OncoTrack
Methods for systematic next generation oncology biomarker development

Sadallah Fatiha
30.10.2014 • Japan Health Sciences Foundation Visit • IMI JU Office, Brussels, Belgium
The OncoTrack Consortium

-11 academic and SMEs and 7 from EFPIA spread across 6 European countries

Observer status:

European Medicines Agency

Innovative Medicines Initiative

Pharmaceutical Industry
- AstraZeneca
- Bayer Pharma
- Boehringer-Ingelheim
- Janssen Pharmaceutica
- Merck-Serono
- Pfizer
- Roche

Academia & Clinical
- MPI Molecular Genetics
  - Stockholm University
- Uppsala University
- Université Paris-Sud
- Charité Berlin
- Medical Uni. Graz
- Technical Uni. Dresden
- Vall d’Hebron, Barcelona

SMEs
- Alacris Theranostics GmbH
- Experim. Pharmakologie & Onkologie Berlin
- International Prevention Research Institute
  - GABO:mi
OncoTrack Objectives

• **The premise:** most attempts to identify novel biomarkers probably fail because the source data do not sufficiently represent the complexity of the tumour

• OncoTrack is using a systems biology approach to model the tumour cell

• An *in silico* model (ModCell™) is being populated with genomic, transcriptome, genetic, biochemical and pathologic information derived from tumour samples (CTC, free circulating DNA, CSC, xenografts) collected prospectively from patients diagnosed with colon cancer

• This approach allows to analyze signaling pathways in the tumour in unprecedented detail

• **Our Major Deliverable:** Biological validation of the computational prediction of treatment response
OncoTrack

- Provide a common platform to share data and to perform analyses

- Unbiased identification of new biomarkers by:
  Building in-silico models in the “Virtual Patient, individual tumor cells, tumor tissues and patient derived xenografts, using data derived from the detailed molecular characterization (genome, exome, transcriptome, and methylome) of patient tumor, blood, CTC’s, CSC’s, and circulating DNA

- Use the output of the models to identify potential prognostic and predictive biomarkers
**In silico modelling workflow**

- **Tumor sampling**
- **Xenograft Models**
- **Tumor stem cell expansion**
- **Genome/Exome Methylome Transcriptome Sequencing**
- **ModCell™**
- **Patient Specific Models**
- **Drug Response**
- **Candidate Biomarkers**
OncoTrack Achievements

• Patient recruitment approaching completion:
  • 122 primary tumours and 31 metastatic tumours collected

• Over 90 novel xenograft models established:
  • About 60% of transplanted tumour tissues take
  • Xenograft models can be used to explore response to treatment

• Over 70 canceroid cell cultures established for investigation of
tumour progenitor cell biology:
  • Canceroids can be passaged and frozen for storage
  • Drug sensitivity testing in HTS format established

• Genomic and drug sensitivity data is now being used to populate
  in silico models of individual tumours
OncoTrack Achievements - continued

- Core genomic data available for 40 patients
  - Full genome / epigenome / transcriptome / proteome characterisation (characterisation by additional techniques is under way)

- Exome (tumor & germ-line) completed for ~ 50 patients
  - Additional 33 patients in progress

- Drug response data for ~ 60 tumors
  - Drug response information from xenografts and/or 3D cell cultures
  - Molecular characterisation of the experimental models is in progress

- Goal: >100 patients with deep characterisation
Systems Biology and Biomarker Discovery

- Systems biology, *in silico* modeling of a tumour, can be used to predict response to treatment
- The approach uses the combined information from exome, transcriptome, methylome and proteome analysis
- Modeling can be done at the level of individual patients (“n=1 trials”)
- The model may also be used to derive complex biomarkers that may allow more accurate stratification of patients
  - The approach highlights the technical questions surrounding technical validation of biomarkers based on high-dimensional data
  - This innovative approach also raises interesting questions regarding design of trials for clinical validation
Modeling the tumor cellular microenvironment
Over 40 different signaling pathways are integrated:
Cytokine signaling (e.g. CSF, IFNA, IL8), Death receptor signaling (e.g. Fas, TNFa, TRAIL), DNA repair / cell cycle, Ephrin signaling, GCPR/Hormone signaling (e.g. Glucagon, Insulin, Testosterone), Hedgehog signaling, Notch signaling, several RTK signaling (e.g. bNGF, EGF, FGF, IGF, PDGF, VEGF), TGFb signaling (e.g. BMP, TGFb) and Wnt signaling.

<table>
<thead>
<tr>
<th>Network components</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions</td>
<td>4439</td>
</tr>
<tr>
<td>Kinetic parameters</td>
<td>4853</td>
</tr>
<tr>
<td>Components</td>
<td>2839</td>
</tr>
<tr>
<td>Genes</td>
<td>572</td>
</tr>
<tr>
<td>Mutated genes</td>
<td>64</td>
</tr>
<tr>
<td>(5 LoF, 58 GoF, 1 fusion)</td>
<td></td>
</tr>
<tr>
<td>External activators</td>
<td>87</td>
</tr>
<tr>
<td>(growth factors, hormones etc.)</td>
<td></td>
</tr>
<tr>
<td>Inhibitors</td>
<td>56</td>
</tr>
<tr>
<td>(41 drugs)</td>
<td></td>
</tr>
</tbody>
</table>
Thank you

Fatiha Sadallah • Principal Scientific Manager
Fatiha.Sadallah@imi.europa.eu