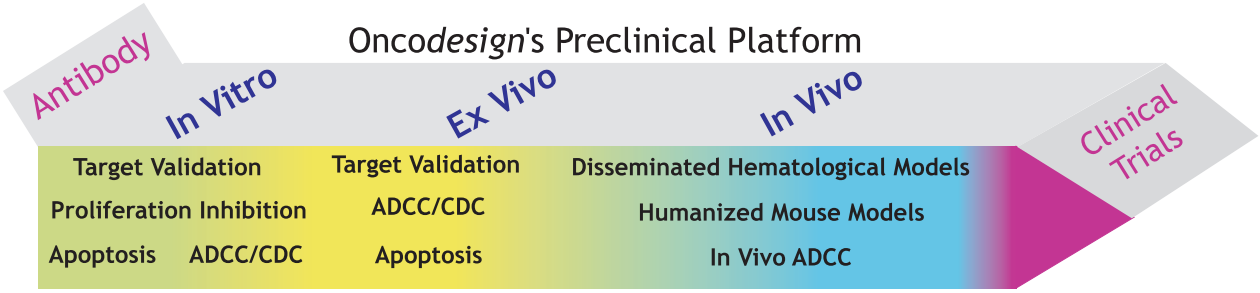
Assessment of Therapeutic Antibodies Targeting Hematological Malignancies

• IMAGING • BIOMARKERS • PRECLINICAL • PHARMACOLOGY • ONCOLOGY •

The complete "preclinical trial" to translate your leukemia targeting antibodies into clinical development

Oncodesign's Preclinical Platform



Monoclonal antibodies, such as Rituximab, are valuable therapies against hematological disorders (leukemia, lymphoma or myeloma), and represent a multi-billion dollar market. Oncodesign's unique models and technology will enable you to translate your mAbs into clinical development with better characterization and more relevant data for clinical use.

Key Benefits

- Target validation using human hematological tumor samples
- Understanding of the molecular mechanism of activity (apoptosis, cytolysis, agonism...)
- Determination of antibody pharmacokinetics and biodistribution
- Evaluation of the antitumor activity in relevant disseminated hematological tumor models
- Analysis of potential synergistic therapy combinations

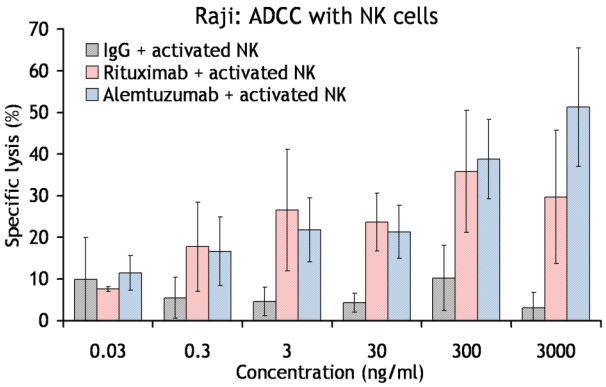
In Vitro Antibody Activity

Fab-mediated effects:

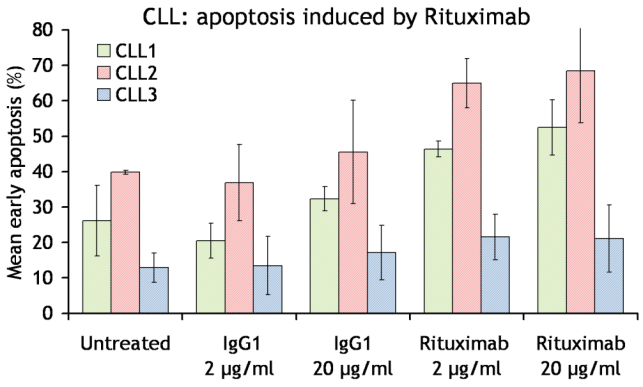
- Validation of targets
  - high-throughput cell line screening
  - flow cytometry, immuno-histochemistry
- Inhibition of proliferation
  - MTS, ATP quantification assay
  - cell cycle cytometry (PI, BrdU, P-histone H3)
- Induction of apoptosis
  - annexin V, caspase flow cytometry

Fc-mediated effects:

- Complement-dependent cytotoxicity (CDC)
- Antibody-dependent cell cytotoxicity (ADCC)
- Antibody-dependent cell phagocytosis (ADCP)
  - ^{51}Cr release, fluorescent dye assay



Ex Vivo Antibody Activity



Fresh human leukemia samples:

- Local hospital agreement
- Patient consent
- Cell subpopulation phenotyping and sorting

Available assays to evaluate:

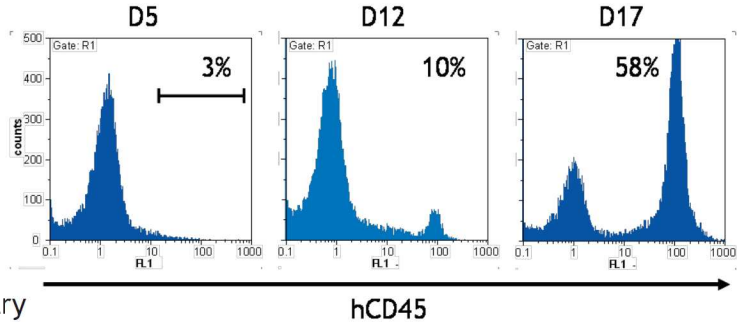
- Antibody target by cytometry
- Induction of apoptosis
- Induction of CDC, ADCC, ADCP

In Vivo Antibody Activity

In vivo hematological tumor models:

- Intraperitoneal or subcutaneously grafted tumors in mice or rats
  - evaluation of antitumor activity

- Disseminated hematological tumor models
  - intravenous injection of tumor cells
  - relevant organ invasion similar to human hematological malignancies
  - cell dissemination assessment by flow cytometry
  - survival and/or additional endpoints (body weight, behavior, flow cytometry)
  - available variants resistant to reference drugs



FACS analysis at day 5, 12 and 17 after IV injection of NAMALWA cells (hCD45+) in *Scid* mice to determine the kinetics of lymphoma dissemination into bone marrow

Experimental IV disseminated hematological tumor models:

Pathologies	Plasma cell leukemia	ALL	AML	CML	Myeloma	Lymphoma	Burkitt's lymphoma
Cell lines	ARH-77	CCRF-CEM	HL-60	K-562	RPMI 8226	U-937	Daudi NAMALWA Ramos Raji

In Vivo Antibody Pharmacokinetics

- Pharmacokinetics by ELISA
- Biodistribution of radiolabeled antibodies by:
  - whole-body autoradiography
  - organ collection and radioactivity counting
  - PET imaging

Therapeutic Combination

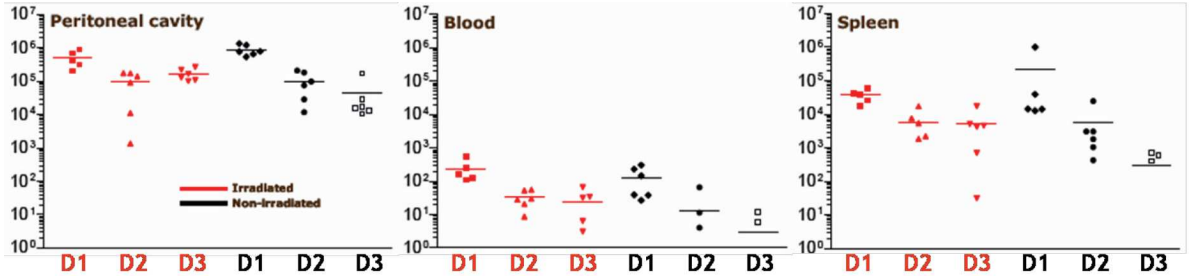
- In vitro cytotoxic assay to determine:
  - most suitable combined therapies
  - optimal schedule of treatment
- In vivo models to evaluate:
  - sequence of administration
  - combined therapy efficacy

Chi-Mice®: Humanized Mouse Models

Humanized mouse models have been usefully applied for studying various human disease states including AIDS, transplantation and autoimmunity. They can be used for the evaluation of antitumor activity related to ADCC.

In order to provide humanized mouse models, we have successfully developed:

- Engraftment of human Peripheral Blood Mononuclear Cells (hPBMCs) or specific immune effector cells
- Examination of human immune effector cells in an in vivo setting by flow cytometry



Absolute number of human NK cells from irradiated (red) and non-irradiated (black) NOD-*Scid* mice injected intraperitoneally with hPBMCs from 3 different donors (D1, D2, D3) and sacrificed at day 18 after engraftment

References Available on our Website in the Media Section

- 2010 ACCR Poster, #394
- 2008 AACR Poster, #1039
- 2007 AACR Poster, #2218
- 2007 AACR Poster, #4112

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