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

**J Jiang, Y Yan, Z Lu, J He, Y Lyu, W Du, X Yang, J Gu, L Hua, X Ye, J Liu and Z Gu**

1. GenenDesign, Shanghai, China; 2. Huashan Hospital, Fudan University, Shanghai, China; 3. Peking Union Medical College Hospital, Beijing, China

#### 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

- **PG**: 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

- Standard drug therapy
- Pathology and validation tests
- Tumor from biopsy or surgery
- Generation of Avatar
- Genetic profiling
- Testing multiple drugs in Avatar
- Identification of target mutations

**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.

---

### GIFTS: Best matching cancer model for treatment prediction

#### GIFTS method for cancer drug treatment selection

- **Standard drug therapy**
- **Pathology and validation tests**
- **Tumor from biopsy or surgery**
- **Generation of Avatar**
- **Genetic profiling**
- **Testing multiple drugs in Avatar**
- **Identification of target mutations**

**GIFTS** (Genomic Information Fitting based Therapeutics Selection) is a method by which a cancer patient genomic information is matched to GenenDesign PDX model genomic profiles to find the best genetic fit and thus related therapeutic options in GenenDesign Drug Response Database.

---

### Comparison of Avatar (PDX) and patient drug responses

**Chemotherapy in NSCLC cancer**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient pathological diagnosis</th>
<th>Clinical outcome</th>
<th>PDX response</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 50 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Adeno; Low differentiation</td>
<td>alive; 20 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Adeno; Low differentiation</td>
<td>alive; 20 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Adeno; Low differentiation</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 9</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Adeno; Low differentiation</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 12</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
<tr>
<td>Patient 13</td>
<td>Adeno; Low differentiation; metastasis</td>
<td>alive; 35 mo after treatment</td>
<td>respond</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Comparison of GIFTS and clinical drug responses**

**PDX models, genomic profiles and drug responses for GIFTS analysis**

<table>
<thead>
<tr>
<th>Tumor origin</th>
<th>Number of primary PDX models</th>
<th>Number of resistance PDX models</th>
<th>Genomic profiles</th>
<th>Drug response data sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>152</td>
<td>45</td>
<td>&gt;100</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Stomach</td>
<td>21</td>
<td>30</td>
<td>&gt;100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>6</td>
<td>&gt;60</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Esophagus</td>
<td>209</td>
<td>3</td>
<td>&gt;60</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

**GIFTS with Lung PDX models**

- Drug responses in matched PDX models
- **GIFTS**: Cancer LUN#038

---

### Comparison of Avatar (PDX) and patient drug responses

**Targeted therapy in gastric cancer**

- **Patient 14**: Her2 amplification; c-Met overexpression
- **Patient 15**: FGFR2 amplification

#### 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 unsensitivity 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 therapies selection
- Independent of Avatar establishment
- Whole cancer genomic matching in addition to drug target identification
- Complement to other genomic profiling platforms
- 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 1-2 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 mice Avatars with patient clinical responses, we found close correlations between them in both sensitivity and unsensitivity.

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.