Introduction / Abstract

Most preclinical investigations in Oncology research are performed using permanent cancer cell lines that have been kept in continuous in vitro passages since decades. These plastic-cultured cells became very different from their original tumors since accumulated genetic abnormalities and multiple selections of subclones occurred over time. The use of fresh patient-derived tumor samples for ex vivo assays and for establishment of new relevant in vivo tumor models allows investigating the anti-tumor activity of new therapies directly linked with clinical reality. In this respect, Oncodesign® has developed a large and international network of clinical centers for the collection of a large number of fresh patient-derived tumor biopsies from all cancer pathologies and from healthy tissues. The collection of these samples is done under ethically approved master agreements and with the signed consent of each patient. The patient’s clinical history, the anamnestic results (T/t, IFI and FCV) and tissue banking are centralized in our internal approved biological resource center.

Examples of ex vivo assays will be presented based on patient-derived acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia and other hematopathologies using chromium release and Annexin V FACS assays. These studies aimed to demonstrate the CDC, ADCC and apoptosis induction of new therapeutic antibodies compared with approved antibodies such as Rituximab and Alemtuzumab used as positive controls. Some xenograft derived models were used to study the direct dose-response effect of new chemotherapy agents through adoptive immunotherapy (dendritic cells used as positive controls).

The highly collected and stored samples set up in the BRC allows to establish new in vivo tumor models in different strains of mice and rats. The full characterization of the genetic patterns of the xenograft derived tumors was compared with the original collected human tumors and with the clinical data of the patient. A panel of “Standard of care” compounds was tested in these new tumor models for pharmacological characterization. The expansion of such tumors at early passages in mice was used to implement a reproducible ex vivo 3D assay. The assay was developed to investigate the potential anti-tumor activity of conventional and targeted therapies, and allows sufficient throughput for use during drug discovery lead optimisation. Ex vivo drug effects were then correlated with in vivo results using the same panel of tumorigenicity.

The use of fresh patient-derived tumors in drug discovery and early preclinical development of new therapies aimed at correlating results with clinical reality. Moreover, these processes from the clinical tumor collection to the in vitro drug efficacy study through ex vivo assays should help the preclinical drug selection, development and clinical positioning as well as companion biomarker identification.

Oncodesign® BRC

Collection opportunities

Ex vivo drug evaluation in hematological malignancies

Ex vivo drug evaluation in solid tumors

OncoDesign BRC has developed an international network to provide (all fresh) biological samples needed for preclinical investigations.

The BRC associated to the Chi-mice® platform allows the establishment of new advanced and predictive experimental models.

The combination of patient-derived models with reconstituted human immune system in mice aims to improve efficient translational drug discovery and drug positioning in Oncology and other related pathologies.

Conclusions

Oncodesign® has built up an unique private approved biologic resource center in accordance with European legal and ethical rules.

Oncodesign® BRC has developed an international network to provide (all fresh) biological samples needed for preclinical investigations.

The BRC associated to the Chi-mice® platform allows the establishment of new advanced and predictive experimental models.

The combination of patient-derived models with reconstituted human immune system in mice aims to improve efficient translational drug discovery and drug positioning in Oncology and other related pathologies.

Ex vivo drug evaluation in hematological malignancies

Ex vivo drug evaluation in solid tumors

Similar tumor response ranges have been observed in mice and in 53 colorectal patient-derived models (1) with some advantages for rituximab as seen in this example (18-68% vs 22-55% response rates in mice vs patients). In addition, the xenograft panel of colorectal tumors was sensitive to RAD001, sorafenib and sunitinib and was not sensitive to lapatinib ex vivo treatments.

Ex vivo drug evaluation in solid tumors

In vivo drug evaluation

Whole body traditional H2O-rewarmed mice were miculated via the intravenous route with C6-36 cells injected from UCB samples. H2O-rewarmed mice were used to assess the drugs’ potency and sensitivity of transplanted human cells in vivo, detecting both mouse and human tumor markers. Twenty six weeks after humanization, tumoral burden were induced by preferential xenograft human patient-derived ovarian tumor fragment (DON-58) into the right flank of humanized NOD mice (n=6).

Take and growth rate of T060-I02 patient-derived tumor was not modified when xenograft was transplanted H2O-rewarmed.