



Madhuri Paul



Roberta Buono



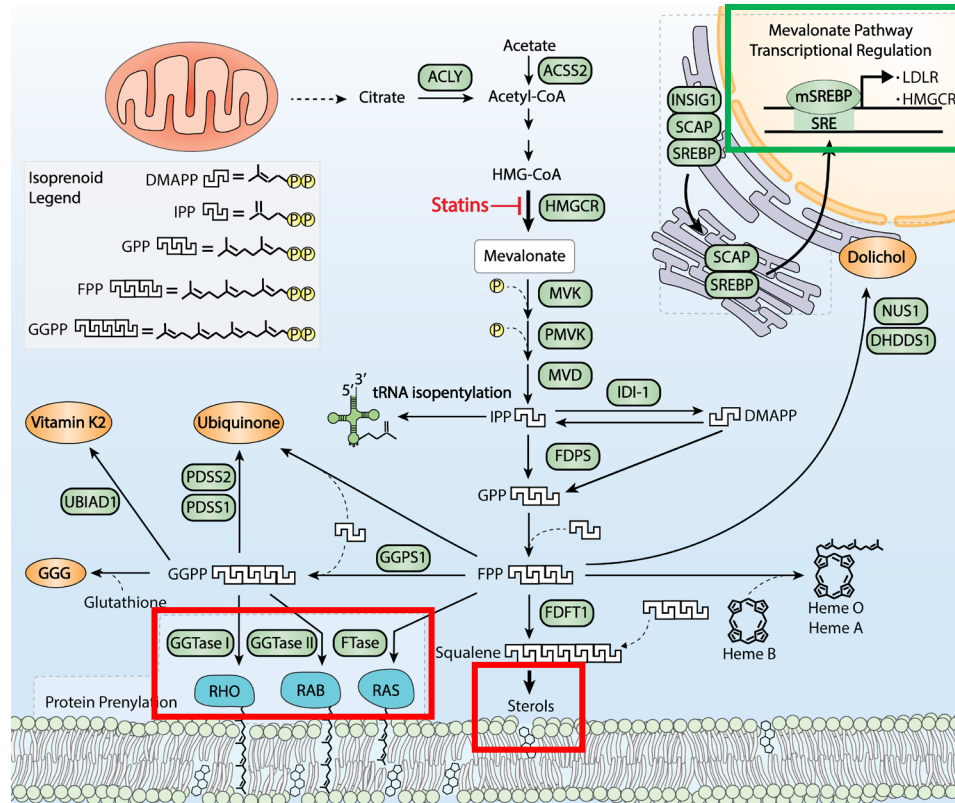
Ian Wong

How do statins trigger AML cell death?

David Fruman, PhD

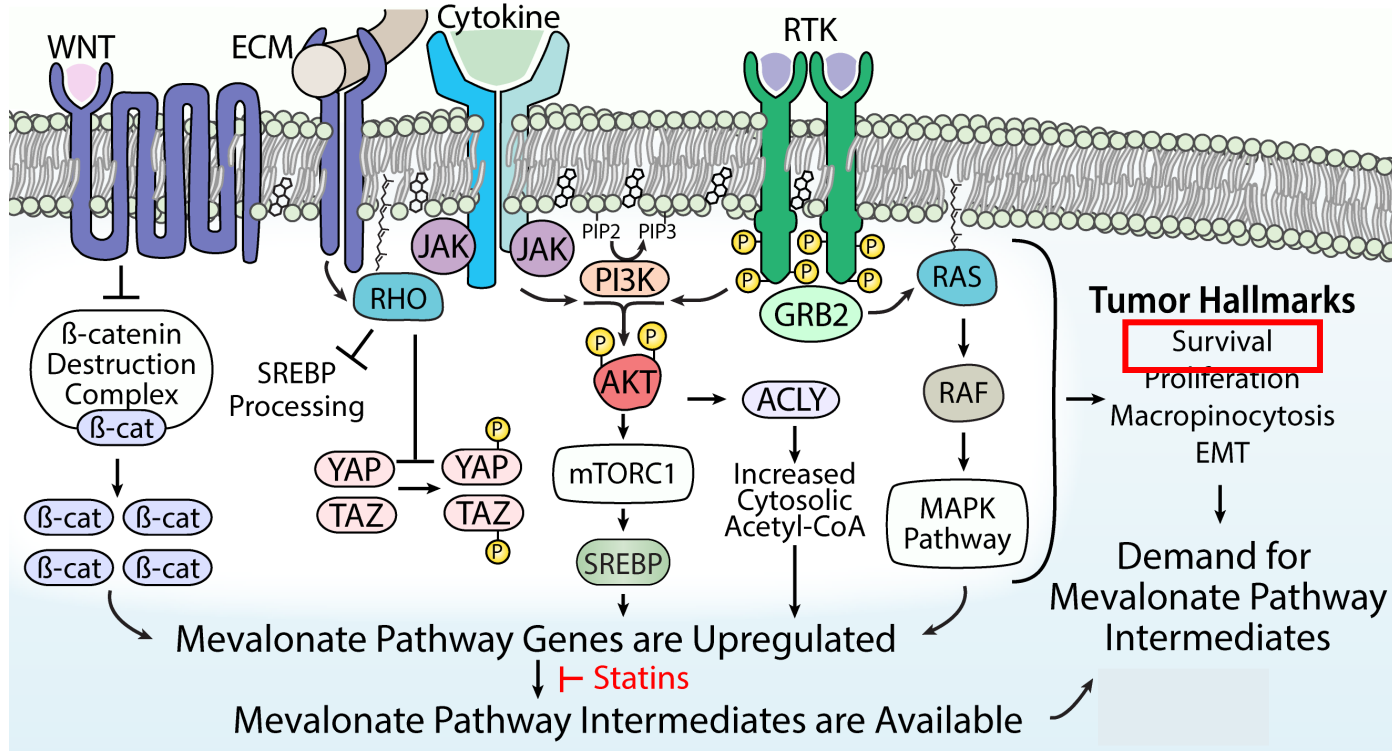
Professor and Chair, Department of Molecular Biology & Biochemistry
Associate Director for Basic Science, CFCCC

Mevalonate pathway is a targetable cancer dependency



D Juarez and DA Fruman, *Trends in Cancer* 2021

Oncogene pathways increase mevalonate demand and supply



D Juarez and DA Fruman, *Trends in Cancer* 2021

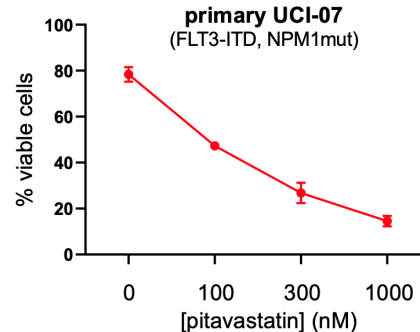
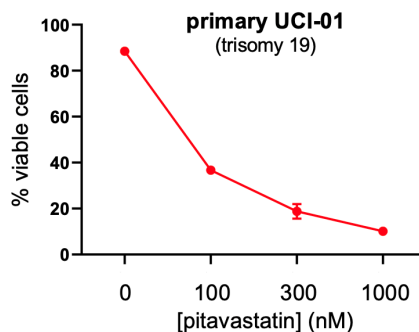
Statins in oncology: untapped potential

- Well-tolerated, cost-effective
- Statins can cause apoptosis in cancer cell lines (esp. blood cancers: AML, myeloma)

> [Leukemia](#). 1994 Feb;8(2):274-80.

Selective inhibition of primary acute myeloid leukaemia cell growth by lovastatin

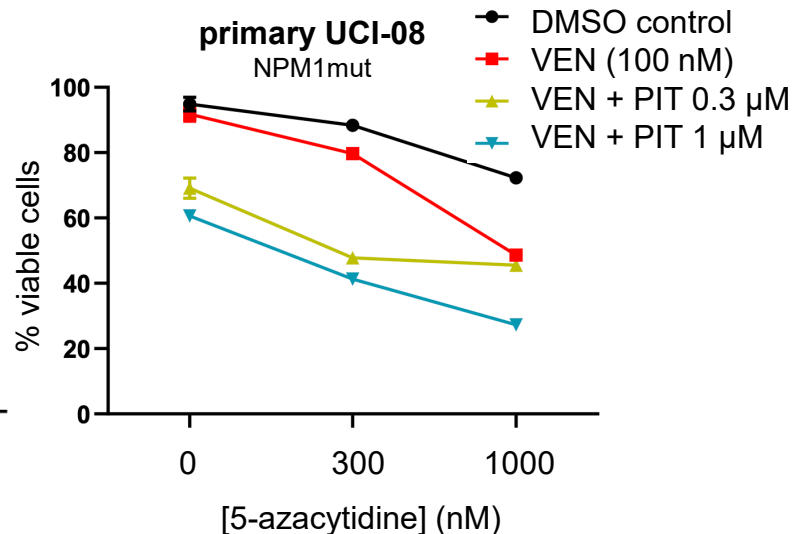
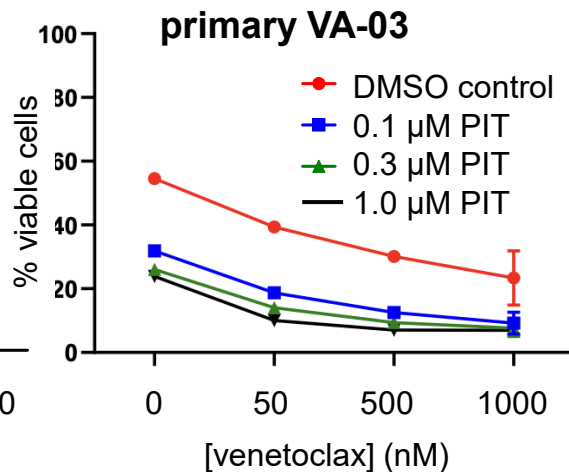
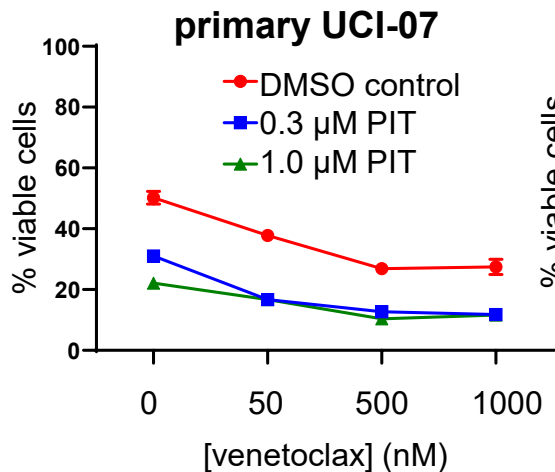
A Newman ¹, R D Clutterbuck, R L Powles, J L Millar



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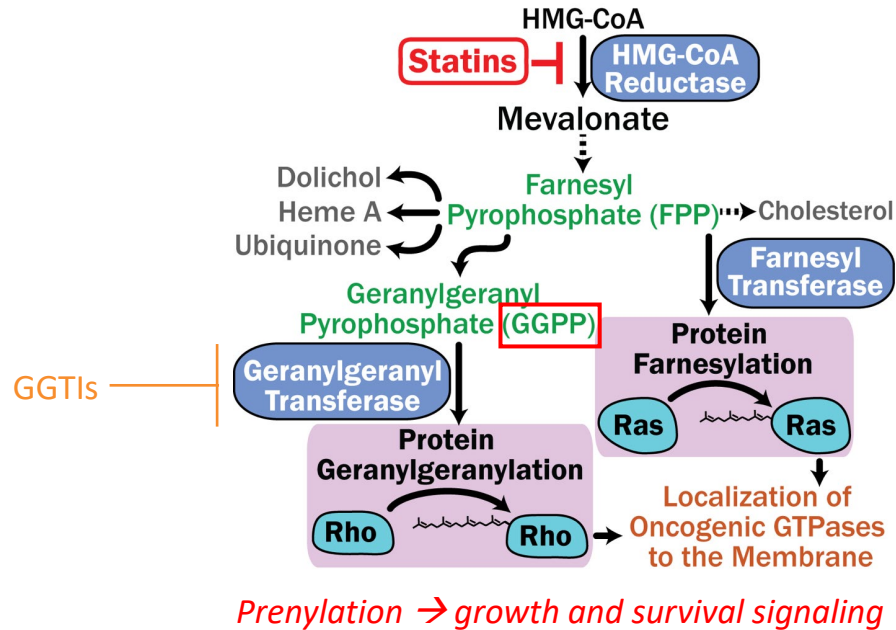
Angela Fleischman
(Heme Biobank)

Pitavastatin enhances cytotoxicity of AML standard-of-care agents



What is the mechanism for statin-mediated apoptosis?

Statins suppress prenylation of signaling proteins



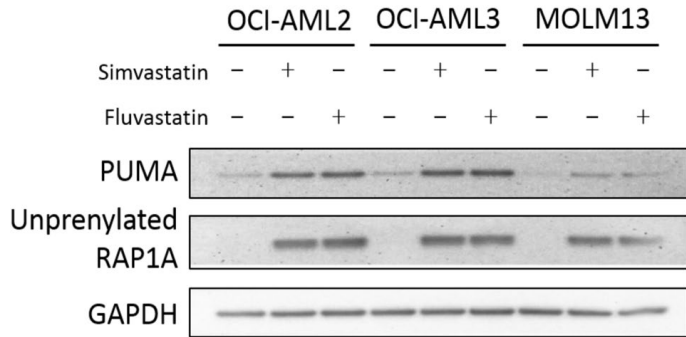
Leukemia (2001) 15, 1398-1407
© 2001 Nature Publishing Group All rights reserved 0887-6924/01 \$15.00
www.nature.com/leu

Blocking protein geranylgeranylation is essential for lovastatin-induced apoptosis of human acute myeloid leukemia cells

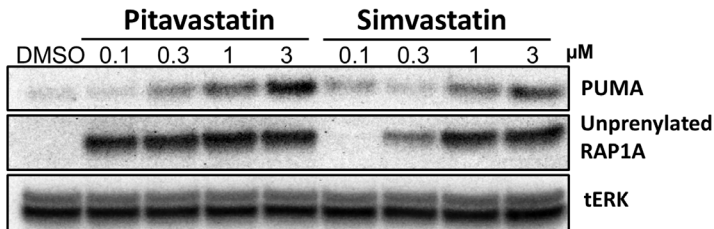
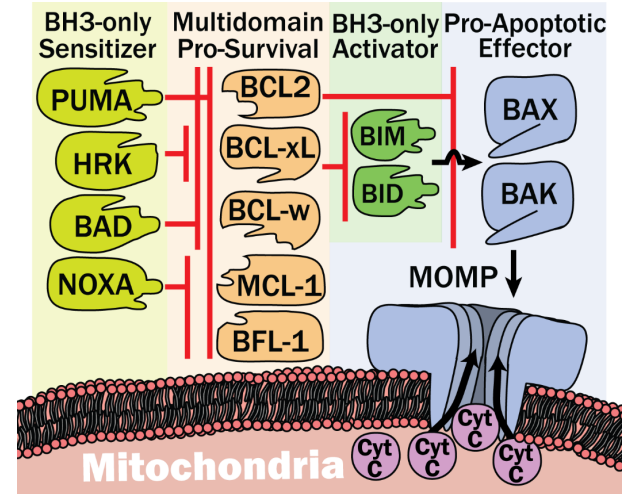
Z Xia^{1,3}, MM Tan¹, W Wei-Lynn Wong^{1,2}, J Dimitroulakos^{1,4}, MD Minden^{1,2} and LZ Penn^{1,2}

¹Department of Cellular and Molecular Biology, Ontario Cancer Institute, University Health Network, Toronto; and ²Department of Medical Biophysics, University of Toronto, Toronto, Canada

Statins increase PUMA expression in blood cancer cell lines



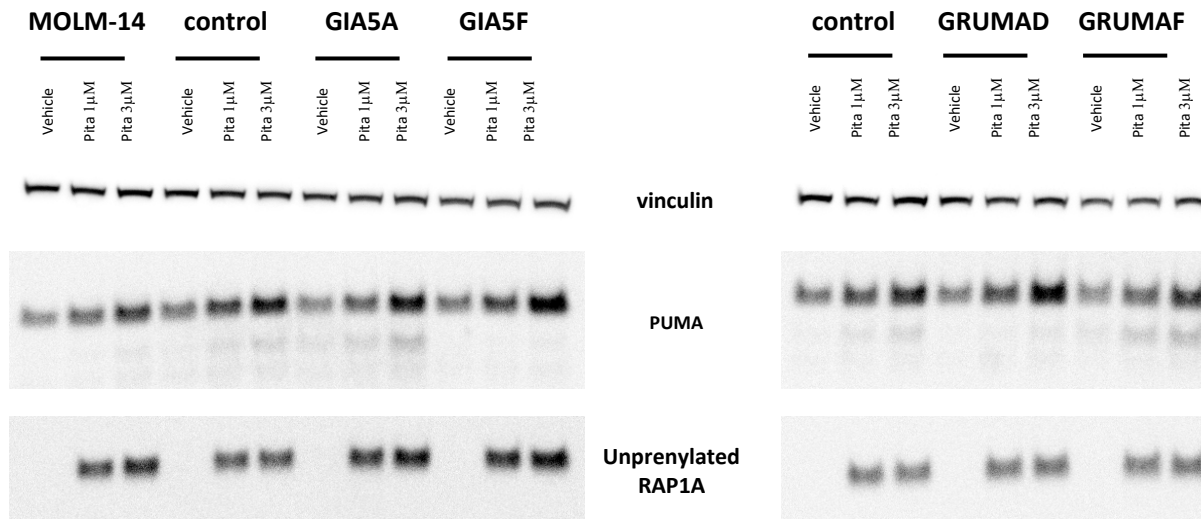
J. Scott Lee et al., Sci. Transl. Med. 2018; 10(445)



D. Juarez et al., Cancer Res. Comm. 2023, 3: 2497

PUMA upregulation is p53-independent

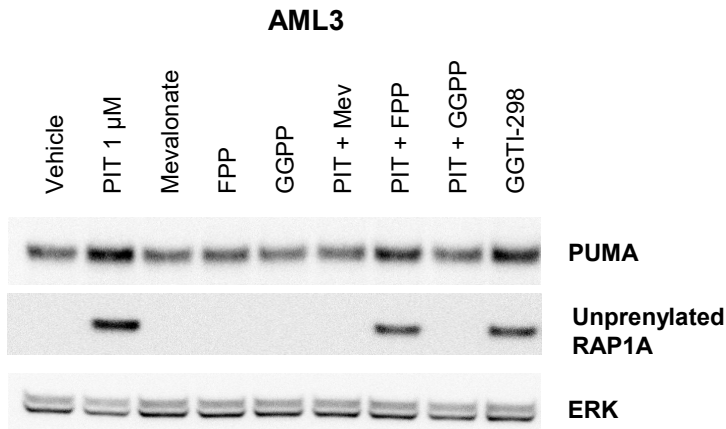
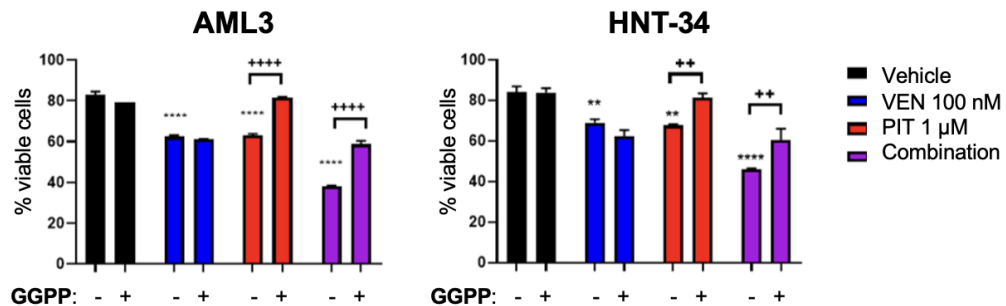
MOLM-14 cell lines and TP53-mutant derivatives



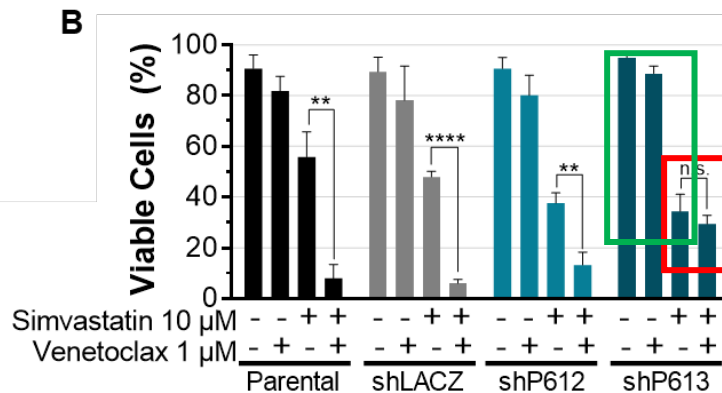
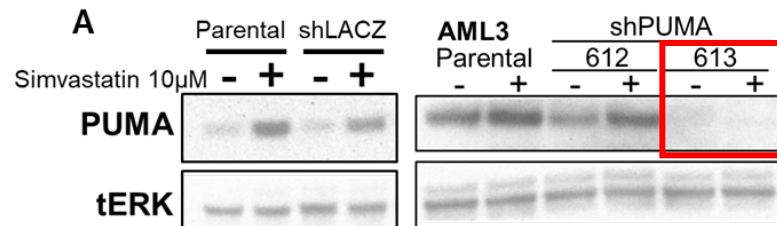
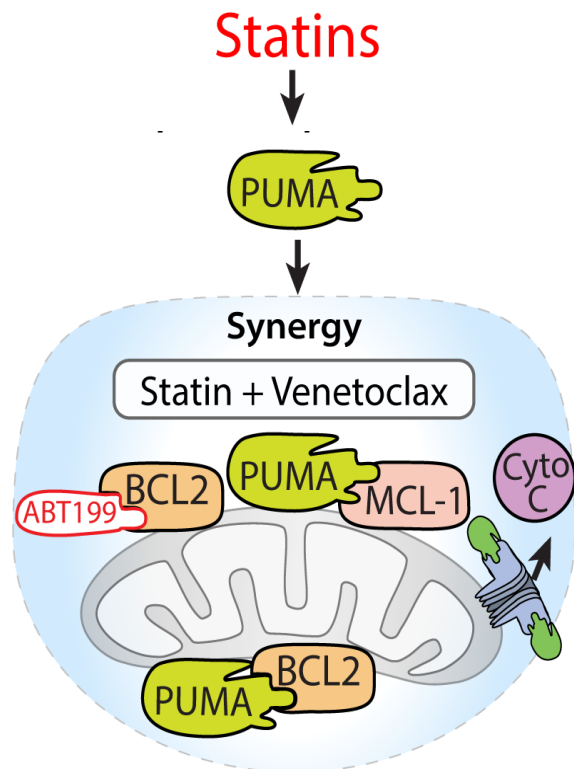
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MOLM-14 cells and derivatives
provided by Sarah Skuli and Martin Carroll (U-Penn)

GGPP rescues cytotoxicity and PUMA upregulation

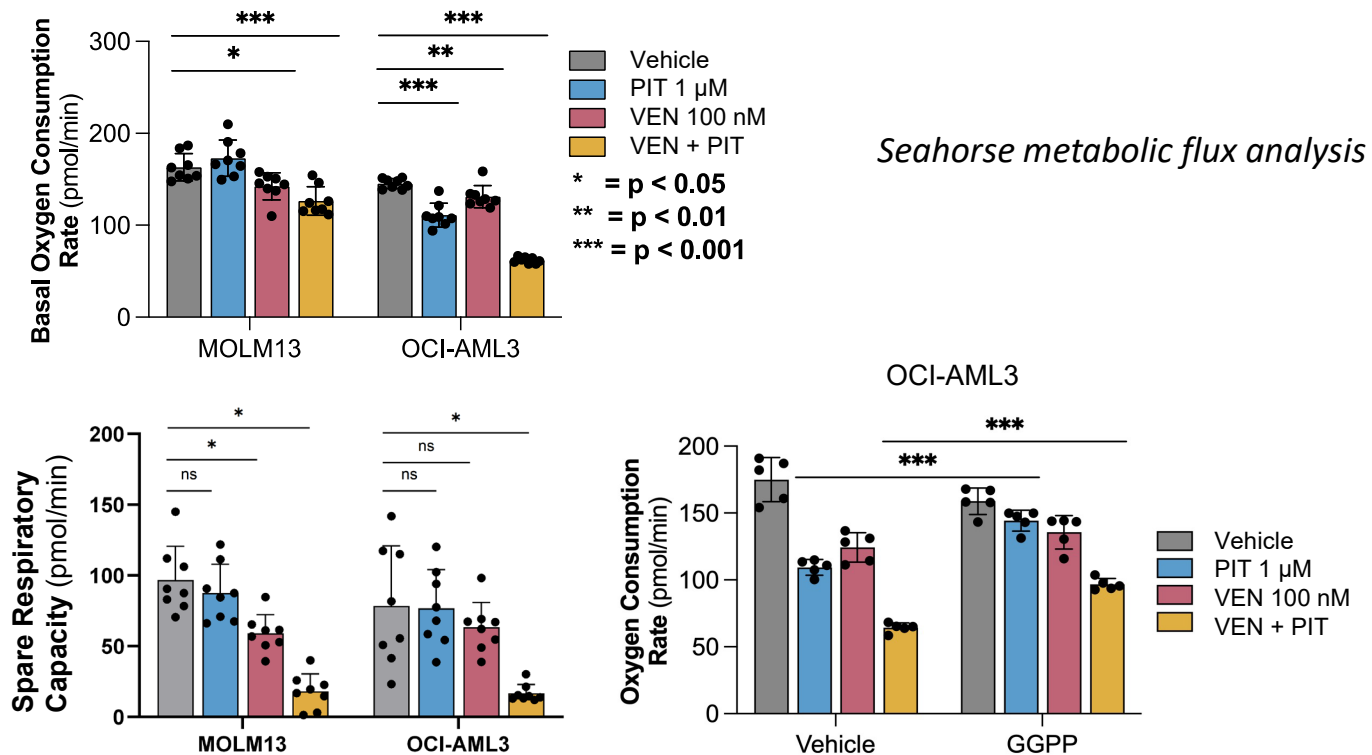


PUMA contributes to cytotoxicity but is not the whole story



J. Scott Lee et al., Sci. Transl. Med. 2018; 10(445)

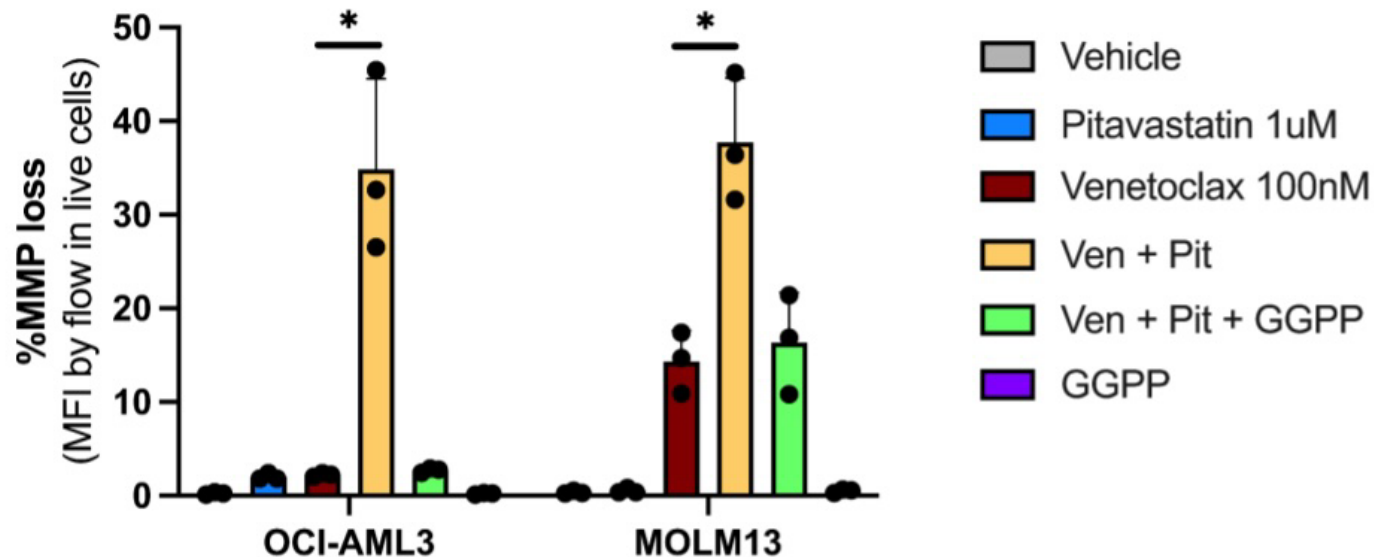
Pitavastatin and venetoclax suppress mitochondrial metabolism



Sarah Skuli
 Martin Carroll
 U-Penn

Pitavastatin and venetoclax cause loss of membrane potential

16hr treatment: MMP loss measured by TMRE staining



Mitochondrial inhibitors circumvent adaptive resistance to venetoclax and cytarabine combination therapy in acute myeloid leukemia

Claudie Bosc^{1,2,3}, Estelle Saland^{1,2,3}, Aurélie Bousard⁴, Noémie Gadaud^{1,2,3,5,6}, Marie Sabatier^{1,2,3}, Guillaume Cognet^{1,2,3}, Thomas Farge^{1,2,3}, Emeline Boet^{1,2,3}, Mathilde Gotanègre^{1,2,3}, Nesrine Aroua^{1,2,3}, Pierre-Luc Mouchel^{1,2,3,5,6}, Nathaniel Polley^{1,2,3}, Clément Larrue^{1,2,3}, Eléonore Kaphan^{1,2,3}, Muriel Picard⁷, Ambrine Sahal^{1,2,3}, Latifa Jarrou^{1,2,3}, Marie Tosolini¹, Florian Rambow⁴, Florence Cabon^{1,2,3}, Nathalie Nicot⁸, Laura Poillet-Perez^{1,2,3}, Yujue Wang⁹, Xiaoyang Su⁹, Quentin Fovez¹⁰, Jérôme Kluzza¹⁰, Rafael José Argüello¹¹, Céline Mazzotti^{1,12}, Hervé Avet-Loiseau^{1,12}, François Vergez^{1,2,3,5,6}, Jérôme Tamburini¹³, Jean-Jacques Fournié^{1,12}, Ing S. Tiong¹⁴, Andrew H. Wei¹⁴, Tony Kaoma¹⁵, Jean-Christophe Marine⁴, Christian Récher^{1,2,3,5,6}, Lucille Stuani^{1,2,3,16}, Carine Joffre^{1,2,3,16} and Jean-Emmanuel Sarry^{1,2,3}

Targeting Mitochondrial Structure Sensitizes Acute Myeloid Leukemia to Venetoclax Treatment

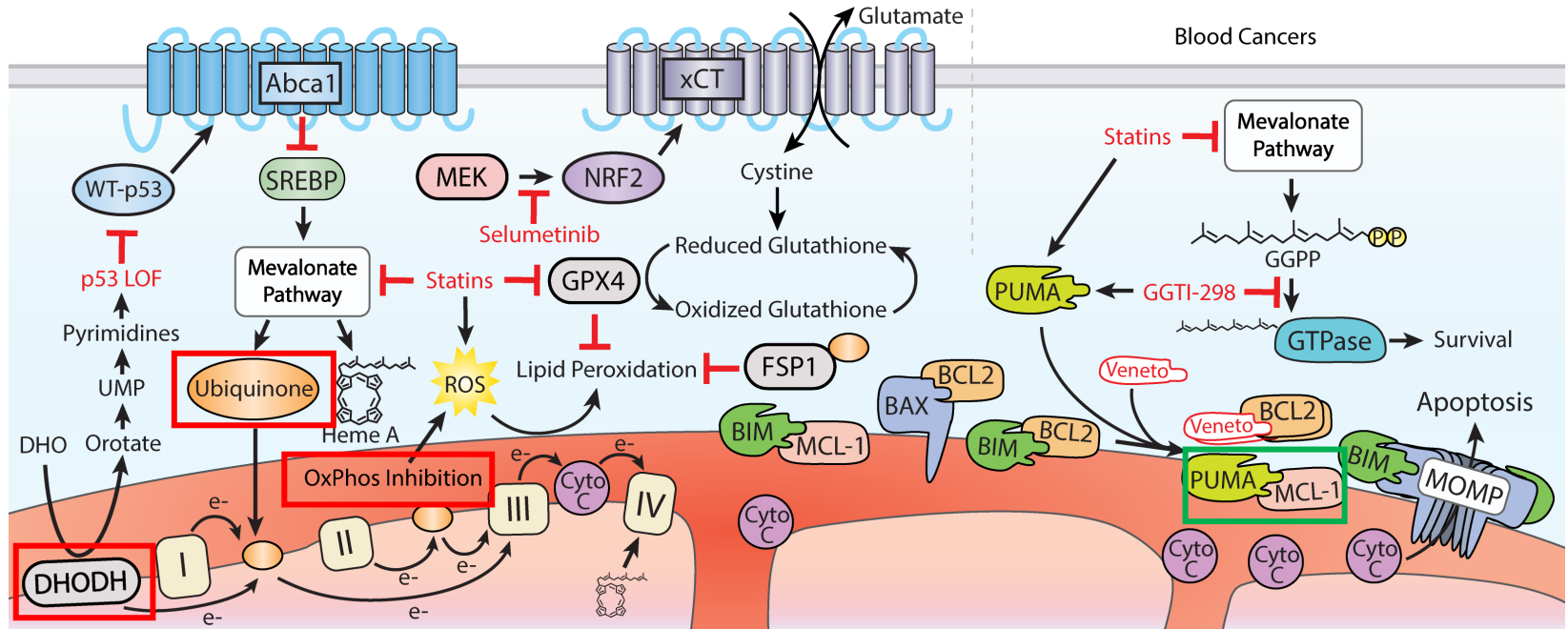
Xufeng Chen^{1,2}, Christina Glytsou^{1,2}, Hua Zhou³, Sonali Narang², Denis E. Reyna^{4,5,6}, Andrea Lopez^{4,5,6}, Theodore Sakellaropoulos^{1,2}, Yixiao Gong^{1,2,7}, Andreas Kloetgen^{1,2}, Yoon Sing Yap^{1,2}, Eric Wang^{1,2}, Evripidis Gavathiotis^{4,5,6}, Aristotelis Tsirigos^{1,2,3}, Raoul Tibes², and Iannis Aifantis^{1,2}

Article

Cotargeting of Mitochondrial Complex I and Bcl-2 Shows Antileukemic Activity against Acute Myeloid Leukemia Cells Reliant on Oxidative Phosphorylation

Fangbing Liu¹, Hasini A. Kalpage², Deying Wang³, Holly Edwards^{4,5}, Maik Hüttemann², Jun Ma¹, Yongwei Su^{1,4,5}, Jenna Carter⁶, Xinyu Li¹, Lisa Polin^{4,5}, Juiwanna Kushner^{4,5}, Sijana H. Dzinic^{4,5}, Kathryn White^{4,5}, Guan Wang^{1,*}, Jeffrey W. Taub^{7,8} and Yubin Ge^{4,5,6,*}

Working Model: statins disrupt mitochondrial physiology



D Juarez and DA Fruman, *Trends in Cancer* 2021

Next questions

- Can statin cytotoxicity be rescued by restoring mitochondrial function?
(Ubiquinone, α keto-butyrate, aspartate)
- Metabolomics, mito structure, mito mass
- Which GTPases are critical for maintaining mitochondrial health and suppressing PUMA?
 - CRISPR screen for small GTPases, GEFs, GAPs

Next questions

- Can statin cytotoxicity be rescued by restoring mitochondrial function? (Ubiquinone, α keto-butyrate, aspartate)
- Metabolomics, mito structure, mito mass
- Which GTPases are critical for maintaining mitochondrial health and suppressing PUMA?
 - CRISPR screen for small GTPases, GEFs, GAPs
- Does addition of pitavastatin to VEN regimens prolong survival in *TP53*-mutant AML? Phase 2 in planning stage...



Dr. Elizabeth Brèm

Acknowledgements

Fruman Lab

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Collaborators

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Orlando Bueno

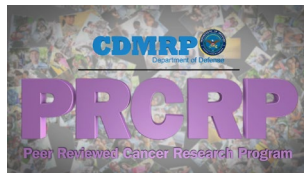
Joel Levenson, **AbbVie**

Sarah Skuli

Martin Carroll, **UPENN**



LEUKEMIA &
LYMPHOMA
SOCIETY®



UCI Collaborators

Elizabeth Brèm

Susan O'Brien

Angela Fleischman

Cholsoon Jang

Thank You
