miR-ACLE (miRNA mimic) to treat Non-Hodgkin lymphomas

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R&D Manager

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Spanish National Centre for Cardiovascular Research (CNIC)

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1. The Institution

The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is a **leading international research center** dedicated to understanding the basis of cardiovascular health and disease and to translating this knowledge into improved patient care.

The CNIC (http://www.cnic.es) is a very ambitious scientific project whose main goals are to promote excellent scientific research, to train scientists, and to facilitate the transfer of basic scientific knowledge to clinical research and to technological innovative applications. Despite being a young Institute, The CNIC is one of the main biomedical research centres in Spain, having been awarded by the Spanish Ministry of Science and Innovation with the **"Severo Ochoa Centers of Excellence Program" two consecutive times.**

2. The Product

- The present invention claims the use of a microRNA, **miR-ACLE**, for the treatment of mature B cell neoplasias.

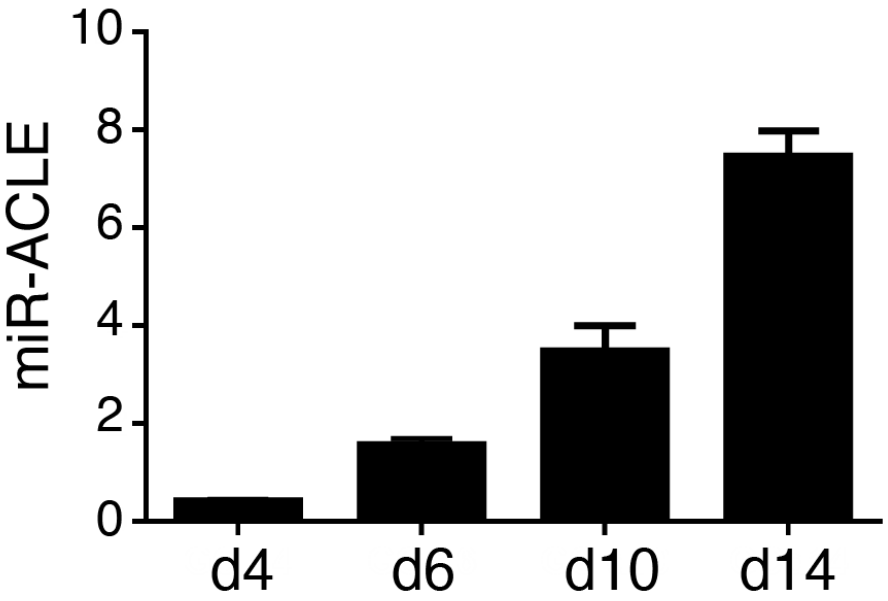
- Mature B cell lymphomas are originated from Germinal Center B cells and can present with aggressive forms, such as diffuse large B cell lymphoma (DLBCL).

- Roughly 50% of DLBCL cases are resistant to current therapies or relapse after treatment.

- **miR-ACLE is a miRNA mimic.** miRNA mimics are small, chemically modified double-stranded RNAs that mimic endogenous miRNAs and enable miRNA functional analysis by up-regulation of miRNA activity**.**

- The patent application also claims different miRNA compositions, as well as compounds that mimic the miRNA activity of MIRacle, including pharmaceutically acceptable carriers and the route of administration.

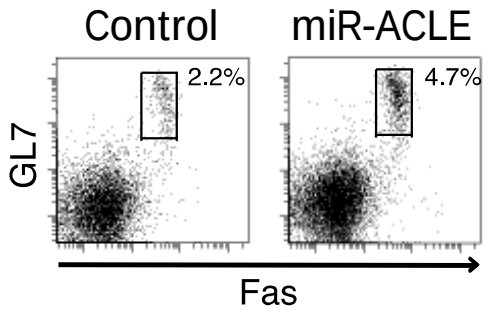
MIRacle is specifically expressed in Germinal Center B cells

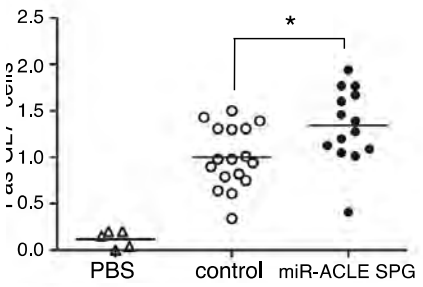


miR-ACLE expression during T-dependent immune response

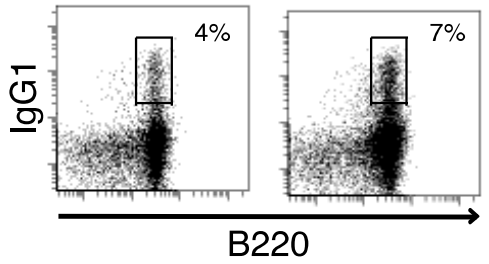
miR-ACLE impairs the germinal center response

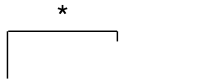
Germinal Center B cells



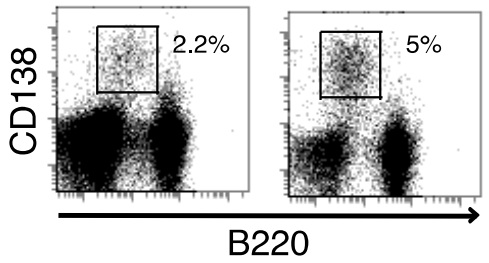


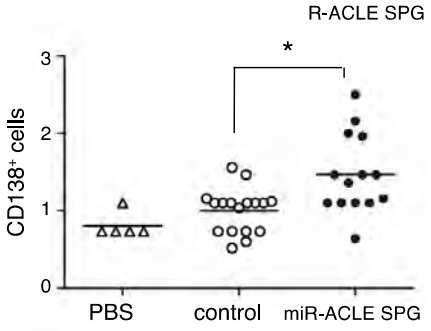
Switched cells





Plasma cells





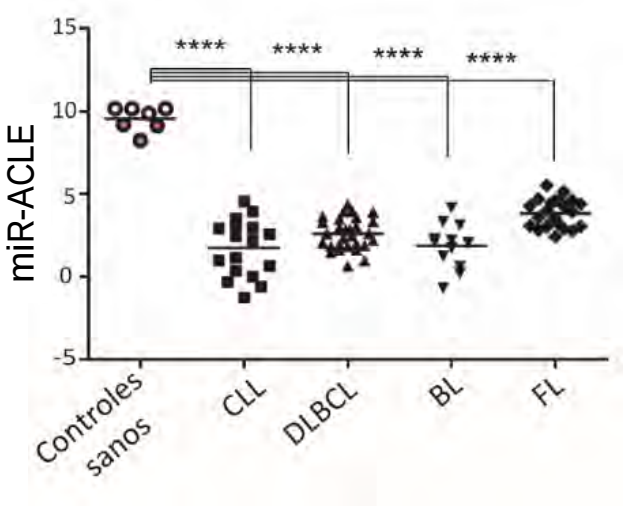
miR-ACLE inhibition in vivo with SPONGE contruct

miR-ACLE negatively regulates the Germinal Center reaction

miR-ACLE in human lymphomas?

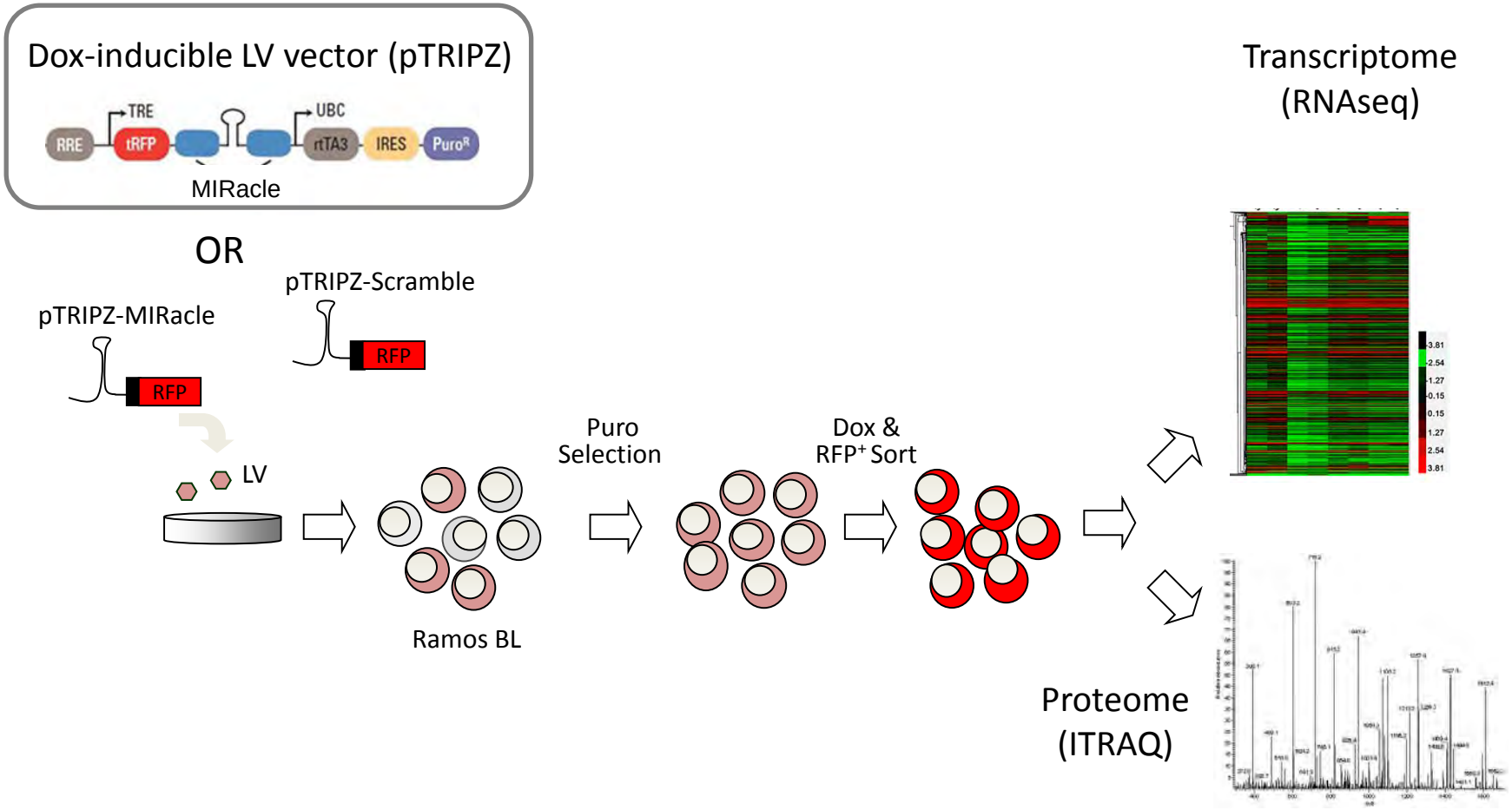
miR-ACLE is frequently lost in B cell neoplasms

Primary tumors



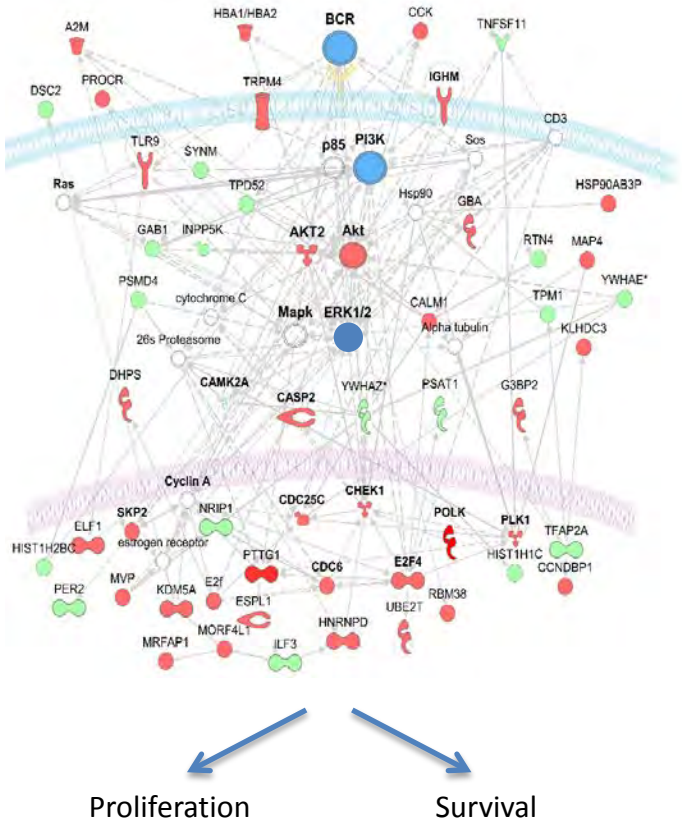
Mechanism?

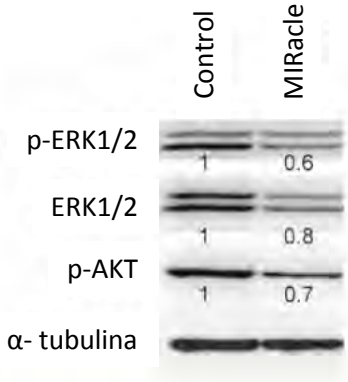
Finding miR-ACLE mechanism with genomewide approaches

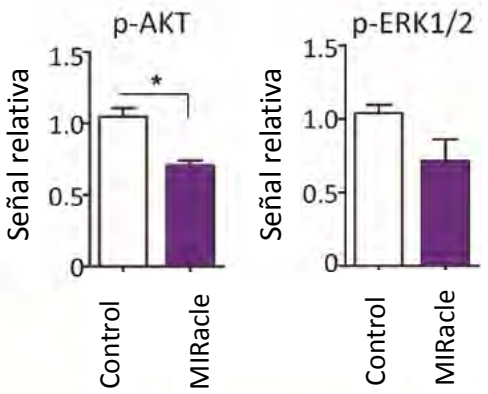


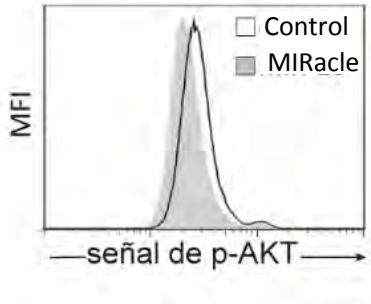
2. The Product

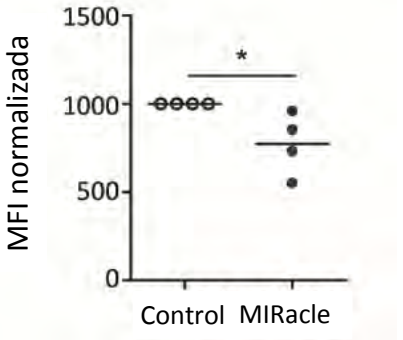
miR-ACLE impairs BCR signaling
BCR signaling is required for survival of most B cell lymphomas





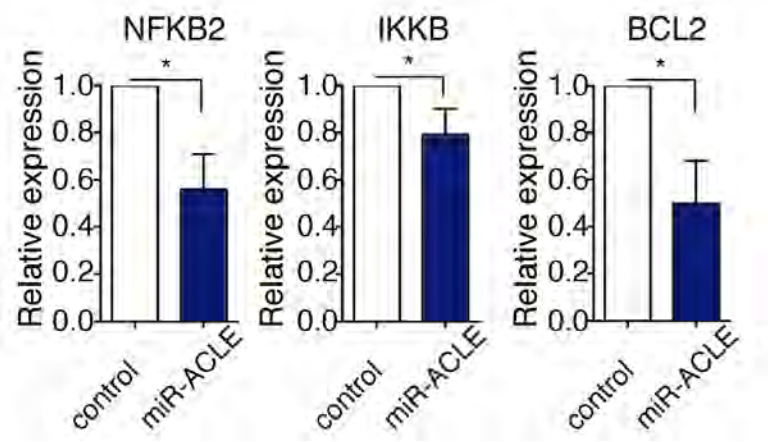




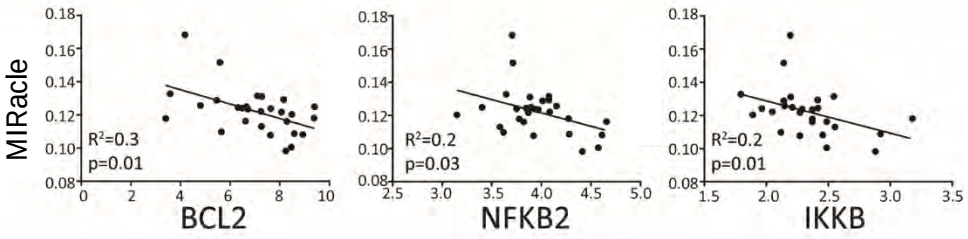


miR-ACLE reduces BCL2, NFKB2 and IKKB expression

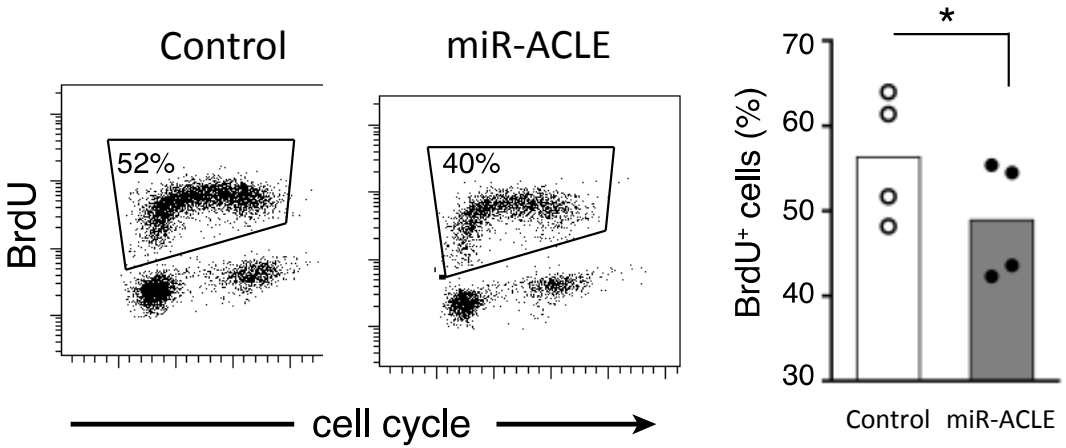
BCL2/NFKB2/IKKB expression in control or miR-ACLE-expressing lymphoma cells



Anti-correlation of miR-ACLE and BCL2/NFKB2/IKKB expression in ABC-DLBCL

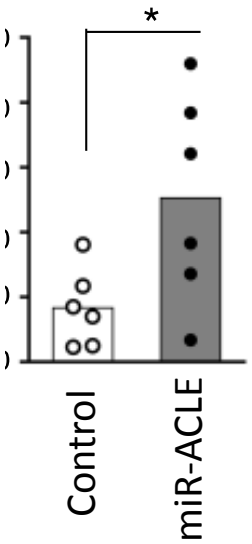


miR-ACLE impairs proliferation of lymphoma cells

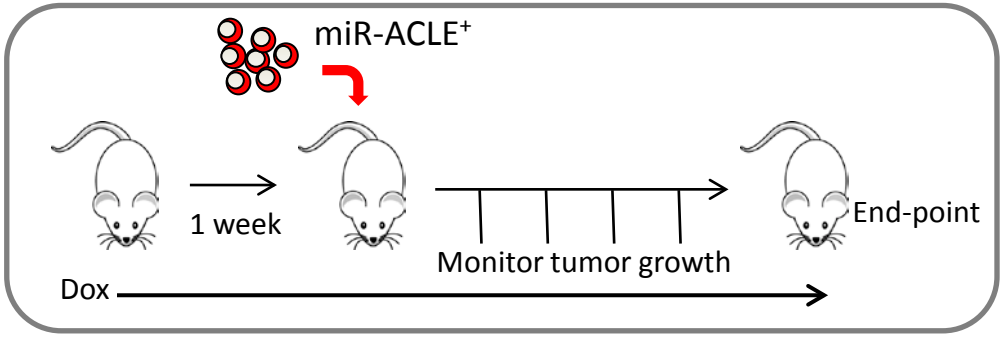


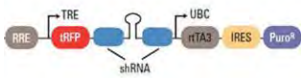
miR-ACLE promotes cell death in lymphoma cells in vitro

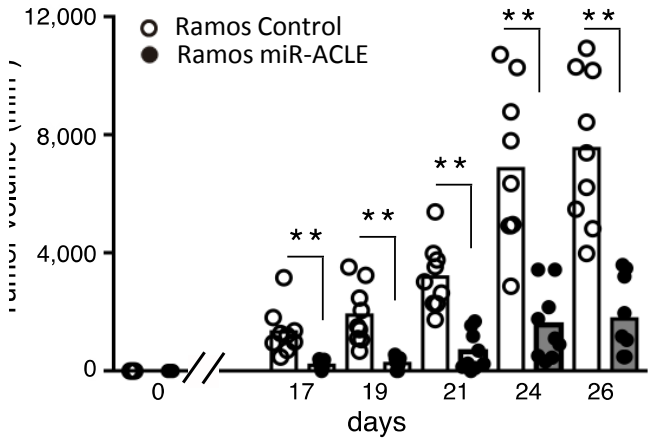
Stauro Control miR-ACLE

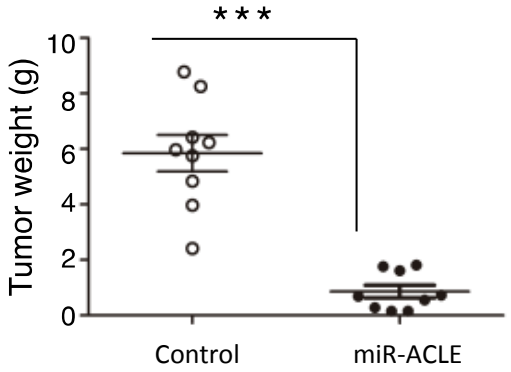


miR-ACLE re-expression impairs the growth of BL xenografts



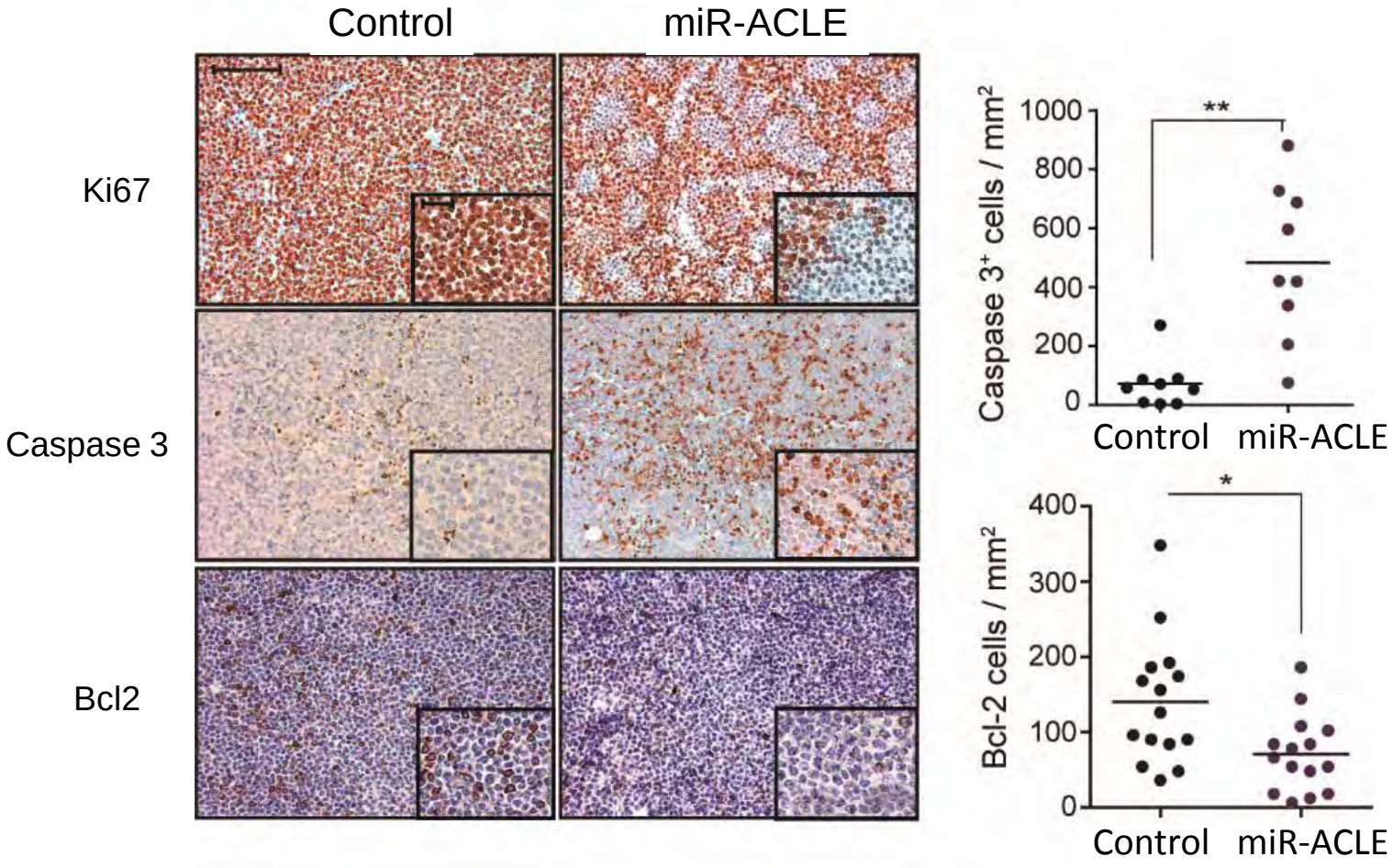




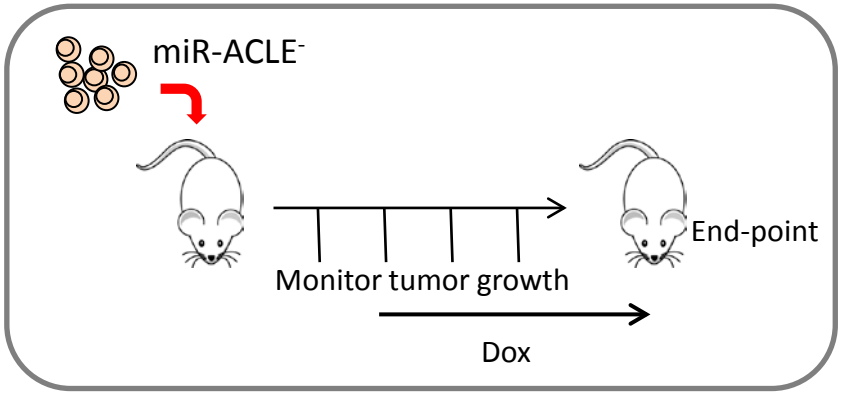


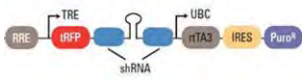
*Same results in Raji BL and in MD-901 ABC-DLBCL

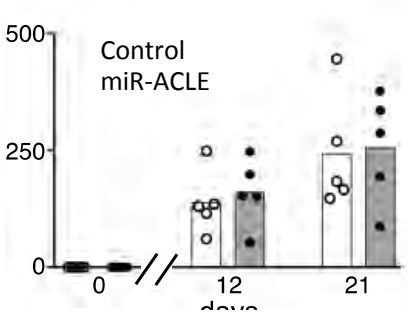
miR-ACLE impairs proliferation and survival of BL xenografts

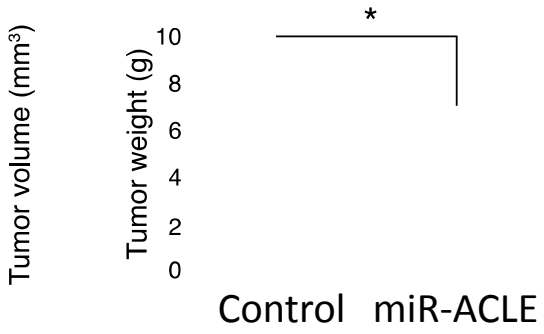


miR-ACLE suppresses established BL xenografts

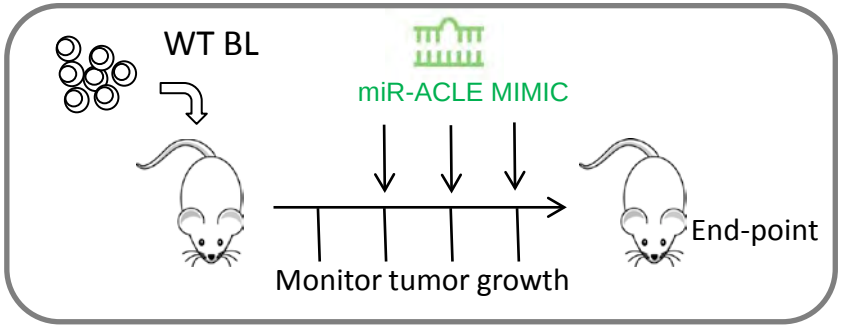




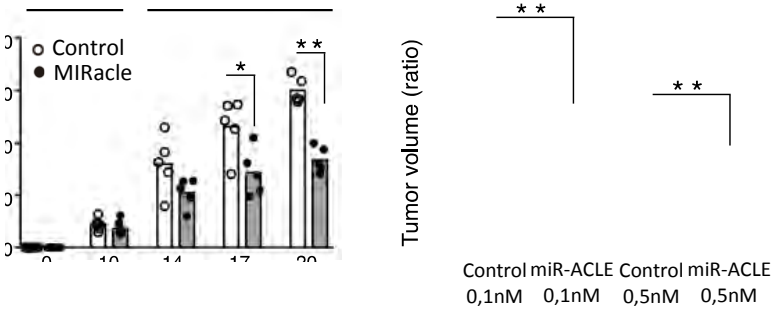




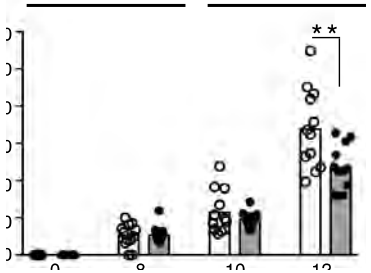
Synthetic miR-ACLE suppresses established BL xenografts



Intratumoral treatment



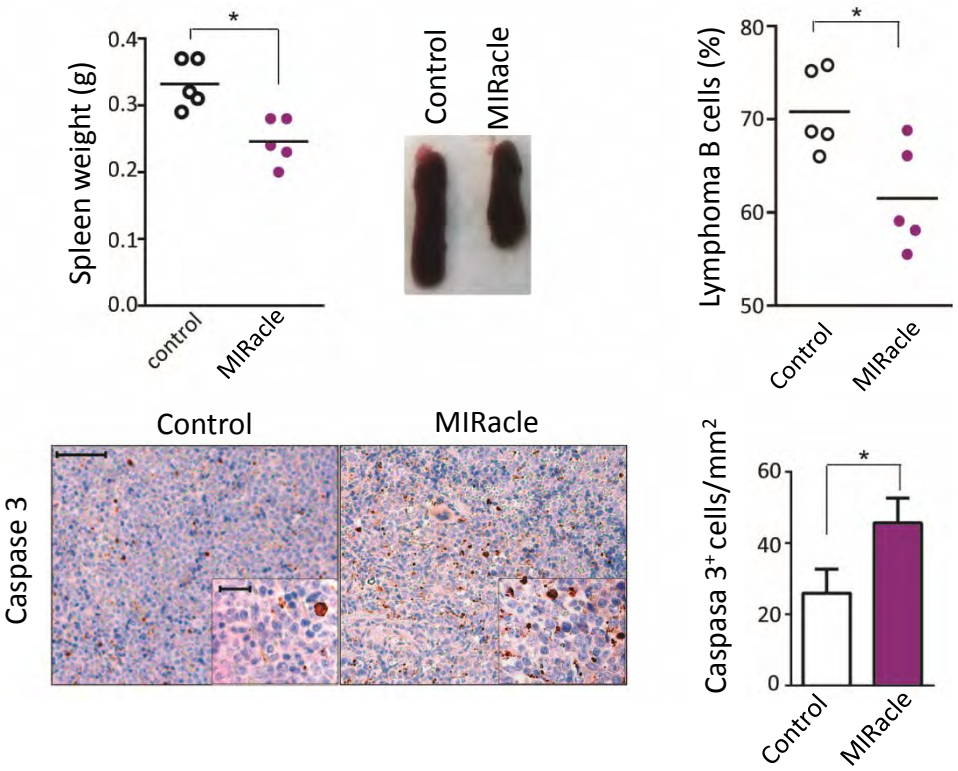
Intravenous treatment



2. The Product

miR-ACLE therapeutic potential is conserved mouse primary tumors

MIMIC



b) Innovative mechanisms of action

- miR-ACLE is a negative regulator of germinal center reaction
- miR-ACLE is lost in human B cell neoplasms
- miR-ACLE impairs proliferation and survival of lymphoma cells
- Replacing miR-ACLE expression in lymphomas inhibits tumor growth
- miR-ACLE is amenable to use in its synthetic form and both by local and systemic administration

Thus,

- miR-ACLE is potentially a novel therapeutic approach to aggressive B cell neoplasms
- miR-ACLE may avoid or complement the use of traditional chemotherapy treatment

c) Differential features facing the market

- Non-Hodgkin lymphomas (NHL) are high prevalent diseases in western societies and their treatment has a great economic impact. Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults, accounting for 30-40% of all NHL in western countries.

- We aim to develop a cheaper and more effective therapeutic alternative for NHL that may render high benefits in terms of diminishing the relative cost of the treatment and of improving the life quality and survival of patients.

- In addition, our proposed therapeutic approach aspires to be the "treatment of choice" in NHL patients not responding to R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), the treatment of choice in aggressive subtypes of NHL.

d) Current status of development

- We are currently expanding our tests on *miR-ACLE* toxicity in vitro and in vivo in the context of **ERC Proof of Concept Grant.** miR-ACLE will be administered intravenously into wild type mice and complete histopathological and biochemical toxicity analyses will be performed.

- *miR-ACLE* versus R-CHOP treatments are currently being compared both in vitro and in mouse models, including xenografts and primary tumors. Singergic effects of both treatments will also be assessed.

e) IPR protection

Number EP15382249
Priority date 14/05/2015
Aplicants CNIC

The patent application claims different miRNA compositions, as well as compounds that mimic the miRNA activity of miR-ACLE, including pharmaceutically acceptable carriers and the route of administration.

f) Pitfalls & Risks to be considered

- **Use of protected modified miRNAs**

  We are open to study:

  ✓ different miRNA modifications

  ✓Permeable molecules similar to miR-ACLE

3. Partnering Opportunities

We are interested in a cooperation with pharma industry in the following aspects:

- Development of *miR-ACLE* formulations with higher activity
- Co-development of the current patent portfolio to generate a suitable product to license and further analyze in Clinical trials.
- Licensing of the current patent porfolio