



Preclinical models of B-cell malignancies

Presented by :



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PLATEXLYMPH, an innovative collaborative initiative for developing preclinical models from patient samples with lymphoid hematological disorders.

Preclinical models are essential tools for increasing technology readiness levels (TRL) and advancing drug candidates along the translational pipeline. The generation of robust proof-of-concept data is a critical step before clinical evaluation.

Because experimental systems can only partially recapitulate the complexity of living organisms, it is essential to rely on **well-characterized and controlled models addressing specific biological questions**, with clearly defined limits for clinical extrapolation.

Among emerging preclinical approaches, models derived from primary patient cells, commonly referred to as **patient-derived models** (PDMs), have gained increasing interest. **When combined with clinical and molecular patient data, these models provide highly relevant platforms for studying disease biology and evaluating innovative therapeutic strategies.**

The Platexlymph - Institut Carnot CALYM consortium **brings together six research teams specializing in lymphoid malignancies**, including B-cell lymphomas (FL, DLBCL, MCL), multiple myeloma, Waldenström macroglobulinemia and chronic lymphocytic leukemia.

Within this consortium, several **complementary lymphoma models derived from patient samples** are currently being developed : 2D+ culture models, diverse 3D models, *in-ovo* models and murine models.

These preclinical lymphoma models provide both biological and clinical opportunities.

From a biological perspective, they enable **functional and immunological investigations**, including the study of multicellular interactions through the partial reconstruction of the tumor microenvironment.

They also support the **generation of high-resolution datasets** such as multi-omics, spatial transcriptomics and single-cell analyses.

From a translational perspective, these systems represent valuable platforms for **target identification, biomarker discovery and the screening of innovative therapeutic approaches**, including targeted therapies and immunotherapies, in **correlation with patient treatment histories and responses.**

This work received support from the Carnot Institute CALYM under the “Carnot Initiative” managed by the French National Research Agency (ANR).

SUMMARY

2D+ MODELS

2D

2D+ Co-culture Platforms

3D MODELS



Advanced 3D
Lymphoma Models

Versatile 3D Alginate Bead Culture Platform

IN OVO MODELS



Innovative *In Ovo* Lymphoma
Xenograft Model (CAM Assay)

MURINE MODELS



Systemic Xenograft
and Patient-Derived
Xenograft Models

In Vivo Xenograft
Mouse Models for
Lymphoid
Malignancies

Genetically
Engineered *In Vivo*
Lymphoma Model



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TECHNOLOGY DESCRIPTION

Technology / Model

Advanced 2D co-culture systems designed to reproduce key tumor microenvironment (TME) interactions and enabling sustained B-cell survival, proliferation, and functional interactions.

These 2D+ model combines lymphoma cells with different TME settings such as:

- B-cell spheroid structures sustained by supportive stromal cells
- Cytokine stimulation (cocktail adapted for each malignancy)
- Lymphoid or Monocyte-based microenvironmental support
- Autologous bone marrow ex vivo culture

Disease Indications

- Non-restrictive
- Designed for studying all lymphoid malignancies

Model Availability

- Clinically annotated Patient-derived samples:
 - Mantle Cell Lymphoma cohorts: Refract-Lyma (Nantes)
 - Multiple Myeloma cohort: MYRACLE (Nantes)
 - DLBCL and FL primary samples (Rennes)
 - Healthy donor samples: lymph nodes, tonsils, PBMCs (Rennes)
- Well-characterized cell lines:
 - GCB lymphoma cell lines, DLBCL, FL (Rennes)
 - MCL and MM cell lines (Nantes)

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

- Cytotoxic agents
- Cytostatic compounds
- Epigenetic drugs (epidrugs)
- Targeted therapies (ex: BCL-2, BTK, Proteasome)
- B cell-targeted monoclonal antibodies
- Immunotherapies (ex: bispecific antibodies)

Integrated Cutting-Edge Technologies

- CRISPR/Cas9 genome editing of cell lines
- Genome editing also developed in primary MCL cells
- Advanced multiparametric immunophenotyping (spectral technology)
- Multi-omics approaches: Genomics, Transcriptomics (Bulk or single cell), Proteomics
- NGS pipelines
- Cytokine and soluble factor quantification assays
- Integration with translational and clinical datasets

Comprehensive Read-outs

- Tumor cell killing and kinetic evaluation of toxicity
- Drug Testing and IC50 determination on patient cells and cell lines
- Evaluation of B-cell differentiation in normal human PBMC in response to drugs
- B- and T-cell activation and exhaustion profiling
- Immune synapse characterization
- Deep immunophenotyping of patient samples

KEY COMPETITIVE ADVANTAGES

This system enables the maintenance and activation of malignant B cells while reproducing key signals from the lymphoid and bone marrow niches. It allows investigation of drug response mechanisms and resistance pathways.

- Animal-free preclinical platform, aligned with 3R principles and evolving regulatory expectations
- Rapid and straightforward implementation, enabling fast experimental turnaround
- Efficient maintenance cell viability and proliferation of primary tumor cell viability and proliferation
- A model well-adapted for fragile and difficult-to-culture cells
- Ability to model several key tumor microenvironment interactions
- Highly suitable for mechanistic studies and targeted therapy evaluation

KEY PUBLICATIONS

Chiron et al, Blood 2016 / Papin et al, Leukemia 2019 / Decombis, Haematologica 2022 / Durand et al, Haematologica 2024 / Madiot et al, Leukemia 2026 (LCM)/ Durand et al, Hemasphere 2024 / Durand et al, Blood 2022 / Gomez-Bougie et al, Blood 2018 (MM) / Caron G et al, iScience (under revision)



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TECHNOLOGY DESCRIPTION

Technology / Model

Advanced 3D lymphoma models designed to reproduce the complex cellular architecture of lymphoid malignancies.

- Cell line-derived 3D models
- Patient-Derived Lymphoma Spheroids

Disease Indications

- Follicular Lymphoma (FL)
- Diffuse Large B-Cell Lymphoma (DLBCL)
- Marginal Zone Lymphoma (MZL)
- Mantle Cell Lymphoma (MCL)
- Chronic Lymphocytic Leukemia (CLL)

Model Availability

- Well-characterized lymphoma cell lines representing the biological heterogeneity of the diseases.
- Clinically annotated Patient-derived primary samples from well-established cohorts
- Disease stages: diagnosis, relapse, relapsed/refractory
- Sample origin: peripheral blood, lymph node, spleen
- Response to treatment

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

- Targeted therapies: key signaling pathway inhibitors (BTK, PI3K, AKT, BCL2, etc.)
- Standard-of-care chemotherapy: CHOP
- Immunotherapies and T-cell-based approaches: monoclonal antibodies, immune checkpoint inhibitors, bispecific antibodies, and related modalities

Integrated Cutting-Edge Technologies

- High-dimensional flow and spectral cytometry
- Advanced microscopy platforms (IHC, multiplex IF, Operetta, SPIM, confocal)
- Multi-omics approaches: Genomics, Transcriptomics, Proteomics including spatial transcriptomics and proteomics (Xenium, CODEX)
- Single-cell RNA-sequencing

Comprehensive Read-outs

- Tumor cell killing and depletion
- T-cell activation and cytotoxicity
- B- and T-cell activation and exhaustion profiling
- Deep immunophenotyping of patient samples
- Immune cell and therapeutic antibody infiltration (3D tumor structures)
- Morphological analysis of 3D spheroid structures
- Immune synapse characterization in complementary experiments (2D systems)
- Direct correlation with patient clinical parameters (treatment response, age, sex, prior lines of therapy, etc.)



KEY COMPETITIVE ADVANTAGES

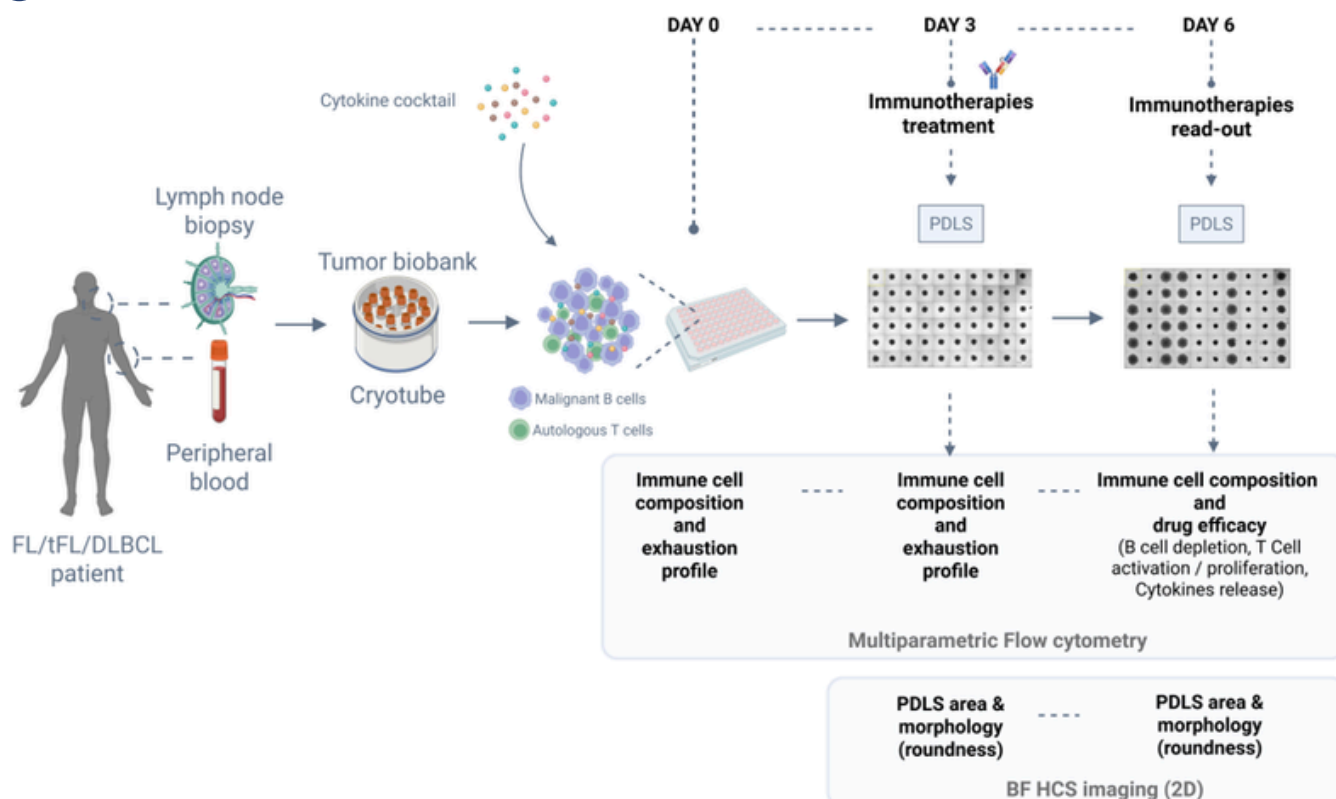
For cell lines-derived 3D models:

- Animal-free preclinical platform, aligned with 3R principles and regulatory evolution
- Cost-effective and highly scalable
- Robust reproducibility and repeatability
- Rapid and easy establishment
- Fully compatible with immune co-culture systems
- Ideal for high-throughput drug screening
- Short culture-to-readout timelines, enabling fast decision-making

For Patient-Derived Lymphoma Spheroids:

- Animal-free preclinical platform, aligned with 3R principles and regulatory evolution
- Rapid generation from patient material
- Clinically relevant drug screening platform
- Short experimental timelines
- Flexible reconstitution strategies (selective depletion or enrichment of specific cell populations)
- Presence of the key cellular players and components of the tumor microenvironment (Lymphoid immune cells, Myeloid cells, Optional stromal components) involved in immunotherapy responses, making the model particularly suitable for immuno-oncology studies
- Strong translational value with demonstrated correlation to in vivo treatment response (e.g., glofitamab)

FIGURES / ADDITIONAL INFOGRAPHICS



KEY PUBLICATIONS

Gava et al Cancers 2021 / Faria et al JITC 2023 / Araujo-Ayala F et al, Leukemia 2023 / Dobano-Lopez et al Blood Cancer J 2024 / Marcoux et al Blood 2026/ Gava et al Hemasphere in press

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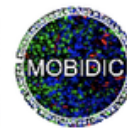
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TECHNOLOGY DESCRIPTION

Technology / Model

- Advanced 3D cell culture model based on alginate bead encapsulation, enabling long-term culture and controlled microenvironmental conditions.

Disease Indications

- Non-restrictive
- Compatible with a wide range of cell types, including hematopoietic and fibroblastic cells

Model Availability

- Cell lines: adaptable to all commonly used hematological cell lines
- Patient-derived primary cells: compatible with primary patient samples (expandable collections)

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

Very large compound compatibility:

E.g., small molecules, biologics as targeted therapies (key signaling pathway inhibitors (BTK, PI3K, AKT), and immunotherapies (monoclonal and bispecific antibodies), complex therapeutic agents (peptides, nanoparticles, liposomes, etc.)

Comprehensive Read-outs

Unlimited analyses enabled by a transparent, permeable and fully dissociable alginate shell.

E.g., Tumor cell killing and depletion; B and T cell activation and exhaustion profiling, immunophenotyping, immune cell and therapeutic antibody infiltration, etc.

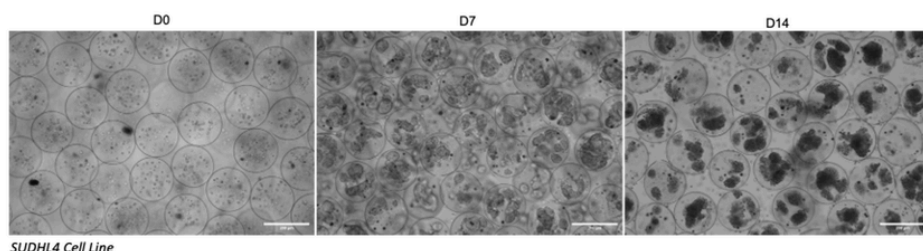
Enabling & Associated Technologies

- Microfluidics enabling customization of the 3D microenvironment (e.g., mechanical constraints, co-encapsulation of different cell types mimicking tumor microenvironment)
- Click chemistry-based functionalization of alginate to mimic key features of the extracellular matrix

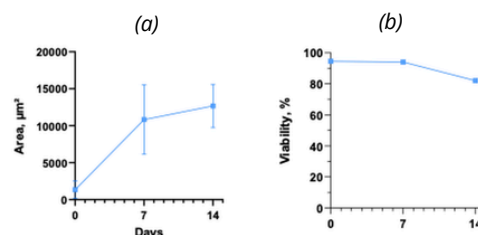
KEY COMPETITIVE ADVANTAGES

- Animal-free preclinical platform, aligned with 3R principles and regulatory evolution
- Highly versatile 3D model suitable for a broad range of fundamental and translational research applications
- Non-disease-restricted technology, enabling cross-indication studies
- Ideal for high-content and high-throughput drug screening across diverse therapeutic classes

FIGURES / ADDITIONAL INFOGRAPHICS



SUDHL4 Cell Line



Fourteen-day growth of SUDHL4 cells in alginate beads + Quantitative assessment of cell growth (b) and cell viability over time (a)

KEY PUBLICATIONS

Lamaison et al Blood Advances 2021



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TECHNOLOGY DESCRIPTION

Technology / Model

In ovo tumor xenograft model on the chick chorioallantoic membrane (CAM).

Human lymphoma cells - either established cell lines or primary patient-derived tumor cells - are grafted onto the chorioallantoic membrane of chicken embryos.

This highly versatile model enables:

- Rapid and robust graft vascularization
- Reproducible tumor growth within days
- Local or systemic administration of therapeutic compounds
- Efficient screening of anti-cancer therapies in a physiologically relevant microenvironment

Disease Indications

- *In ovo* tumor xenograft model on the chick chorioallantoic membrane (CAM)
- Human lymphoma cells - either established cell lines or primary patient-derived tumor cells - are grafted onto the chorioallantoic membrane of chicken embryos. This highly versatile model enables:
- Rapid and robust graft vascularization
- Reproducible tumor growth within days
- Local or systemic administration of therapeutic compounds
- Efficient screening of anti-cancer therapies in a physiologically relevant microenvironment

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

The CAM lymphoma model supports evaluation of a wide range of anti-cancer strategies:

- Targeted therapies : kinase inhibitors, pathway modulators and epigenetic drugs
- Standard-of-care chemotherapies
- Innovative therapeutic combinations including immunotherapies: evaluation of synergistic or combinatorial strategies, monoclonal antibodies, immune checkpoint inhibitors (e.g., anti-PD1, anti-PD-L1) and bispecific antibodies

Model Availability

- Well-characterized lymphoma cell lines.
- Clinically annotated patient-derived primary samples (lymph nodes) :
- Diagnosis, molecular status, treatment history available
- Personalized *ex vivo* approaches - Precision medicine-oriented testing
- Feasibility for therapeutic proof-of-concept studies and drug response evaluation



APPLICATIONS & CAPABILITIES

Integrated Cutting-Edge Technologies

- CAM micro-surgery and xenografting expertise
- Paraffin-embedded and cryosection histology
- Immunohistochemistry platforms
- Human-specific RT-qPCR assays
- Avian-specific RT-qPCR assays
- Avian ELISA assays
- Image-assisted tumor quantification (ImageJ)
- Dose-response pharmacological studies
- Multi-condition experimental screening design

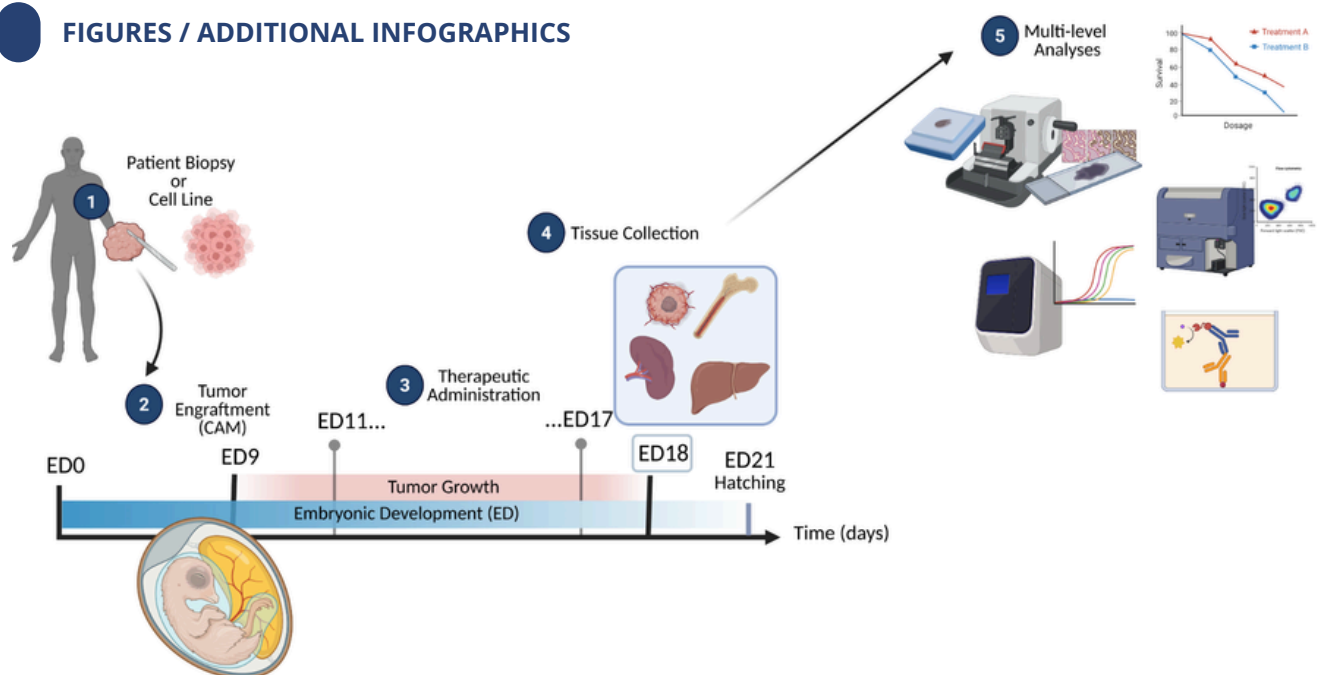
Comprehensive Read-outs

- Macroscopic Endpoints
- Tumor mass quantification (volume and weight)
- Embryo survival assessment
- Histological and Cellular Analyses (Immunohistochemistry):
 - Tumor viability (cleaved caspases)
 - Proliferation (Ki-67)
 - Tumor organization and architecture
 - Lymphoma subtype-specific markers
- Molecular Read-Outs (avian-ELISA and RT-qPCR-human specific gene expression)
 - Avian cytokines: IL-6, IFN- γ , IL-10
 - Apoptosis and survival pathways
 - Signaling pathways and tumor microenvironment-related genes

KEY COMPETITIVE ADVANTAGES

- Reduced regulatory burden (outside EU Directive 2010/63)
- Robust translational interface between in vitro assays and murine in vivo models
- Short experimental timelines (7–10 days from grafting to read-out)
- Low-cost, high-throughput screening capacity
- Fully vascularized, biologically relevant tumor microenvironment
- High inter-batch reproducibility
- Early assessment of antitumor efficacy
- Functional validation of molecular targets
- Compatibility with both mechanistic studies and pharmacological evaluation
- Highly suited for personalized approaches using patient-derived material

FIGURES / ADDITIONAL INFOGRAPHICS



KEY PUBLICATIONS

Caillot et al *Leukemia* 2026 under review/ Madiot et al *Leukemia* 2026/ Laguerre et al, *International Journal of Pharmaceutics* 2025/ Durand et al *Journal of Experimental & Clinical Cancer Research* 2024/ Caillot et al *Molecular Oncology* 2023/ Decombis et al *Blood* 2023



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CANCER & IMMUNOLOGY

TECHNOLOGY DESCRIPTION

Technology / Model

In vivo systemic xenograft models through intravenous tail vein injection into NSG immunodeficient mice.

This approach enables the development of disseminated lymphoma models, reproducing key aspects of systemic tumor spread and organ infiltration.

Disease Indications

- Mantle Cell Lymphoma (MCL)

Model Availability

- Well-characterized MCL cell lines : CDX models
- Patient-derived tumor samples: PDX models

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

- All clinical relevant targeted therapies, including BCL2 or BTK inhibitors

Comprehensive Read-outs

- Tumor volume and weight measurements
- Overall survival analysis
- Percentage of circulating tumor cells in peripheral blood

Integrated Technologies

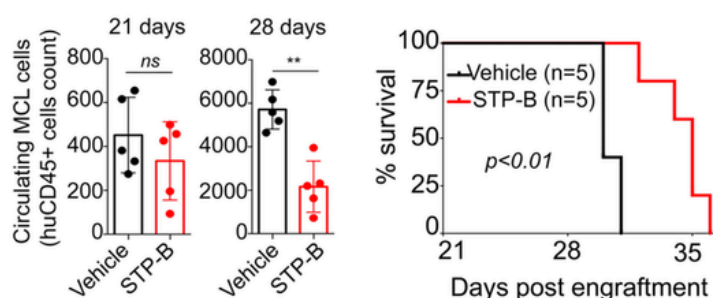
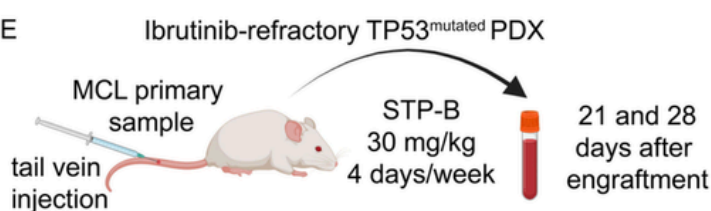
- Flow cytometry for characterization of: circulating tumor cells and tumor cells isolated from spleen or other infiltrated tissues

KEY COMPETITIVE ADVANTAGES

- Well-established murine xenograft model,
- Robust xenograft engraftment
- Accurate modeling of tumor growth and systemic disease spread
- Suitable for evaluation of targeted therapies
- Enables investigation of therapeutic resistance mechanisms
- High experimental reproducibility
- Strong histopathological and molecular fidelity to the original disease
- Preservation of inter- and intra-patient tumor heterogeneity in PDX models

FIGURES / ADDITIONAL INFOGRAPHICS

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KEY PUBLICATIONS

Decombis et al, Blood 2023 / Durand et al, Haematologica 2024



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TECHNOLOGY DESCRIPTION

Technology / Model

In vivo xenograft models based on subcutaneous injection of tumor cell lines into NSG immunodeficient mice.

These models enable the evaluation of tumor growth dynamics and therapeutic responses in a controlled *in vivo* environment.

Disease Indications

- Mantle Cell Lymphoma (MCL)
- Multiple Myeloma (MM)

Model Availability

Well-characterized lymphoma and myeloma cell lines, enabling robust and reproducible tumor engraftment in NSG mice.

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

- All clinical relevant targeted therapies, including BCL2 or BTK inhibitors

Comprehensive Read-outs

The model allows monitoring of key *in vivo* endpoints:

- Tumor volume and weight measurements
- Overall survival analysis

Integrated Technologies

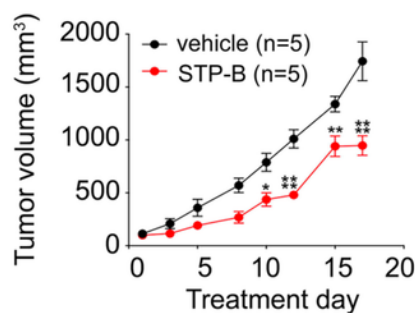
- The platform can be combined with complementary analytical approaches for tumor characterization, depending on experimental design.

KEY COMPETITIVE ADVANTAGES

- Well-established murine xenograft model,
- Cost-effective
- Highly reproducible and well-characterized
- Well-suited for targeted therapy assessment
- Efficient screening platform prior to validation in more complex models such as patient-derived xenografts (PDX)

FIGURES / ADDITIONAL INFOGRAPHICS

D Blastoid MCL xenograft model



KEY PUBLICATIONS

Durand, *Hemasphere* 2024 / Durand, *Haematologica* 2024

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TECHNOLOGY DESCRIPTION

Technology / Model

Innovative *in vivo* murine knock-in model carrying the Myd88^{L252P} mutation inserted into the Rosa26 locus, coupled with a YFP fluorescent reporter for precise cell tracking and disease monitoring.

Disease Indications

- Waldenström's Macroglobulinemia
- Diffuse Large B-Cell Lymphoma (DLBCL), ABC subtype

Model Availability

- Genetically engineered embryonic stem cells enabling robust and reproducible generation of the *in vivo* model

APPLICATIONS & CAPABILITIES

Therapeutic Modalities Evaluated

- Immunotherapies, including antibody-based strategies

Comprehensive Read-outs

- Molecular profiling (gene expression, signaling pathways)
- Cellular phenotyping (immune and tumor compartments)
- Tissue-level and histopathological characterization : immunohistochemistry and immunofluorescence
- *In vivo* cell tracking enabled by YFP fluorescent labelling

KEY COMPETITIVE ADVANTAGES

- Faithful recapitulation of Waldenström's macroglobulinemia
- Clinically relevant ABC-type DLBCL modeling, driven by Myd88^{L252P}
- Endogenous expression of the oncogenic mutation, ensuring physiological disease development
- Powerful immunotherapy evaluation in an intact immune system
- Fluorescent reporter-based disease monitoring, enabling precise spatial and temporal analyses

KEY PUBLICATIONS

Ouk et al., Frontiers in Immunology, 2021 / Lemasson et al. Hemasphere, 2025