

CLL-Specific Aspects of B-cell Receptor Signaling

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IWCLL 2019

UNIVERSITY OF
Southampton

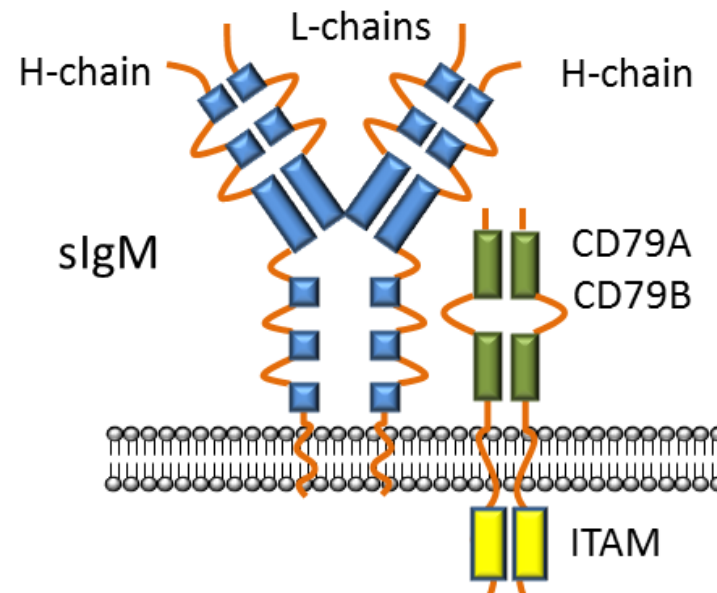
Overview

A (brief) introduction to the B-cell receptor in CLL
Targeted inhibition of BCR-induced mRNA translation

Disclosures; None

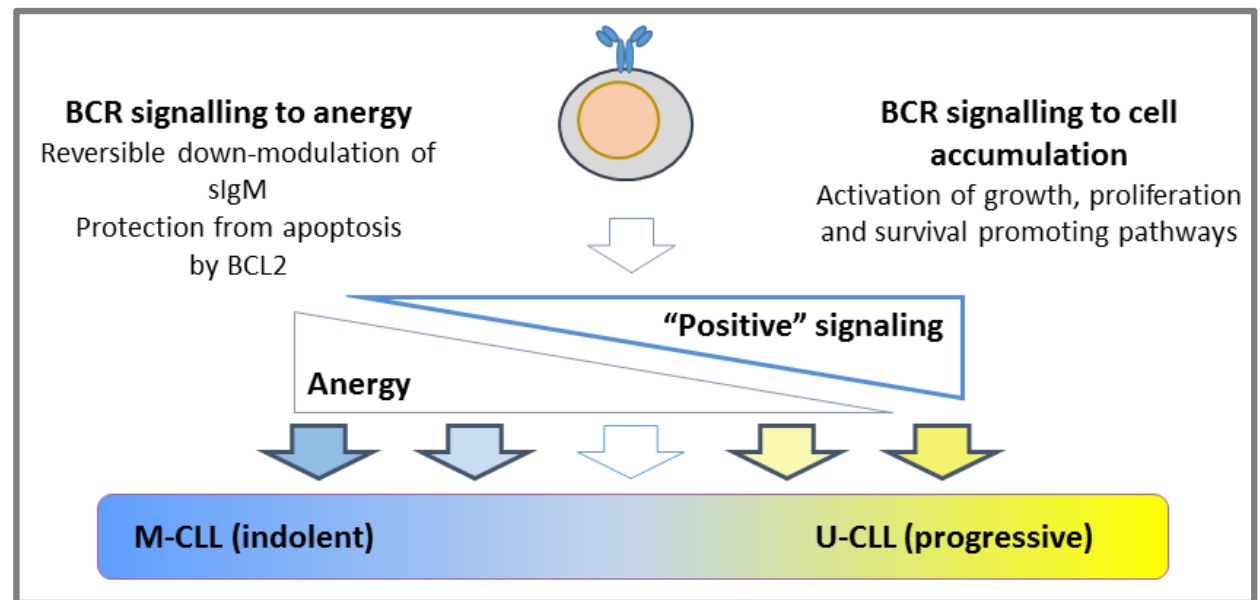
The B-cell receptor

- Two main functions
 - Signalling
 - Antigen internalisation
- Variable responses to ligand
 - Proliferation, survival, activation
 - Apoptosis
 - Anergy



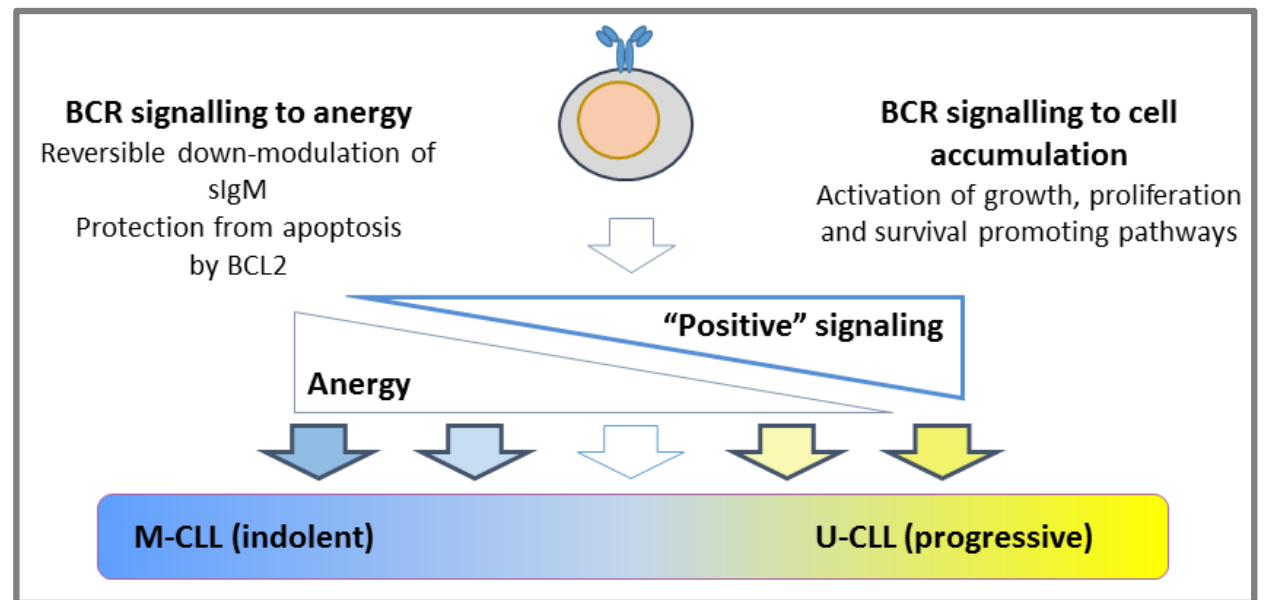
“CLL-specific” features of the BCR

- Low levels expression and function of the BCR
- “BCR-driven” disease
 - Clinical responses to kinase inhibitors
- Anergy *versus* proliferative signalling

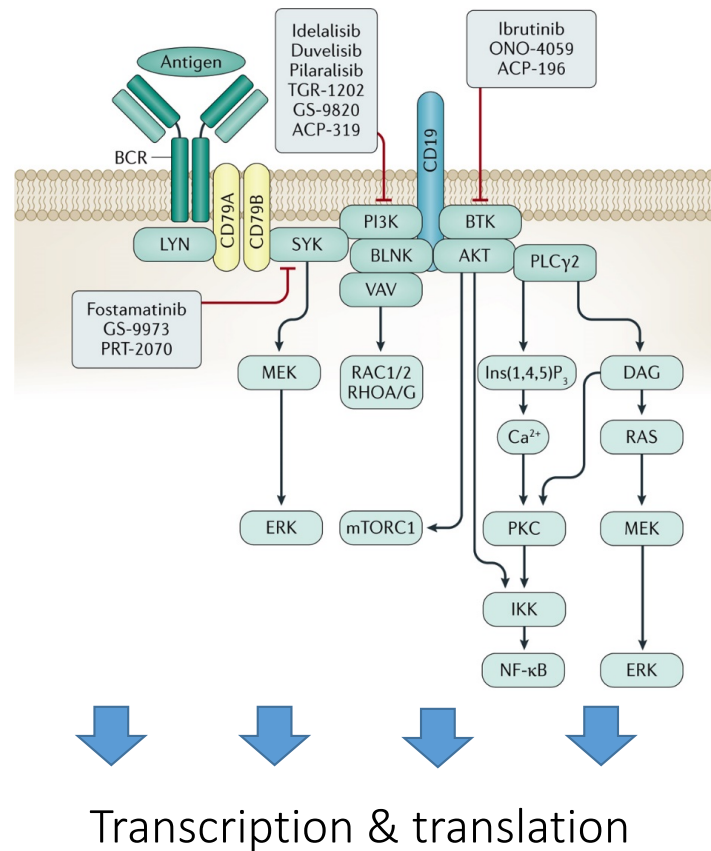


“CLL-specific” features of the BCR

- Is BCR function in CLL distinct from normal B cells?
- Role of genetics?
 - BCL2 overexpression
- Which normal B cells to compare to?

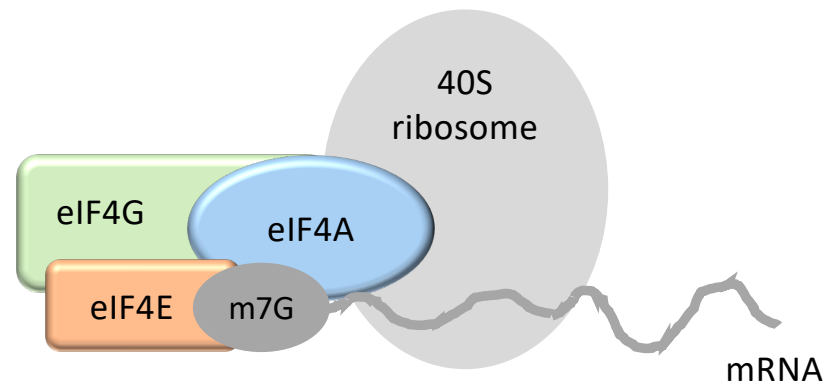


Drug targeting of BCR pathways



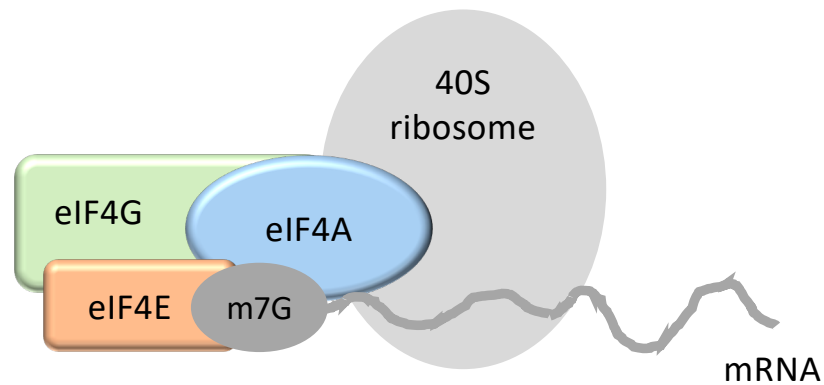
Kipps et al. Nature Reviews
Disease Primers. 2017

mRNA translation



eIF4G	Scaffold
eIF4A	Helicase
eIF4E	cap-binding

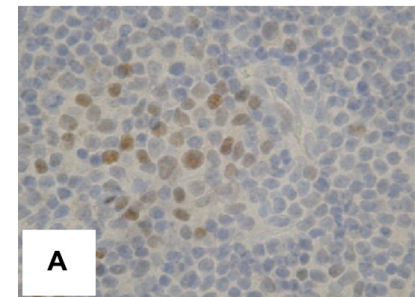
mRNA translation



eIF4G Scaffold
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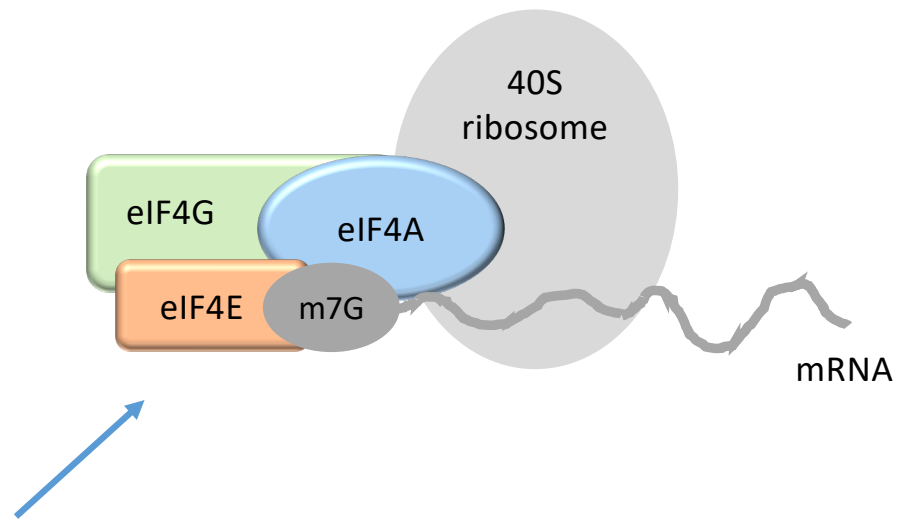
MYC induced by BCR stimulation

MYC expression in CLL proliferation centre



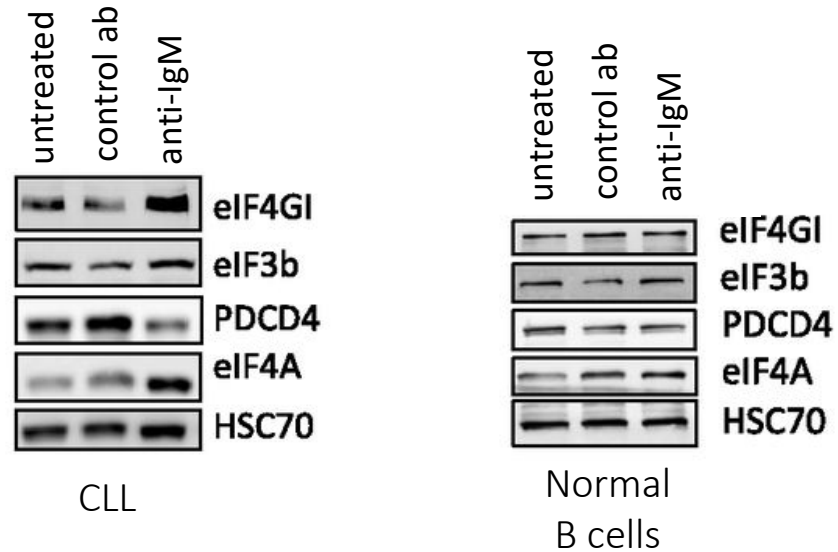
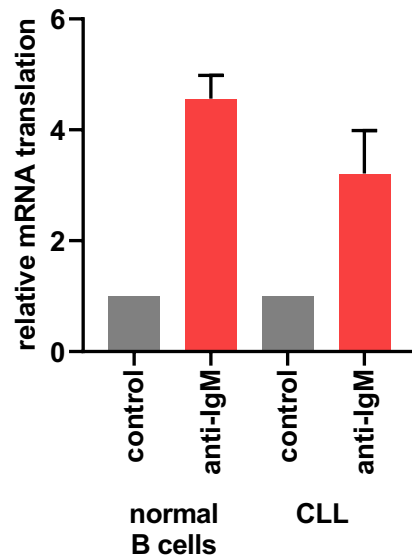
Krysov et al Blood 2014

mRNA translation



Drug inhibition

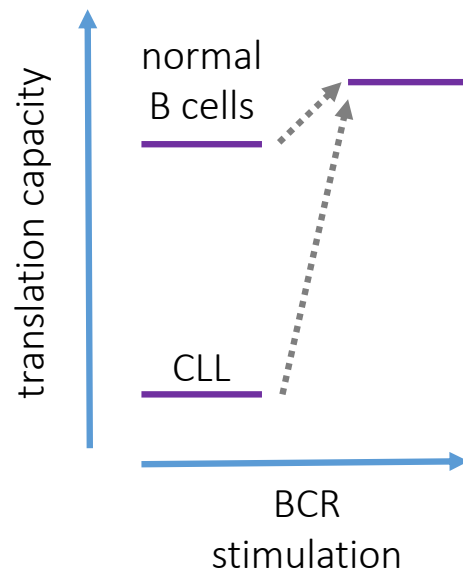
Mechanisms of anti-IgM-induced mRNA translation differ between CLL and normal B cells




Signal competent CLL samples

Yeomans et al. Blood 2016

Potential basis for differential regulation of mRNA translation



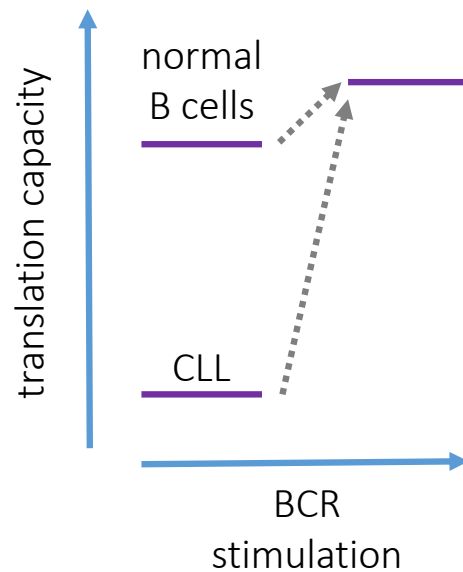
OPEN

Citation: *Cell Death and Disease* (2016) 7, e2249; doi:10.1038/cddis.2016.148
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www.nature.com/cddis

A ribosome-related signature in peripheral blood CLL B cells is linked to reduced survival following treatment

T Sbarrato¹, E Horvilleur¹, T Pöyry¹, K Hill², LC Chaplin¹, RV Spriggs¹, M Stoneley¹, L Wilson¹, S Jayne³, T Vulliamy⁴, D Beck³, I Dokal⁴, MJS Dyer³, AM Yeomans⁵, G Packham⁵, M Bushell¹, SD Wagner^{2,3} and AE Willis^{1,1}

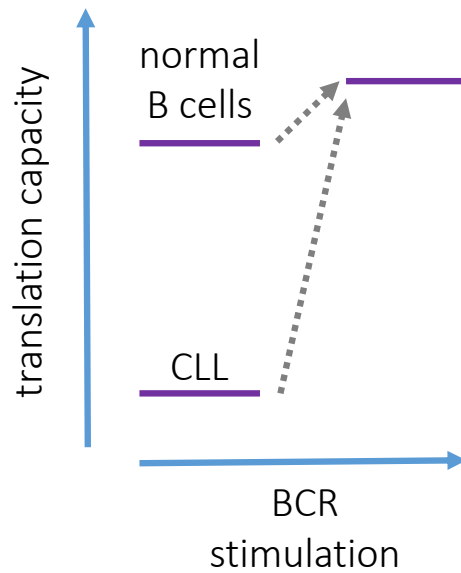
Potential basis for differential regulation of mRNA translation



Metabolic Reprogramming Is Required for Antibody Production That Is Suppressed in Anergic but Exaggerated in Chronically BAFF-Exposed B Cells

Alfredo Caro-Maldonado,^{*,†,‡} Ruoning Wang,[§] Amanda G. Nichols,^{*,†,‡} Masayuki Kuraoka,[†] Sandra Milasta,[¶] Lillian D. Sun,^{*,†,‡} Amanda L. Gavin,^{||} E. Dale Abel,[#] Garnett Kelsoe,[†] Douglas R. Green,[¶] and Jeffrey C. Rathmell^{*,†,‡}

Potential basis for differential regulation of mRNA translation



Selective inhibition of translation initiation factors in CLL cells?

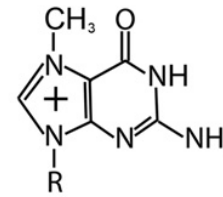
eIF4E inhibition



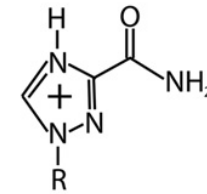
Ribavirin

Synthetic nucleoside

Anti-viral



m⁷-guanosine



Ribavirin

PNAS

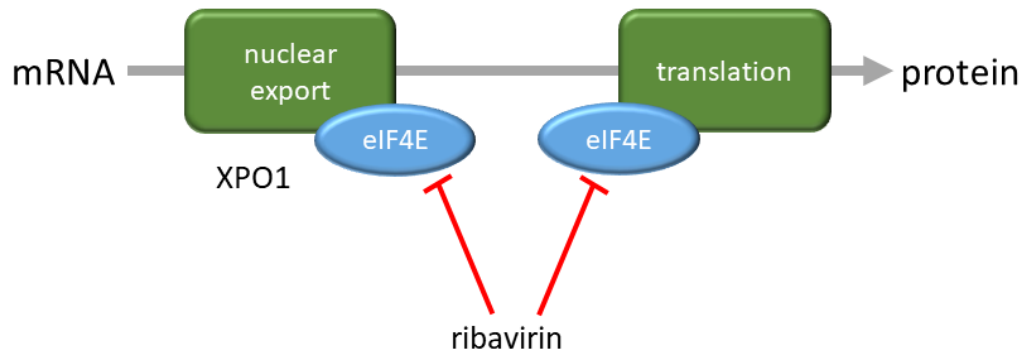
Ribavirin suppresses eIF4E-mediated oncogenic transformation by physical mimicry of the 7-methyl guanosine mRNA cap

Alex Kentsis*, Ivan Topisirovic*[†], Biljana Culjkovic*[†], Ling Shao[‡], and Katherine L. Borden*^{†§}

*Structural Biology Program, Department of Physiology and Biophysics, and [†]Center for Immunobiology, Mount Sinai School of Medicine, New York University, New York, NY 10029

Edited by Peter K. Vogt, The Scripps Research Institute, La Jolla, CA, and approved November 8, 2004 (received for review September 17, 2004)

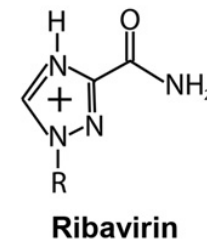
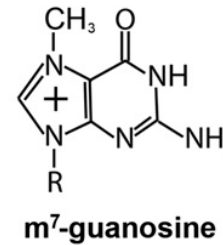
eIF4E inhibition



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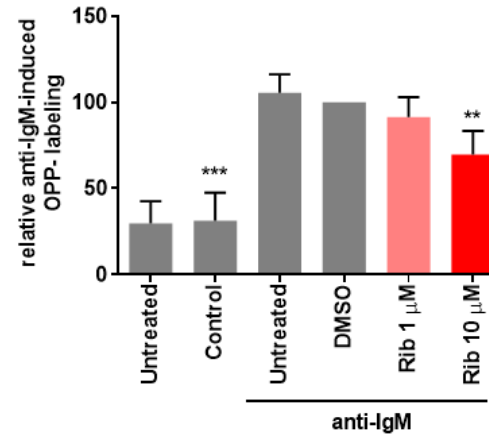
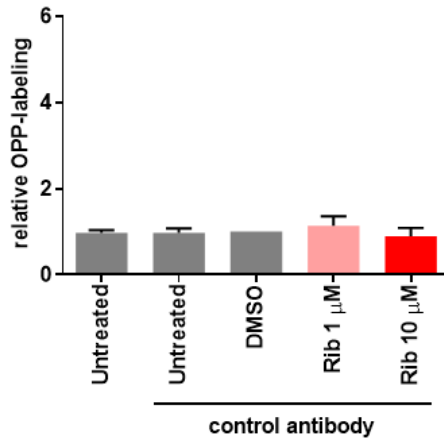
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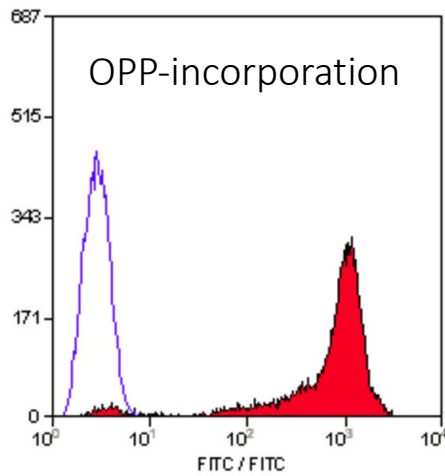
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Ribavirin reduces anti-IgM-induced global mRNA translation

CLL cells
(CD5⁺CD19⁺)

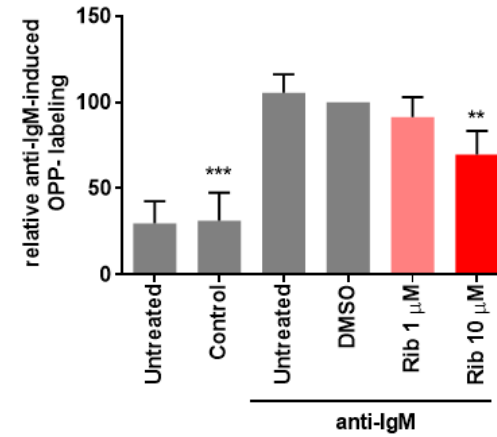
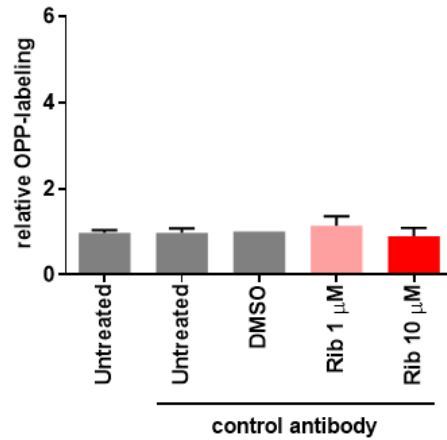


10 μ M – readily achievable with current dosing as anti-viral

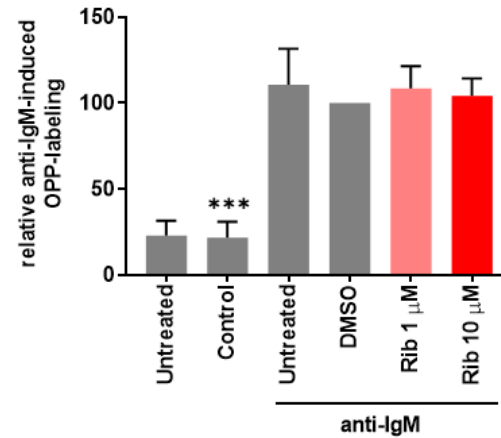
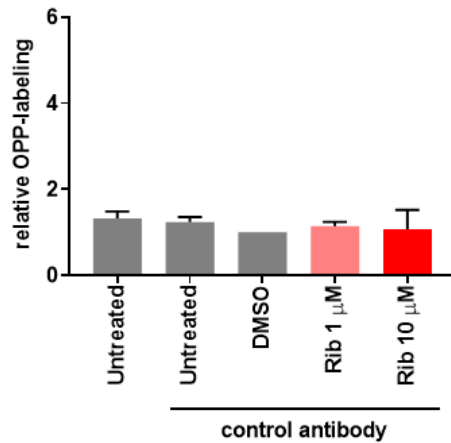


Ribavirin reduces anti-IgM-induced global mRNA translation

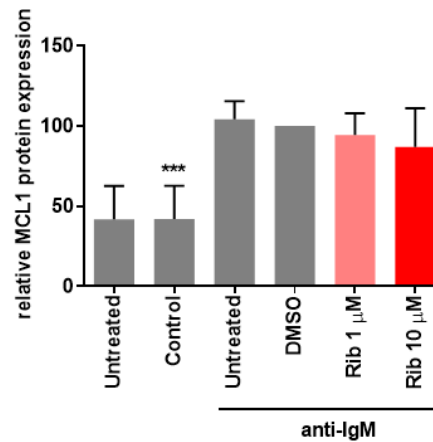
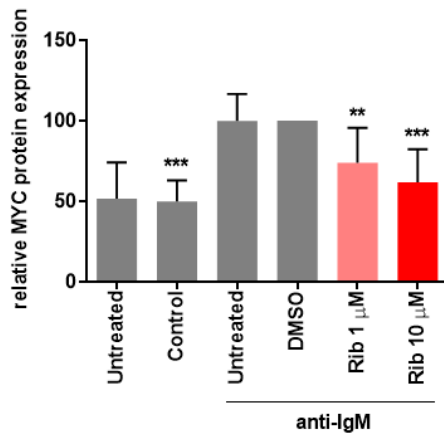
CLL cells
(CD5⁺CD19⁺)



Normal B cells
(IgG⁻CD5⁻CD19⁺)

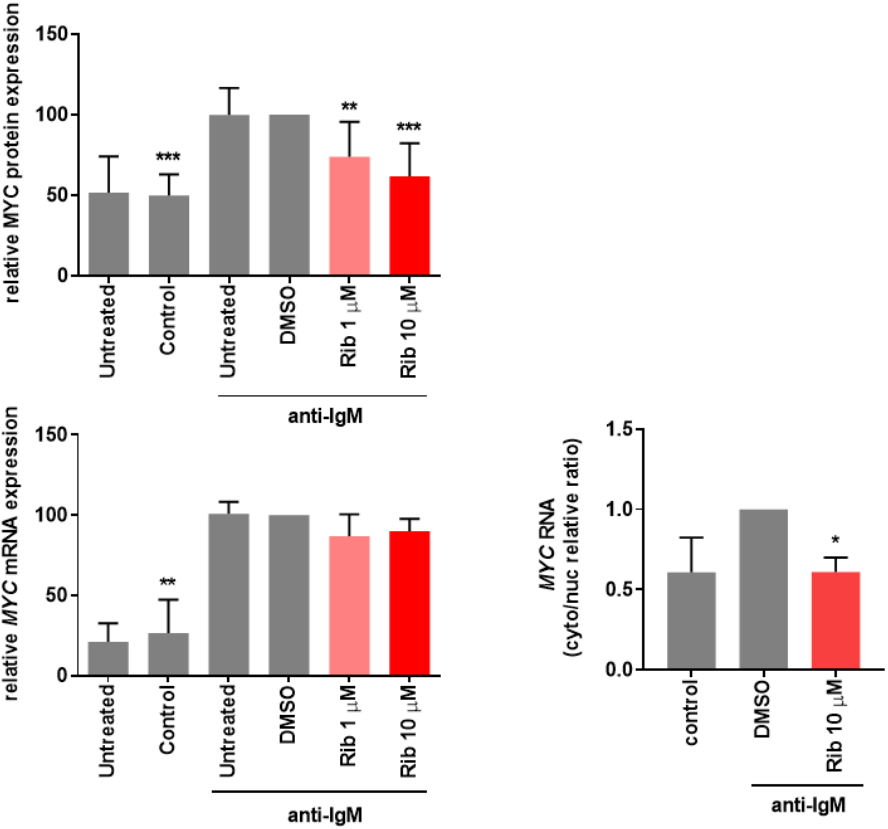


Ribavirin effectively reduces MYC expression via effects on mRNA nuclear transport

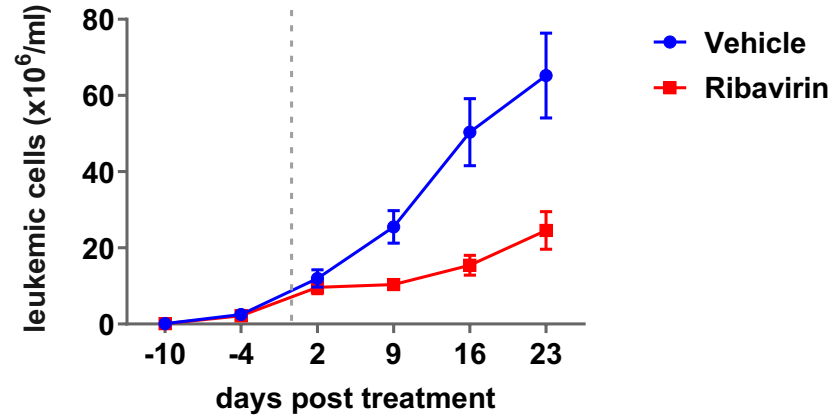


Little induction of apoptosis with ribavirin (10 μ M) at up to 72 hours

Ribavirin effectively reduces MYC expression via effects on mRNA nuclear transport

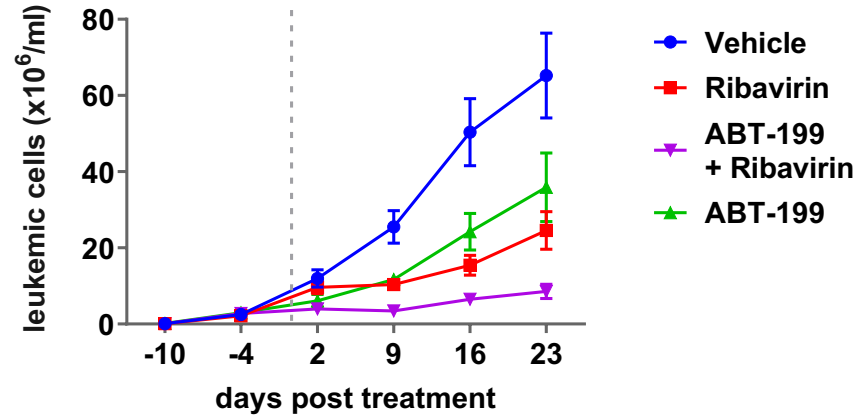


In vivo activity of ribavirin



Adoptive transfer of E μ -*TCL1* leukemic cells into C57BL/6 mice
Ribavirin 80 mg/kg ip daily

In vivo activity of ribavirin



Adoptive transfer of $E\mu\text{-}TCL1$ leukemic cells into C57BL/6 mice
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Summary

- BCR signalling is a key determinant of behaviour of CLL cells
- Behaviour of CLL cells may largely reflect normal influences of antigen on B cells

Summary

- BCR signalling is a key determinant of behaviour of CLL cells
- Behaviour of CLL cells may largely reflect normal influences of antigen on B cells
- Differences in regulation of mRNA translation between normal B cells and CLL cells may provide therapeutic opportunities
- Ribavirin partially reduces anti-IgM-induced global mRNA translation in CLL cells, but not “normal” B cells
- Ribavirin effectively prevents accumulation of MYC (and cyclin D1) in anti-IgM-treated CLL cells, potentially via interfering with eIF4E-dependent RNA nuclear export
- Ribavirin is effective in an E μ -*TCL1* mouse model

Acknowledgements

- Sarah Wilmore
- Alison Yeomans
- Laura Karydis
- Matt Carter
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- Liz Lemm
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- Jonathan Strefford
- Freda Stevenson

