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Developing a panel of orthotopic syngeneic tumor models for IO drug discovery

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Background

Immuno-oncology (IO) therapy is the focus of drug discovery in recent years. Unlike chemotherapy or targeted agents, the pharmacological efficacy of immune-oncology therapies needs to be evaluated in animal models with functional immune system. Syngeneic tumor models are established by inoculating mouse cancer cell lines to immunocompetent mice with the same genetic background. The host mice have complete immune activity and show histocompatibility with homograft tumor tissues, which can maximize the simulation of the real tumor microenvironment.

Subcutaneous syngeneic models are easily established and have been widely used; however, the subcutaneous tumors lack organ-specific stromal-tumor interactions that are critical for disease progression in patients. Orthotopic tumor models are established in organ-specific sites, facilitating metastatic spread, supporting immune and stromal component interactions, and providing a more disease-relevant tumor microenvironment for IO therapy assessment.

Method

In order to facilitate the development of IO drug, we have established a panel of orthotopic syngeneic tumor models. We generated a series of luciferase-labeled bioluminescent mouse tumor cell lines, which were then engrafted into the organ of interest to establish orthotopic models. Bioluminescent imaging (BLI) enabled non-invasive in vivo imaging of orthotopic tumor burden, the real time tumor growth, and the response to therapies, monitored by quantitative bioluminescent signals.

Results

Table 1 WuXi AppTec OIU orthotopic syngeneic models

Cancer type	Model	Mouse strain	Inoculation site
Bladder	MBT-2-luc	C3H	Bladder
	MB49-luc	C57BL/6	Bladder
Brain	GL261-luc	C57BL/6	Intracranial
Breast	4T1-luc	BALB/c	Mammany fat pad (MFP) Intravenous
	E0771-luc	C57BL/6 Albino	Mammany fat pad (MFP) Intra-caudal arterial Intra-tibia
	EMT6	BALB/c	Mammany fat pad (MFP)
Colorectal	CT-26-luc	BALB/c	Colon
Liver	H22-luc	BALB/c	Liver
Kidney	Renca-luc	BALB/c	Kidney
Lymphoma	A20-luc	BALB/c	Intravenous
Mastocytoma	P815-luc	DBA/2	Intravenous Subcutaneous
Melanoma	B16-F10-luc-G5	C57BL/6 Albino	Intravenous
Osteosarcoma	K7M2 wt	BALB/c	Intravenous

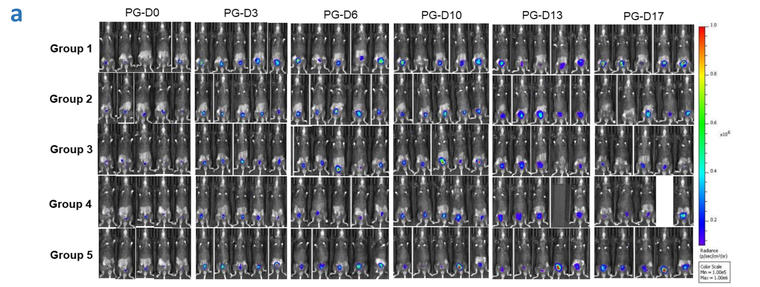

Fig 1 Establishment of MB49-luc bladder orthotopic model

a. Mice were treated with Gemcitabine and anti-mouse PD-1. Bioluminescent imaging of mice over 18 days (n=5).
b. Tumor weight data shows Gemcitabine works well in MB49-luc bladder orthotopic model.

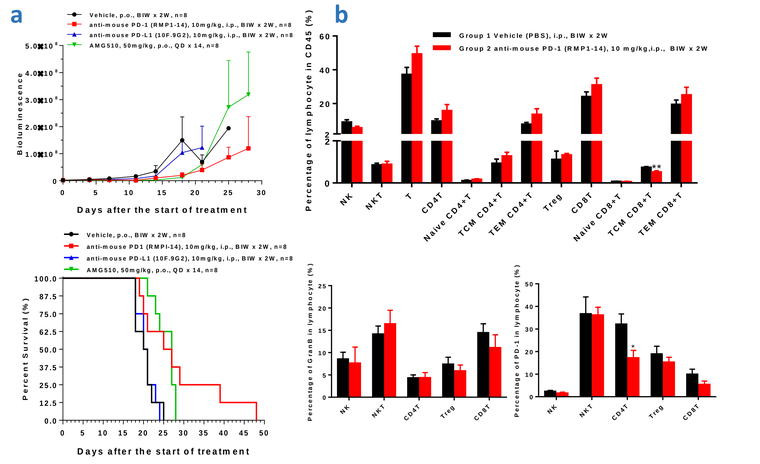

Fig 2 Combinatorial strategies in GL261-luc intracranial model

a. Anti-mouse PD-1 monotherapy produces some anti-tumor activity in GL261-luc intracranial model. GL261 tumor is detected with KRAS G12C mutation per in house data, the model also shows good response to KRAS G12C inhibitor AMG510.
b. Brain samples from control and anti-mouse PD-1 treated mice were analyzed by flow cytometry. Data shows percentage, Granzyme B and PD-1 expression of T & NK cell subsets. **c.** Combinatorial efficacy of anti-mouse PD-1 and Radiation or AMG510 in GL261-luc intracranial model.

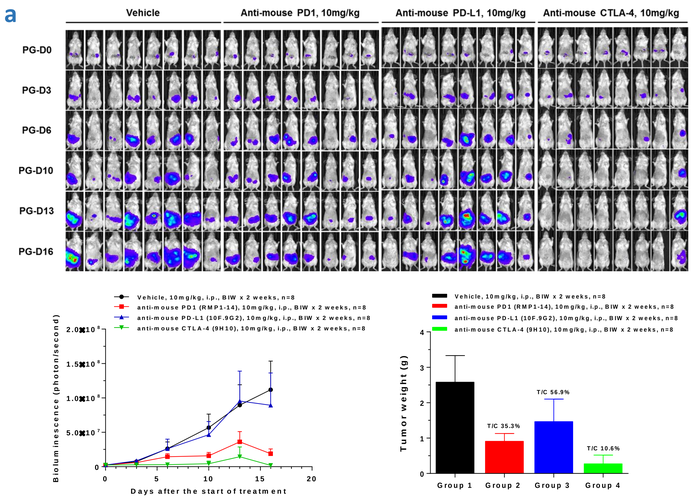

Fig 3 Check point inhibitors in CT-26-luc colon orthotopic model

a. Efficacy of anti-mouse PD-1, anti-mouse PD-L1 and anti-mouse CTLA-4 in CT-26-luc colon orthotopic model. **b.** Different immune cell composition in subcutaneous vs. orthotopic tumors, flow cytometry data shows decreased macrophage and increased CD11b+ DC in CT-26-luc orthotopic tumor.

Conclusion

Overall, these established orthotopic syngeneic tumor models recapitulate the clinically relevant tumor microenvironment and serve as a useful tool in the pre-clinical evaluation of immunotherapies.