

Lymphoma Group

Summary

Our research focuses on translating discoveries in the molecular pathogenesis of lymphomas into the identification of new diagnostic and therapeutic markers targeting essential oncogenic and cell survival mechanisms – ‘molecular diagnosis-driven targeted therapy’. We foresee that lymphoma research will continue to be the incubator where new cancer paradigms are generated and high-throughput technologies demonstrate capacity for identifying essential cancer mechanisms.

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 biological models for lymphoma diagnosis and prognosis
- Identify new molecular markers and predictive models

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 was 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 in the 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 Haemathology, 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.

He has contributed to over 195 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.

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





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

Highlights

Lymphoma machinery: integrative genomics

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

Our efforts in 2009 have focused on the generation and integration of data generated using the following high-throughput techniques:

- DNA gains and losses characterised by CGH oligonucleotide arrays
- The transcriptome as determined by Gene Expression Profiling
- miRNA signatures
- siRNA silencing of selected genes and pathways

This combined analysis is facilitating the identification of functional signatures for the classification of lymphomas, thus 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. These data facilitate hypotheses on potential changes in somatic mutations in B-cell receptor genes and pathways that are being investigated in a project using Next Generation Parallel Sequencing in collaboration with Agilent and the CNIO Genomics Unit.

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

Spider web of interaction between downregulated miRs and upregulated genes

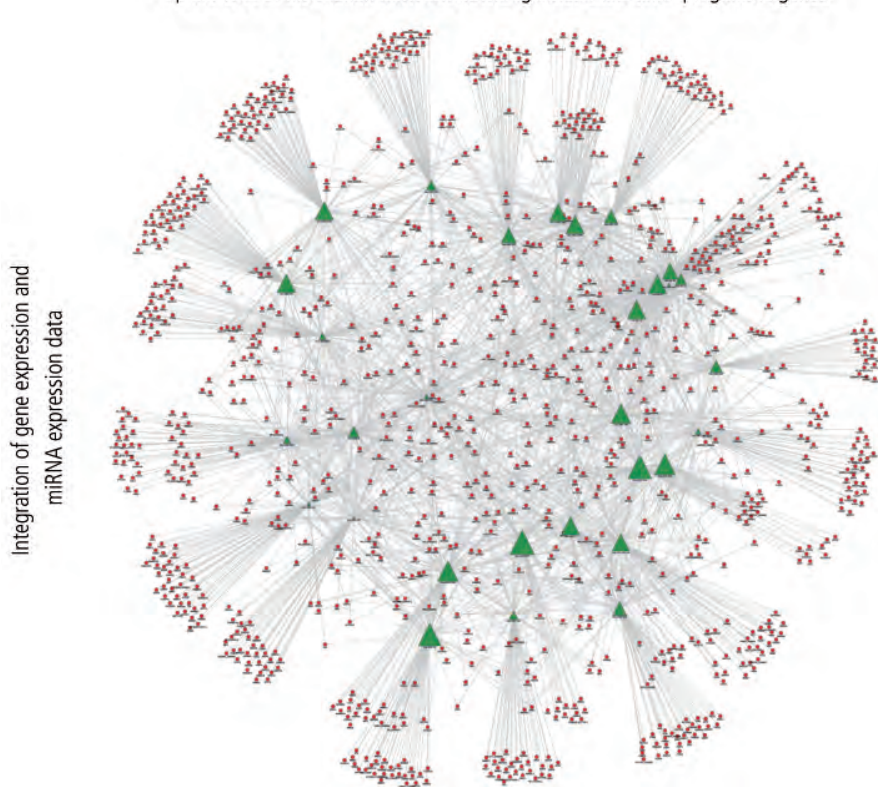


Figure 1: Spiderweb of the interaction between downregulated miRNAs and upregulated genes in Mantle Cell Lymphoma pathogenesis. Downregulated miRNAs are targeting multiple genes essential for cell survival pathways.

is carried out through the development of *in vitro* and *in vivo* models exploiting synergies with the CNIO Experimental Therapeutics Programme and some pharmaceutical companies (Eli Lilly). 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 for which we have earned the reputation as being a reference centre for 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, AID, and others have been characterised with the help of the CNIO's Monoclonal Antibody Unit:

Specific 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.

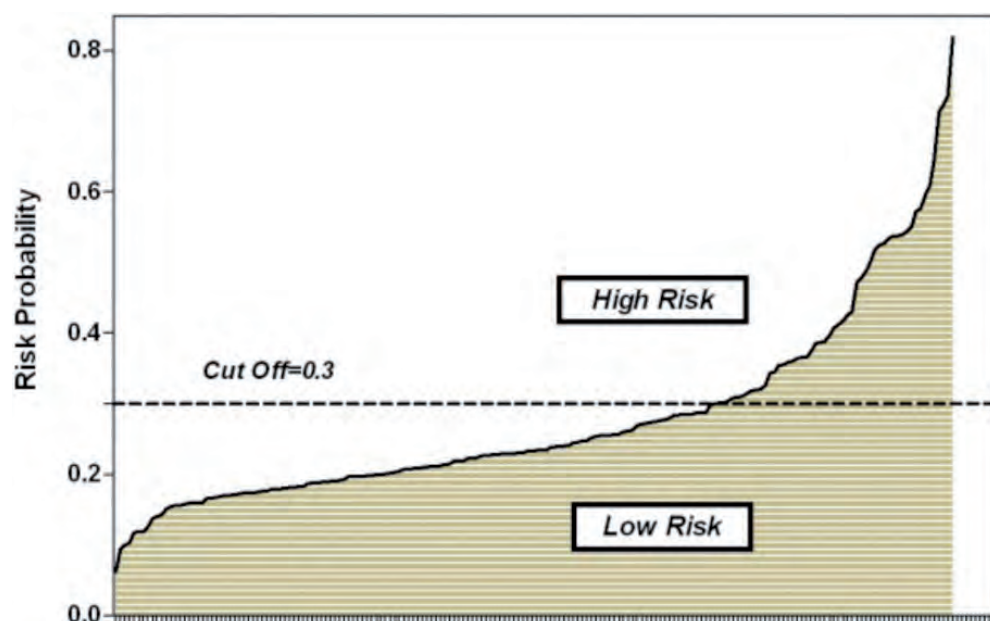


Figure 2: Identification of individual molecular risk score in advanced Hodgkin Lymphoma patients treated with ABVD. QT-PCR analysis of 12 genes in paraffin-embedded tissue.

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