Epigenetic Basis and Therapies for Follicular Lymphomas

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Disclosures

Research Funding: Janssen, Epizyme, Daiichi Sankyo

Consulting: BMS, Epizyme, Jubilant, Exo-Therapeutics, Astra Zeneca, KDAC, Treeline

Summary

Epigenetic Dysregulation is a Hallmark of Follicular Lymphoma

Epigenetic mutations in FL primarily mediate their effects by reprogramming immune microenvironment and signaling

Epigenetic mutations are not redundant and may have surprising ways of cooperating

Epigenetic precision therapy could serve as critical “adjuvant” precision treatments to immunotherapy approaches

A modern classification of FL may require a combination of genetic and microenvironment studies

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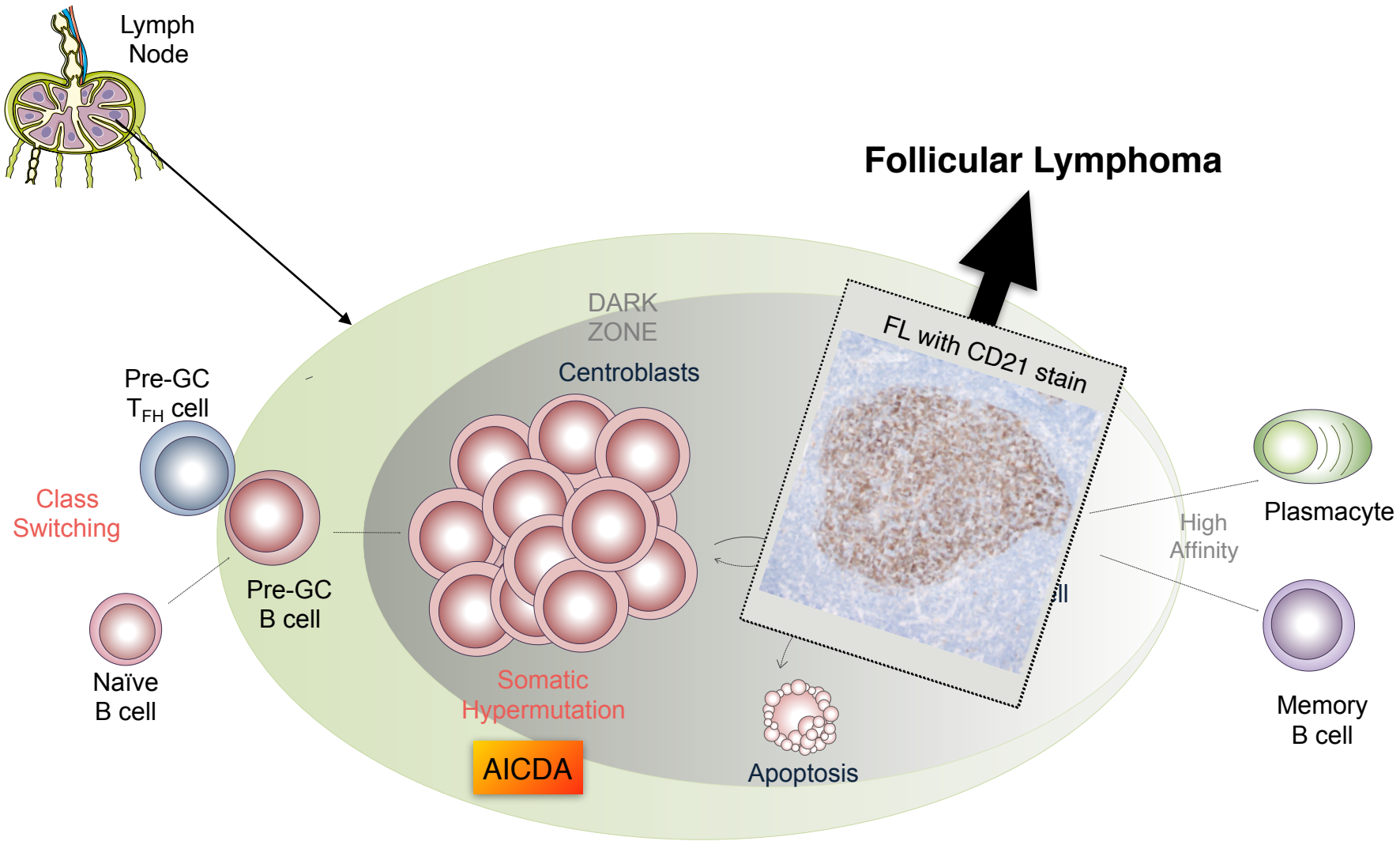
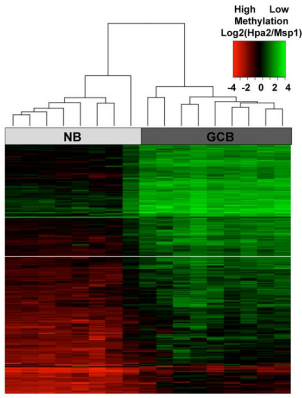
FLs arise from germinal centers and generally reflect light zone immune microenvironment



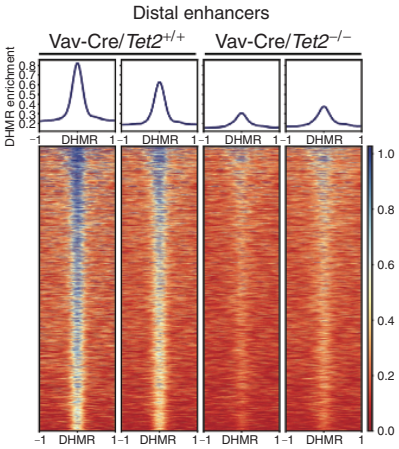
Adapted from Hatzi and Melnick, Trends in Molecular Medicine, 2014

GC B cell immune synapse induces profound epigenetic and 3D architectural reprogramming

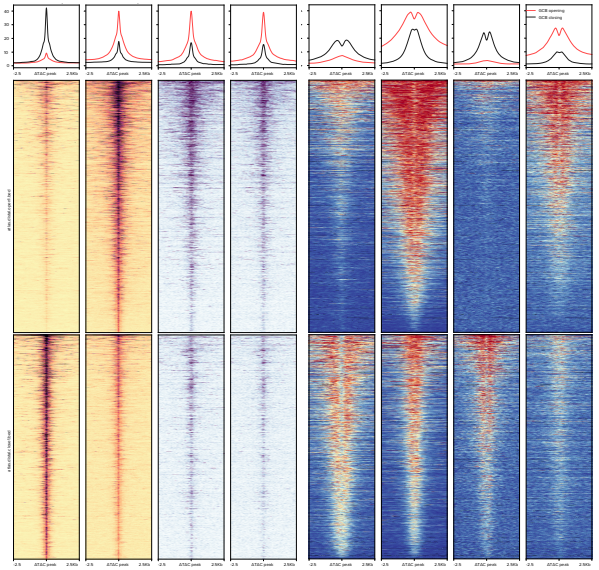
Cytosine Methylation



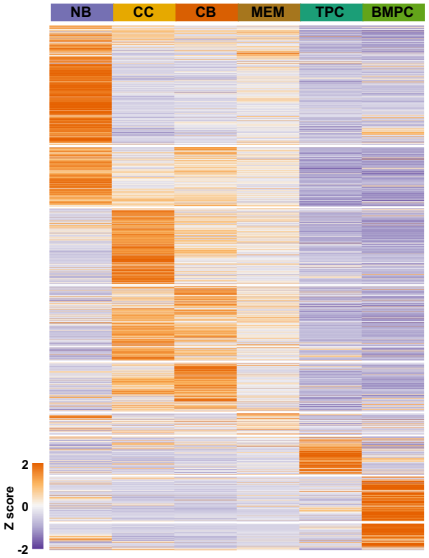
5'hydroxmethylcytosine



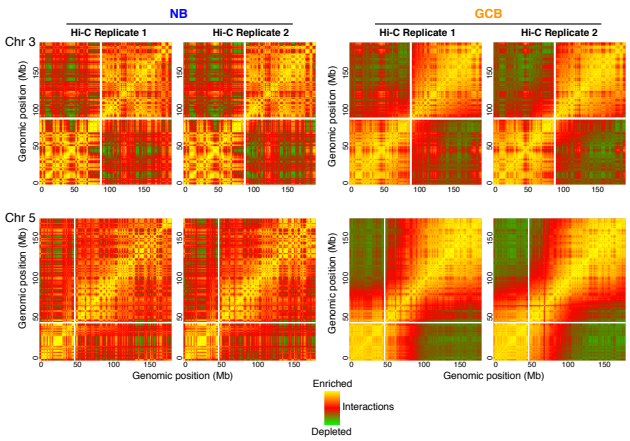
Histone Marks



Non-coding transcriptome



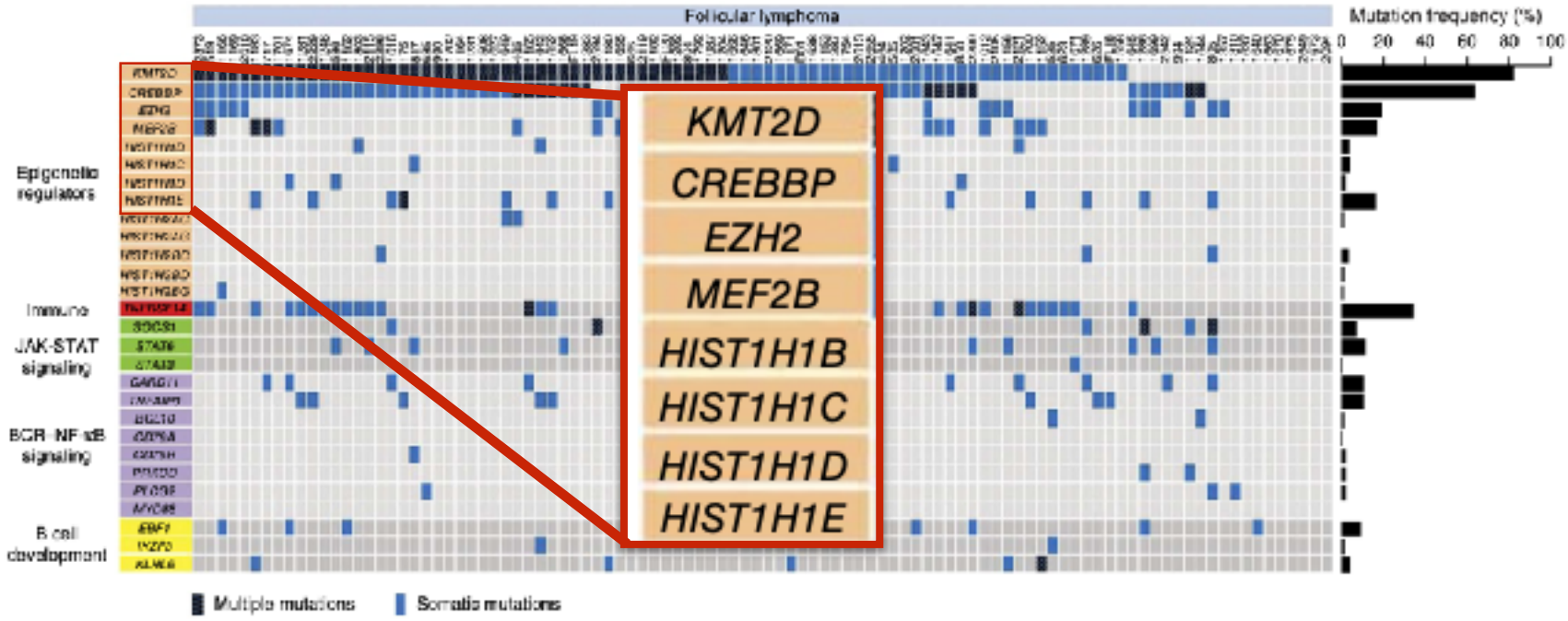
HiC/Hi-ChIP Nuclear Architecture



Shaknovich et.al. Blood 2010
Velichutina et.al. Blood 2010
Shaknovich et al Blood 2011
De et.al. PLOS Genetics 2013
Clozel et.al. Cancer Discovery 2013
Hatzi et al Cell Reports 2013
Béguelin et.al. Cancer Cell 2013
Chambwe et.al. Blood 2014
Ortega et.al. Nature Medicine 2015
Dominguez et.al. Cell Reports 2015
Bunting et.al. Immunity 2016
Béguelin et.al. Cancer Cell 2016
Jiang et.al. Cancer Discovery 2017
Béguelin et.al. Nature Communications 2018
Teater et.al. Nature Communications 2018
Dominguez et.al. Cancer Discovery 2018
Aguirre et.al. Nature Communications 2019
Hatzi et.al. Nature Immunology 2019
Mondello et.al. Cancer Discovery 2020
Rosikiewicz et.al. Science Advances 2020
Béguelin et.al. Cell 2020
Chu et.al. Molecular Cell 2020
Yusufova et.al. Nature 2021
Rivas et.al. Nature Immunology 2021
Rivas et al Frontiers Immunology 2021
Doane et al Nature Immunology, 2021
Leung et al Cancer Discovery 2022

Epigenetic mutations are the dominant hallmark of FLs

Okosun et al, Nature Genetics 2014



Disruption of immune synapse (GC-exit) induced epigenetic effects is a universal feature in FL

Velichutina et al Blood 2010
Cerchietti et al J Clin Investigation 2010
Beguelin et al Cancer Cell 2013
Huang et al Nature Immunology 2013
Hatzi 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
Hatzi et al - Nature Immunology 2019
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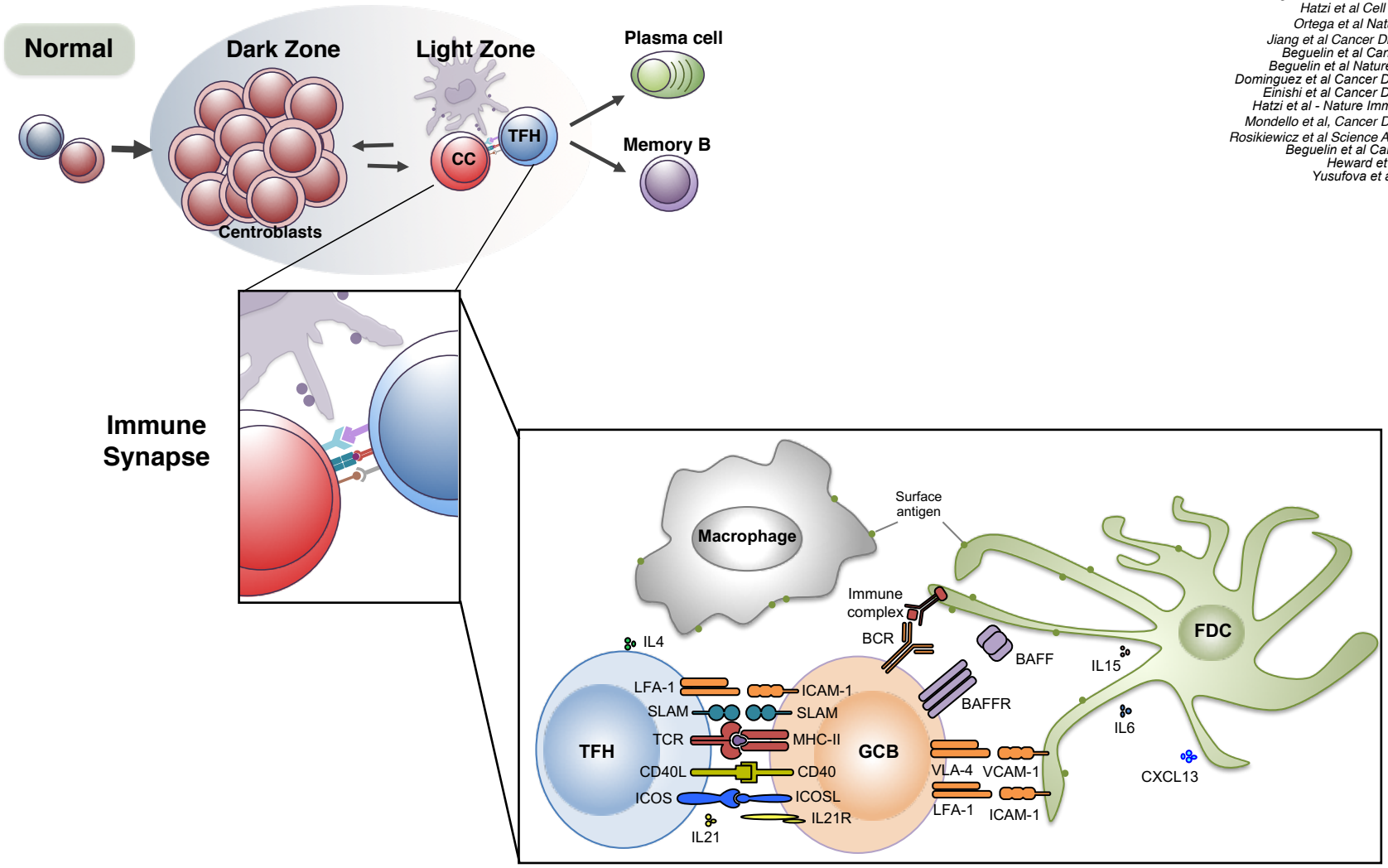
Rosikiewicz et al Science Advances 2020
Beguelin et al Cancer Cell 2020
Heward et al Blood 2021
Yusufova et al Nature 2021



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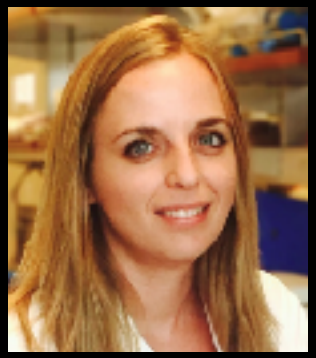
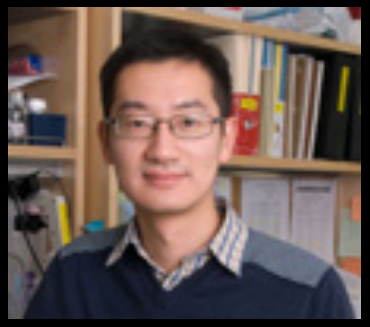


Katerina Hatzi PhD

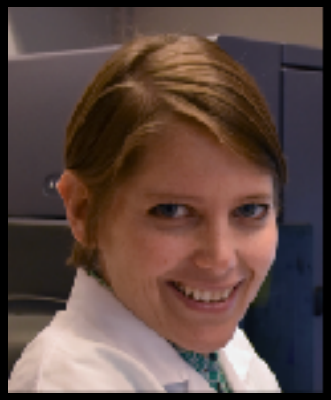
Isaac Boss PhD



Yanwen Jiang PhD

Patrizia Mondello MD PhD

Matt Teater PhD



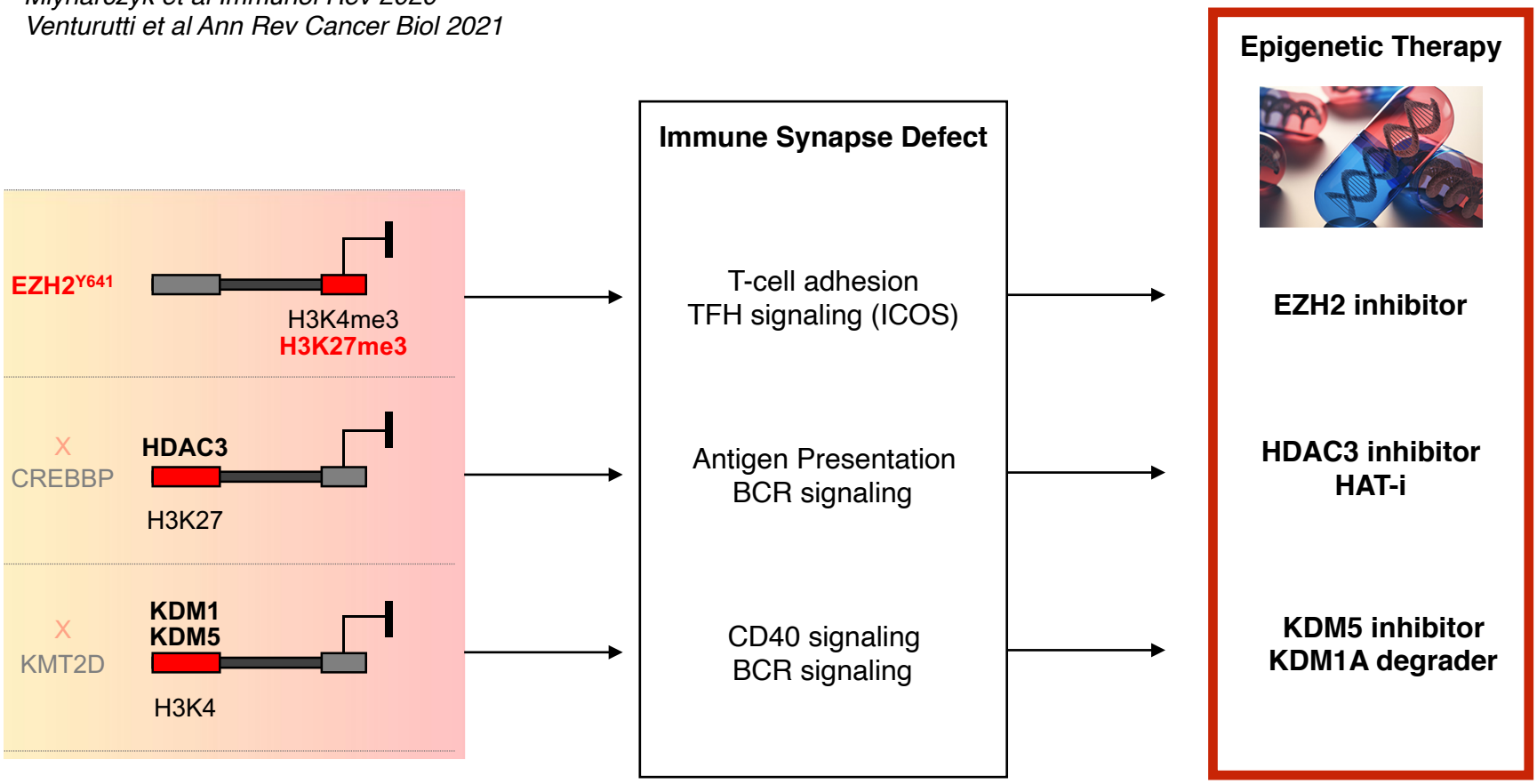
Wendy Beguelin PhD

Pilar Dominguez PhD

Nevin Yusufova PhD

Epigenetic mutations confer specific therapeutic vulnerabilities

Mlynarczyk et al Immunol Rev 2020
Venturutti et al Ann Rev Cancer Biol 2021



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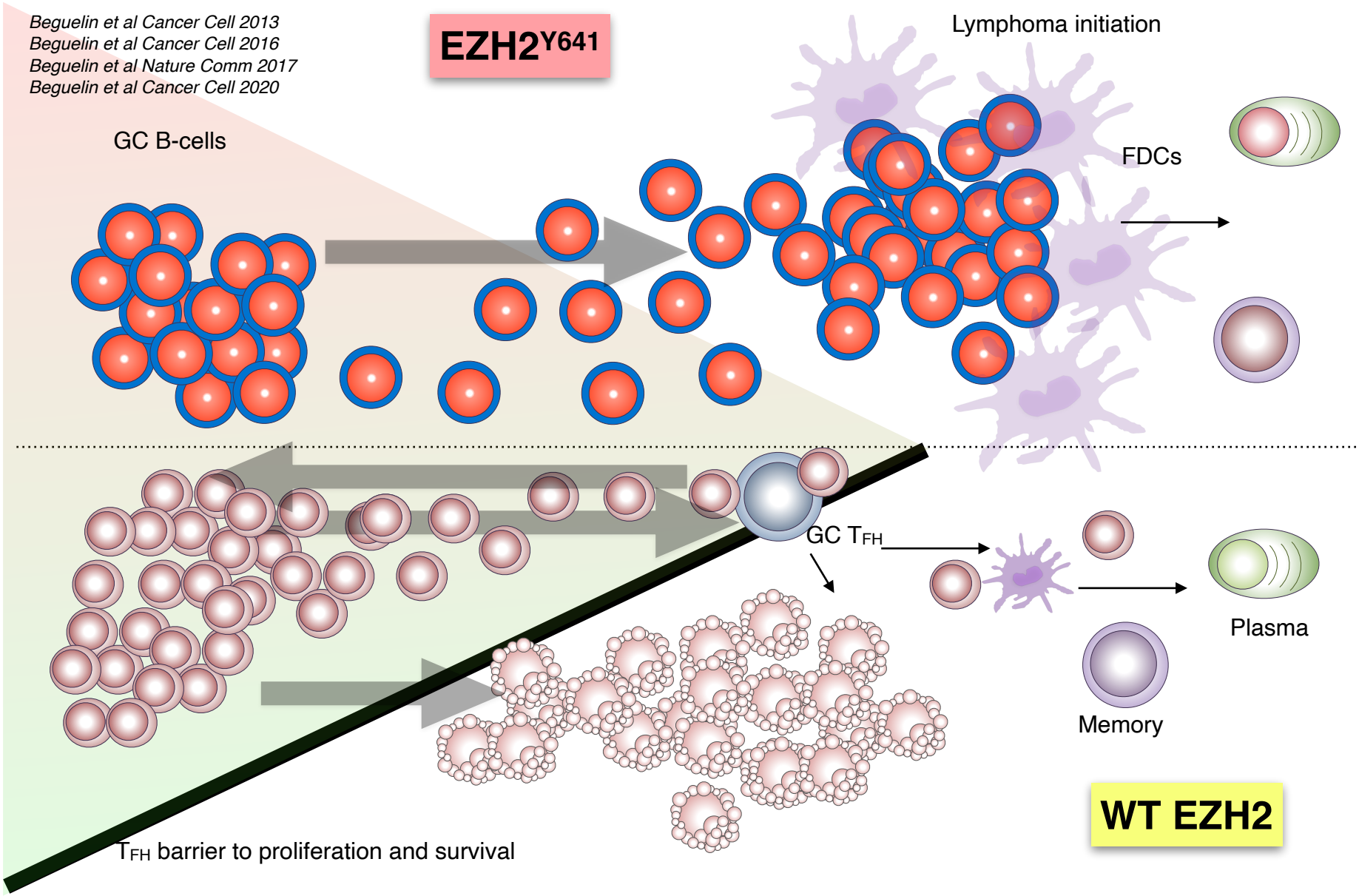
Mondello et al, Cancer Discovery 2020
Rosikiewicz et al Science Advances 2020
Beguelin et al Cancer Cell 2020
Heward et al Blood 2021

Zhang et al Nature Med 2015
Zhang et al Cancer Discover 2017
Garcia Ramirez Blood 2017
Hashwah et al PNAS 2017
Mewer et al Immunity 2019

EZH2 mutations reprogram the light zone immune niche to initiate lymphomagenesis



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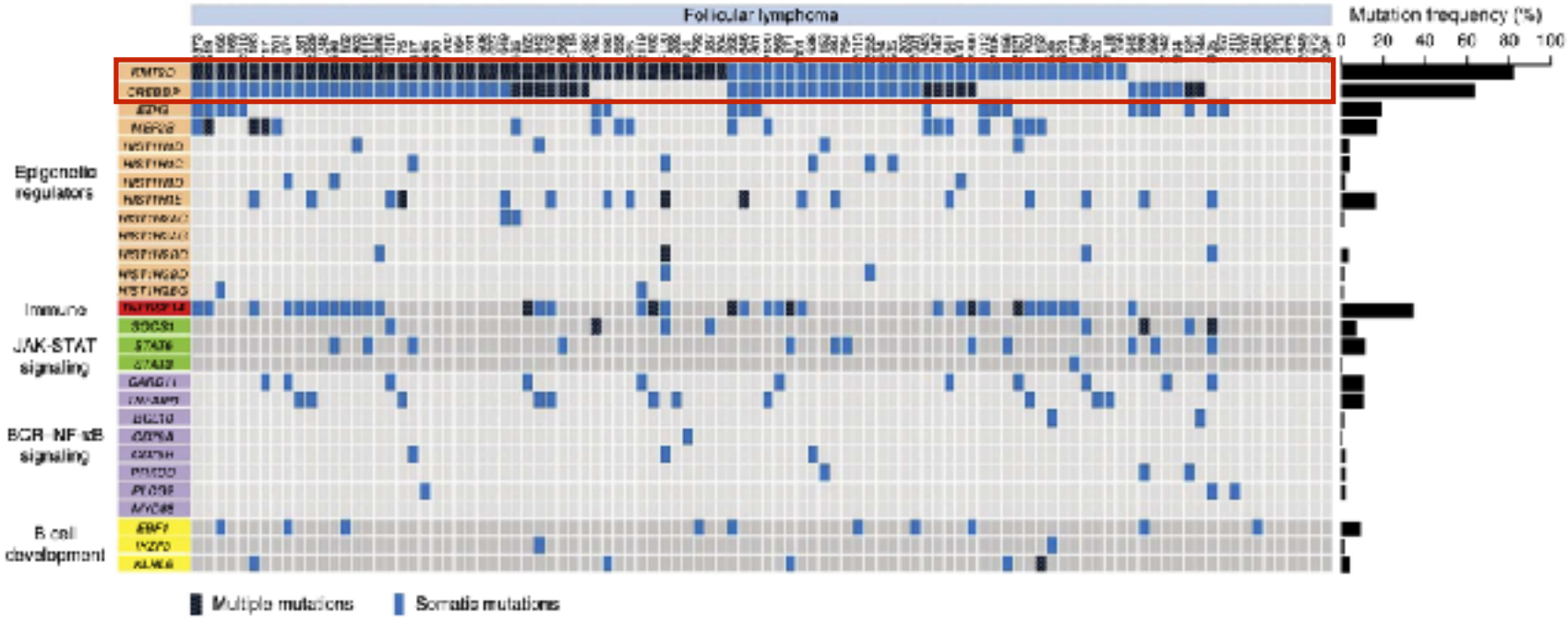
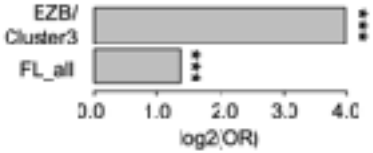
Somatic mutations of KMT2D and CREBBP are highly co-occurrent in FL and GCB-DLBCL

Okosun et al, Nature Genetics 2014

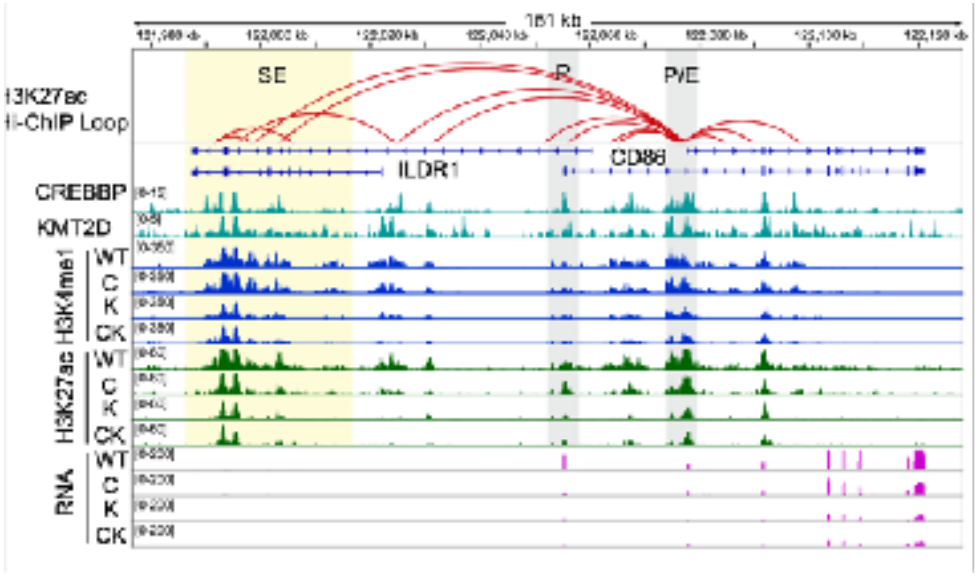


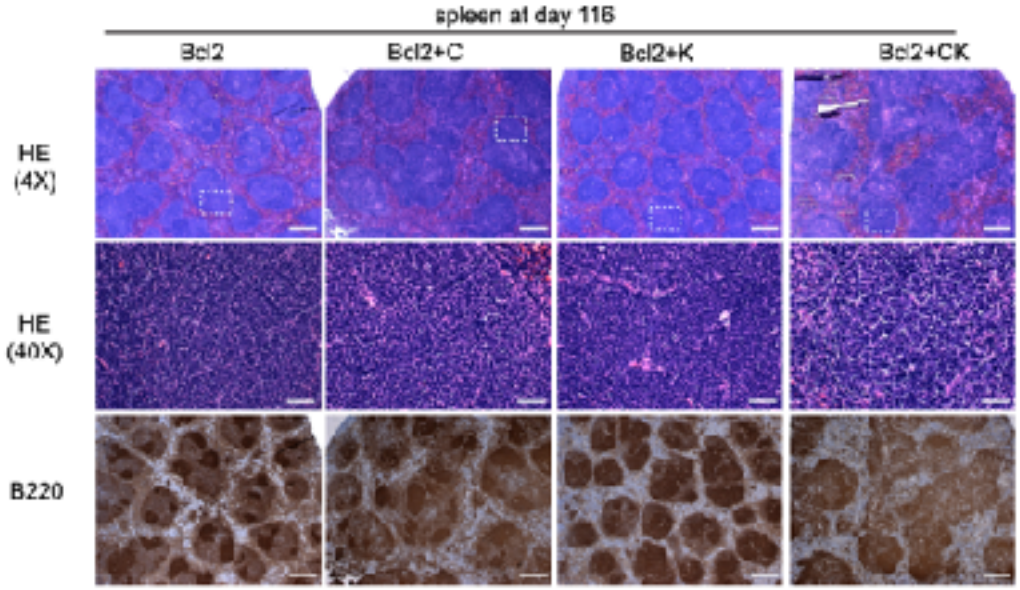


Highly significant co-occurrence in FL and GCB-DLBCL

GC B cell immune synapse leads to profound epigenetic and 3D architectural reprogramming

Chin, Li and Yang, unpublished





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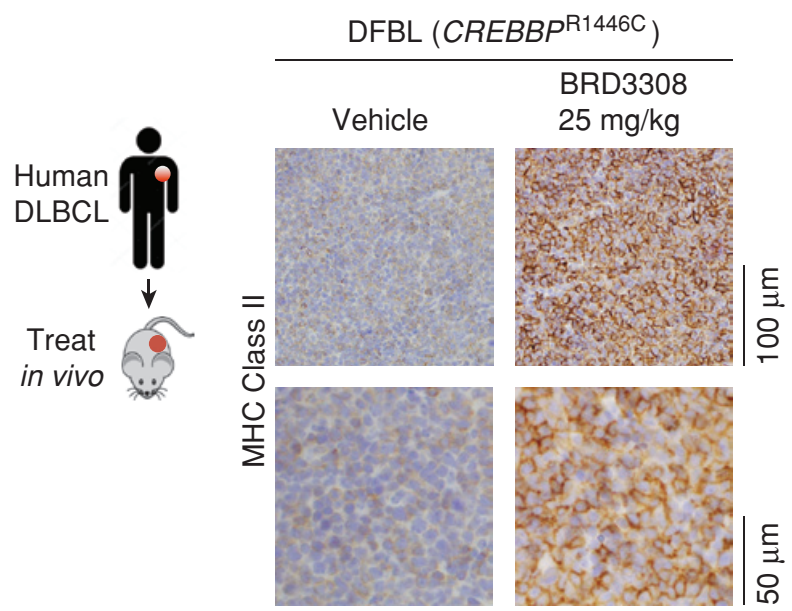
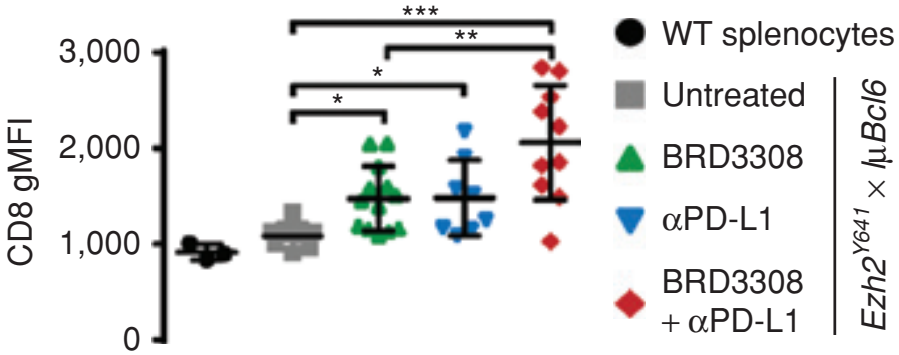
HDAC3i reverse silencing of MHC II and potentiate checkpoint inhibitor activity in vivo

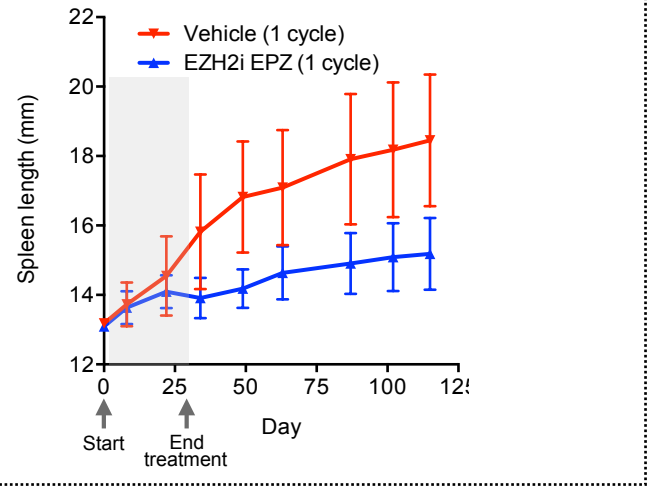
Jiang et al Cancer Discovery 2017
Mondello et al, Cancer Discovery 2020

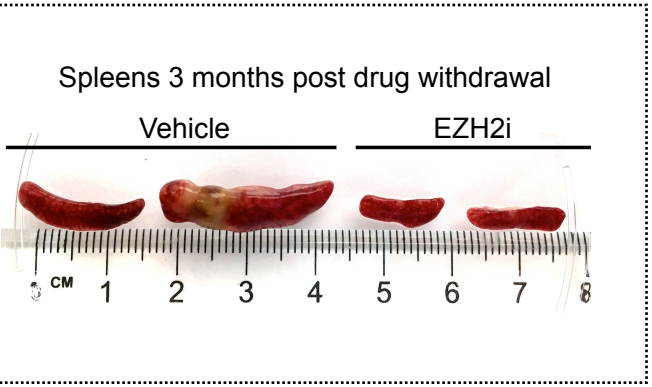


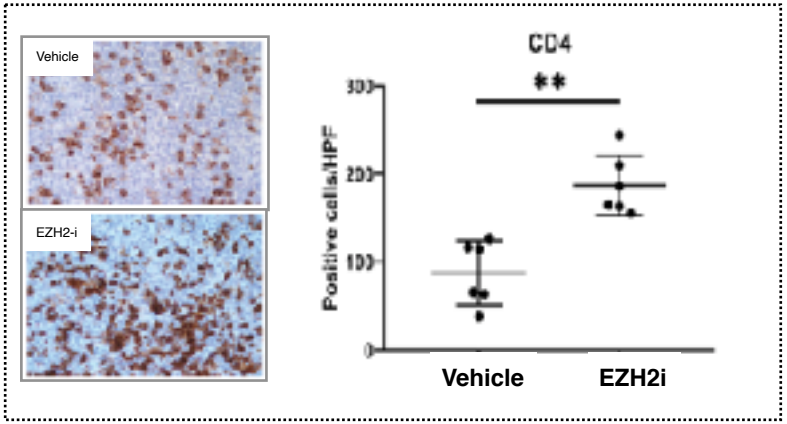


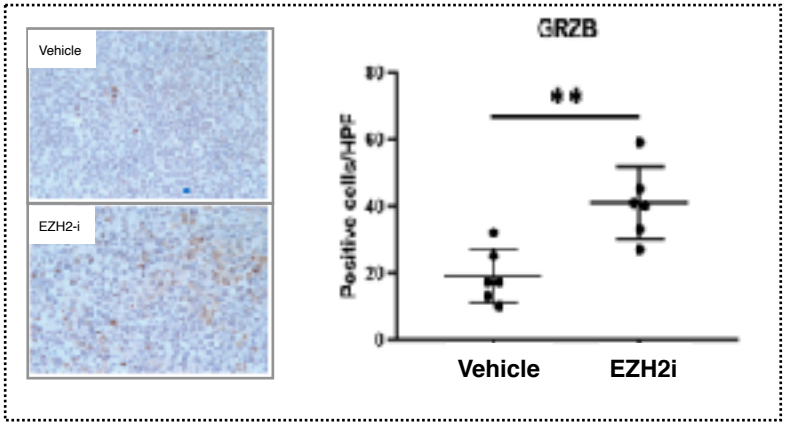
EZH2-i induce prolonged anti-lymphoma effect and immune reactivation

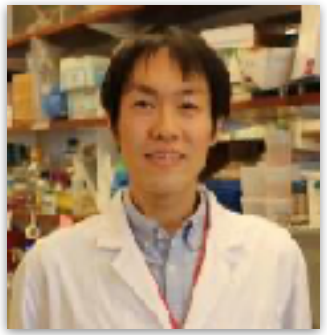
Takata et al, J Clin Invest 2022







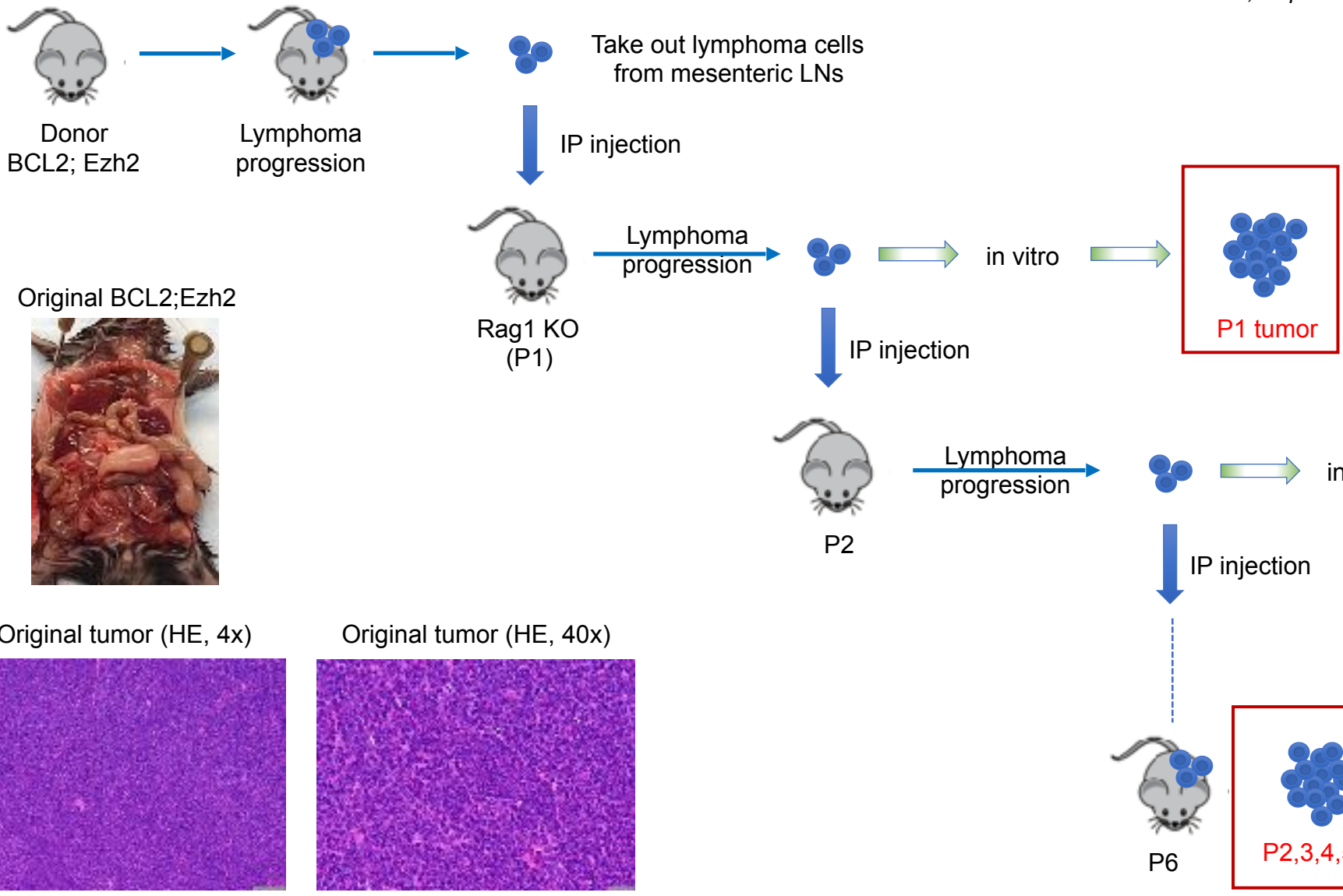




Yusuke Isshiki MD PhD

Development of the first FL cell line, and first model for syngeneic experimental therapeutic studies for FL

Yusuke Isshiki, Unpublished



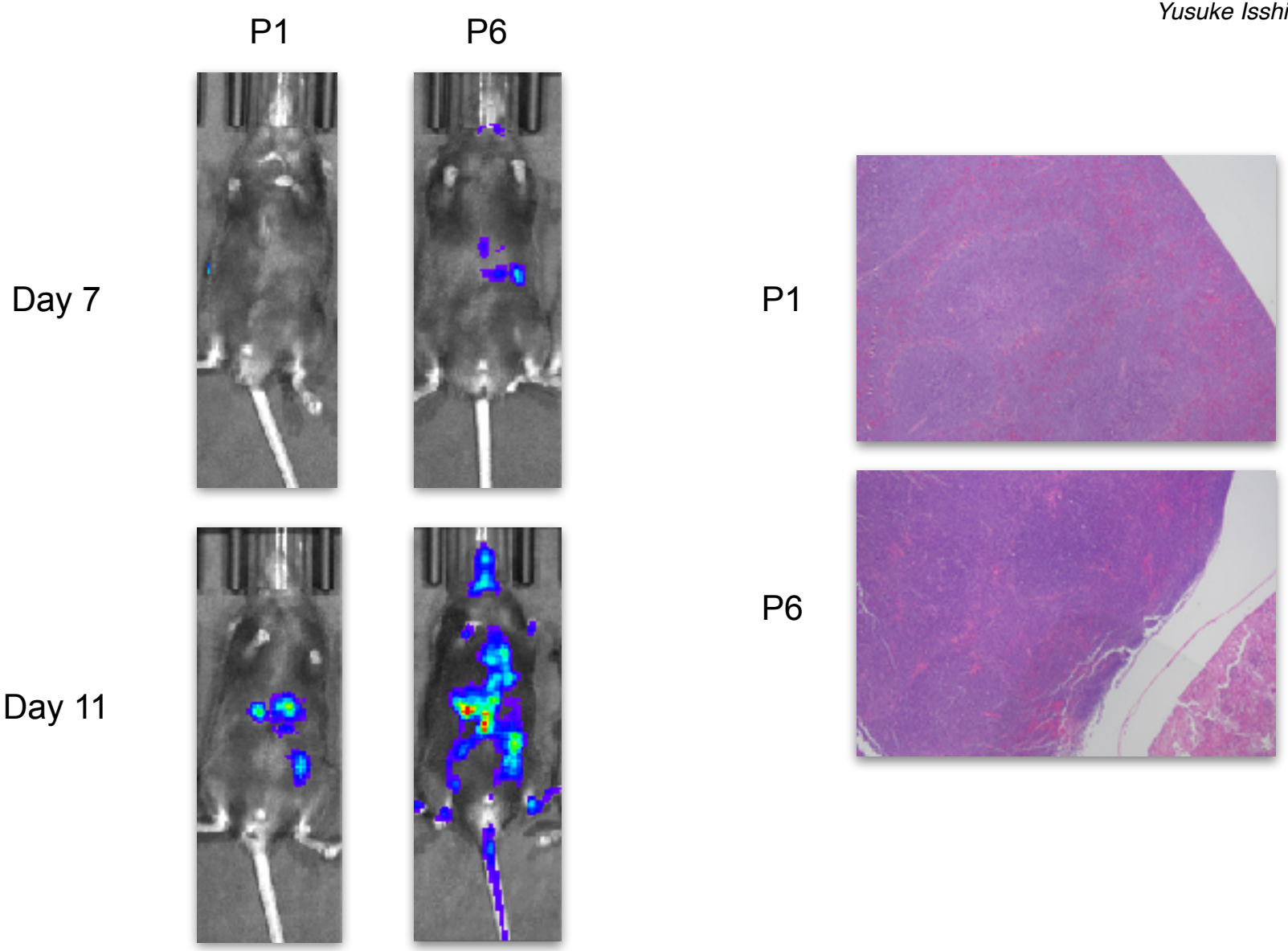
Original BCL2;Ezh2

Original tumor (HE, 4x)

Original tumor (HE, 40x)

FL cell lines establish FLs in syngeneic mice

Yusuke Isshiki, Unpublished



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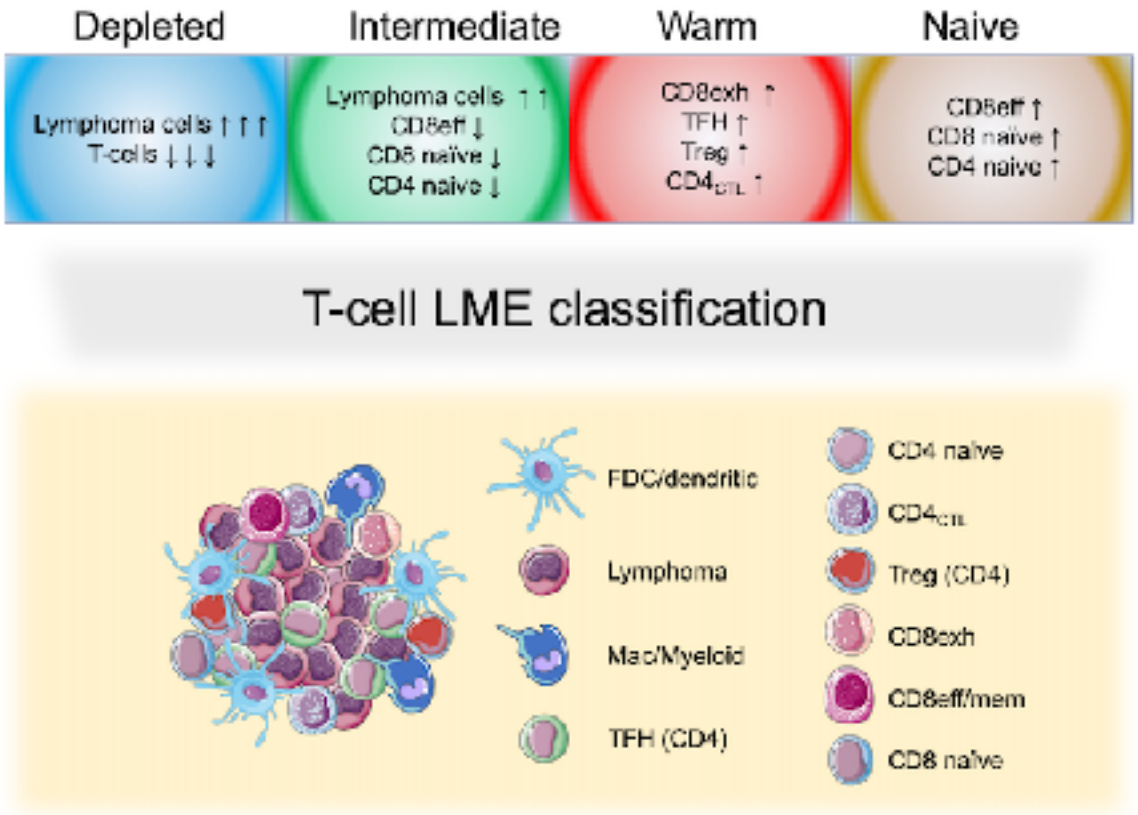
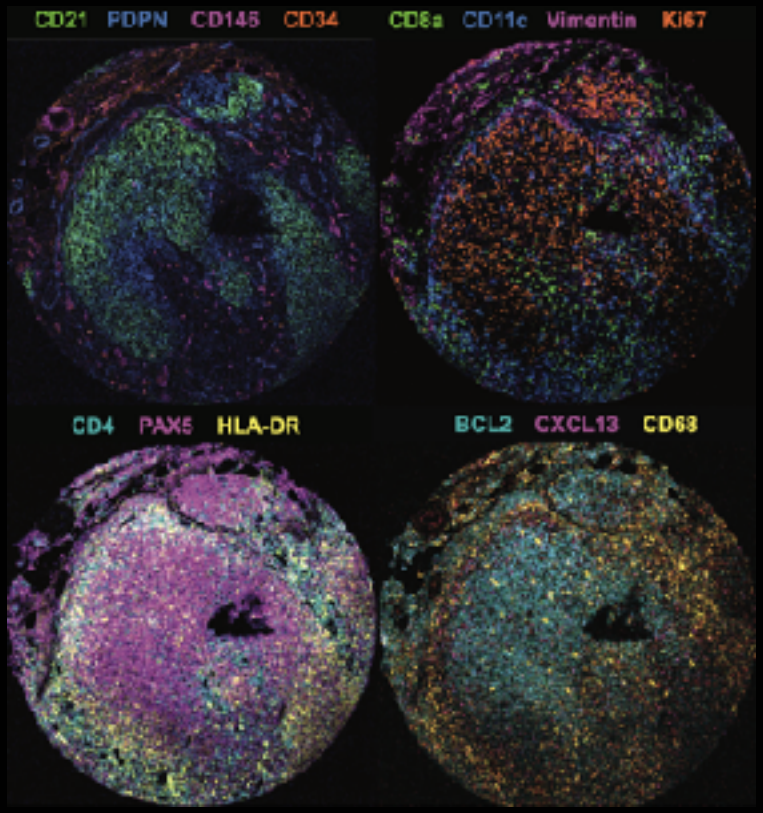
Potential for immune-ME to sub-classify FLs

A Melnick, Blood Cancer Discovery - based on data published by from ***Han et al, Blood Cancer Discovery 2022***



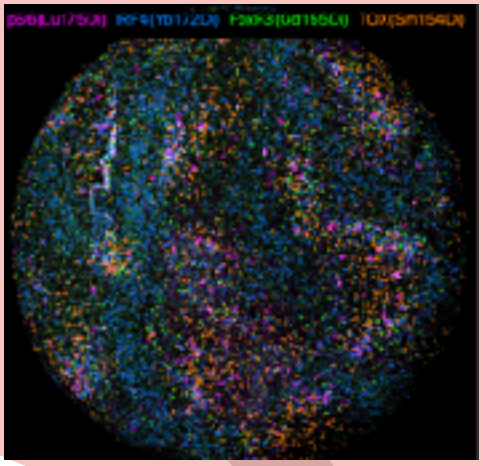
Hyperion Imaging Mass Cytometry, 68 antibodies - staining in one FL patient



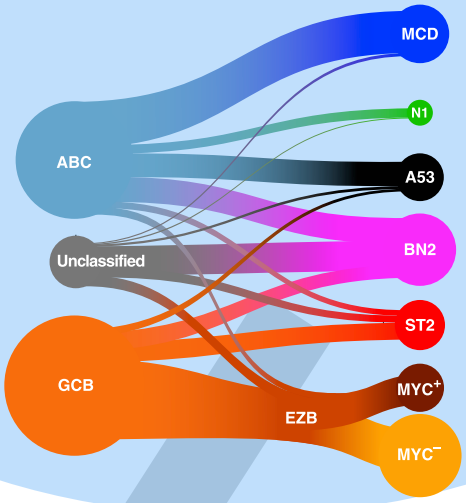
Dylan McNally, unpublished data

A possible future for precision diagnostics and therapy in FL

Microenvironment



Genetic features



Precision LME analysis

Targeted Panels

Precision diagnosis
Epigenetic immune adjuvant therapy

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Acknowledgements

Collaborators

WCM
Roberta Zapposodi
Leandro Cerchietti
Effie Apostolou
Marcin Imilienski
Olivier Elemento
Chris Mason
George Kalishvili
Lisa Roth
Ethel Cesarman
Giorgio Inghirami
John Leonard
Peter Martin
Steven Josefewicz
Samie Jaffrey

MSKCC
Ross Levine
Mike Kharas
Guido Wendel
Omar Abdel-Wahab
Yael David
Ahmet Dogan

BCCA
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Andy Weng
Ryan Morin

Rockefeller
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UF
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Northwestern U
Ali Shilatifard
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Einstein
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Yale
Ann Haberman
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Mark Shlomchik

Erasmus
Ruud Delwel
Bob Lowenberg
Bas Wouters
Peter Valk

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Izidore Lossos
Rhamin Shiekettar

MDACC
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NYU
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Tamar Schlick
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Iannis Aifantis
Aris Tsirigos
Chris Park

Princeton
Shawn Davidson

HZI
Michael Meyer-Hermann

INSERM
Karin Tarte
Michel Cogne
Phillip Gaudard
Francois Lemonier

U Toronto
Gil Prive
Tak Mak

PeterMac
Ricky Johnstone

Funding

National Cancer Institute

NASA

Leukemia and Lymphoma Society

Falk Foundation

Lymphoma Research Foundation

Starr Cancer Consortium

Chemotherapy Foundation

Sam Waxman Cancer Research Fdtn

Janssen Pharmaceuticals