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International Workshop on CLL
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Abstract ID#2052

Pyroptosis as a drugable cell death pathway in Chronic Lymphocytic Leukemia: The other side of inflammation

Florencia Rammauro [1], Angimar Uriepero [2], Daniel Prieto [2], María E. Marquez [2], Catalina Berca [2], Mercedes Segovia [1], Sofía Russo [1], Victoria Remedi [3], Ana C. Oliver [4], Raúl Gabus [3], Marcelo Hill [1] and Pablo Oppezzo [2]

Institut Pasteur de Montevideo

poppezzo@pasteur.edu.uy

RL on CLL
Research Laboratory on Chronic Lymphocytic Leukemia

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Disclosures

Sponsored laboratory research and/or educational courses

- **Abbvie**
- **GSK**

Introduction

- ✓ Pseudofollicular proliferation centers are classical anatomical structures in CLL patients also observed in inflamed tissues of patients with chronic autoimmune/inflammatory disorders. (*Caligaris-Cappio, Haematologica, 2011)*

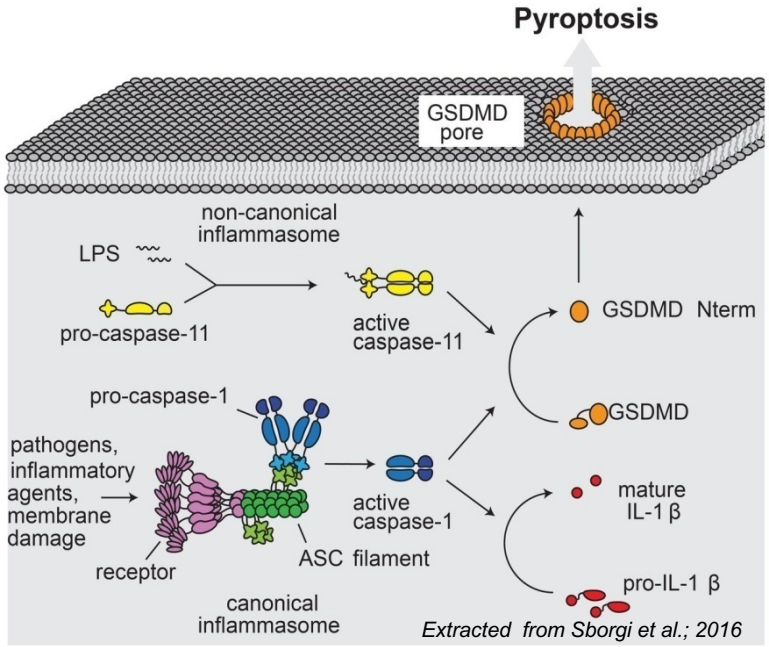
- ✓ It`s mostly accepted that an inflammatory microenvironment is at the basis of disease progression *(Schulz et al., Haematologica, 2011; Paggetti et al., Blood, 2015 and Prieto et al., Blood, 2017, Palma, et. al., Br J Haematol, 2018).*

- ✓ However, the role of the inflammatory response in CLL is not fully understood, and additional therapies focused in manipulate the chronic inflammation in this leukemia have not been described.

Does inflammation support disease progression or not?

Goal

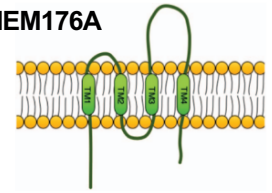
To study inflammasome activation in CLL cells of progressor and indolent patients

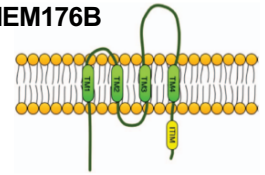


- ✓ Inflammasomes are cytosolic complexes that regulate the activation of inflammatory caspases and cause **pyroptosis.**

- ✓ Inflammasome activation is sensitive to ion fluxes.

- ✓ The cation channels **TMEM176A** and **TMEM176B** as novel inflammasome inhibitors, *(Segovia and Russo et al, Cancer Cell, 2019).*





How is the expression pattern of these proteins in CLL?

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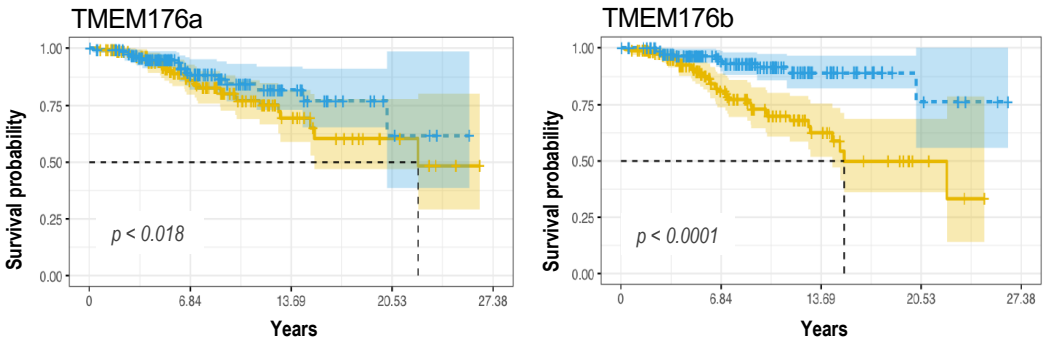
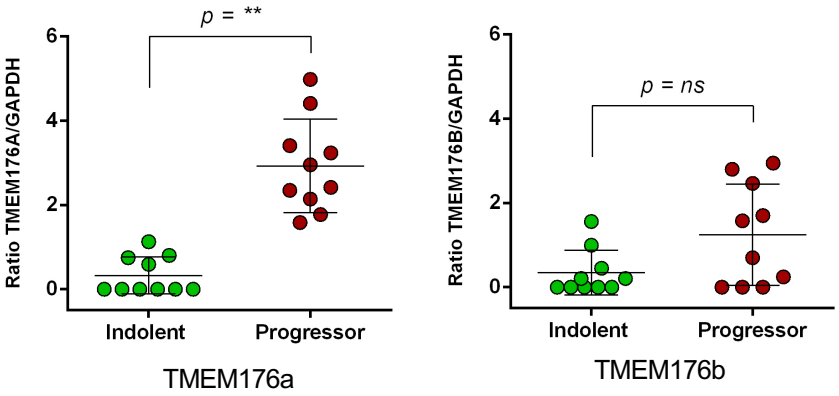
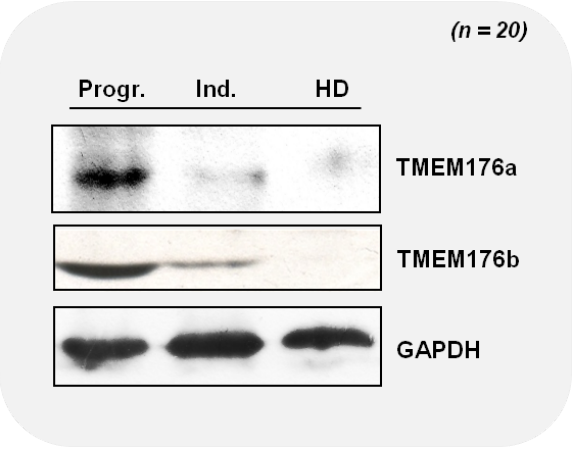
Results: TMEM176A/B expresión in CLL cells



Transcriptome analysis of 304 CLL patients – Data from International Cancer Genome Consortium



Lower survival in CLL patients is associated with higher expression of TMEM176a/b at mRNA level



TMEM176a is significantly overexpressed in CLL cells from progressor patients at protein levels

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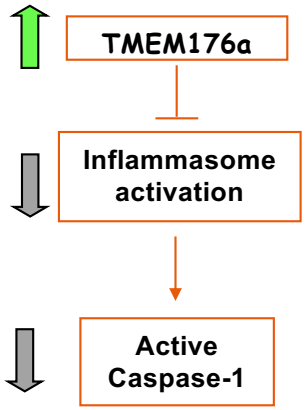
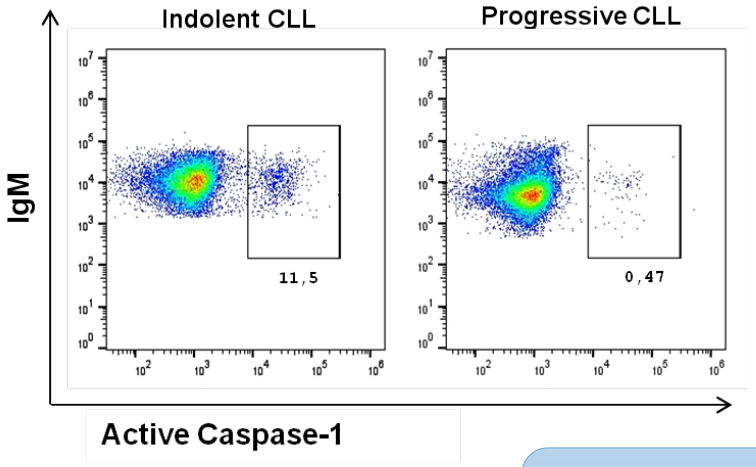
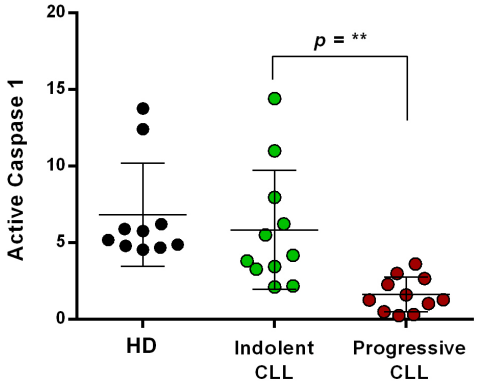
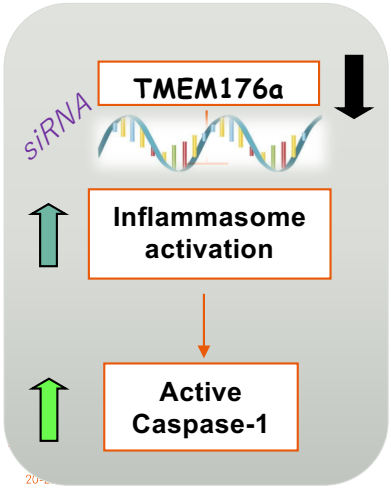
Results:

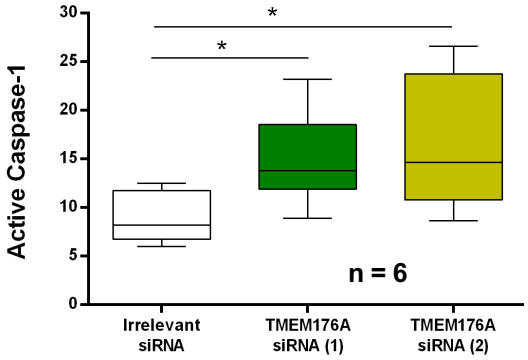
Casp1 activation in CLL cells









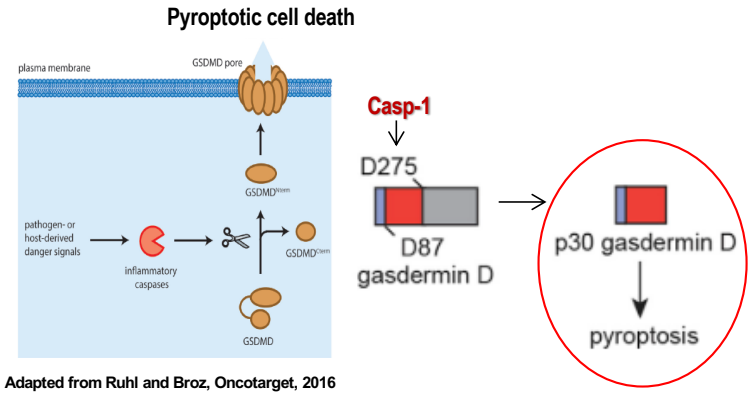


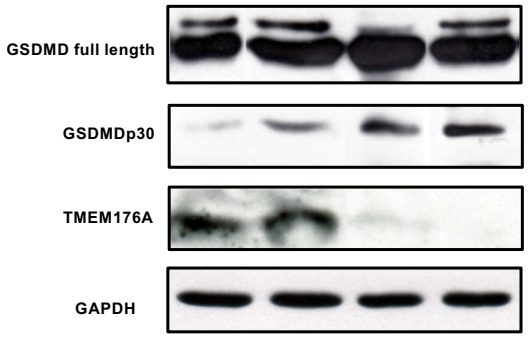
CLL cells from progressor patients have lower Casp1 activation, than indolent patients

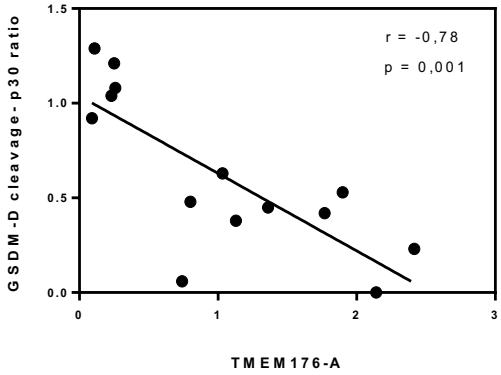
This effect can be reversed by TMEM176a knock down in CLL cells of aggressive cases

Results:

Pyroptosis in CLL







Hypothesis

Aggressive CLLs

TMEM176a ↑↑↑

Active Casp-1

Pyroptosis

Survival of the tumor clone

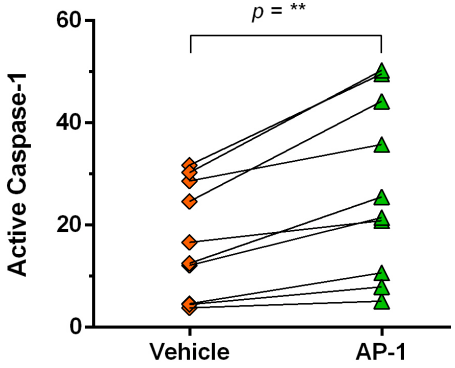
If pyroptosis is a regulated cell death in CLL, could be TMEM176a an additional therapeutic target?

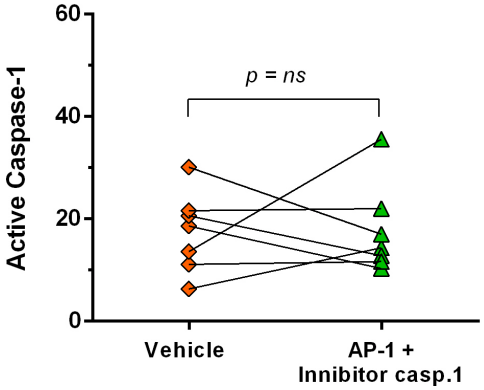
In progressor patients high

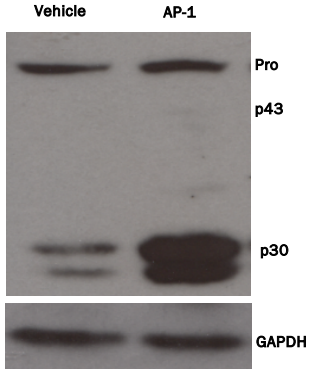
its

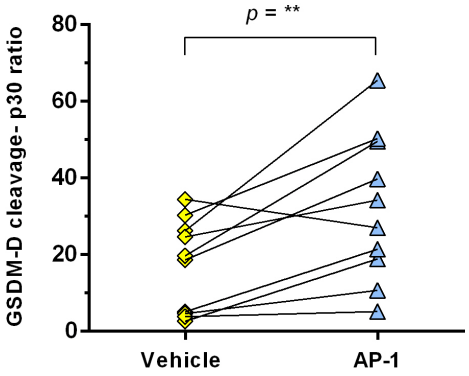
pyroptotic cell death in CLL

Results: Pyroptosis as a drugable cell death pathway







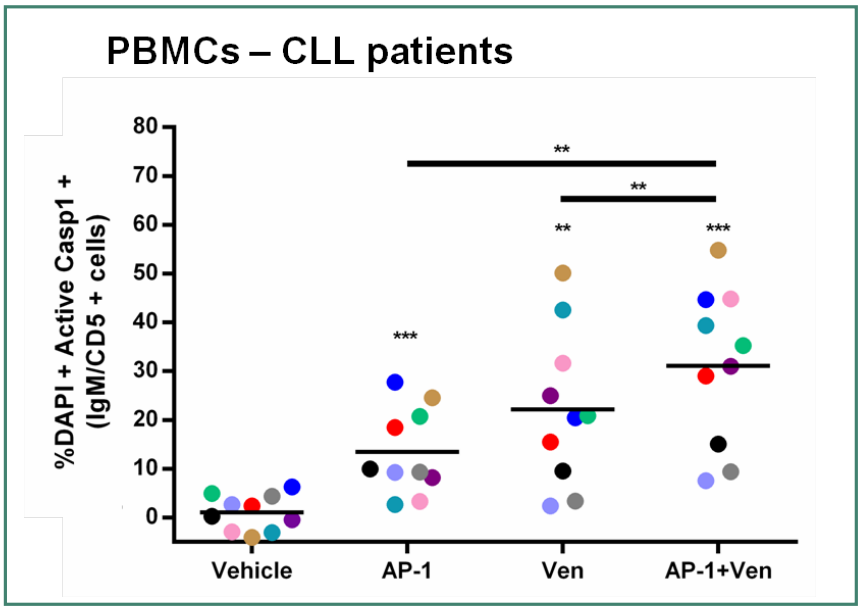


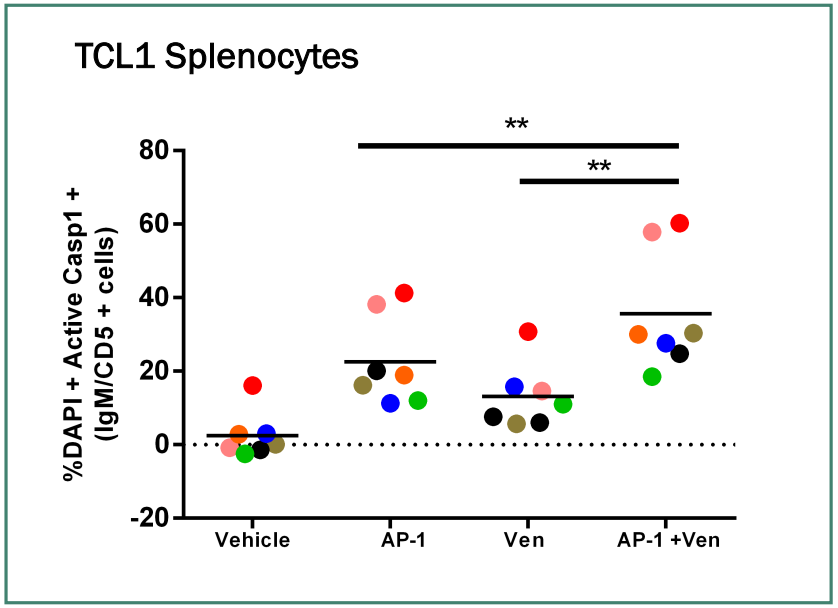
We hypostasize that the combination of drugs targeting pyroptosis (AP-1) and apoptosis (Venetoclax) could improve therapeutic strategies in CLL.

This difference is lost when a casp1 inhibitor is added.

through pyroptosis.

Results: Venetoclax in combination with AP-1





Venetoclax in combination with AP-1 increase cell death, in comparison with each individual therapy in primary CLL cells and in TCL1 splenocytes

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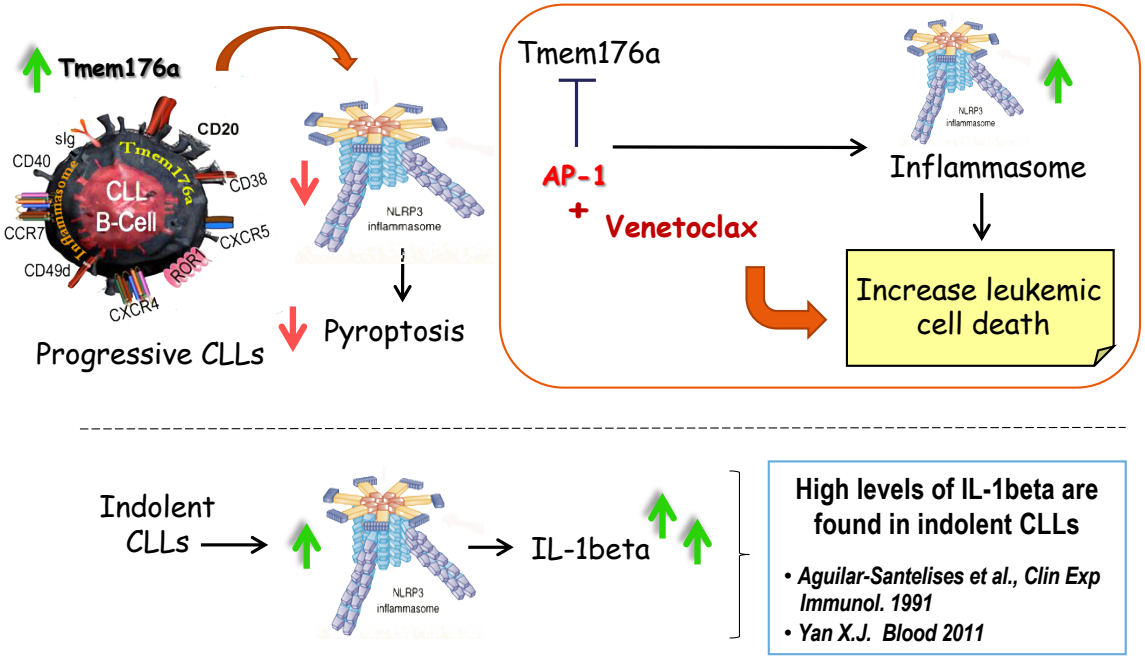
Conclusions and Perspectives

- ✓ **TMEM176a is overexpressed in progressor patients and correlated with lower Casp1 activation and decreased p30 GSDMD.**
- ✓ **TMEM176a downregulates inflammasome activation preventing pyroptosis in progressive CLLs.**
- ✓ **Inhibition of TMEM176a by a specific inhibitors (siRNA or AP-1) produces pyroptotic cell death of the tumor clone.**
- ✓ **Venetoclax in combination with AP-1 increase the extent of leukemic cell death.**



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To the patients...