

Lymphoma Group



Miguel Ángel Piris

Group Leader

Miguel Ángel Piris was born in Zaragoza, Spain in 1952. He received his MD degree from the *Universidad Complutense de Madrid* in 1977 and his First Class Honours PhD degree from the *Universidad Autónoma de Madrid* in 1991.

He trained as a Pathologist at the *Hospital Virgen de la Salud*, Toledo, and the *Fundación Jiménez Díaz* in Madrid. In 1982 he carried out his advanced training at the Pathology Institute, University of Kiel, Germany. He then moved to the John Radcliffe Hospital at the University of Oxford, UK in 1989.

Piris is a Member of the WHO lymphoma/leukaemia panel, the International Lymphoma Study Group, Past-President of the European Association of Haematology, and Head of the Spanish Network of Lymphoma Groups within the Spanish Cancer Group Network. Until the year 2000 he served as Consultant and Chief of Section at the Pathology Department of the *Complejo Hospitalario de Toledo*, and has since been appointed as Director of the CNIO's Molecular Pathology Programme and Leader of the CNIO Lymphoma Group.

Since the year 2000 his work has focused on the application of high-throughput molecular techniques to the identification of new diagnostic markers.

In 2010 he was elected as Member of the German Academy of Sciences *Leopoldina*. He has contributed to over 215 articles published in international scientific journals of prestige. Most of his research has focused on lymphoid neoplasms, with numerous contributions to the classification, molecular pathogenesis and analysis of the alterations in the control of the cell cycle, transcriptional regulation and survival signalling.

Summary

Our research aims to better understand the pathogenesis of lymphoma, identifying the essential survival pathways and mutated genes to subsequently translate discovery on the molecular pathogenesis of lymphomas into new diagnostic and therapeutic markers recognising essential oncogenic and cell survival mechanisms. We use "molecular diagnosis-driven targeted therapy" to describe this approach.

Following the latest data generated from our laboratory and those of others, we are focusing on the molecular mechanisms and therapeutic potential involving B-cell and T-cell receptor-derived signalling and associated pathways.

Ultimately, in collaboration with our colleagues in the clinic, we pursue the rapid translation of results generated in the laboratory to the clinical setting.

Strategic Goals

- Translate knowledge on the molecular machinery of lymphoma into the identification of markers for the development of targeted drugs and patient stratification
- Develop new molecular models for lymphoma diagnosis and prognosis
- To gain further insight into the molecular pathogenesis of lymphoma





Staff scientists: Nerea Martínez, Santiago Montes, Socorro M. Rodríguez and Margarita Sánchez-Beato. **Post-doctoral fellows:** Cristina I. Gómez and M. Pilar Sancho (until June). **Graduate students:** Lorena Di Lisio, Elena Doménech, Beatriz Herreros, Daniel Martín, Esperanza Martín, Lina S. Odqvist, Beatriz Sánchez and Magdalena B. Wozniak (until June). **Technicians:** M. Encarnación Castillo, M. Mar López, Cristina Morgades (June-August), Helena Pisonero, Luis Miguel Rodríguez (until May), M. Elena Rodríguez and Pierfrancesco Vargiu.

Highlights

Lymphoma machinery: integrative genomics

Integrative genomic lymphoma analysis contributes to the identification of the main lymphoma survival mechanisms and pathways and identifies crucial genes implicated in this process.

Our efforts in 2010 have focused on the generation and integration of data generated using the following high-throughput techniques:

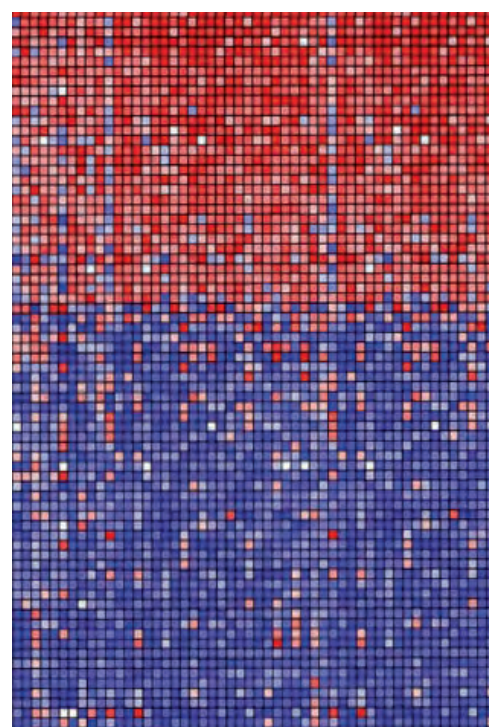
- Gene signatures, as determined by gene expression profiling
- miRNA signatures
- siRNA silencing of selected genes and pathways
- DNA gains and losses characterised by CGH oligonucleotide arrays
- Gene mutations, using Next Generation Sequencing

This combined analysis is facilitating the identification of the essential pathways and genes in lymphoma pathogenesis, therefore permitting construction of a therapy-oriented lymphoma classification.

The results of these studies highlight the role of B-cell receptor signalling and other survival mechanisms in the regulation of tumoural B-cell proliferation.

Identification of biomarkers for targeted therapy

Integrative genomics analysis reveals potential new therapeutic approaches through the silencing of B-cell receptor (BCR) pathways using currently available and newly developed drugs. This project is carried out through the development of *in vitro* and *in vivo* models exploiting synergies with the CNIO's Experimental Therapeutics Programme and some pharmaceutical companies. We are actively investigating



whether PIM, NIK, PI3K and SYK silencing constitutes an appropriate therapy for B and T-cell lymphomas. The project aims at associating newly developed drugs with diagnostic markers for patient stratification and pharmacodynamic biomarkers that provide information regarding the inhibition of selected targets.

Molecular markers for lymphoma diagnosis and prognosis

This research is closely connected with routine diagnostic work performed in our laboratory. Through this work, we are recognised as a reference centre by multiple clinical centres and clinical trials in and out of Spain.

Specific projects under development include:

- Construction of Predictor Models based on routinely applicable techniques. Analysis of lymphoma samples is allowing

us to develop biological predictors that can be used for clinical decisions based on the simultaneous analysis of multiple markers (mRNA, miRNAs, proteins).

- Validation in prospective series is being developed using disease-specific tools such as low-density oligonucleotide microarrays or QT-RT-PCR for transcript quantification. This is being applied to a standardised series of patients diagnosed with Hodgkin Lymphoma and Diffuse Large B-cell Lymphoma.

New markers for diagnosis including GCET1, PD1, MND4, and AID have been characterised with the help of the CNIO's Monoclonal Antibody Unit:

- Particular attention is paid to the identification of cellular and viral miRNAs whose expression may help explain lymphoma pathogenesis and enrich the battery of diagnostic and prognostic markers.

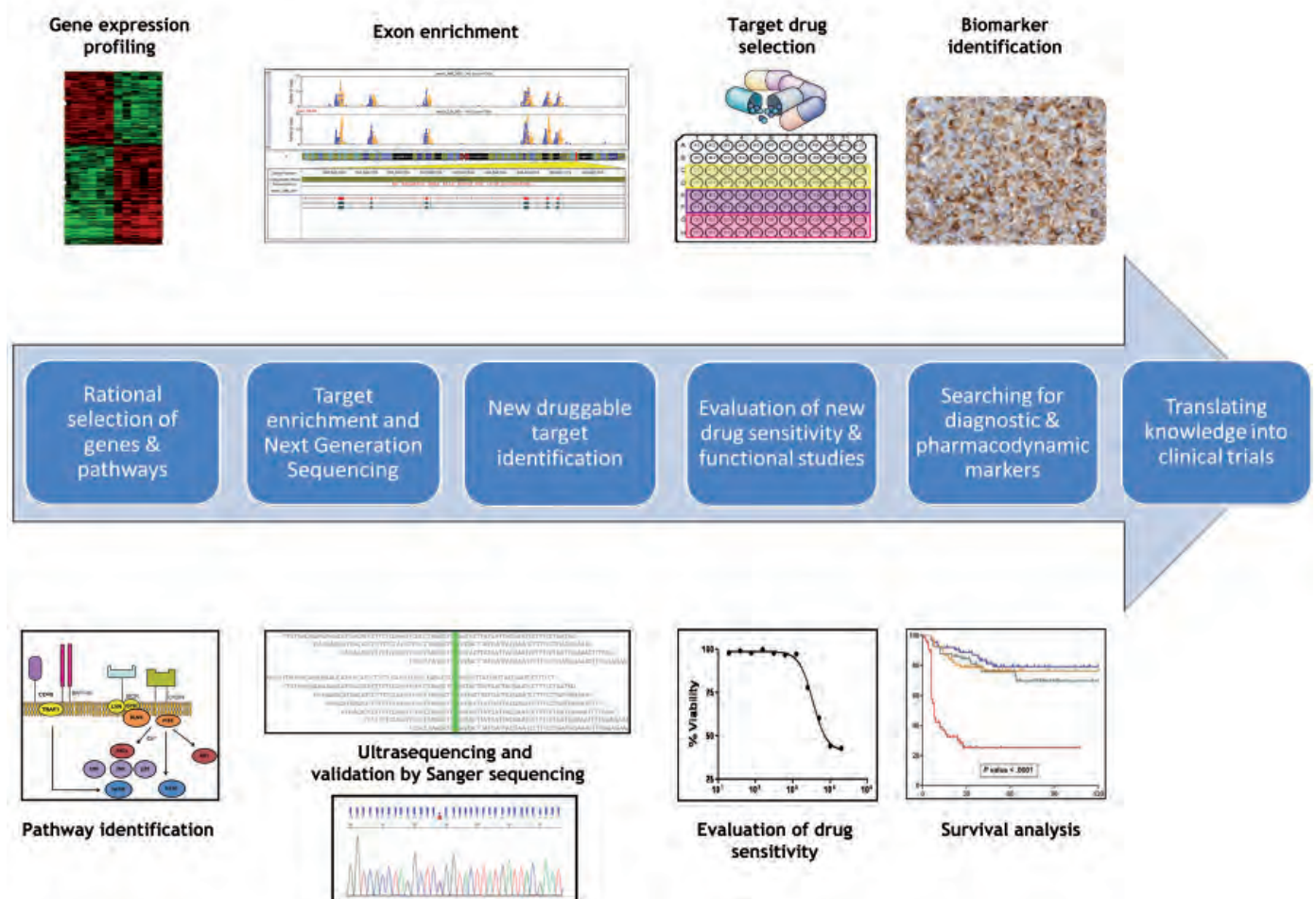


Figure 1: Targeted therapy in Lymphoma. This diagram summarises the series of steps to follow for the selection of drugs, identification of markers and clinical translation of the research results.

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Awards and Recognition

Member, German Academy of Sciences *Leopoldina*