Studying cancer drug resistance in patient derived xenograft tumor models

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AACR 2014
#1212

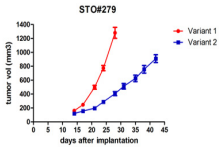
Abstract

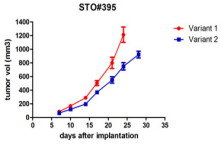
Anti-cancer drugs, either targeted therapies or cytotoxic chemotherapies, prove to be effective in treating certain cancer patients. However, in most cases, tumors recur and become resistant to the treatment after a period of time. In order to tackle this widely occurring clinical problem, there are urgent needs to understand the underlying drug resistance mechanisms, to discover drug resistance targets and drug resistance biomarkers and to develop new therapies or combination therapies. Currently, the main approach to study cancer drug resistance includes analyzing clinical samples and developing drug resistance models *in vitro*. Numerous potential resistance mechanisms have been identified. However, validation of these findings in a clinical-like setting and testing therapies in preclinical studies require *in vivo* tumor models of drug resistance.

Heterogeneity in PDX Tumor Models

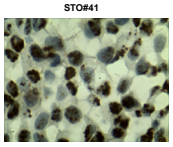
During the establishment and characterization of GD PDX tumor models, different layers of heterogeneity of human tumors are observed. First, at P3-P5, although the majority of PDX tumors display consistent tumor growth characteristics among tumors of the same lineage, some showed heterogeneity in growth rate. Secondly, molecular profiling further reveals intra-tumor heterogeneity at the cellular level. Thirdly, when being treated, different tumors derived from the same PDX tumor model may display drastically different responses to the therapy, predicting the existence of resistant subpopulations. We define the PDX tumor subpopulations with different reproducible phenotypes as PDX tumor variants.

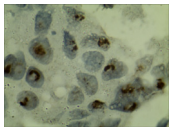
Variation in tumor growth rate



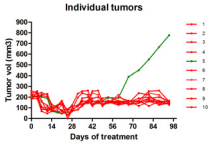


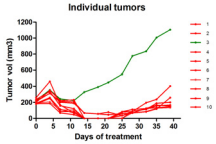
Variation in genetic background





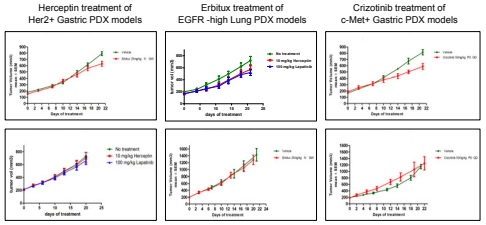
Variation in drug response



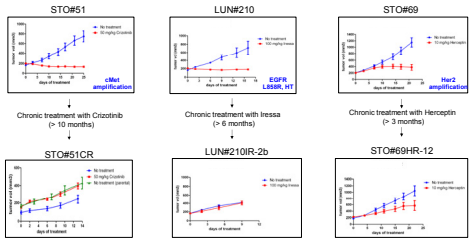


Development of Drug Resistant Variants from PDX Tumor Models

***De novo* resistance to target therapies**



Acquired resistance to target therapies



Resistance variants derived from GenenDesign PDX tumor models

Drug	Target	PDX tumor model	Acquired resistant variants
Herceptin	Her2 amplification	Gastric cancer	3
Lapatinib	Her2 amplification	Gastric cancer	7
Crizotinib	ALK fusion	Gastric cancer	2
Crizotinib	C-Met amplification/overexpression	Gastric cancer	6
Iressa/Tarceva	EGFR mutation	Lung cancer	3
FOLFOX		Gastric cancer	9
Paclitaxel		Gastric cancer	6
Paclitaxel		Lung cancer	5
Cisplatin		Lung cancer	4
Docetaxel		Gastric cancer	1

Molecular Analysis of Resistance Models

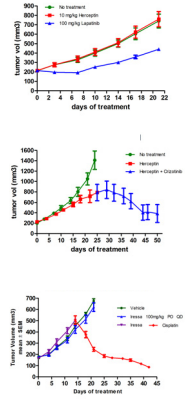
Molecular profiling of the drug resistant variants reveals multiple potential mechanisms that can be tested further by using 2nd generation targeted therapies or combining the initial drug with therapies targeting the additional oncogenic abnormalities.

Genetic abnormalities in Her2+_Herceptin-resistance gastric PDX models

Genetic Abnormality	c-Met amplification and overexpression	Pten deletion	EGFR overexpression	CCNE1 amplification	PIK3CA mutation	FGFR2 amplification	FGFR1 amplification	Not available
Number of Models	3	2	1	2	1	2	2	2

Test of New or Combination Therapy against Drug Resistance

Resistance model	Initial therapeutic target	Additional genetic abnormality	Treatment	Response
STO#53	Her2 amplification	EGFR high expression	Herceptin	Progression
			Lapatinib	Tumor growth inhibition
STO#69HR12	Her2 amplification	c-Met high expression	Herceptin	Progression
			Herceptin + Crizotinib	Regression
LUN#210IR2b	EGFR L858R	EGFR T790M	Iressa	Progression
			Cisplatin	Regression
			Afatinib	TBD



Summary

1. There is extensive tumor cell heterogeneity in PDX tumor models.
2. Drug resistance models (variants) can be derived from PDX tumor models.
3. Drug resistance mechanisms in PDX tumor models are similar to clinical findings.
4. Resistance models (variants) can be used to test new therapies or combination therapies.