OVERVIEW

The Haematological Malignancies Clinical Research Unit focuses on the identification of new molecular biomarkers and drivers of diseases and the development of novel therapeutic approaches. Moreover, we are developing novel strategies and cutting-edge technology tools to better characterise and monitor minimal residual disease to anticipate cancer outcomes. We have contributed to elucidating the molecular determinants of critical molecular processes in haematological malignancies such as splicing, ribosome biogenesis, nucleolus biology, and mechanoreception.

In the Haematological Malignancies Clinical Research Unit at CNIO we investigate:

→ **Splicing**: Traditional haematological neoplasms (leukaemia, myeloma, lymphoma): new diagnostic approaches, biomarkers, and treatments.
→ **Nucleolus biology and ribosome biogenesis**: Novel drivers of haematological malignancies such as bone marrow failures.
→ **Mechanoreception**: Novel drivers of haematological neoplasms.
→ **Ultra-deep sequencing**: Minimal residual disease (MRD) monitoring (LiqBio-MRD).
→ **Immunotherapy**: NK-CARs, BITES, T-CARs and immune checkpoints inhibitors.

“Our results establish that RNA splicing inhibition, alone or combined with venetoclax, could be useful for the treatment of newly diagnosed or relapsed/refractory AML.”
In this study, we screened 84 patients with follicular lymphoma (FL) for somatic mutations suitable as liquid biopsy MRD biomarkers using a targeted next-generation sequencing (NGS) panel. We found trackable mutations in 95% of the lymph node samples and 80% of the liquid biopsy baseline samples. We then used an ultra-deep sequencing approach with ≥10^5 sensitivity (LiqBMDR) to track those mutations on 151 follow-up liquid biopsy samples from 54 treated patients. The results demonstrated that LiqBMDR is robust and non-invasive approach, complementary to metabolic imaging, for identifying patients with FL at high risk of having their treatment fail, and should be considered in future response-adapted clinical trials.

**REFERENCES**

Post-translational splicing modifications as a key mechanism in cytarabine resistance in acute myeloid leukaemia (AML)

Despite the approval of several drugs for AML, cytarabine is still widely used as a therapeutic approach. However, 85% of patients show resistance and only 10% overcome the disease. Using RNA-seq and phosphoproteomics, we show that RNA splicing and serine-arginine-rich (SR) protein phosphorylation were altered during cytarabine resistance. Moreover, phosphorylation of SR proteins at diagnosis was significantly lower in responder than in non-responder patients, pointing to their utility to predict response. These changes correlated with altered transcriptional profiles of SR protein target genes. Notably, splicing inhibitors were therapeutically effective in treating sensitive and resistant AML cells as monotherapy or in combination with other approved drugs. The E1EB-8800 and venetoclax combination showed the best efficacy in vitro, demonstrating synergistic effect in patient samples and no toxicity in healthy haematopoietic progenitors. Our results establish that RNA splicing inhibition, alone or combined with venetoclax, could be useful for the newly diagnosed or relapsed/refractory AML.

**Real-life disease monitoring in follicular lymphoma patients using liquid biopsy ultra-deep sequencing and PET/CT**

In this study, we screened 84 patients with follicular lymphoma (FL) for somatic mutations suitable as liquid biopsy MRD biomarkers using a targeted next-generation sequencing (NGS) panel. We found trackable mutations in 95% of the lymph node samples and 80% of the liquid biopsy baseline samples. We then used an ultra-deep sequencing approach with ≥10^5 sensitivity (LiqBMDR) to track those mutations on 151 follow-up liquid biopsy samples from 54 treated patients. The results demonstrated that LiqBMDR is robust and non-invasive approach, complementary to metabolic imaging, for identifying patients with FL at high risk of having their treatment fail, and should be considered in future response-adapted clinical trials.

**PUBLICATIONS**


**AWARDS AND RECOGNITION**


**EQUULEUS**

Laura Córdoba: Fulbright Pre-doctoral Research Grant,

Santiago Barrio: Pre-doctoral Fellowship, Tulane Physician’s Foundation,

Josep Gisbert: Fulbright Post-doctoral Research Grant,

Juan Rodés: Spanish Society for Biochemistry and Molecular Biology. Biod. Presentation Award,


Laura Córdoba: Fulbright Pre-doctoral Research Grant.

Jesús Encinas: Young Investigator Award, XX International Myeloma Workshop, Athens, Greece.

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