Prediction of cancer patient responses to different treatments using personalized tumor models or models with matching genomic profiles

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Background

Complexity and heterogeneity in human cancer

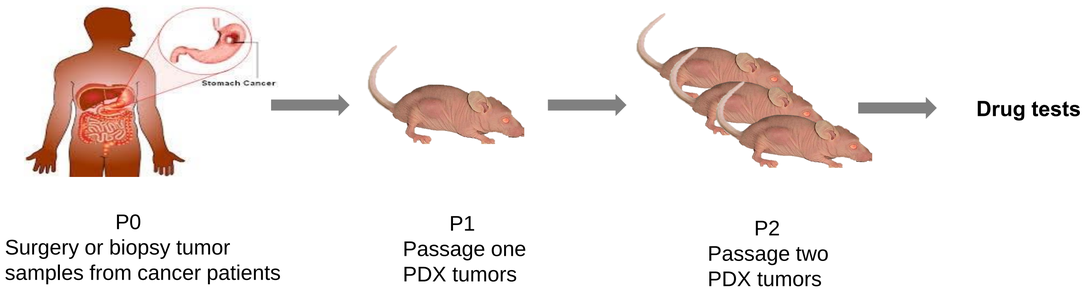
- Hundreds of cancer types from different organs and locations
- High inter-tumor and intra-tumor heterogeneity
- Continuous changes in cancer cells during tumor progression and drug treatment
- Tens of thousands of gene aberrations in cancer genome
- Difficulties in interpretation of cancer genomic aberrations for drug response prediction in most cancer cases

PDX models in cancer drug discovery and patient treatment selection

- Similar pathological and molecular features between PDX models and patient tumor samples
- A large number of PDX models available for preclinical efficacy studies and mouse trials
- A large amount of genomic profile and drug response information associated with PDX models
- Close correlations between PDX models and cancer patients in drug responses
- Usefulness of PDX models as AVATAR has been tested in multiple clinical trials to predict patient outcome

AVATAR: personalized cancer model for treatment prediction

Establishment of Avatar (PDX) model

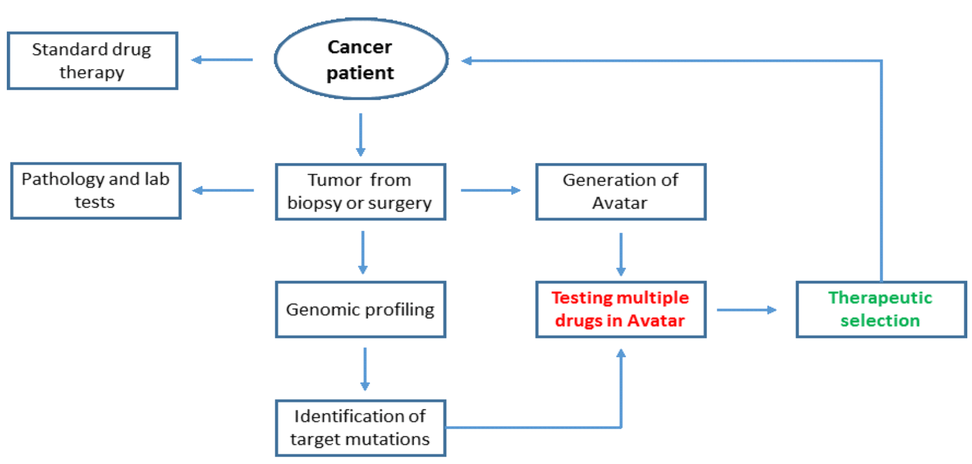


P0
Surgery or biopsy tumor samples from cancer patients

P1
Passage one PDX tumors

P2
Passage two PDX tumors

Avatar method for cancer drug treatment selection



Avatar is a personalized cancer model from a patient and for the patient. It is also known as Patient-Derived Xenograft (PDX) model. It is derived from patient's own tumor sample from surgery or biopsy, and tested with multiple cancer drugs.

Comparison of Avatar (PDX) and patient drug responses

Chemotherapy in NSCLC cancer

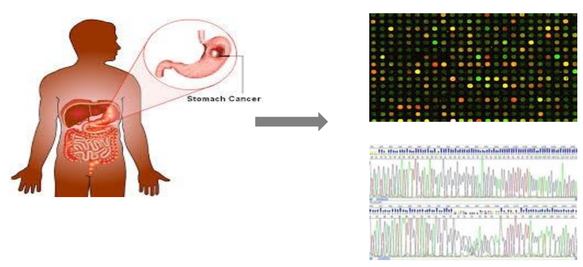
Patient/ Avatar	Patient pathological diagnosis	Clinical outcome	PDX response	Correlation
Patient 1	Adeno; Low differentiation; metastasis	alive; 36 mo after treatment	respond	>70%
Patient 2	Adeno; Low differentiation; Metastasis	alive; 37 mo after treatment	stablize	
Patient 3	Adeno; Low differentiation	alive; 29 mo after treatment	respond	
Patient 4	Adeno; Moderate differentiation	alive; 26 mo after treatment	respond	
Patient 5	Adeno; Low differentiation; Metastasis	alive; 24 mo after treatment	respond	
Patient 6	Adeno; Low differentiation; Metastasis	dead; 10 mo after treatment	progress	
Patient 7	Adeno; Low differentiation	dead; 11 mo after treatment	progress	
Patient 8	Adeno; Low differentiation; Metastasis	dead; 8 mo after treatment	stablize	
Patient 9	Adeno; Low differentiation	dead; 12 mo after treatment	respond	
Patient 10	LCLC	dead; 9 mo after treatment	progress	
Patient 11	Adeno; Moderate differentiation; Metastasis	dead; 12 mo after treatment	progress	
Patient 12	Adeno; Low differentiation	dead; 13 mo after treatment	progress	
Patient 13	Adeno; Low differentiation; Metastasis	dead; 6 mo after treatment	progress	

Targeted therapy in gastric cancer

Patient/Avatar	Cancer type	Drug target	Treatment	Patient response	PDX response	Correlation
Patient 14	Gastric cancer	Her2 amplification; c-Met overexpression	Herceptin	respond	regress	yes
			Paclitaxel	NA	regress	NA
			FOLFOX	NA	progress	NA
			Crizotinib	NA	progress	NA
Patient 15	Gastric cancer	FGFR2 amplification	FOLFOX	progress	progress	yes
			FGFR inhibitor	respond	regress	yes
			Paclitaxel	NA	stasis	NA
			Irinotecan	NA	stasis	NA
			Dovitinib	NA	stasis	NA
			Ponatinib	NA	progress	NA

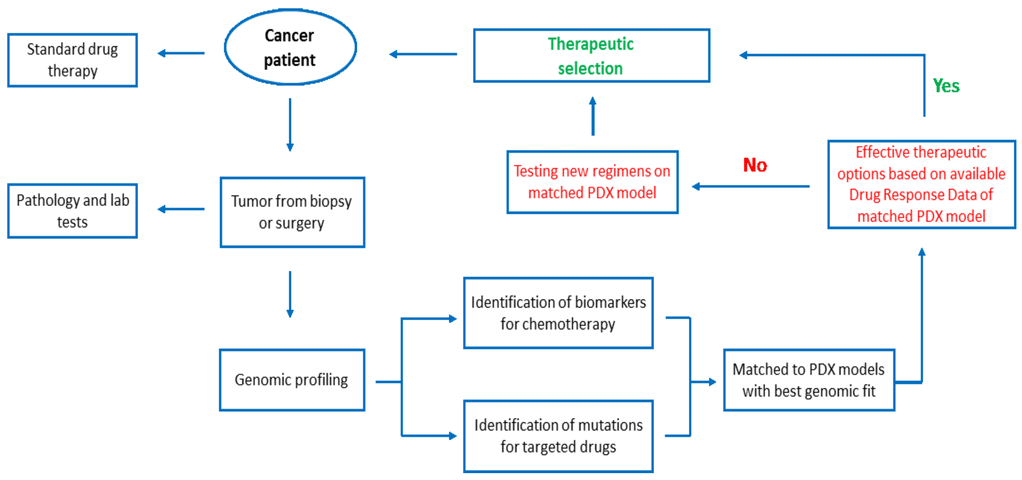
GIFTS: Best matching cancer model for treatment prediction

Genomic profile analysis of patient tumor sample



Methods	Profiling
Exome-Seq	DNA mutations and insertion/deletions
RNA-Seq	RNA expression, fusion and alternative splicing
SNP microarray	DNA copy number variations
PCR sequencing	Hot spot mutations

GIFTS method for cancer drug treatment selection



GIFTS (**G**enomic **I**nformation **F**itting based **T**herapeutics **S**election) is a method by which a cancer patient genomic information is matched to GenenDesign PDX model genomic profiles to find the best genomic fit and thus related therapeutic options in GenenDesign Drug Response Database.

Comparison of GIFTS and clinical drug responses

PDX models, genomic profiles and drug responses for GIFTS analysis

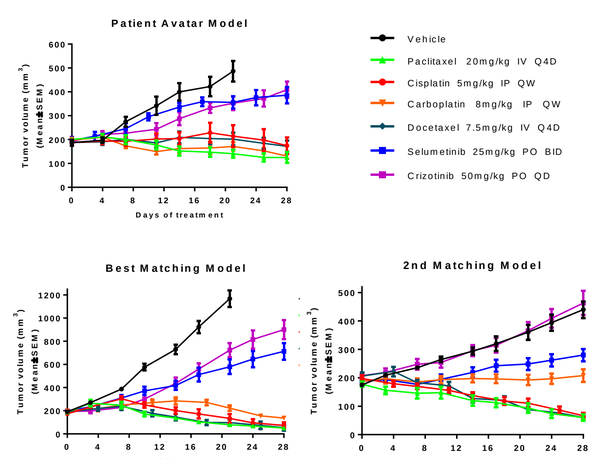
Tumor origin	Number of primary PDX models	Number of resistance PDX models	Genomic profiles	Drug response data sets
Lung	152	45	>100	>1000
Stomach	219	50	>100	>350
Liver	59	6	>50	>260
Esophagus	209	3	>60	>210

GIFTS with Lung PDX models

Number of cancer genes used in GIFTS	Patients		Matched PDX models	
	ID	Number of existing functional mutations	ID	Number of matched functional mutations
A panel of >600 cancer genes	LUN#038	27	1st best match	9
			2nd best match	8
	LUN#157	31	1st best match	8
			2nd best match	6
	LUN#257	18	best match	6

GIFTS		Treatment						
		Paclitaxel	Docetaxel	Cisplatin	Carboplatin	Taxol+platin	Selumetinib	Crizotinib
Case 1 (LUN#038)	Patient	NA	NA	NA	NA		NA	NA
	1st best match							
	2nd best match							
Case 2 (LUN#157)	Patient	NA	NA	NA	NA		NA	NA
	1st best match							
	2nd best match							
Case 3 (LUN#257)	Patient	NA	NA	NA	NA		NA	
	best match							

Drug responses in matched PDX models GIFTS – Case1 LUN#038



Advantages of AVATAR

Personalized cancer model
- From patient's own tumor sample from surgery or biopsy

Multiple drug tests at the same time
- Chemotherapy or targeted drug; single agent or combination therapy

Functional evidence based prediction on patient drug response
- Drug sensitivity or unresponsiveness in avatars were shown to be correlated with clinical results
- Choose the best drug treatments; Avoid the ineffective treatments

Derived drug resistance models for future treatment selection
- The course of drug resistance development in Avatar is similar to that in clinical patients

Advantages of GIFTS

Direct and effective usage of genomic profiles for both chemo and targeted therapeutics selection
- Independent of Avatar establishment
- Whole cancer genomic matching in addition to drug target identification
- Complement to other genomic profiling platforms

Quick prediction on patient drug responses
- A large number of available PDX models to find a match
- Available drug response information from the matching PDX models
- Treatment selection can be made in < 1 month

Easy new drug tests in matched PDX models
- New drugs or combinations can be tested in a short period of time

Summary

More than 50 Avatars have been successfully established so far and been tested with chemotherapeutic and targeted drugs *in vivo*. Based on our >320 in-house drug testing results of these Avatar models, a drug that could cause stabilization or regression of the PDX tumors was identified in >80% models. By comparing drug responses in mouse Avatars with patient clinical results, we found close correlations between them in both sensitivity and unresponsiveness.

Through bioinformatics analysis of PDX model genomic and drug response information, we were able to identify biomarkers for predicting drug sensitivity or resistance. These biomarkers have been used in matching cancer patient genomic profiles to those of PDX models in GenenDesign database using GIFTS method. Our preliminary results show that there are high degree of similarities in drug response profiles between patients and their matched PDX models.