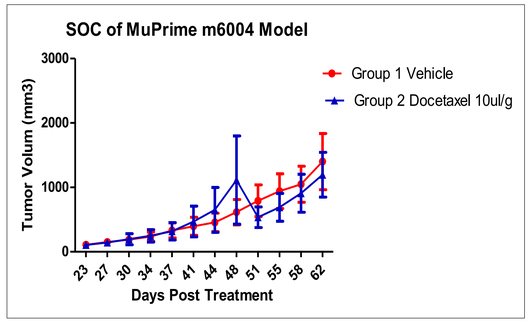

Figure 2: Stander of Care by treated the animals with Docetaxel..

Conclusions

1. We successfully build mouse tumor derived allografts for immune-oncology research by using genetically engineered mutant mouse cancer and other spontaneous tumor models
2. We have successfully established 6 MuPrime™ models including breast cancer, B-lymphoma and prostatic carcoma, etc. They grow robustly after engraftment
3. Our MuPrime™ will be a useful platform with normal immunity for drug evaluation, particularly for immune-oncology therapeutics.