Patient-Derived Xenograft (PDX) models as an emerging way to personalized medicine in translational cancer research

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Towards precision cancer medicine

Targeted drug → Target

Target alterations → Sensitizing alterations

Response → De-sensitizing alterations

Tissue/context-specific modifiers
Further elements of complexity

- **Intratumoral heterogeneity**
  - De-sensitizing lesions only present in a fraction of the cancer cells may lead to early recurrence

- **Intracellular signaling is governed by networks**
  - Dynamic adaptation to altered signaling.

- **Tumor-host interactions**
  - Tumor growth and response also depends on stroma, vasculature, inflammation and immune response
Patient-Derived mouse Xenografts (PDXs): the “Avatar” concept
Patient-Derived mouse Xenografts (PDXs): the “Avatar” concept
Propagation, biobanking and profiling of PDXs

Surgery

↓

“P0”

- Formalin
- Liquid nitrogen
- RNA later → -80°C

Mice

Implants

Molecular profiling
Propagation, biobanking and profiling of PDXs

“Pn”

- Formalin
- Liquid nitrogen
- RNA later → -80°C

Mice Implants

Vital Freezing

In vivo drug efficacy studies

Molecular profiling
PDX preclinical study designs

1. Collection of annotated PDXs or 'xenopatients'
2. Testing of a drug regimen
3. Correlation of response
4. Identification of resistance mechanisms
5. Biomarker discovery
6. Testing of new treatment regimens
7. Initiation of new clinical trials
8. Patient enrolled in a clinical trial
PDX preclinical study designs

(a) Collection of annotated PDXs or ‘xenopatients’
- Testing of a drug regimen
- Correlation of response
- Identification of resistance mechanisms
- Biomarker discovery
- Testing of new treatment regimens
- Initiation of new clinical trials

(b) Correlation of response
- Identification of resistance mechanisms
- Testing of new combined treatments
- Biomarker discovery
- Tumour volume
- Drug X
- Time (days)
- Vehicle

- Testing of a drug regimen in a clinical trial
- Test of patient enrolled in a clinical trial
- Development of avatar models

Nature Reviews | Cancer
PDX preclinical study designs

**a** Collection of annotated PDXs or ‘xenopatients’

- Testing of a drug regimen
- Correlation of response
- Identification of resistance mechanisms
- Biomarker discovery

Tumour volume over time (days)

**b** Correlation of response
- Identification of resistance mechanisms
- Testing of new combined treatments
- Biomarker discovery

Testing of a drug regimen in a clinical trial

**c** Bioinformatics analysis retrieves best proxy

Molecular profiling by NGS

Testing of a series or combination of drugs

- Information for treatment options
- Prognostic indicators

Tumour volume over time (days)
CRC PDXs at Candiolo

\[ n = 180 \]

\[ n = 110 \]

\[ n = 515 \]

Bertotti et al, Cancer Discovery 2011
Predictive biomarkers of response to cetuximab

Genetic status affects PDX response like in patients

Bertotti et al, Cancer Discovery 2011
Predictive biomarkers of response to cetuximab

Genetic selection affects response rate

*RAS/RAF wild-type only*
Predictive biomarkers of response to cetuximab

Other genetic biomarkers of resistance?

Bertotti et al, Cancer Discovery 2011
Predictive biomarkers of response to cetuximab
HER2 amplification is enriched in cetuximab-resistant PDXs
Only certain anti-EGFR + anti-HER2 combinations induce tumour shrinkage in HER2-amplified CRCs.
The HERACLES trial: Targeting HER2 in KRAS WT, cetuximab-resistant mCRC

*Heracles and the Hydra (Early Hellenistic Period), Musei Capitolini, Rome*
The HERACLES Trial: from “Xenopatients” to patients

Sartore-Bianchi et al., *Lancet Oncology* 2016
Opportunities arising from a European PDX community

- Recapitulate inter-tumor heterogeneity through assembly of large collections
- “Pan-cancer” preclinical approaches may become feasible
- Standardization and benchmarking of pharmacological and molecular profiling
- Wider range of expertise in technological platforms applied to PDX
EurOPDX Consortium at a glance

- **Launched in 2013**
- **19 academic institutions** in Europe and the US, among which **6 Comprehensive Cancer Centres**
- Each institution is part of an hospital or is collaborating with a neighbouring one.
- **Expertise in basic, preclinical, translational and clinical oncology**
Details of the collection for some pathologies

Colorectal cancer (754)
- 291 primary tumors
- 444 liver mets
- 4 lung mets
- 15 other mets

Characterization: 400+ already characterized by transcriptome arrays and targeted sequencing, but also 140+ by WES and 250+ drug monitoring

Breast cancer (161)
- 54 luminal
- 89 triple negative
- 18 HER2+

Characterization: 40+ CGH, 90+ transcriptomic, 40+ WES, 55+ drug monitoring

Lung cancer (71)
- 59 NSCLC
- 12 SCLC

Characterization: targeted seq, 20+ transcriptomic

Skin melanoma (136)
- 20+ WES, 40+ gene panel, drug monitoring

Pancreatic cancer (235)

Characterization: 120+ transcriptomic, 100+ CGH, 120+ WES, 20+ WGS, 70+ RNAseq, 70+ MiR

1500+ subcutaneous and orthotopic models - 30+ different pathologies

More info on www.europdx.eu
Standards

- **minimal information on the models**: workshop in Nov. 2014 + development of global standards in collaboration with EBI-EMBL (Terry Meehan) > Article Meehan TF et al., published in a special informatics issue of Cancer Research on November 1st
EDIREx: EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts

- Successful Proposal to call INFRAIA-2-2017 “Integrating Activities for Starting Communities” – Activities start in 2018
- To fulfill a clear need for access to PDX models from the scientific community:
  - Model delivery/deposit
  - Drug efficacy studies
# The EDIREX partnership

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EDIRex – A 4-year project

WP1 – (Virtual) access to a European distributed collection of PDX
IT tools (data handling, capturing and visualisation) / public database(s)

WP2 – Harmonise PDX Biobanking ad quality control
Biobanking and QC SOPs & Installation of LAS in the 7 nodes

WP3 – Cross-validation study
Across 7 nodes and additional preclinical platforms (orth./cells/humanised/imaging)

WP4 – Trans-national access
Shipping PDX cryopreserved samples & in vivo studies in the 7 nodes - Training

WP5 – Ethics

WP6 – Performance & Long-term sustainability

WP7 – Dissemination & Communication
Communication tools, Dissemination activities – User outreach

Beyond the project / Sustainability
A precision oncology perspective

Patients
- Clinical data
- Histology
- Molecular profiles

Patient-derived models (xenografts, cell cultures)
- Histology
- Molecular profiles
- Pharmacology

Public data
- Molecular datasets
- Pharmacogenomics
- Biomarker signatures

Data integration, analysis and visualisation

Individual patient

Diagnosis, prognosis and therapeutic decision.

Capture, Storage, Standardisation

New biomarker / stratification hypotheses

Data mining

Bioinformatician/ Translational researcher

Integrative visual reports
Possible interactions with INFRAFRONTIER

• Phenotyping/imaging capabilities
  – Drug efficacy studies
  – Modeling metastasis
  – Monitoring side effects of drug combinations

• Genetic engineering to improve PDX models
  – Facilitating tumour engraftment
  – Facilitating reconstitution of a human immune system
  – "Humanizing" mouse MHC

• Integrating PDX and mouse tumorigenesis models

• "Health passport", QC etc.

• Biobanking
Visit www.europdx.eu for the latest news about the Consortium

Contact:
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SAVE THE DATE

2nd EurOPDX Workshop

October 1-3, 2018
Weggis, Switzerland

More info available through our website in Nov.-Dec. 2017