# Oncodesign® Translational Drug Discovery Process

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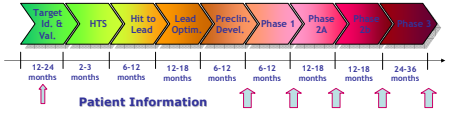
## Introduction

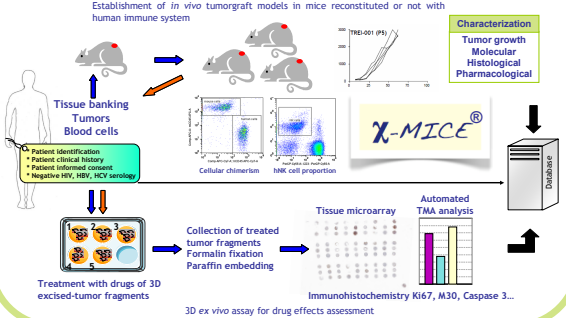
We present our "Translational Drug Discovery process", which is based on multiple research platforms that are used as flexible building blocks to design an optimal process to advance compounds and position them towards precise oncology applications. These platforms include cellular models, *in vivo* xenografts in mice and rats, pathophysiology based phenotypic models and a multi-modality imaging platform. Recent additions are based on fresh patient-derived tumor tissues and include *ex vivo* 3D models and low passage tumorgrafts. We have in addition initiated a program to discover $^{18}$F-labeled kinase inhibitor-based biomarkers/imaging tracers for use in PET applications. Our research base was recently completed with the addition of a diverse collection of potent and selective kinase inhibitors and the associated proprietary chemical technology.

## Oncology Drug Discovery Process



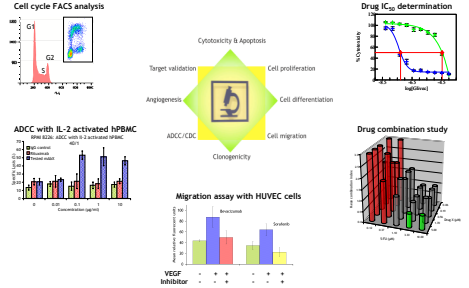

Oncology drug discovery remains today a largely sequential process, in most cases starting from a molecular target with some initial but often limited relevance to the disease. It takes multiple years and investments in the order of 5-10 million US$ before a compound is validated in advanced efficacy and safety models. In addition, due to the remoteness of many of the models to real disease pathophysiology and the resulting low predictability, attrition rates in clinical phases remain very high. There is an urgent need to create a tighter and earlier link between compound development and the patient to correctly position early targeted approaches towards clinical applications.

## Patient-derived models: Logistics



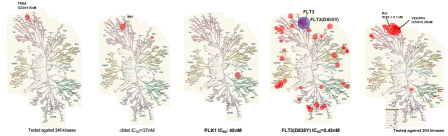

## *In vitro* conventional pharmacology

- Large panel of cell lines:
  - > 300 lines covering 90% of human cancers
  - Characterized growth kinetics
  - Responses to standard-of-care ($IC_{50}$ database)
  - Drug resistant cell lines
- Access to fresh patient tumor samples:
  - Tissue collection from local hospitals
  - Healthy blood and derived cell fraction collection
  - Consent statement and serological testing
  - Patient/cell subpopulation phenotyping




## Medicinal Chemistry

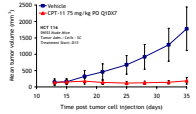
- Nanocyclix® technology
  - Design and synthesis of new molecules
  - Increasing potency and selectivity of kinase inhibitors




- Development of companion pharmacodynamic PET tracers
  - IMAK*inib*®: joint development of kinase inhibitor based therapeutics and $^{18}$F-labeled PET ligands
  - **Radiochemistry expertise,** including cyclotron on site

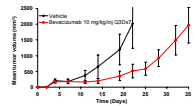
## *In vivo* conventional pharmacology

Anti-tumor activity study of CPT-11 on *Nude* mice bearing subcutaneous HCT 116 human colon carcinoma

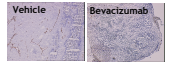



- Large panel of *in vivo* models:
  - > 100 xenograft models in athymic mice and rats
  - > 20 syngenic models
  - Disseminated, orthotopic or metastatic models
  - Known activity of standard-of-care.

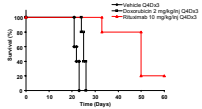
Anti-tumor activity study of bevacizumab on *Nude* mice bearing subcutaneous A-673 human rhabdomyosarcoma



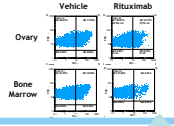

Bevacizumab efficacy on A-673 tumor vessel density (CD31 immunohistochemistry)




Anti-tumor activity study of rituximab and doxorubicin in Scid mice bearing disseminated Ramos lymphoma

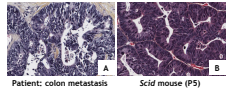



FACS analysis of human CD45 positive Ramos cells in mice organs at D20

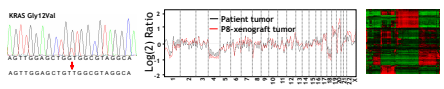



## *In vivo* and *ex vivo* pharmacology with patient-derived models*

Histological analysis reveals a high degree of similarity between the patient tumor (A) and the derived xenograft model in mouse (B) (e.g. colon adenocarcinoma from liver metastasis)

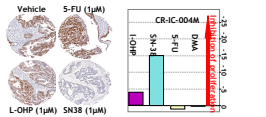



The molecular profiles of the tumors address specific gene mutations (DNA sequencing), chromosome abberation (Comparative Genomic Hybridization-array), gene or protein expression (transcriptomic, proteomic or metabolomic analysis). Such analyses guide the choice of the models in regard to the drug targets and help to correlate the results with potential responsive patients

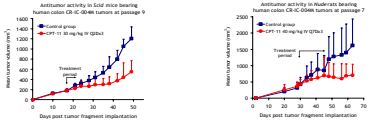



**Pharmacological evaluation suggests the correlation between *ex vivo* and *in vivo* drug response in patient-derived tumors**

3D *ex vivo* 5-FU, SN38 and L-OHP drug effect on cell proliferation (Ki67) of CR-IC-004M colon tumor fragments




*In vivo* anti-tumor activity on subcutaneous colon tumorgrafts in *Scid* mice or *Nude* rats IV treated with CPT-11, 5-FU, or L-OHP. Tumors were responsive to CPT-11 in both models (T/C% max = 16% in mice, 30% in rats) whereas no significant response was observed with 5-FU or L-OHP (not shown)



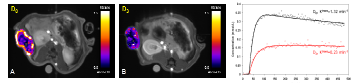

(*) These data have been generated with the contribution of the members of the CReMEC consortium : 2009 AACR poster #309 and 2010 AACR poster #4169

## Translational imaging biomarkers

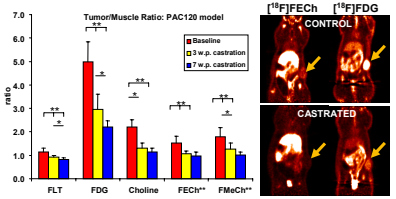
**Oncodesign® and PharmImage® Imaging capabilities :**
- MRI
- PET
- SPECT
- US

→ **Imaging biomarker identification for :**
- patient / model stratification
- pharmacodynamic endpoints
- drug efficacy
- toxicity / safety

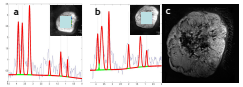
Functional DCE-MRI for tumor perfusion assessment (Ktrans) of anti-angiogenic therapies in tumor-bearing *Nude* rats




Identification of useful PET tracers for hormonal therapies evaluation in PAC120 human prostate cancer model in *Nude* rat*




$^{1}$H-MR Spectroscopy and MRI morphology of the PAC120 human prostate tumor SC xenografted in *Nude* rat




No change in the choline content was observed between baseline (a) and two weeks post castration (b). The heterogeneity of the tumor tissue is clearly depicted in the T2-weighted high resolution images (c).

(*) These data have been generated in collaboration with the Preclinical Imaging Laboratory, Tubingen University, Germany
(**) FECh: fluoroethylcholine; FMeCh: fluoromethylcholine