

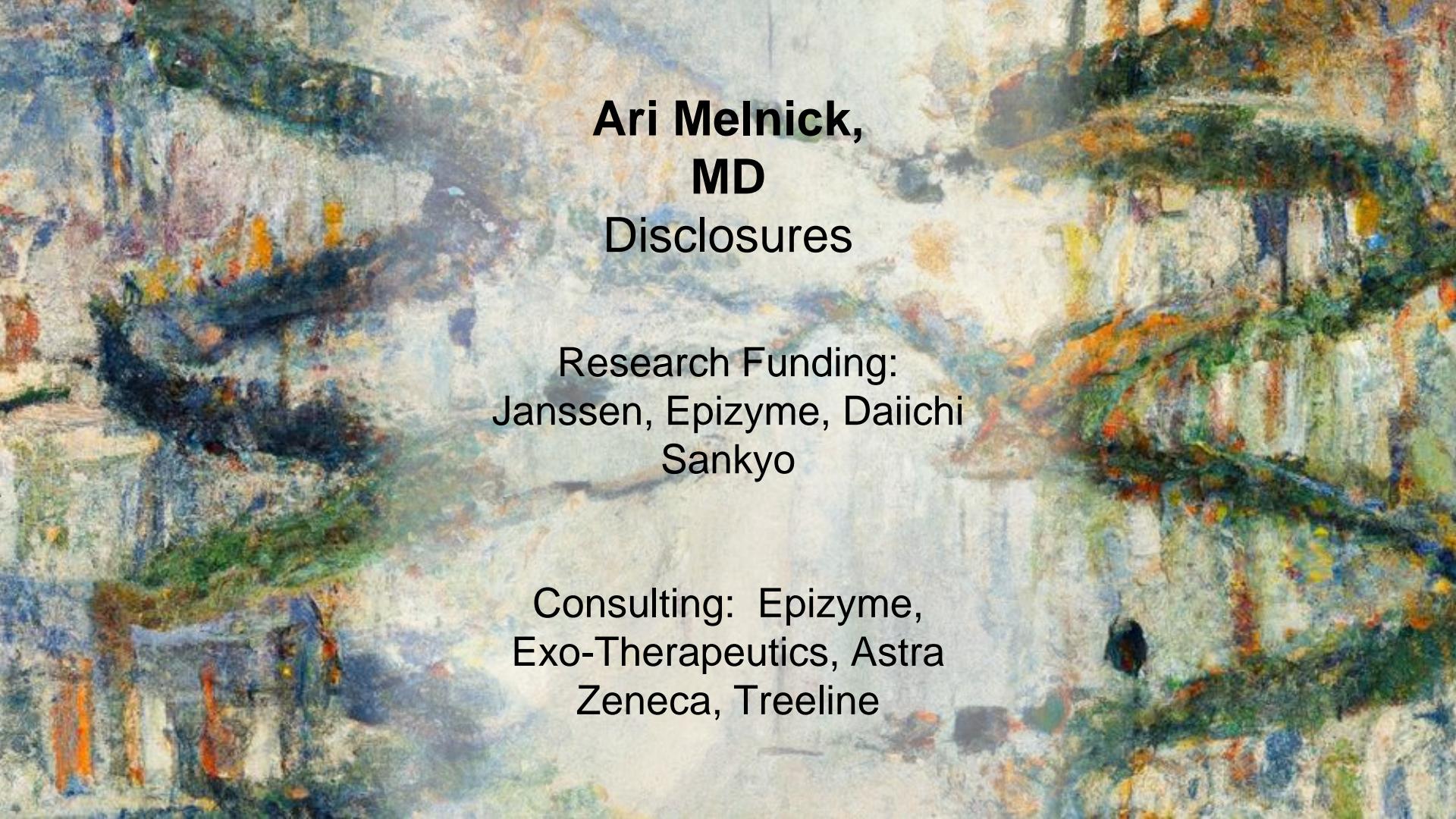
Mechanisms of malignant transformation of the immune system

Ari Melnick, MD

Laurel Gebroe Professor of Hematology and Medical Oncology
Joan and Sanford I. Weill Department of Medicine
Professor of Pharmacology and Immunology



Weill Cornell
Medicine

A classic Impressionist painting featuring a bridge spanning a body of water, with buildings visible across the riverbank. The scene is depicted with visible brushstrokes and a color palette dominated by blues, greens, and earth tones.

Ari Melnick, MD

Disclosures

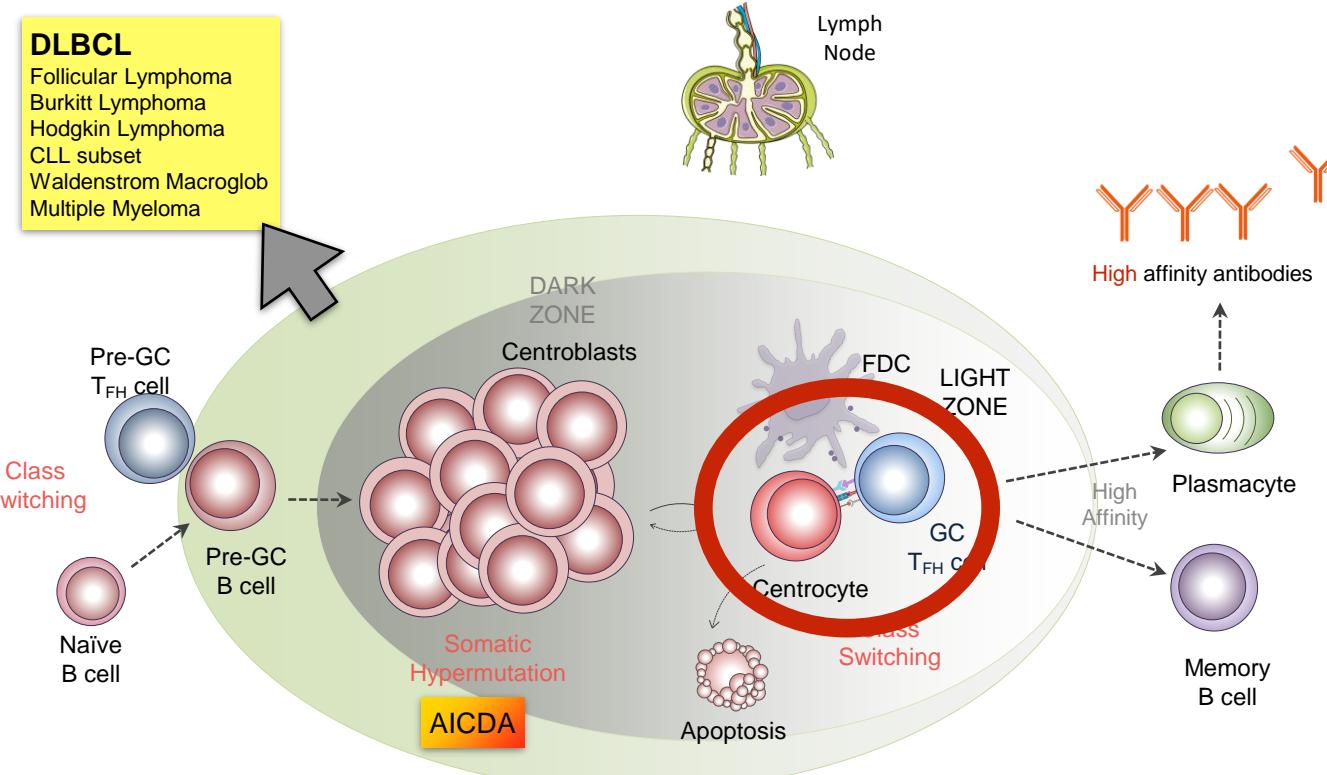
Research Funding:
Janssen, Epizyme, Daiichi
Sankyo

Consulting: Epizyme,
Exo-Therapeutics, Astra
Zeneca, Treeline

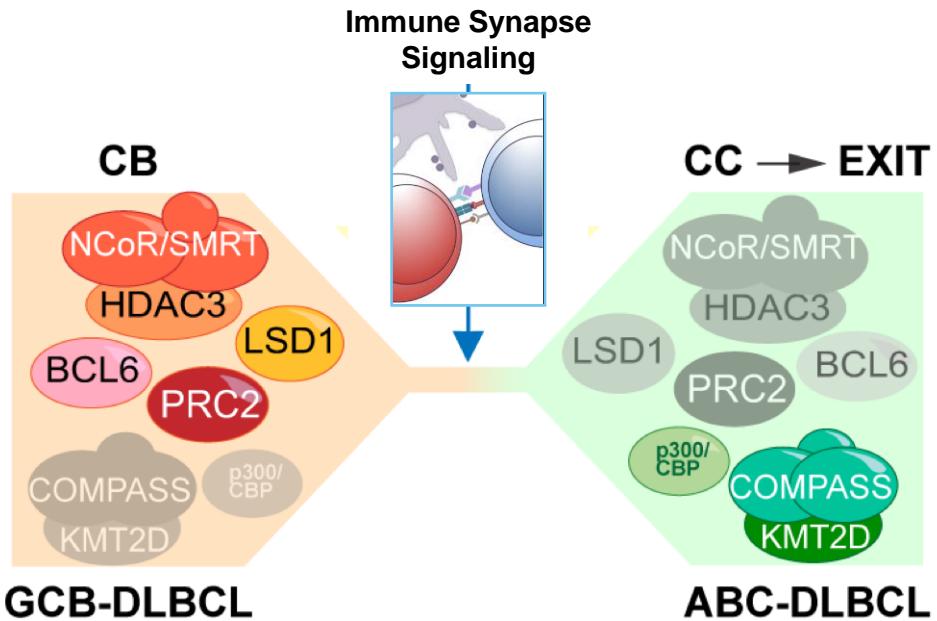


Trying to solve the DLBCL puzzle

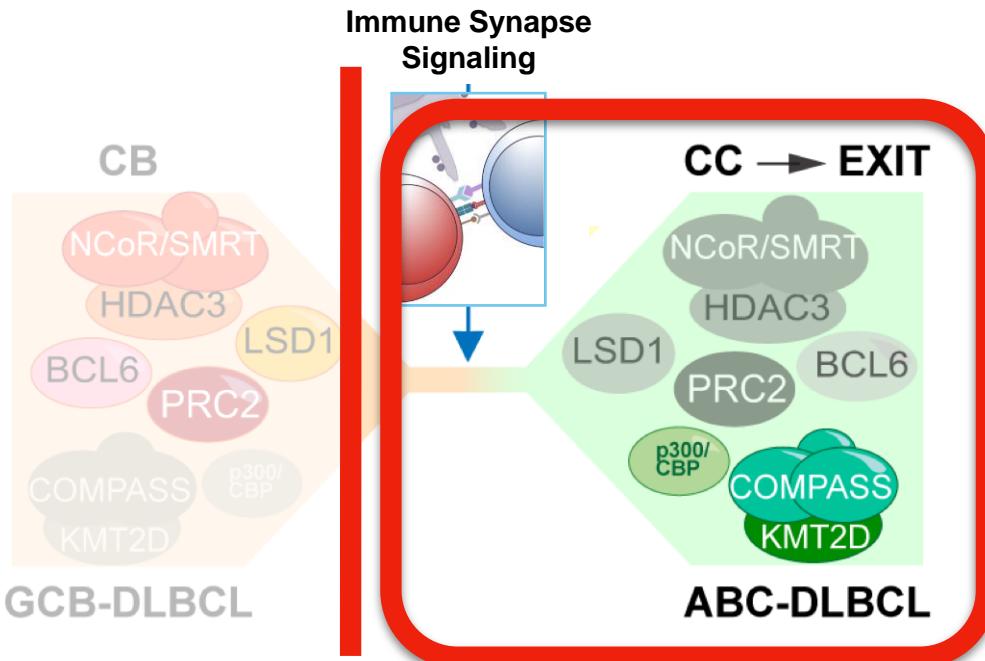
The germinal center reaction is the origin of a majority of hematologic malignancies



The origin, mechanisms and phenotypes of lymphomas are dependent on how immune synapse signaling is perturbed by mutations

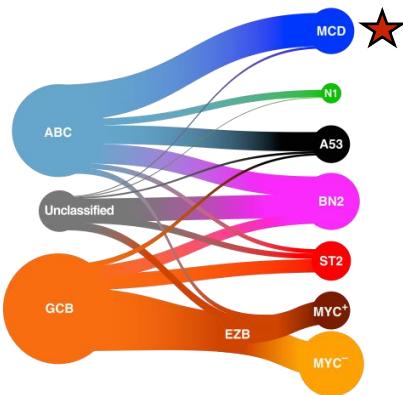


ABC-DLBCLs reflect GC B-cells with **gain of function** immune synapse profiles



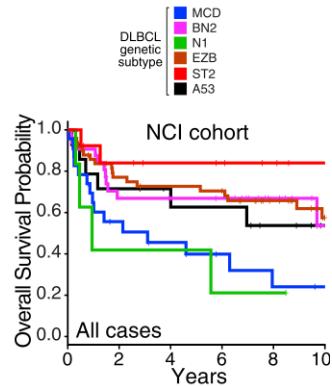
MCD/C5 DLBCLs: inferior clinical outcomes and recurrent mutations

Chapuy et al Nature Med 2018
Schmidt et al NEJM 2018
Wright et al Cancer Cell 2020



Wright et al Cancer Cell 2020
~ Cluster 5 from Chapuy et al Nature Medicine 2018

MCD/C5 DLBCLs have inferior clinical outcomes

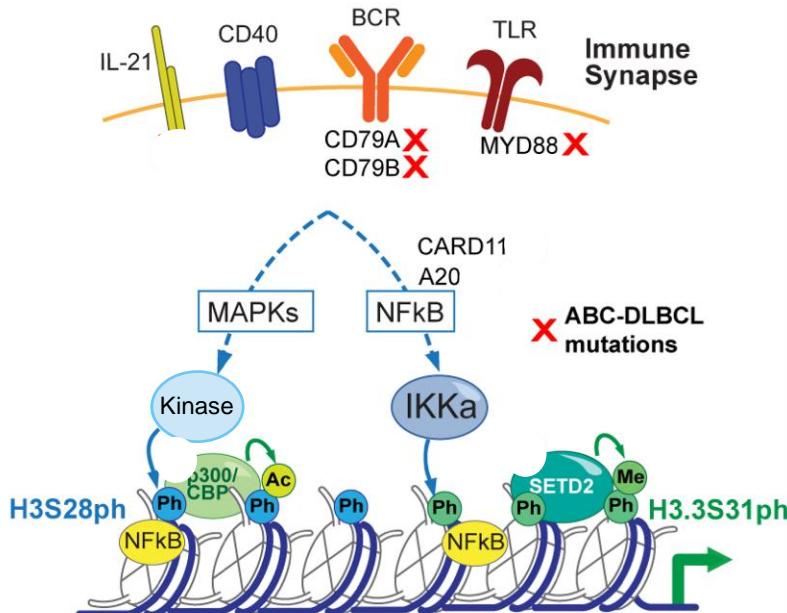
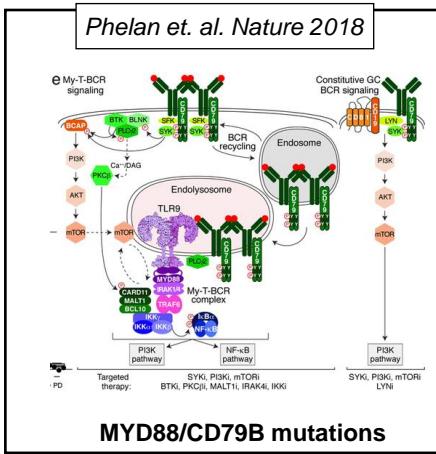


Mostly IgM+ self-reactive BCRs

Transcription factors | Signaling

Mutations
<i>MYD88</i> ^{L265P} ★
<i>CD79B</i>
<i>BTG1</i> ★
<i>TBL1XR1</i> ★
<i>SPIB</i>
<i>PRDM1</i>
<i>SETD1B</i>
<i>TOX</i>
<i>IRF4</i>
<i>ETV6</i>

Chronic active immune synapse signaling in ABC-DLBCL drives lymphoma phenotypes through epigenetic effects



Alexia Martinez de Paz
Steven Josefowicz
Wendy Beguelin

MYD88 mutation induces expansion of autoimmune B-cell clonal precursor cells for MCD-DLBCL

RESEARCH ARTICLE

An Aged/Autoimmune B-cell Program Defines the Early Transformation of Extranodal Lymphomas

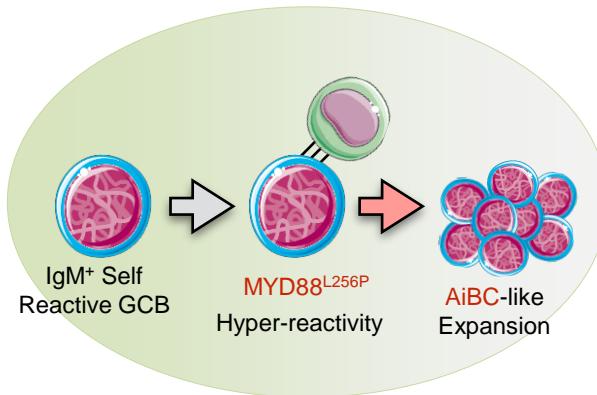


Venturutti et al, Cancer Discovery 2023

Pindzola et al Blood 2022

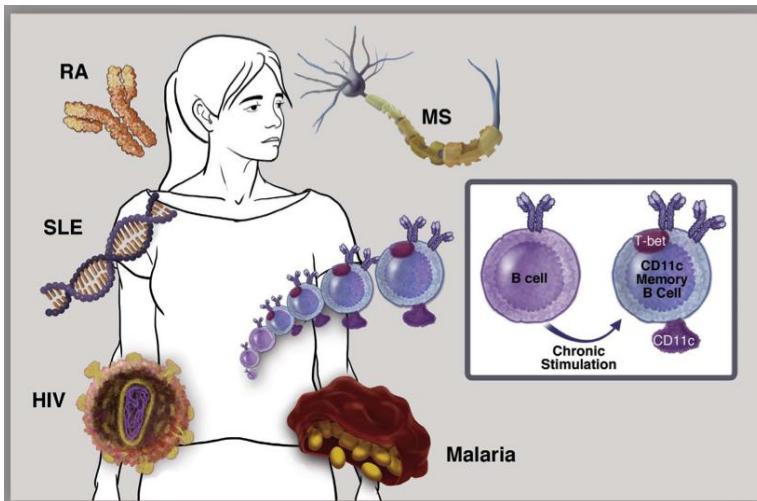


Leandro Venturutti PhD



“AiBC”-Like MBs as prospective cell of origin for MCD/C5 DLBCLs

“AiBC” = “Aged/Autoimmune/Atypical B-cells”



Cellular Immunology 321 (2017) 40–45

Subpopulation of MBs.

CD11c^{hi}TBX21^{hi}

Mediate auto-immune disorders

Expand in frequency with age

- Key features:

Likely GC-derived

Self-renewal potential

Highly reactive to activating signals

Elevated AICDA expression

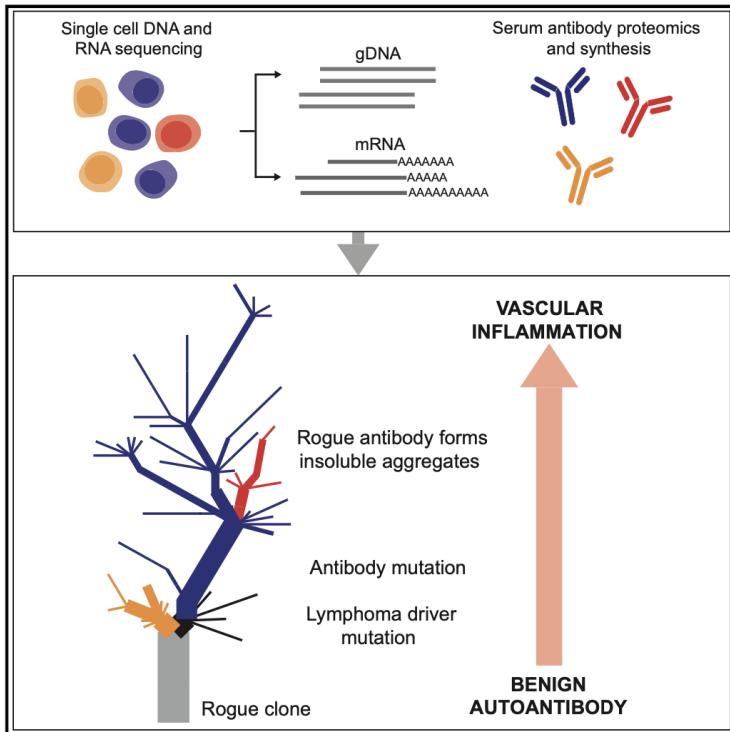
Mostly IgM-type BCR

Tissue-resident or circulating in blood

Genesis/survival dependent on MYD88

Lymphoma Driver Mutations in the Pathogenic Evolution of an Iconic Human Autoantibody

Graphical Abstract

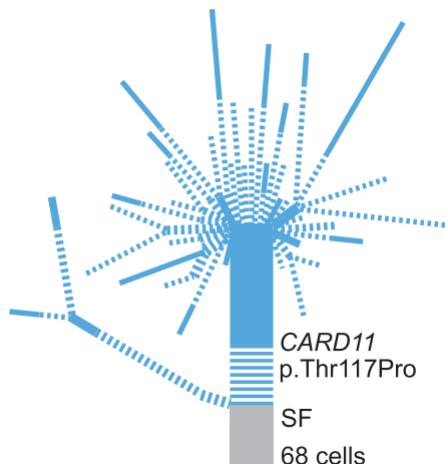


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Christopher C. Goodnow, Joanne H. Reed
2020

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MYD88 mutation induces expansion of autoimmune B-cell clonal precursor cells for MCD-DLBCL

RESEARCH ARTICLE

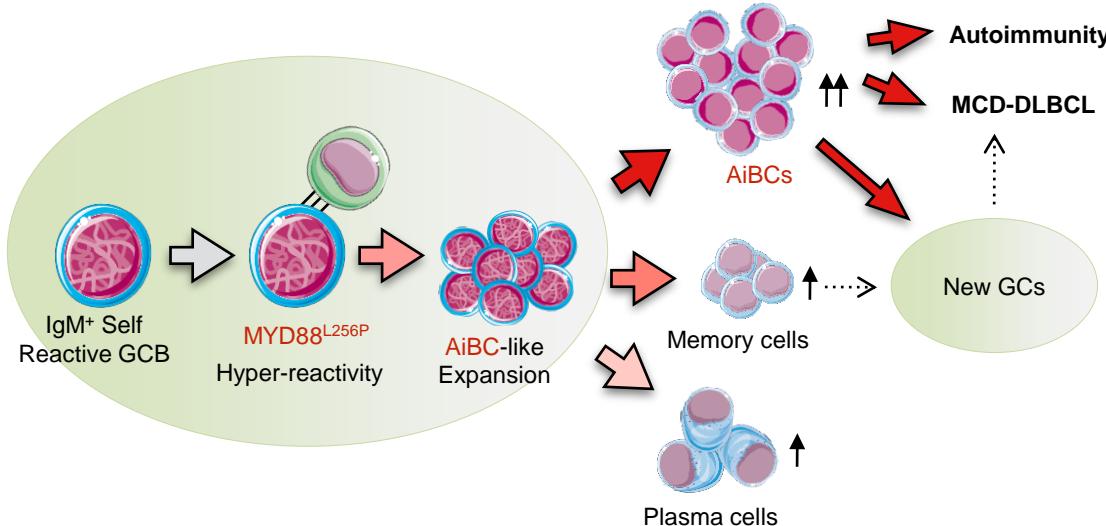
An Aged/Autoimmune B-cell Program Defines the Early Transformation of Extranodal Lymphomas



Leandro Venturutti PhD



Venturutti et al, Cancer Discovery 2023



TBL1XR1 mutation drives MCD-DLBCL through immune synapse transcriptional skewing towards MBC/AiBC

Cell

Article



Leandro Venturutti PhD

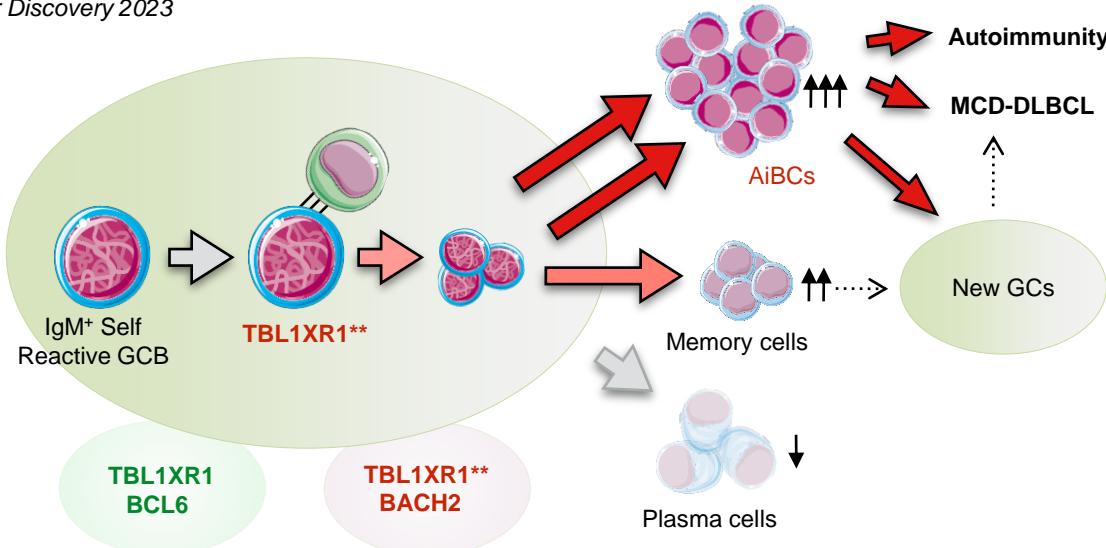


TBL1XR1 Mutations Drive Extranodal Lymphoma by Inducing a Pro-tumorigenic Memory Fate

Venturutti et al, Cell 2020

Venturutti et al, Blood 2020

Venturutti et al Cancer Discovery 2023



BTG1 somatic mutations cluster around hotspots in the N-terminal domain

RESEARCH ARTICLE

LYMPHOMA

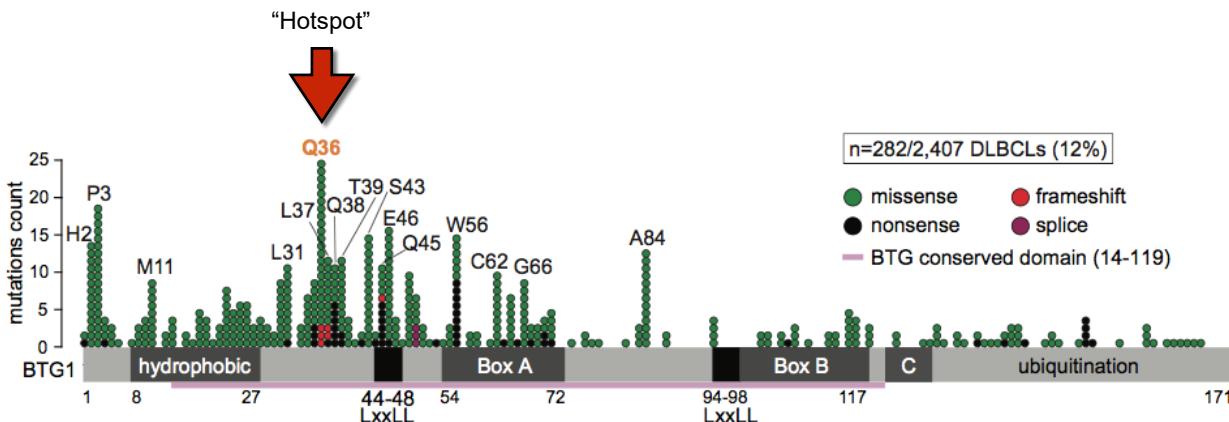
BTG1 mutation yields supercompetitive B cells primed for malignant transformation

Coraline Mlynarczyk^{1,5}, Matt Teater¹, Juhee Pae², Christopher R. Chin^{1,3,4,5}, Ling Wang¹, Theimmozi Arulraj⁶, Darko Barisic¹, Antonin Papin⁷, Kenneth B. Hoehn⁸, Ekaterina Kots⁹, Jonatan Ersching^{2,†}, Arnab Bandyopadhyay⁶, Ersilia Barin¹⁰, Hui Xian Poh¹⁰, Chiara M. Evans^{11,12}, Amy Chadburn⁷, Zhengming Chen¹³, Hao Shen¹, Hannah M. Isles¹, Benedikt Pelzert¹, Ioanna Tsialta¹, Ashley S. Doane^{1,5}, Huimin Geng^{2,4}, Muhammed Hassan Rehman^{1,6}, Jonah Melnick¹, Wyatt Morgan^{1,‡}, Diu T. T. Nguyen^{1,16}, Olivier Elemento^{3,17}, Michael G. Kharas¹¹, Samir R. Jaffrey¹⁰, David W. Scott¹⁸, George Khelashvili^{5,9}, Michael Meyer-Hermann^{6,19}, Gabriel D. Victoria², Ari Melnick^{1,§}

Mlynarczyk et al Science 2023



Coraline Mlynarczyk, PhD



BTG1 mutations cause highly malignant supercompetitive MCD-DLBCL

RESEARCH ARTICLE

LYMPHOMA

***BTG1* mutation yields supercompetitive B cells primed for malignant transformation**

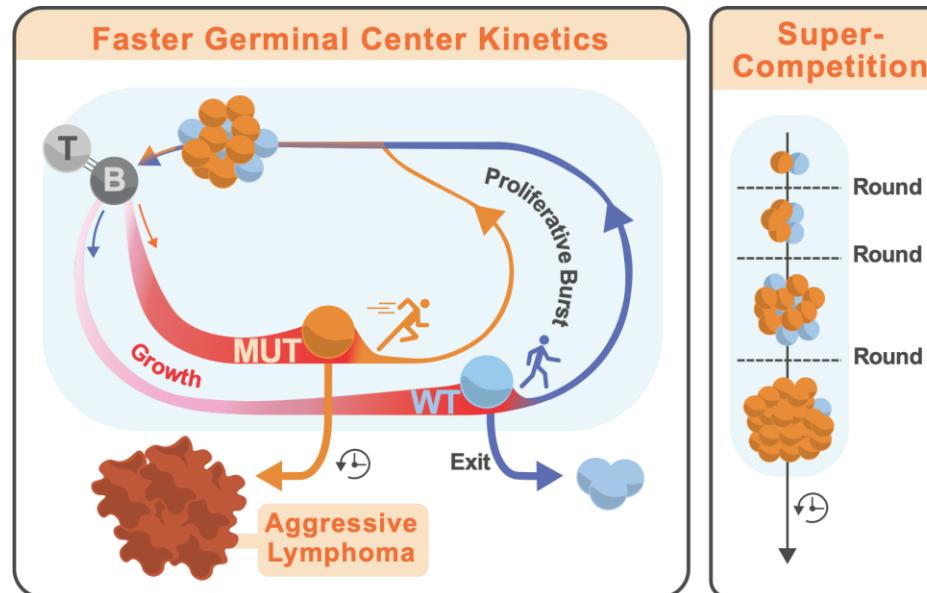
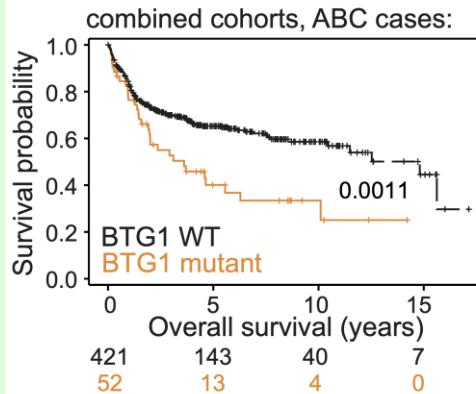
Coraline Mlynarczyk^{1*}, Matt Teaster², Juhee Pae², Christopher R. Chin^{1,3,4,5}, Ling Wang¹, Theinmoezhi Arulraj⁶, Darko Barisic¹, Antonin Papin⁷, Kenneth B. Hoehn⁸, Ekaterina Kots⁹, Jonatan Ersching¹⁰, Arnab Bandopadhyay⁹, Ersilia Barin¹⁰, Hui Xian Poh¹⁰, Chiara M. Evans^{11,12}, Amy Chadburn⁷, Zhengming Che¹³, Hua Shen¹, Hannah M. Isles¹, Benedict Pelzer¹, Ioanna Tsialta¹, Ashley S. Doane^{1,5}, Huimin Geng¹⁴, Muhammad Hassan Rehman¹³, Jonah Melnick¹, Wyatt Morgan¹¹, Diu T. T. Nguyen^{11,16}, Olivier Elemento^{1,17}, Michael G. Kharas¹¹, Samie R. Jaffrey¹⁰, David W. Scott¹⁸, George Khelashvili^{5,9}, Michael Meyer-Hermann^{6,19}, Gabriel D. Victor², Ari Melnick^{1*}



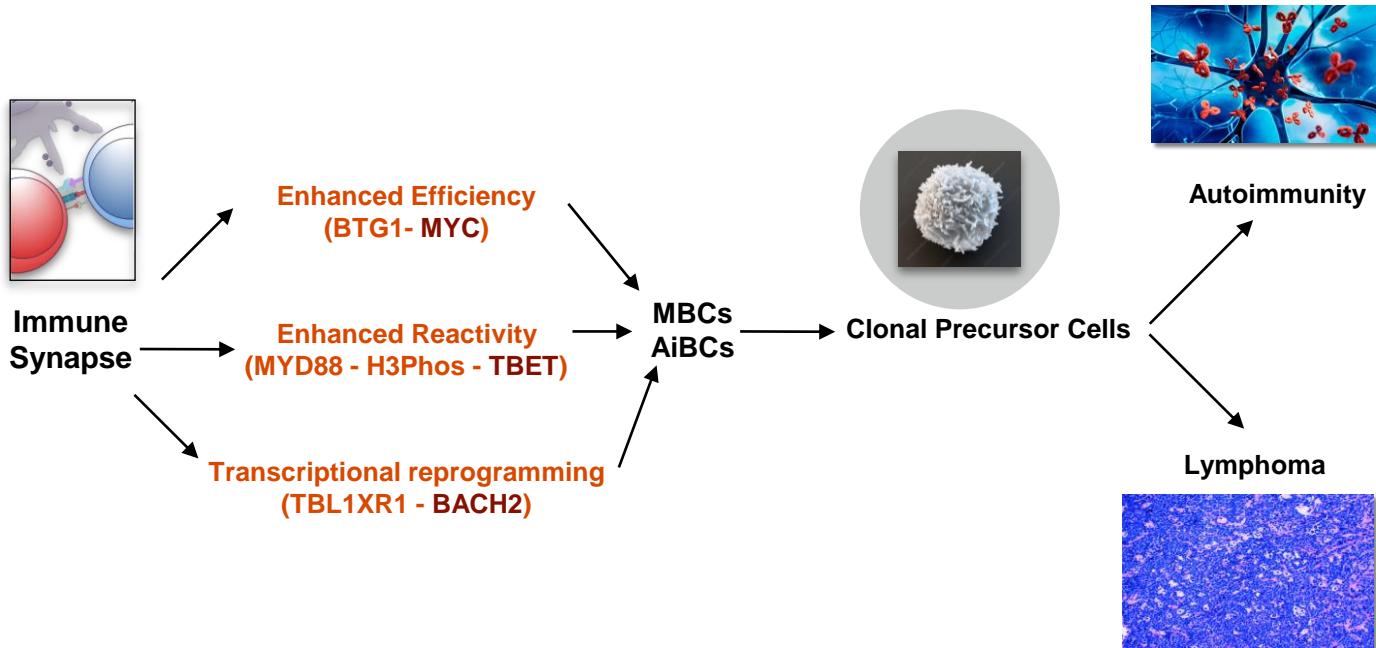
Coraline Mlynarczyk, PhD



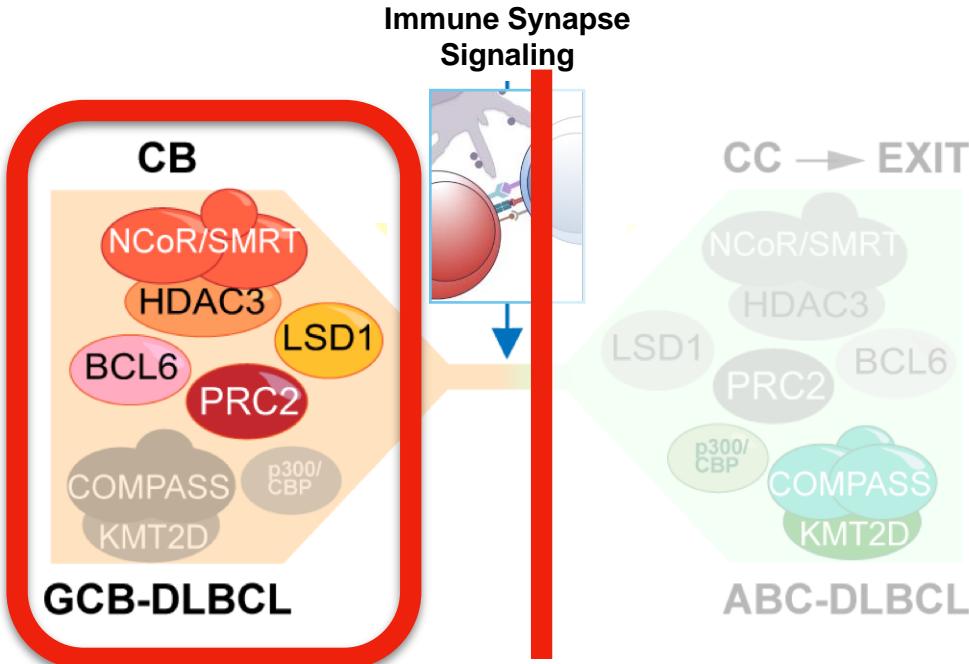
Mlynarczyk et al Science 2023



Trajectories for MCD-DLBCL development from CPCs also linked to auto-immunity



GCB-DLBCLs reflect GC B-cells with **loss of function** immune synapse profiles

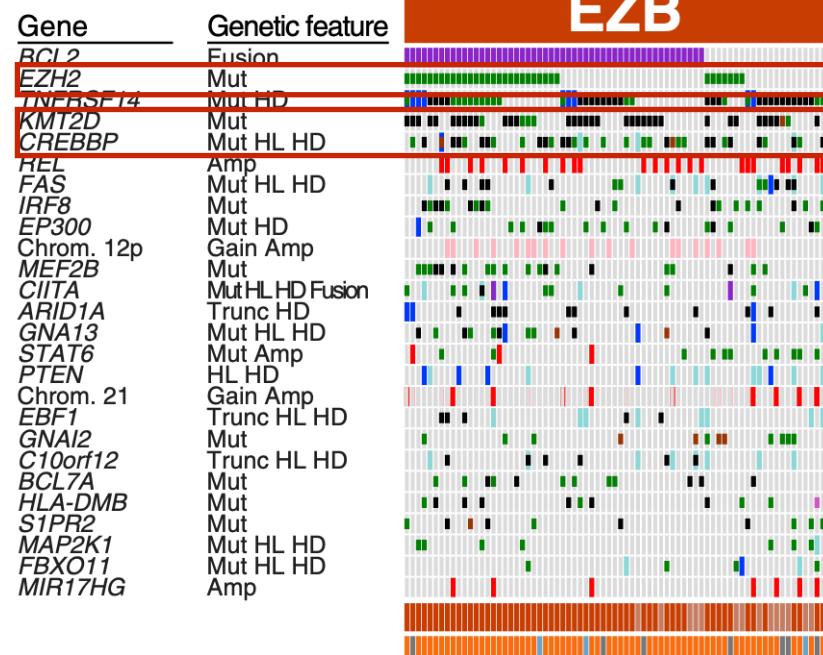
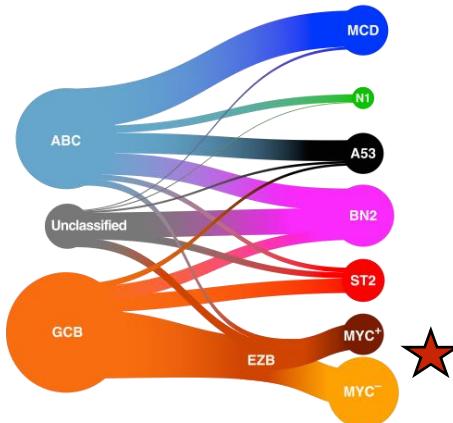


Somatic mutation of histone modifying genes are the hallmark of EZB/C3 DLBCLs

Chapuy et al Nature Med 2018

Schmidt et al NEJM 2018

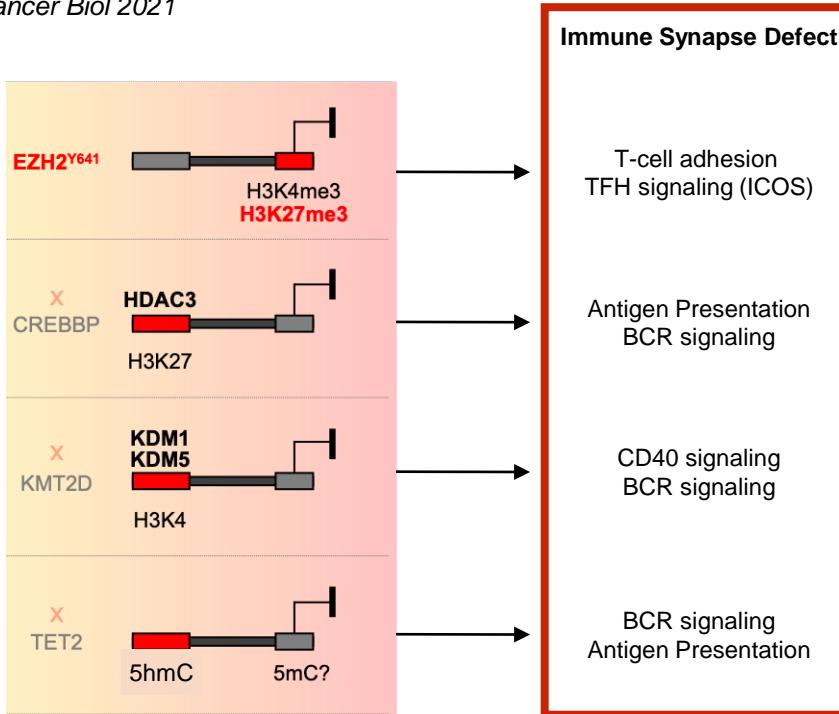
Wright et al Cancer Cell 2020



EZH2, CREBBP, KMT2D and TET2 mutations primarily alter and suppress Immune Synapse gene sets

Mlynarczyk et al *Immunol Rev* 2020

Venturutti et al *Ann Rev Cancer Biol* 2021



- Velichutina et al *Blood* 2010
Cerchietti et al *J Clin Investigation* 2010
Beguelin et al *Cancer Cell* 2013
Huang et al *Nature Immunology* 2013
Hatzis et al *Cell Reports* 2013
Ortega et al *Nature Med* 2015
Jiang et al *Cancer Discovery* 2016
Beguelin et al *Cancer Cell* 2016
Beguelin et al *Nature Comm* 2017
Dominguez et al *Cancer Discovery* 2018
Einishi et al *Cancer Discovery* 2019
Hatzis et al - *Nature Immunology* 2019
Mondello et al, *Cancer Discovery* 2020
Rosikiewicz et al *Science Advances* 2020
Beguelin et al *Cancer Cell* 2020
Chu et al *Molecular Cell* 2020
Doane et al *Nature Immunology* 2021
Rivas et al *Nature Immunology* 2021
Rivas et al *Frontiers Immune* 2021
Takata et al *J Clin Investigation* 2022
Li et al *BioRxiv* 2022

Zhang et al *Nature Med* 2015
Zhang et al *Cancer Discover* 2017
Garcia Ramirez *Blood* 2017
Hashwhah et al *PNAS* 2017

Mutant EZH2 causes strong interactions with FDCs and at the same time impairs interaction with TFH cells

Cancer Cell

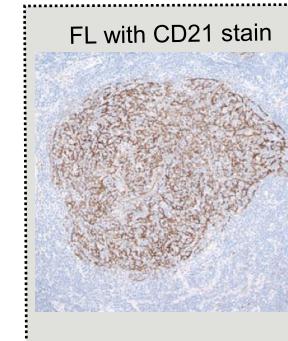
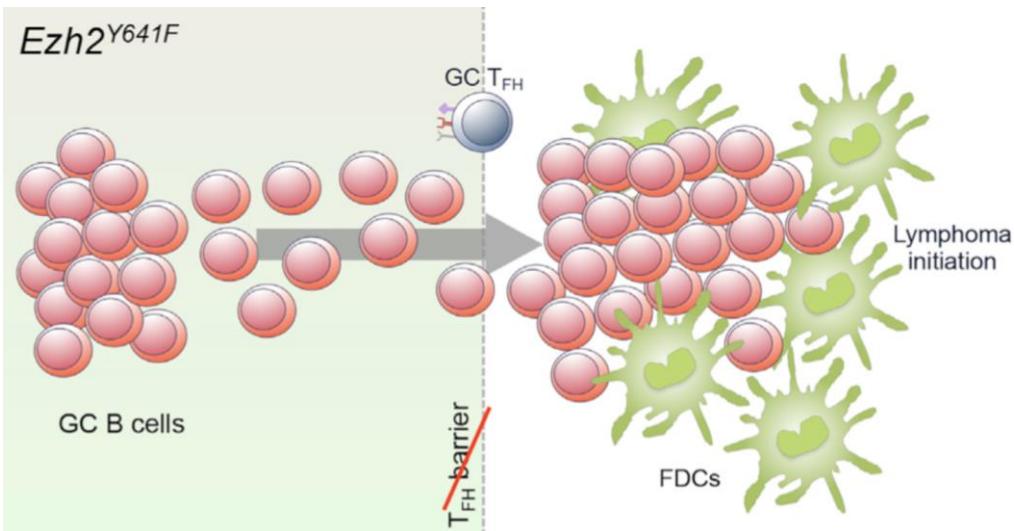
Mutant EZH2 Induces a Pre-malignant Lymphoma Niche by Reprogramming the Immune Response

Beguelin et al Cancer Cell 2013
Beguelin et al Cancer Cell 2016
Beguelin et al Nat Communications 2017
Beguelin et al Cancer Cell 2020

Article



Wendy Beguelin, PhD
Assistant Professor



EZH2-i induce prolonged anti-lymphoma effect and immune reactivation

The Journal of Clinical Investigation

RESEARCH ARTICLE

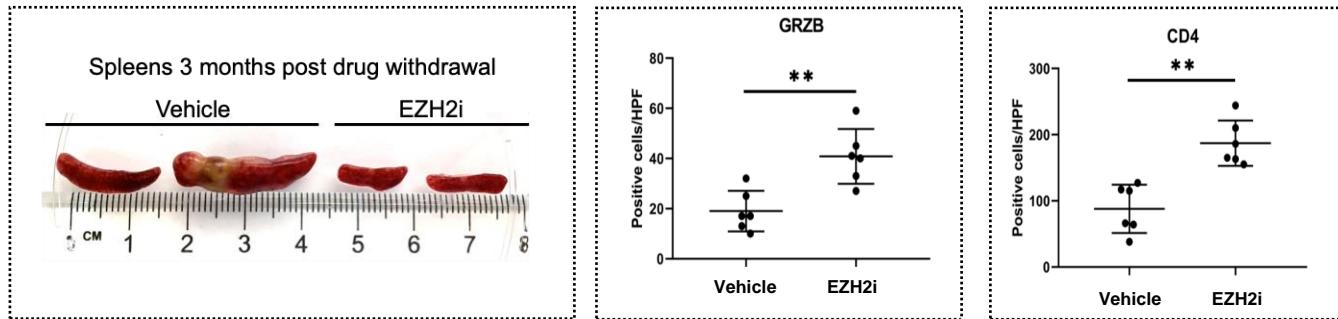
Tumor-associated antigen PRAME exhibits dualistic functions that are targetable in diffuse large B cell lymphoma



Yusuke Isshiki MD PhD



Takata et al., *J Clin Invest.* 2022



With Christian Steidl, BCCA

Problem: there are no relevant syngeneic models for lymphoma

Solution: Syngeneic GEMMs faithfully recapitulating the human DLBCLs

BCL2⁺-EZH2^{Y641F} High Grade FL

BCL2⁺-EZH2^{Y641F} EZB-DLBCL

BCL2⁺-MYC⁺-EZH2^{Y641F} EZB-MYC (DHIT) DLBCL

BCL2⁺-SETD2^{+/-} SETD2 mut DLBCL

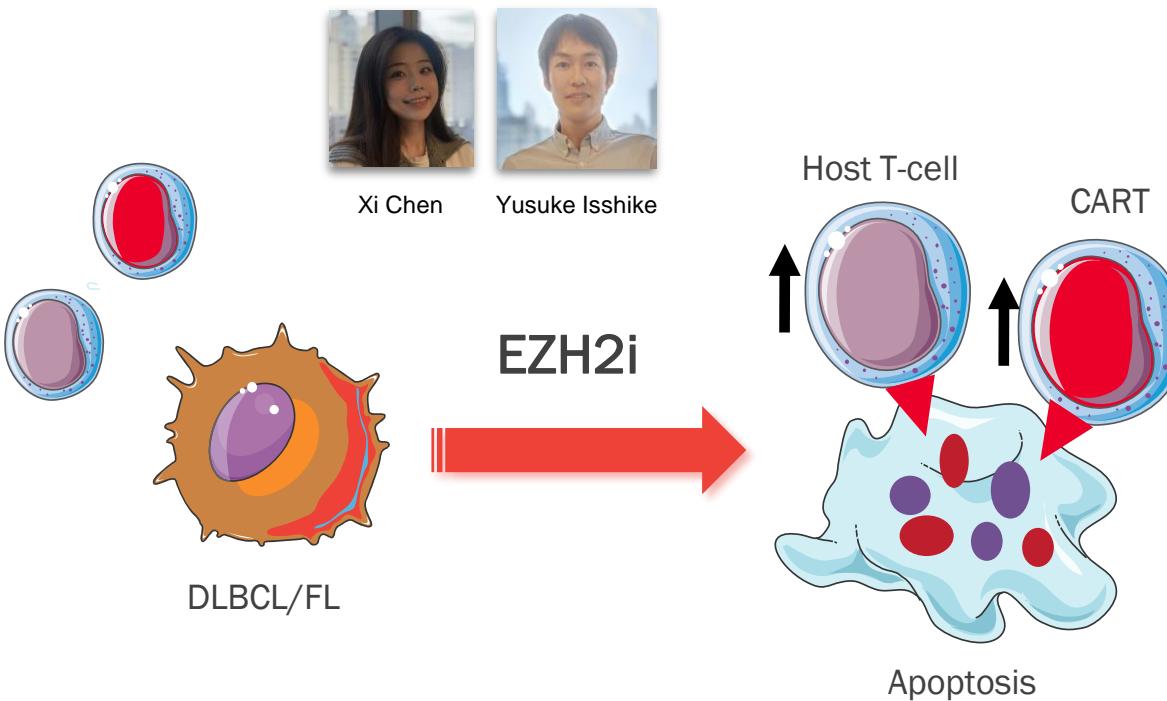
BCL2⁺-MYD88^{L252P} IgM+ ABC-DLBCL-like w plasmacytic differentiation

BCL2⁺-MYD88^{L252P}-CARD11^{L251P} IgM+ ABC-DLBCL

BCL2⁺-MYD88^{L252P}-PRDM1^{-/-} IgM+ ABC-DLBCL

EZH2i enhance DLBCL immunogenicity, reduce Tregs, and enhance efficacy of host T-cells and CAR T-cells

Unpublished data from Yusuke Isshiki, Xi Chen: with **Wendy Beguelin**



Weill Cornell ISTs: TAZ + CART, TAZ + MOSUN

HDAC3i reverse silencing of antigen presentation genes and potentiate checkpoint inhibitor activity in vivo

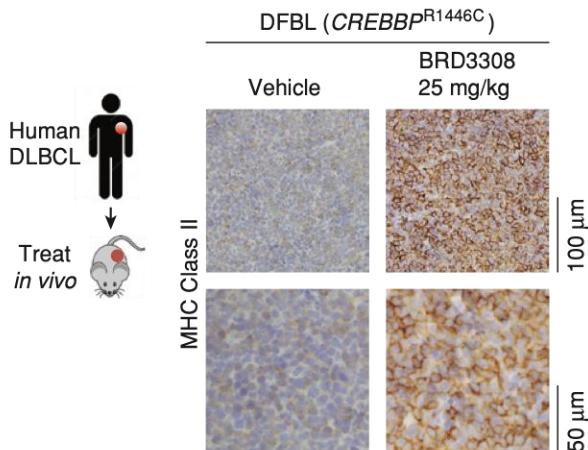
RESEARCH ARTICLE

***CREBBP* Inactivation Promotes the Development of HDAC3-Dependent Lymphomas**

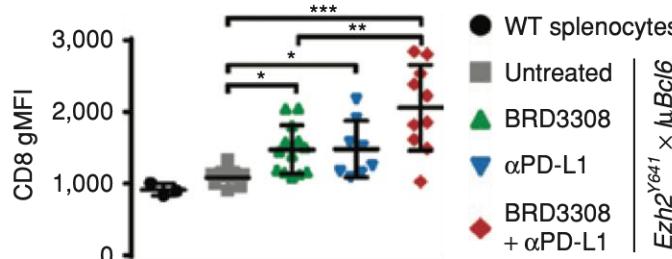
Jiang et al *Cancer Discovery* 2017
Mondello et al, *Cancer Discovery* 2020

RESEARCH ARTICLE

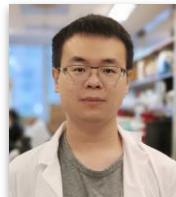
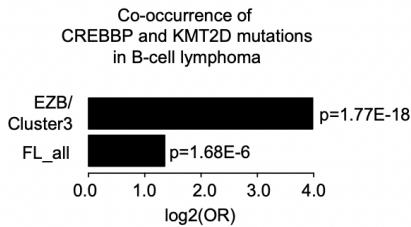
Selective Inhibition of HDAC3 Targets Synthetic Vulnerabilities and Activates Immune Surveillance in Lymphoma



HDAC3i avoid the toxicity of HDACi, and could achieve superior target engagement in vivo



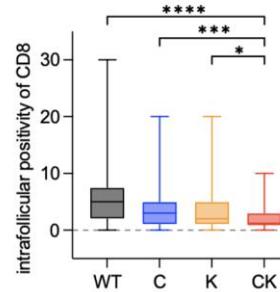
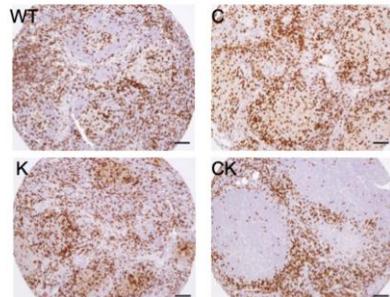
CREBBP+KMT2D double mutant FLs and possibly DLBCLs feature relatively reduced CD8 infiltration



Jie Li, PhD



CD8 IHC of human FL

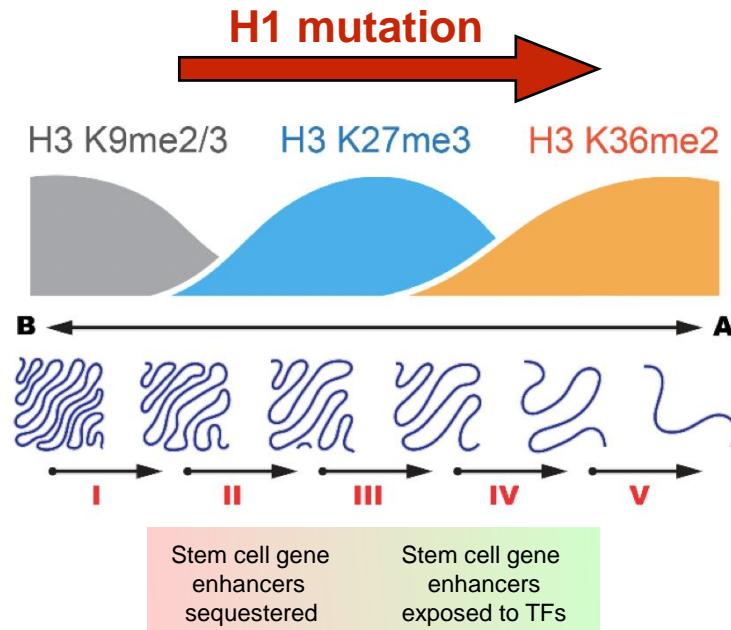


Linker histone 1 mutations may confer stem-like properties through 3D and epigenetic effects

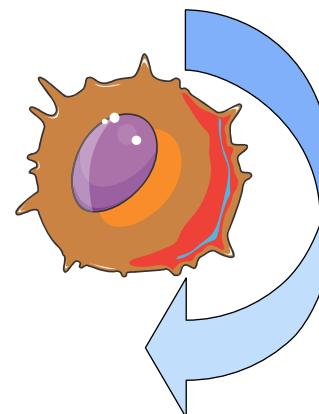
Article

Histone H1 loss drives lymphoma by disrupting 3D chromatin architecture

Yusufova et al Nature 2021



Nevin Yusufova PhD



Self Renewal
Plasticity

SETD2 mutations enhanced mutagenesis and result in highly mutated DLBCLs

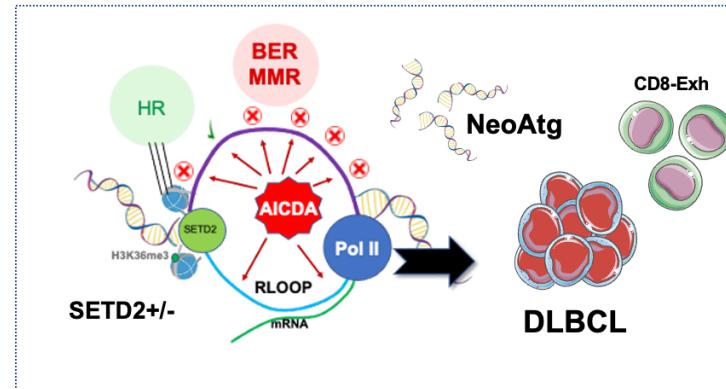
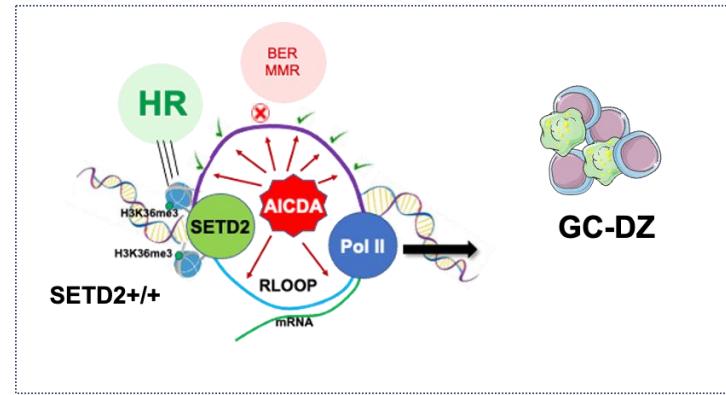
Leung et al, Cancer Discovery 2022

RESEARCH ARTICLE

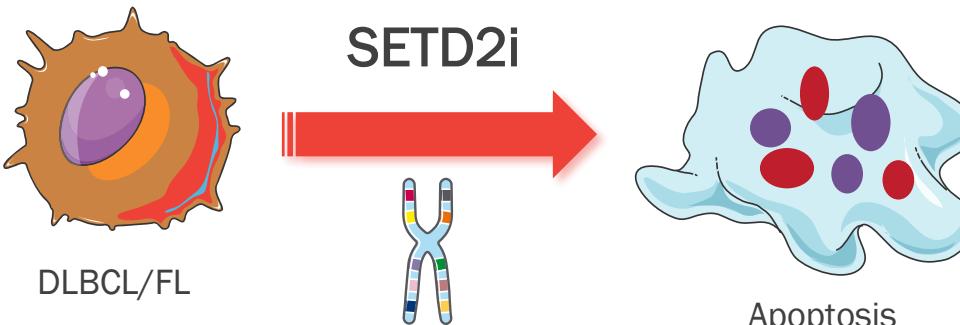
SETD2 Haploinsufficiency Enhances Germinal Center-Associated AICDA Somatic Hypermutation to Drive B-cell Lymphomagenesis



Wilfred Leung DVM PhD

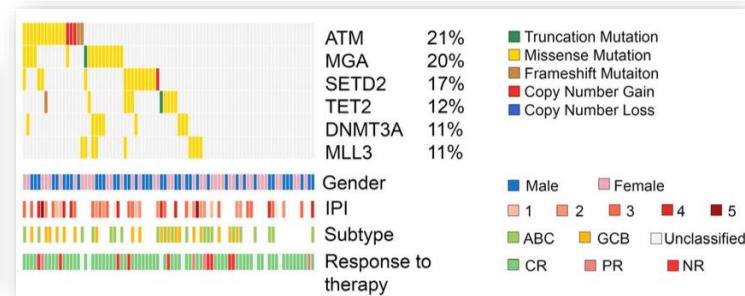


SETD2 mutations are more common in African ancestry patients, with potential for response to SETD2i



First in man:
NCT05121103

Sanket Shah, unpublished



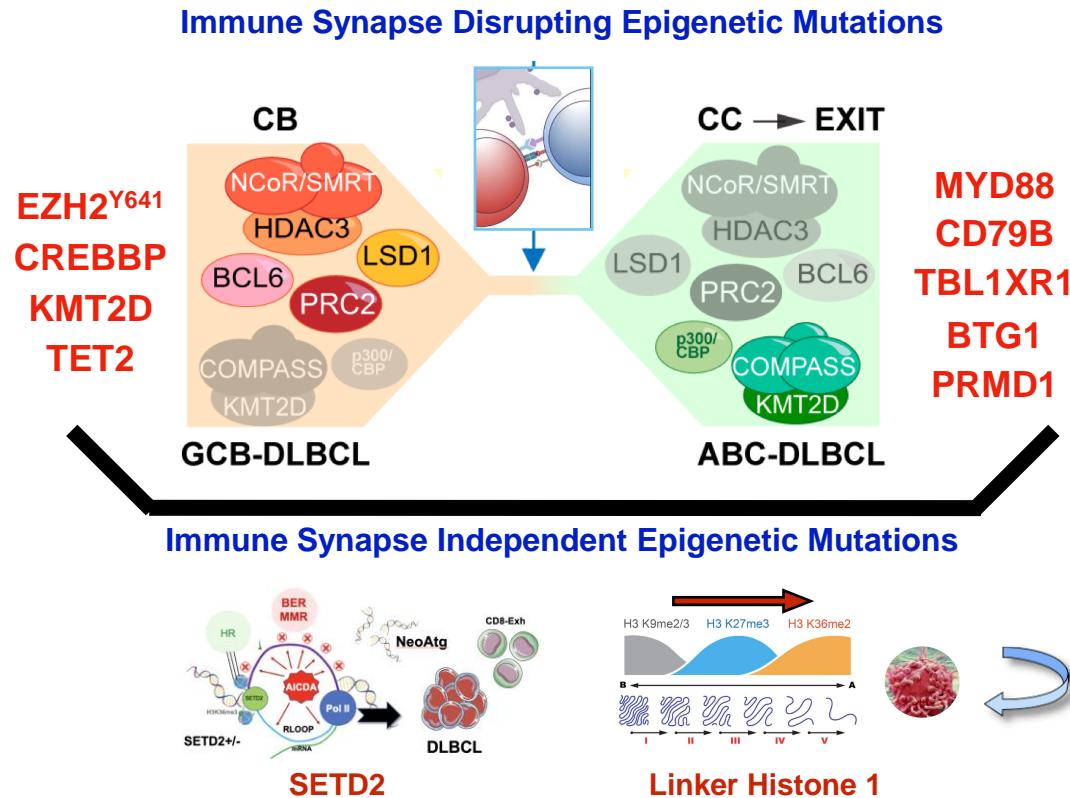


HEALTH DISPARITIES IN HEMATOLOGIC MALIGNANCIES: FROM GENES TO OUTREACH

MAY 12-13, 2023

WEILL CORNELL MEDICINE
BELFER RESEARCH BUILDING, NEW YORK CITY

Three Classes of Epigenetic Drivers in B-cell Lymphomas





Still many pieces to assemble, but getting closer

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Cem Meydan



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Rockefeller

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UF

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Michael Meyer-Hermann

INSERM

Karin Tarte
Michel Cogne
Phillip Gaudard
Francois Lemonier

U Toronto

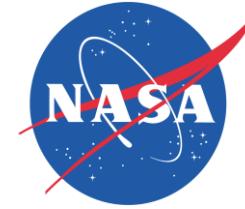
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Falk Foundation

Lymphoma Research Foundation

Starr Cancer Consortium



Chemotherapy Foundation



Sam Waxman Cancer Research Fdtn



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