Building a comprehensive and fully annotated patient tumor derived xenograft (PDX) library mirroring cancer patient population

J Cai*, D Chen, R Kumari, S Guo, J Yang, M Yang, A McKenzie, Z Wang, X Huang, X An, J Liu, J-P Wery, H Li.
Crown Bioscience, Inc., Santa Clara, CA *Presenter

Poster : 1472

In life for life

Introduction

Patient derived xenografts (PDXs) mirror patients' pathology and genetic profiles, and are therefore valued as predictive experimental models for studying oncogenesis and precision treatments. Cancer is not a single disease but diseases of complex genetic components and oncogenic processes. We have built the largest and most comprehensive PDX library with full genetic profiles. Our large library of different disease panels are particularly useful for conducting mouse clinical trial (MCT of HuTrials™), which can be used to discover predictive biomarker and guide clinical study design.

Abstract

Our PDX library contains over 1,600 models derived from patients of both Asian and Western origins, covering over 20 major cancer types. Our PDX models are fully annotated with original clinical pathology diagnosis information, genomic profiling data (GeneChip and NGS), hotspot mutation data, and HLA typing info to enable immuno-oncology research. Majority PDX models have tumor growth and standard of care (SOC) treatment information. Comparing our PDXs' genomic profiles with published patient genomic profiles in literature and TCGA data source (Guo et al., 2015 AACR #1926) revealed a high degree of similarity. Subsets of the models have been comprehensively characterized for special relevance to specific clinical characteristics and specific drug targeting mechanisms (HuPrime® 2.0). These subsets include all clinically observed EGFR mutated NSCLC; c-MET activation diseases; FGFR driven diseases; RET-fusion driven CRC; FLT3-LTD driven AML, IDH mutated AML and CRC; RSPO-fusion driven CRC; BCR-ABL fusion disease, HER2 driven gastric and breast cancers, and ALK fusion NSCLC, etc.. We have also established numerous drug resistant models to various SOCs of both chemotherapy and target therapies. The resistance could be *de novo* or induced. Models which have great metastatic potential have also been identified, enabling the study metastatic mechanisms and for identifying agents to block metastasis. A number of PDXs can grow in humanized mice (HuPrime 3.0), where human immunity has been reconstituted in the immune-compromised mouse background to facilitate immune-oncology research.

Building HuPrime Platform

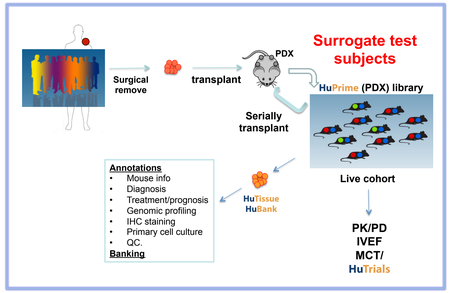

Figure 1. Patient derived xenograft models – HuPrime PDX platform. A. Building HuPrime PDX models and service platform. B. Core components of HuPrime pharmacology service capability.

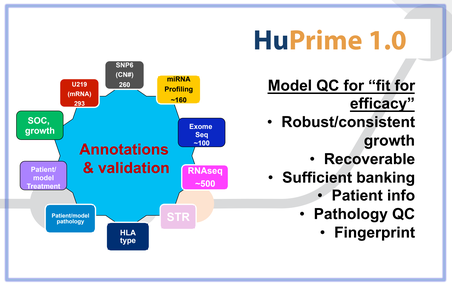

Figure 2. HuPrime model annotation and criteria for IVEF study.

HuPrime Model Collection

Table 1. Summary of Patient derived HuPrime 1.0 tumor models

Cancer Type	Subtype	Established	Total Asian models	Total Caucasian models	Treated model
Acute Lymphoblastic Leukemia		16	16	0	0
Acute Myeloid Leukemia		4	4	0	0
Adrenal		2	2	0	0
Bladder		17	8	9	1
Brain tumor		9	9	0	0
Breast		65	36	29	14
Cervical		17	16	1	0
Cholangiocarcinoma		21	20	1	0
Colonrecta		310	194	116	57
Endometrial		2	0	2	0
Esophageal		41	36	5	1
Fallopian		1	1	0	0
Gallbladder		9	9	0	0
Gastric		179	169	5	8
Gastrointestinal stromal tumor (GIST)		6	1	5	2
Head and neck		85	64	21	9
Kidney		15	13	2	0
Liver	HCC	104	99	4	0
	Other	51	35	15	1
Lung	NSCLC	249	90	159	35
	SCLC	68	4	64	32
	Other	53	39	14	0
Lymphoma	HL	2	2	0	0
	NHL	7	7	0	0
	Other	14	14	0	0
Melanoma		24	6	17	7
Neuroendocrine Tumor		9	9	0	0
Ovarian		72	28	44	10
Pancreatic		131	99	32	0
Sarcoma		12	10	2	0
Testis		1	1	0	0
Thyroid		7	7	0	0
Unclear Primary Site		20	19	1	0
Uterine sarcoma		16	0	16	7
Total		**1642**	**1067**	**564**	**184**

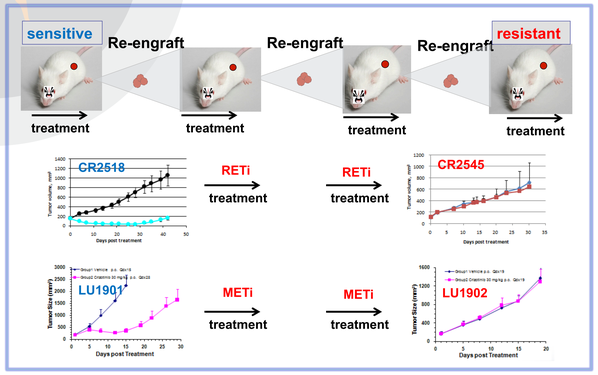

Figure 3. Development of drug resistant HuPrime PDX models by serial drug treatment and re-engraftment.

Special Application

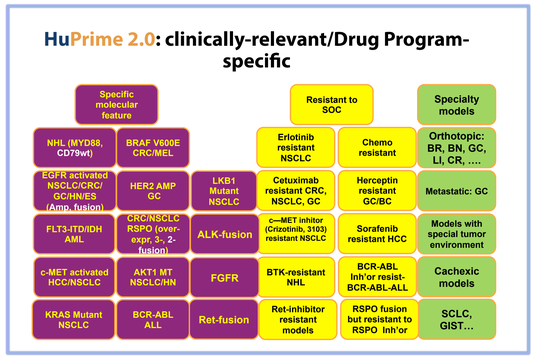

Figure 4. NexGen HuPrime 2.0 PDX models available for specific drug programs.

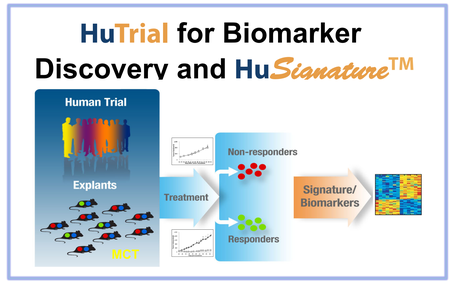

Figure 5. Large scale MCT/HuTrial studies using HuPrime 1.0 PDX models for Biomarker discovery and HuSignature development.

Database

Figure 6. Proprietary HuBase 2.0 - easy data access and powerful search function. http://hubase2.crownbio.com/

Contact: Henry Li, henryli@crownbio.com