NEW SPONTANEOUS AND CARCINOGEN-INDUCED MOUSE-DERIVED ISOGRAFT (MDI) TUMOR MODELS FOR IMMUNE THERAPEUTIC APPROACHES

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Introduction

First findings in the late 1990s and the early 2000s that blockade of immune checkpoint inhibitors (ICI) by antibodies could induce rejection of established tumors and induce immunity also to secondary exposure with these tumor cells, led again to a stronger focus of experimental studies on syngeneic tumor models in immunocompetent animals.

Table 1: Selection of frequently used syngeneic tumor cell lines and their origin.

Tumor cell line	Development	First description
CT26	NMU (N-Nitroso-N-methylurea)	Corbett TH etal, Cancer Res. 1975 Sep;35(9):2434-9.
Panc 02	3-MCA (3-methylcholanthrene)	Corbett TH etal, Cancer Res. 1984 Feb;44(2):717-26.
B16	natural	Teicher BA, Tumor models in Cancer Research
LL-2	natural	Sugiura K, Stock CC, Cancer. 1952 Mar;5(2):382-402.
4T1	natural	Dexter DL etal, Cancer Res. 1978 Oct;38(10):3174-81.
RENCA	natural	Murphy GP, J Natl Cancer Inst. 1973 Apr;50(4):1013-25.

The availability of such models, however, is mainly limited by the small number of genetically-modified (GEM) or long-term passaged cell line-derived tumor models. As many of the cell line-derived models currently used, either naturally developed or were carcinogen-induced in the 1950s to 1970s (see table 1), the idea arose to develop new syngeneic models.

Two different approaches were followed: (A) spontaneously arising tumors in old mice and (B) carcinogen-induced tumors. These new models are propagated in a PDX-like mode via transplantation from animal to animal to maintain a preserved primary tumor phenotype and intratumoral immune cell populations.

Experimental starting position

Table 2: Mouse strains observed for natural tumor development.

Animal number	Mouse strain	Sex	MHC haplotype
0001/14	C57BL/6	female	$H2^b$
0002/14			
0003/14			
0004/14			
0005/14	BALB/c	female	$H2^d$
0006/14			
0007/14			
0008/14			
0009/14	DBA/2N	female	$H2^d$
0010/14			
0011/14			
0012/14			
0013/14	C57BL/6 albino	female	$H2^b$
0014/14			
0015/14			
0016/14			
0017/14	CBA/J	female	$H2^k$
0018/14			
0019/14			
0020/14			
0021/14	C3H/HeJ	female	$H2^k$
0022/14			
0023/14			
0024/14			
0025/14	C57BL/6	male	$H2^b$
0026/14			
0027/14			
0028/14			
0029/14	BALB/c	male	$H2^d$
0030/14			
0031/14			
0032/14			
0033/14	C57BL/6 albino	male	$H2^b$
0034/14			
0035/14			
0036/14			

Table 3: Carcinogen and application site used to induce tumor development in CBA/J mice.

Animal number	Mouse strain	Sex	Carcinogen	Applikation site
2009/16	CBA/J	female	N-Nitroso-N-methylurea (NMU)	subcutaneous
2010/16				
2011/16				
2012/16				
2017/16	CBA/J	female	3-Methylcholanthren (MCA)	subcutaneous
2018/16				
2019/16				
2020/16				
2021/16	CBA/J	female	3-Methylcholanthren (MCA)	per os
2022/16				
2023/16				
2024/16				
2033/16	CBA/J	male	N-Nitroso-N-methylurea (NMU)	subcutaneous
2034/16				
2035/16				
2036/16				
2041/16	CBA/J	male	3-Methylcholanthren (MCA)	subcutaneous
2042/16				
2043/16				
2044/16				
2045/16	CBA/J	male	3-Methylcholanthren (MCA)	per os
2046/16				
2047/16				
2048/16				

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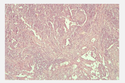
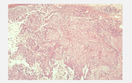
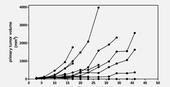
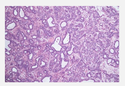
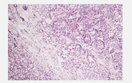
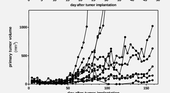
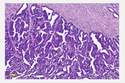
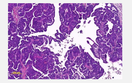
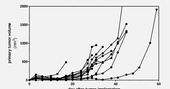
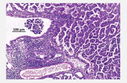
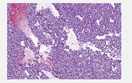
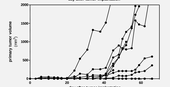
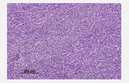
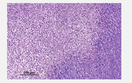
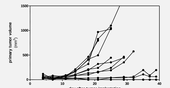
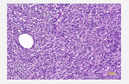
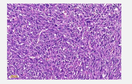
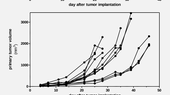
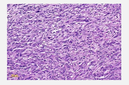
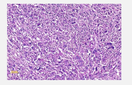
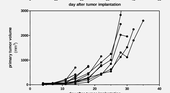
Summary

- Engraftment of tumor pieces which have never been adapted to grow in vitro
- Preserved original tumor histopathology via propagation from animal to animal
- Development of new syngeneic models for testing novel immunotherapies

Results

	Tumor Name	Diagnosis	Location of appearance	HE-staining of original tumor	HE-staining of transplanted tumor	In vivo tumor growth
Spontaneous tumor development	JA-0009	Adenocarcinoma, solid, invasive				
	JA-0017	Adenocarcinoma, solid, significant infiltration with small lymphocytes				
	JA-0023	Adenocarcinoma, exocrine gland origin, moderate peripheral mononnuclear cell infiltration				
	JA-0032	Adenocarcinoma, papillary, lung, surfactant secreting type II pneumocytes				
Carcinogen induced tumor development	JA-2041	Sarcoma, no giant cells, dense lymphocyte infiltration				
	JA-2042	Sarcoma, no giant cells, likely origin is integument of leg				
	JA-2011	Sarcoma, anaplastic, with atypical mononuclear and multinucleate giant cells				
	JA-2019	Sarcoma, no giant cells, invades skeletal muscles and adipose tissue