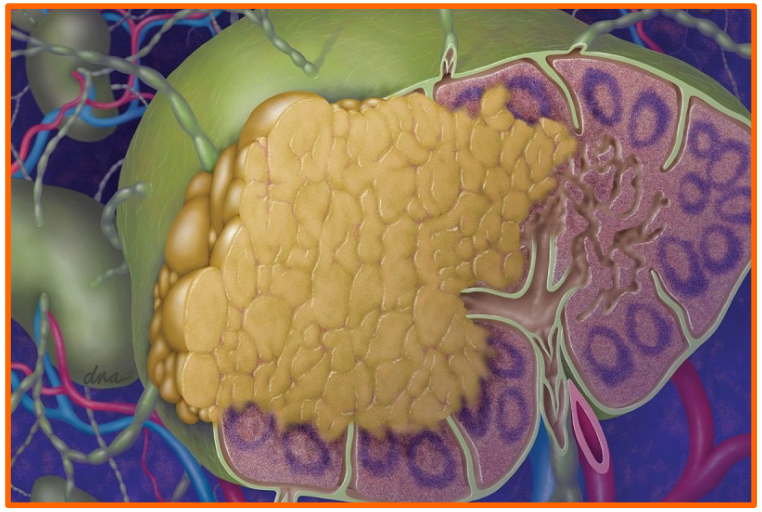
Molecular Pathways in Follicular Lymphoma

Hans-Guido Wendel

Cancer Biology & Genetics Program

Memorial Sloan Kettering Cancer Center

Follicular Lymphoma



Common and incurable

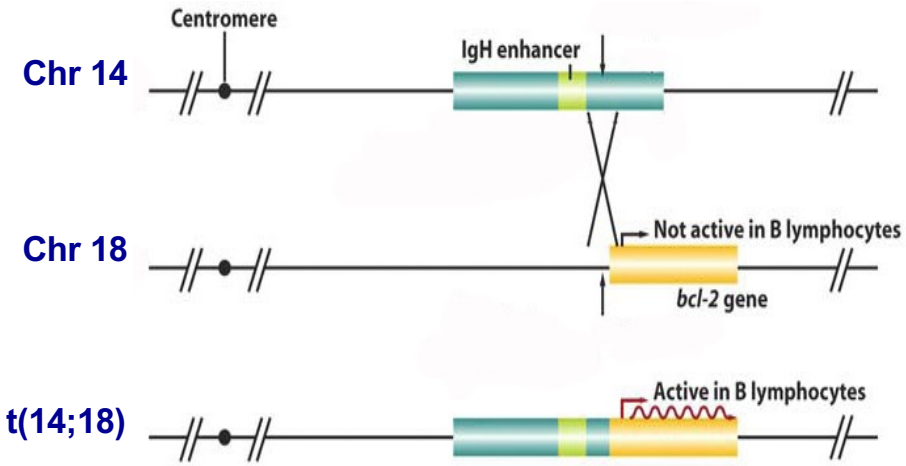
Follicular appearance

Relentless relapses

Eventual transformation into aggressive disease.

The goal is that Insights into molecular mechanisms will lead to rational therapies

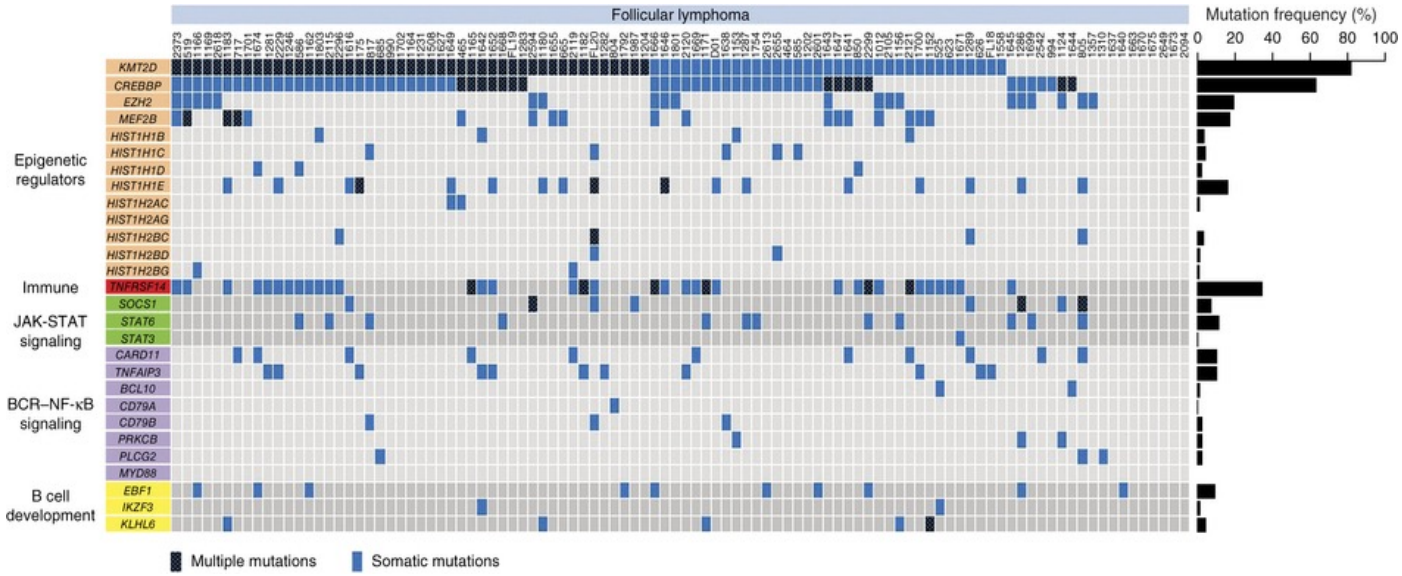
The translocation t(14;18) is the genetic hallmark of FL



- T(14;18) activates expression of BCL2
- Present in >90% of FL
- Likely the initiating lesion
- Detected in 30% of healthy individuals
- BCL2 blocks apoptosis but also delays cell proliferation
- BCL2 inhibition is not very active in FL

These findings imply cooperating genetic lesions and they highlight the lack of BCL2 dependence as a clinical problem

Several groups have catalogued somatic mutations in FL

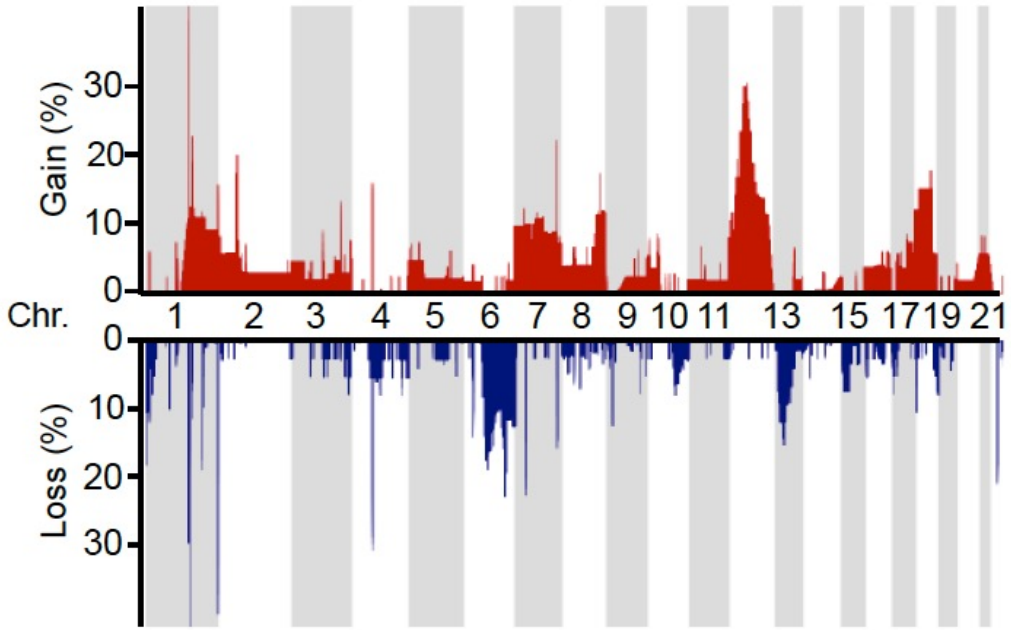


Frequent lesions in
Epigenetic factors: KMT2D, CREBBP/EP300, SETD1B

Immune receptors: TNFRSF14, beta-2 Microglobulin

On the other hand, genome integrity checkpoints (TP53, RB) are not frequently mutated in early FL and are linked to progression.

Chromosomal lesions in FL reveal hotspots and genetic relationships

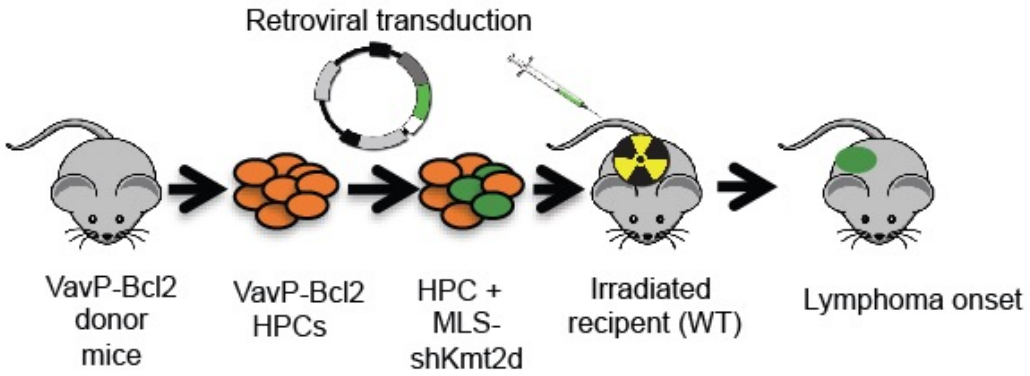


Del 1p36 (>20%) – TNFRSF14 (HVEM) – often mutation of 2nd allele

Del 6q (~15%) – EphA7, TNFAIP/A20, FOXO3, SESTRIN1 are 6q tumor suppressors

Gain 12q14 (>20%) -*mutual exclusive* with loss of RB and ARF/p16, CCND3 mutation
- CDK4, HDM2, SHMT2 are oncogenes at Chr12q14

Interpreting the genetic evidence using a mouse lymphoma model



Origin ✓

Genetics ✓

Pathology ✓

MIcroenvironment: Oricchio et al., CELL 2011 and Boice et al., CELL 2016

RNA translation: Wolfe, Nature 2014, Singh, JEM2019, Sci Transl. med. 2017

Epigenetics: Ortega et al., Nat. medicine 2015; Cancer Disc. 2017

Progression: Oricchio et al. JEM 2011, Schatz, JEM 2012;

MicroRNAs: Mavrakis et al., Nat Cell Bio 2011, Nat. Genet. 2012

Metabolism: S. Parsa et al., Nat Cancer 2020

Aneuploidy: A. Cadete, Nat. com. 2023

Transcription: V Sanghvi et al., Cell 2019

Johann Cruyff (famous philosopher / soccer player):

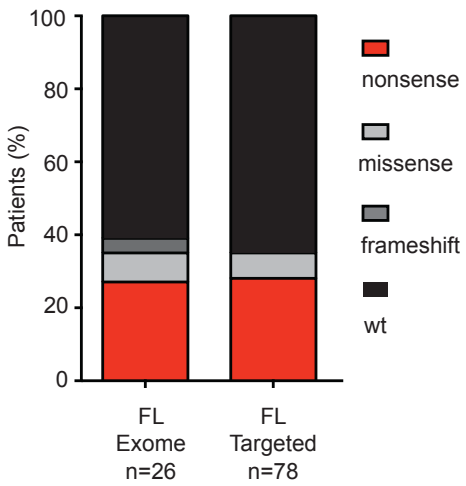
"***Every advantage has a disadvantage***"

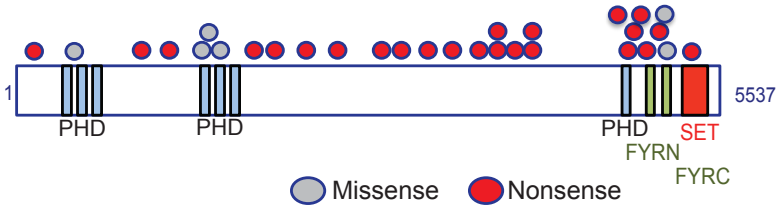
What is the *biological cost* of lymphomagenesis?

1. Epigenetic drivers of lymphomagenesis

Ana Ortega, Ana Cadete, H. Guido Wendel
Memorial Sloan-Kettering

KMT2D is a H3K4$^{me1/me2}$ histone methyl transferase and the most frequently mutated gene in FL

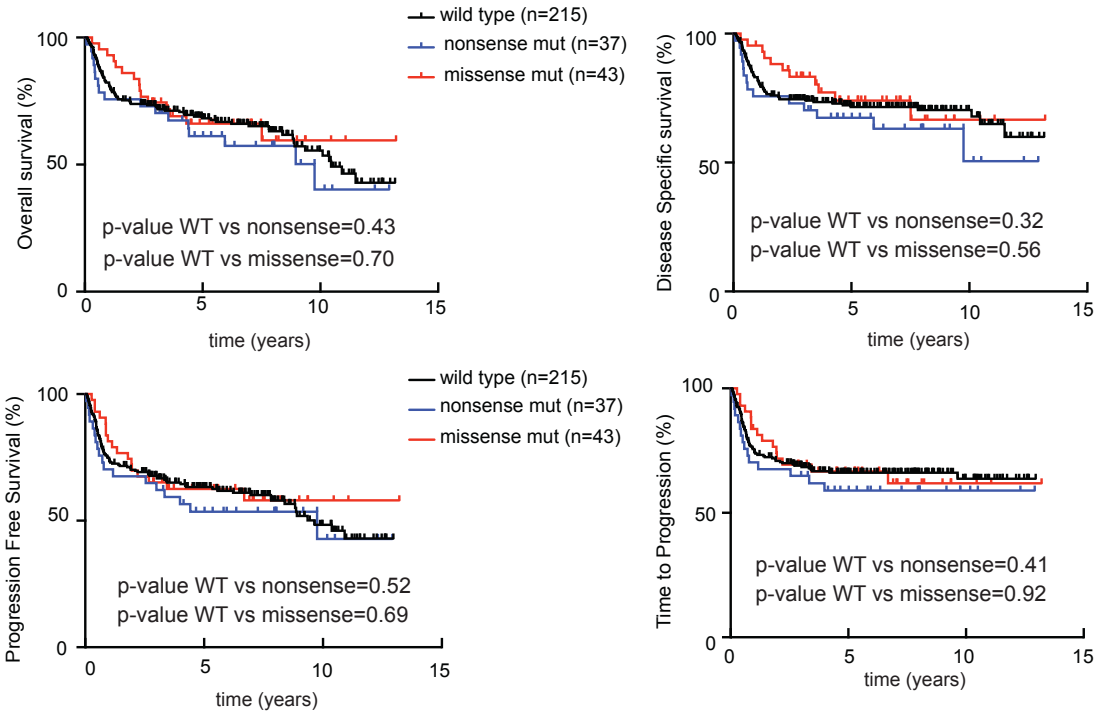




The mutation pattern suggests loss of KMT2D function

KMT2D lesions are not linked to grade or outcomes

KMT2D mutation	Grade				p-value		
	I	II	III	total	I vs II	I vs III	II vs III
wt	16	29	17	62			
nonsense	5	16	8	29	0.15	0.22	0.20
missense	5	0	1	6	0.01	0.11	0.38
frameshift	1	0	0	1	0.37	0.50	1.00
total	11	16	9	36	**0.18**	**0.20**	**0.20**



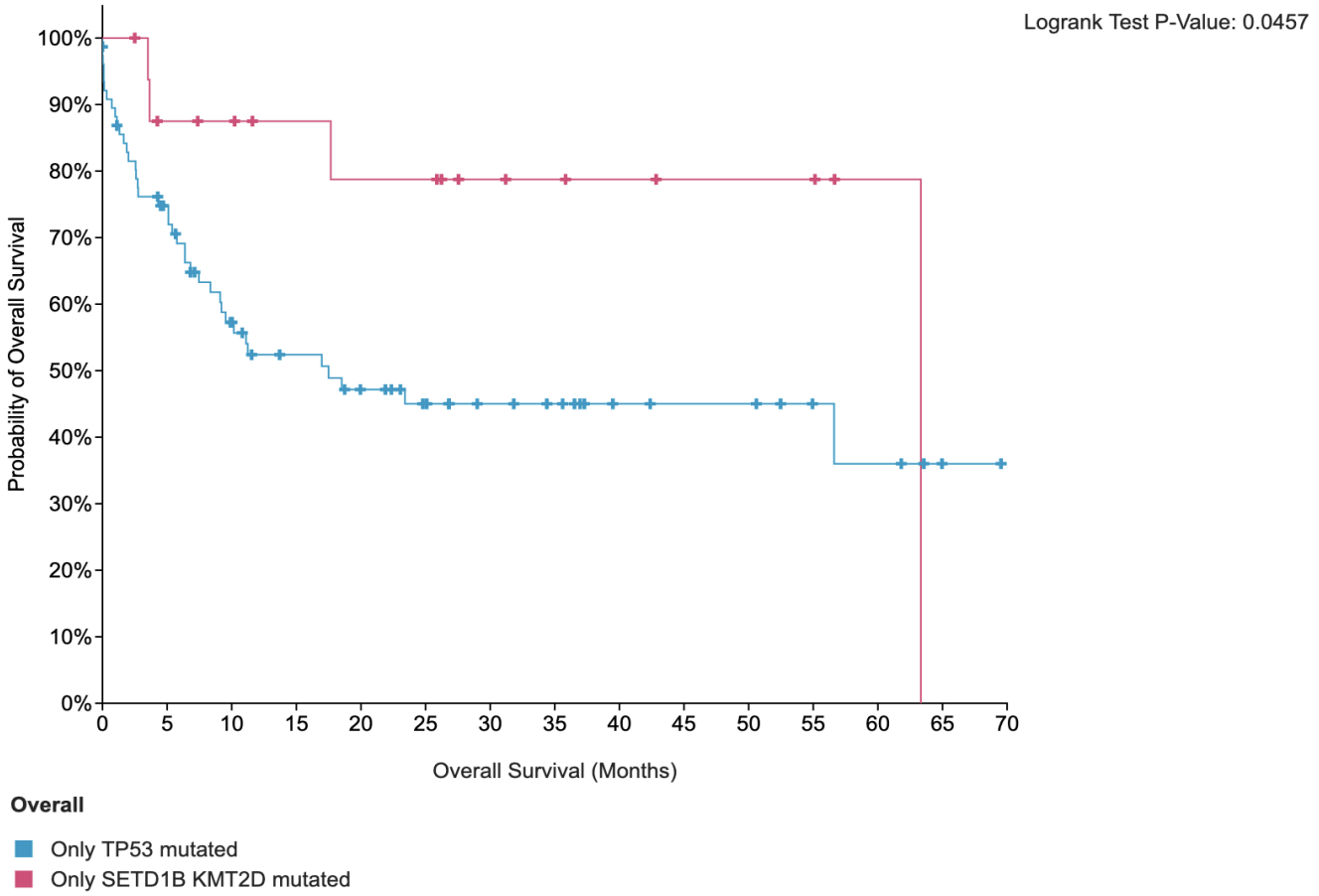
Heritable Kabuki Syndrome is linked to a B cell defect

- KMS caused by KMT2D mutation in 50-80%
  (rarely KDM6A mutation)

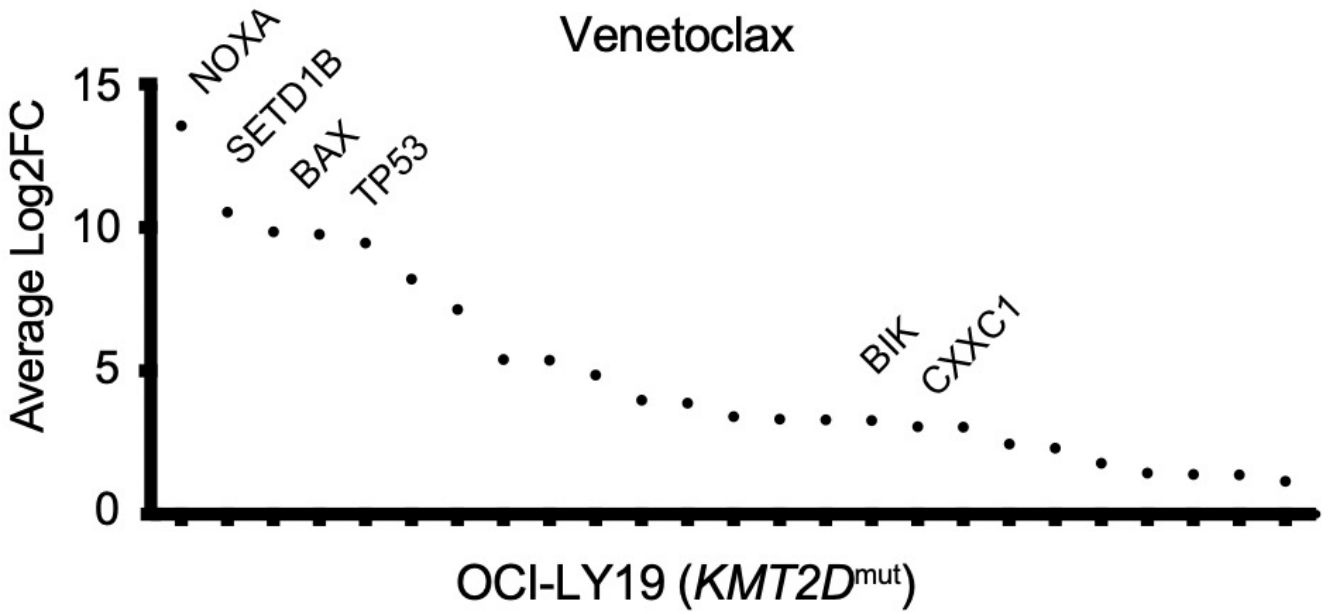
- Features include:
  Facial changes
  Modest immune defect
  Frequent mid ear infections
  Tumor link is not established

Nicked form kabukisyndrome.com

Loss of SETD1B does not have the clinical effect of p53 loss

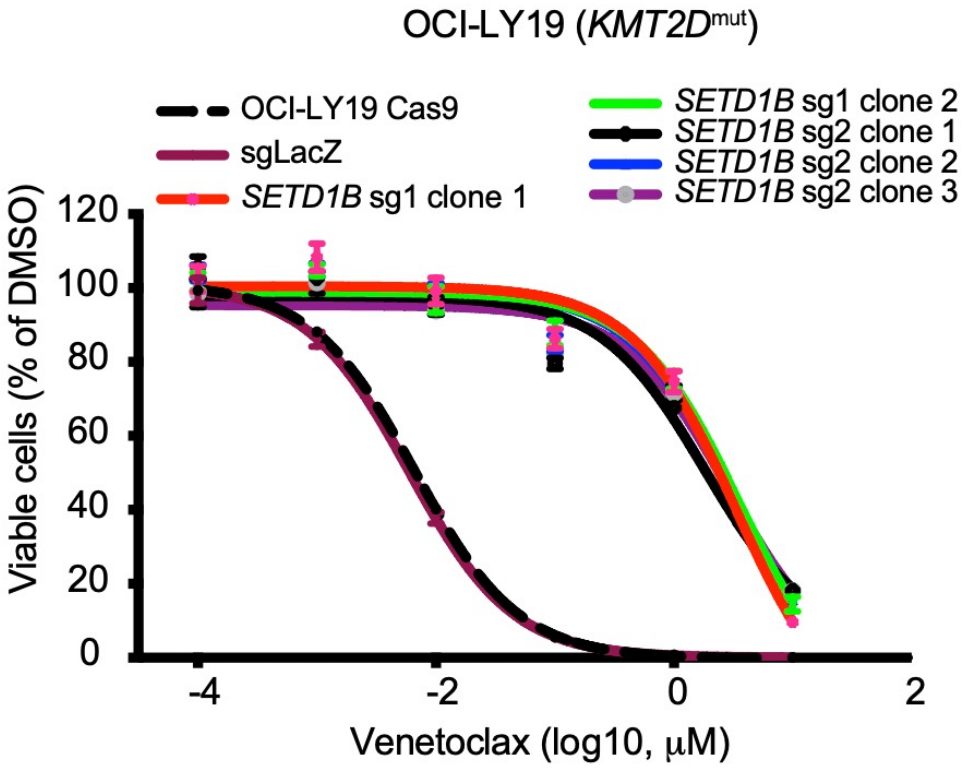


Genetic screens identify SETD1B in Venetoclax resistance

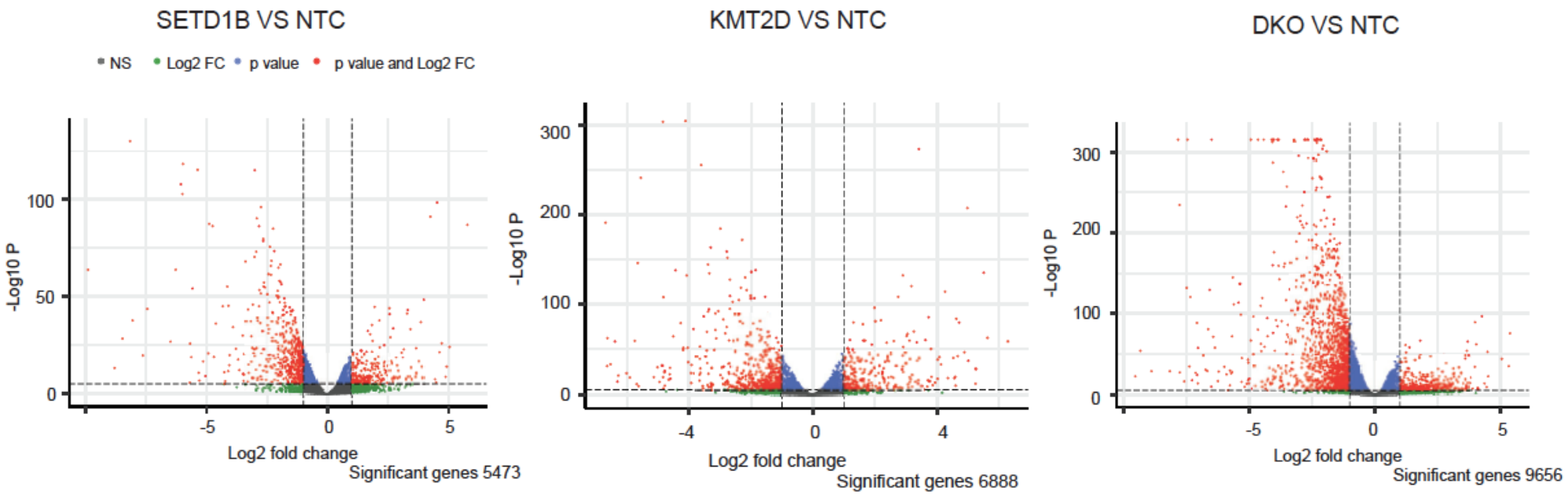


We see a similar resistance to MCL1 inhibition and KMT2D does not have this effect

SETD1B causes a large shift in Venetoclax sensitivity

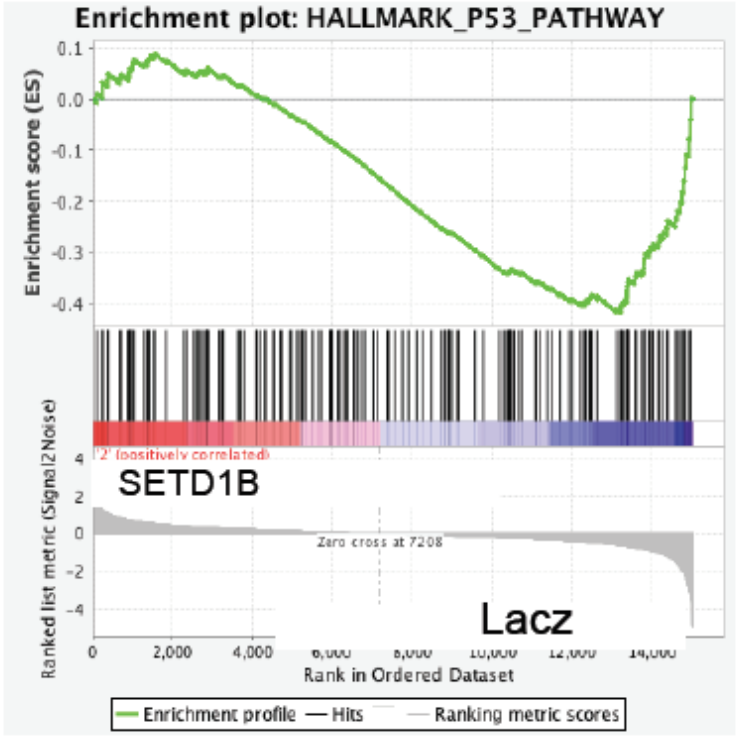


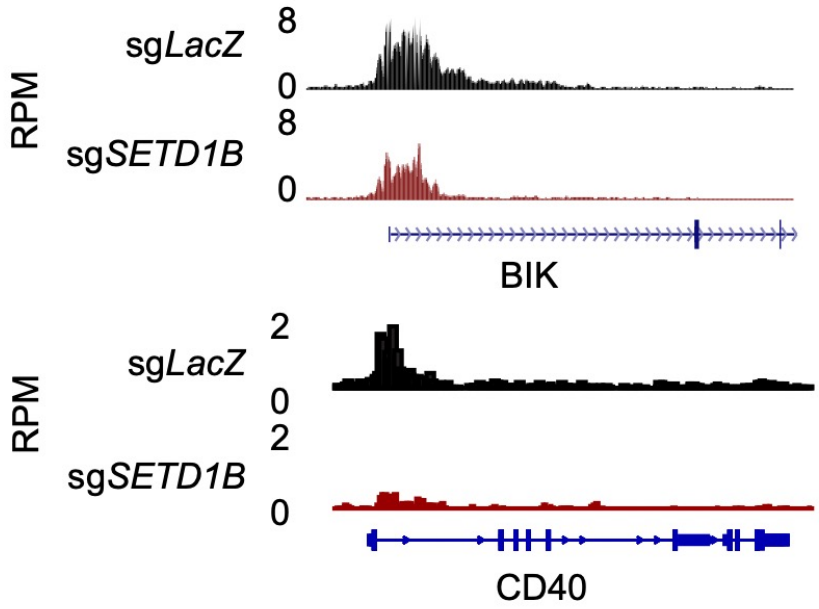
Isolating the expression changes of SETD1B and KMT2D in isogenic cells



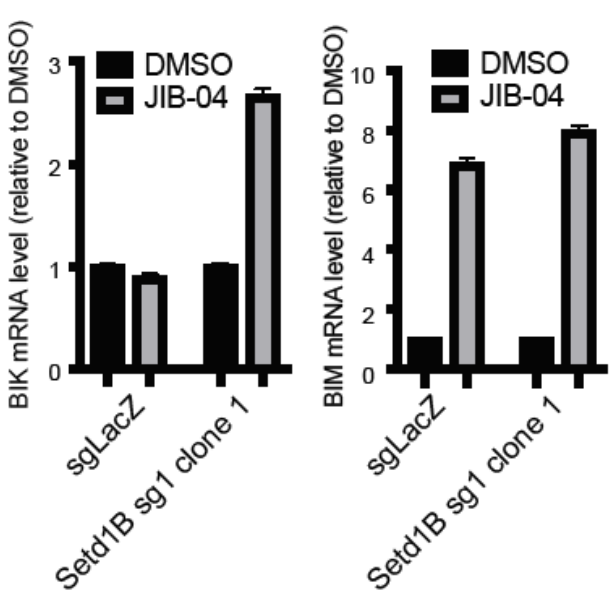
Both additive and unique effects of SETD1B

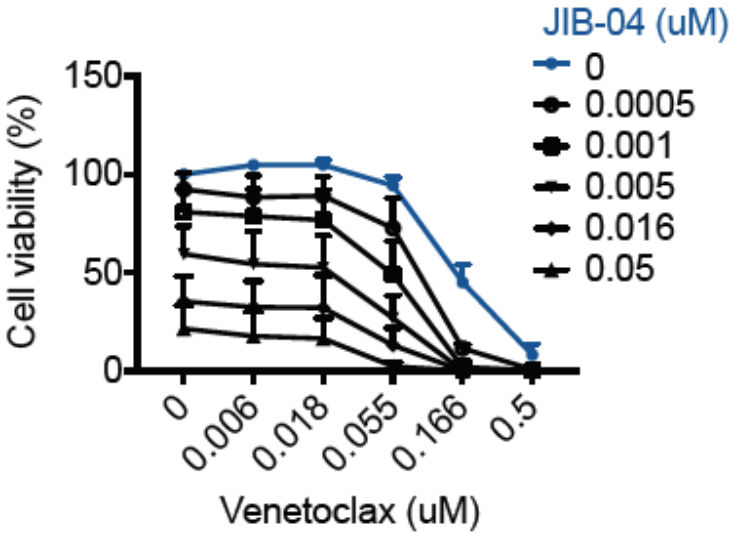
Gene expression and H3K4^{me3} ChIPSeq data point to the p53 response and apoptosis





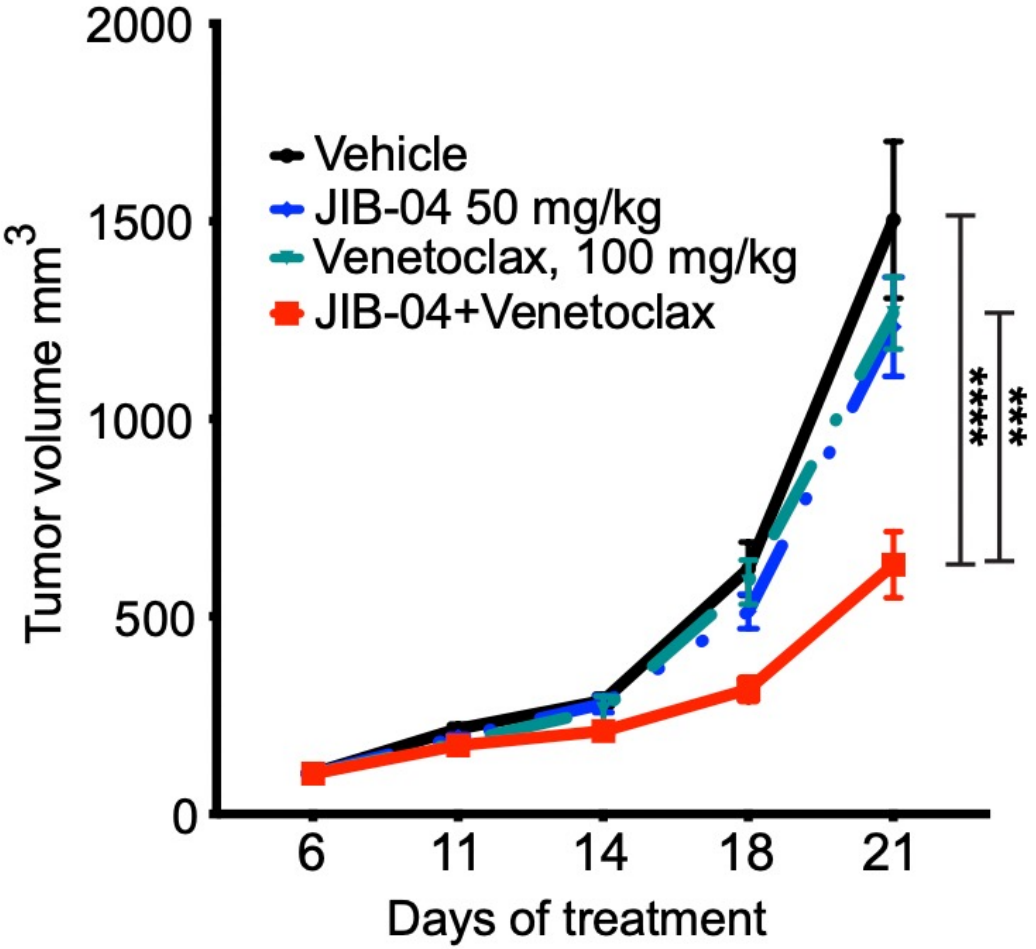
Inhibition of the corresonding KDM5A histone demethylase KDM5A activates expression of BH3 proteins and synergizes with Venetoclax





…and restores Venetoclax sensitivity in vitro

KDM5 inhibition overcomes Venetoclax resistance in xenografts



The combination is well tolerated without frank signs of toxicity

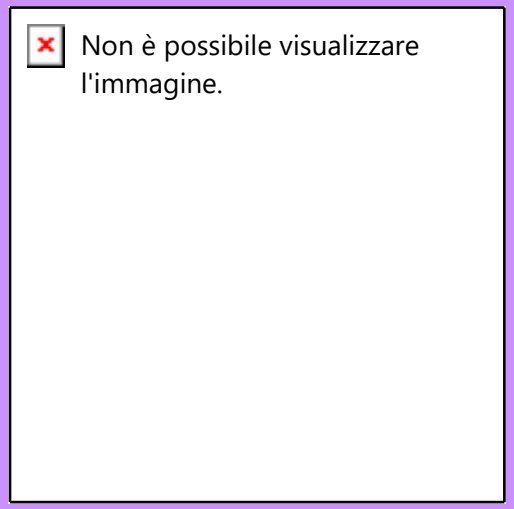
Epigenetic lesions in lymphoma

KMT2D controls different growth and proliferation programs
and has a role in Ig class switch and production.

CREBBP/EP300 mediates histone acetylation and defects cause a decrease in
Expression of immune receptors (MHCII, b2M).
HDAc3 inhibition counters these effects.

SETD1B loss causes defects in cell death and Venetoclax resistance.
KDM5A inhibition reverses these effects in vivo with good safety.

KMT2D and SETD1B in lymphoma



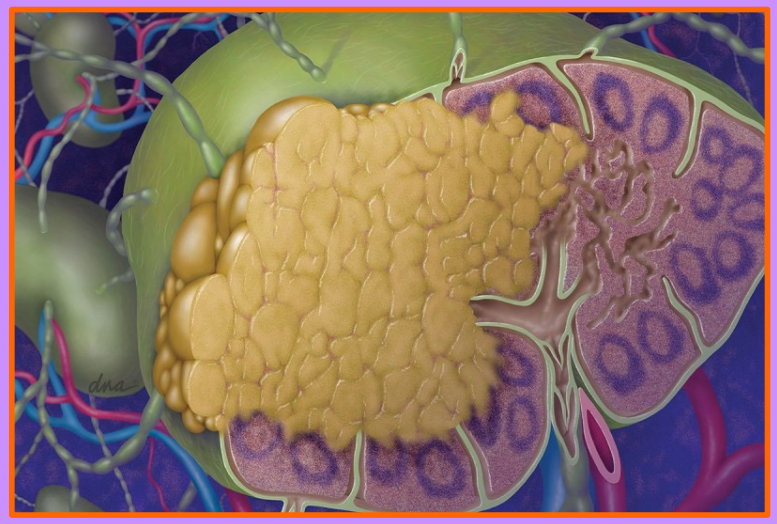
Ana Ortega
(now CNIO)

Ana Portelinha
(MSK)

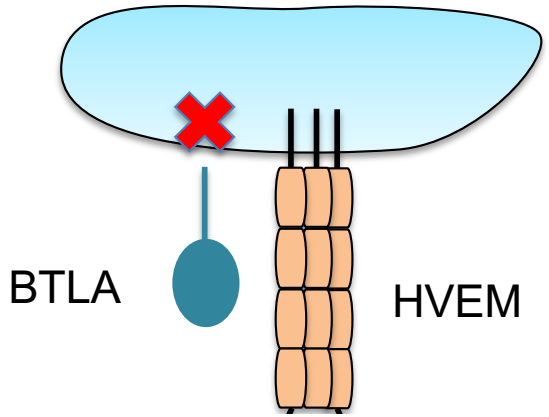
Collaborations with A. Melnik, J. Fitzgibbon, A. Younes, A. Dogan, G. Salles.
(Funding support from LRF and Astra Zeneca)

2. Immune checkpoint mutations

Michael Boice, Darin Salloum, H. Guido Wendel
Memorial Sloan-Kettering



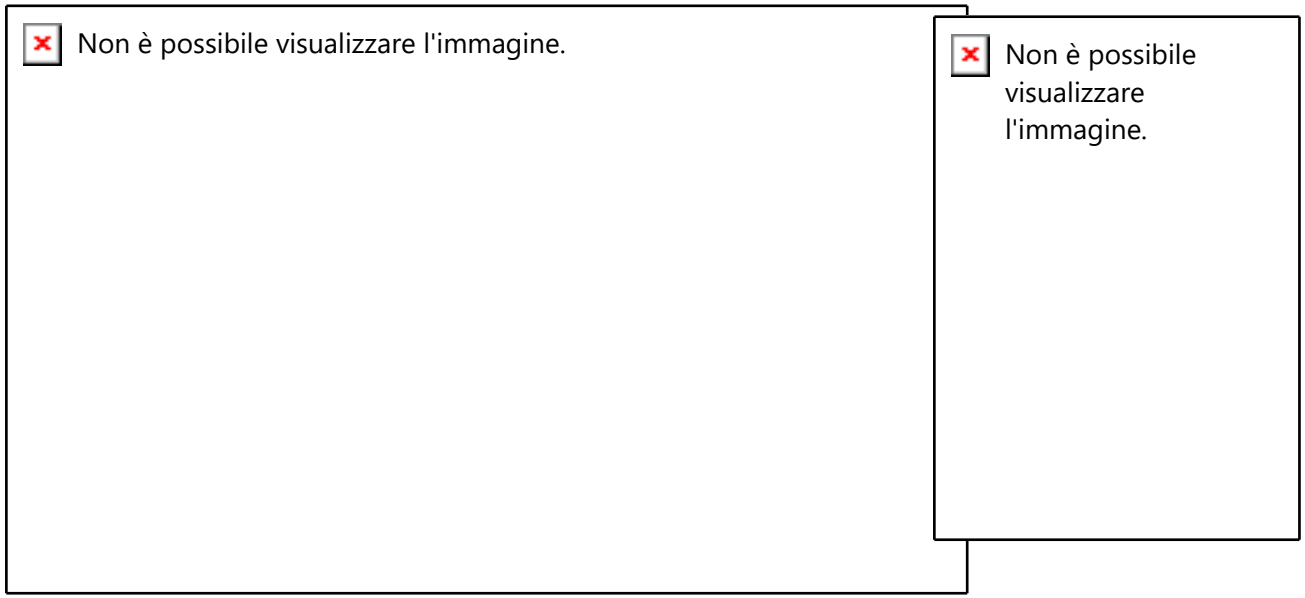
The receptors TNFRSF14 (HVEM) and BTLA form an B cell checkpoint



In B cells HVEM binds the inhibitory BTLA receptor *in trans* or *in cis*.

This interaction stops B cell growth.

The HVEM/TNFRSF14 receptor is mutated or deleted in ~45% of FL



Lymphomas that are wild type for HVEM/TNFRSF14 typically lose expression of BTLA

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Tissue array (n = 198; p = 0.001)

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Together, the interaction between HVEM and BTLA is lost in ~75% of FLs.

Loss of HVEM or BTLA causes lymphomas in vivo

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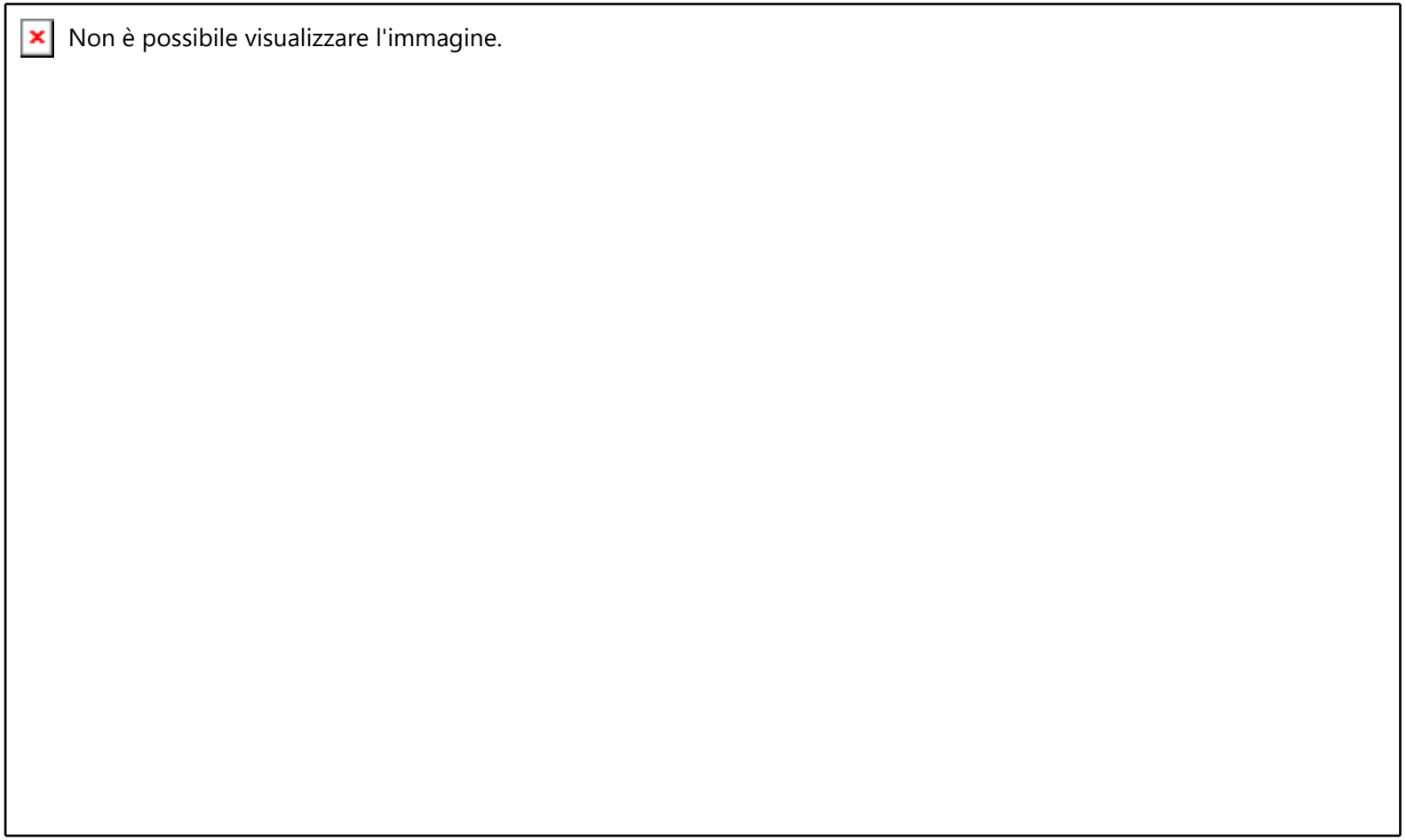
We use genetically engineered lymphomas to study mechanism and therapy

HVEM deficient FLs show stroma activation and TFH recruitment

Reactive GC | Lymphoma | HVEM Lymphoma

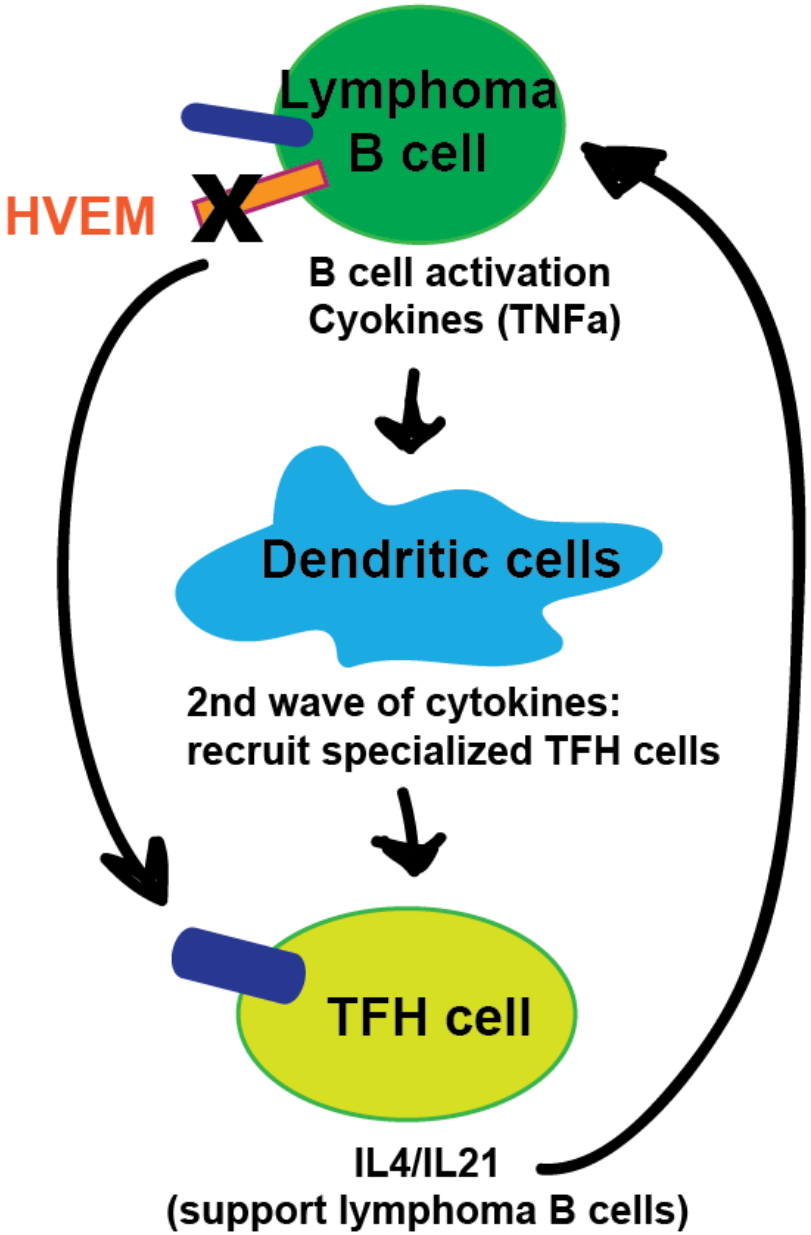


B cells

FRCs

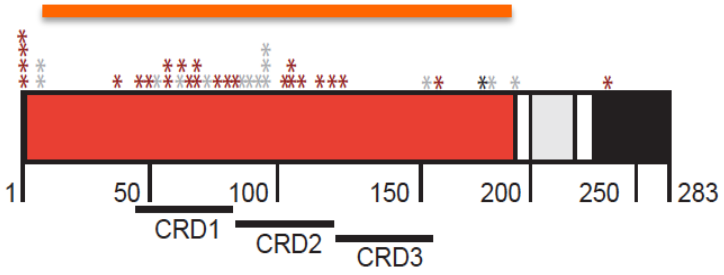
FDCs

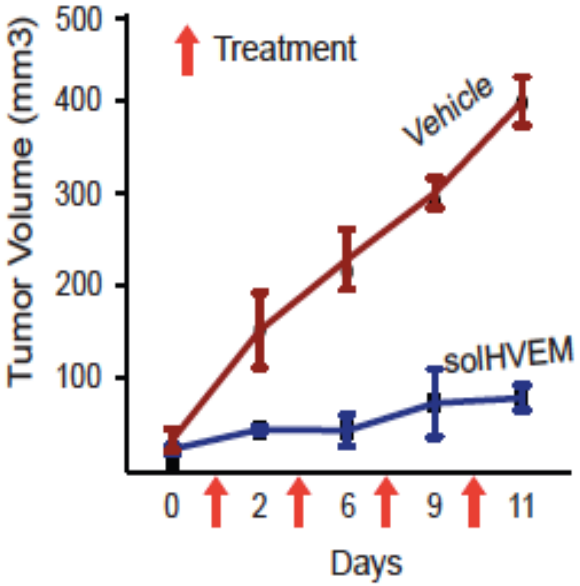
HVEM loss activates B cells *and* creates a supportive niche



The HVEM extracellular protein domain has therapeutic effects

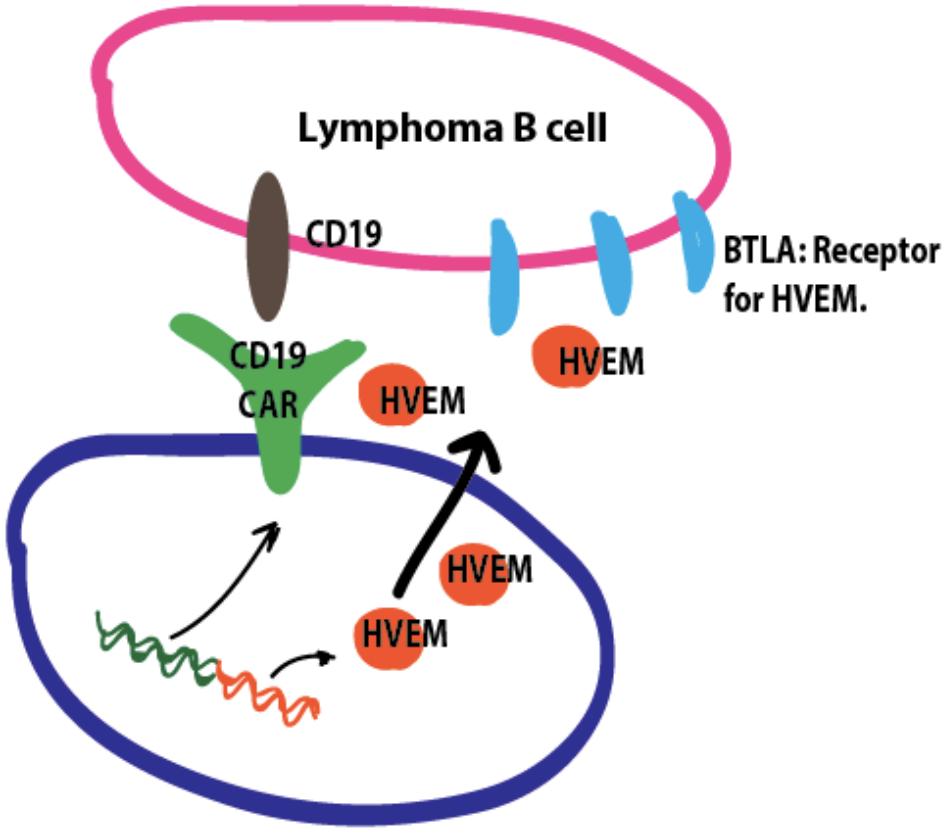
SolHVEM (P37-V202) protein



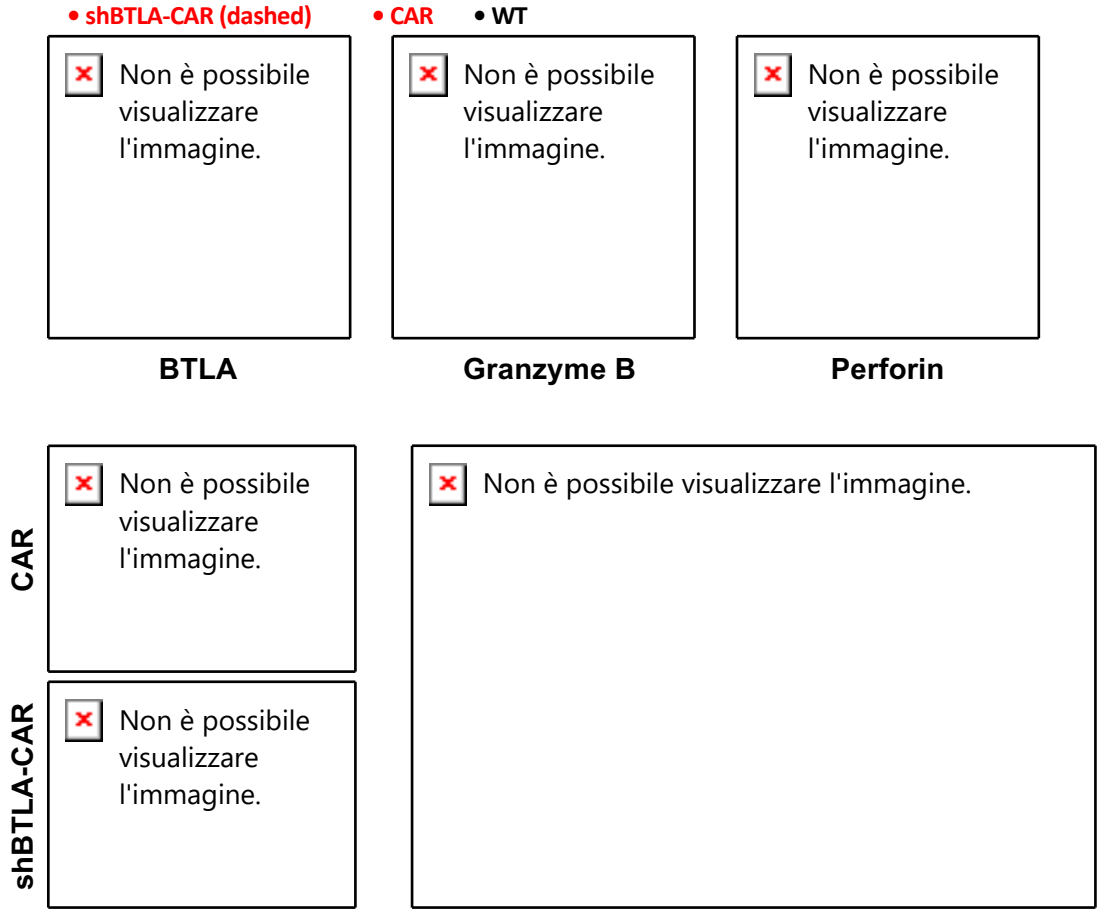


MYC/BCL2 mouse lymphomas; HVEM injected into the tumor 20μg

CAR-T cells as "micro-pharmacies" that produce the HVEM protein at the tumor



To deliver HVEM, we must engineer CAR T cells that don't have BTLA and these cells show much superior lymphoma cell killing



The HVEM-BTLA checkpoint in lymphoma and CAR T cells

The HVEM-BTLA checkpoint is lost in the majority of human FLs.
This has direct effects on B cells and creates a supportive niche through TFH recruitment.

CAR T cells can deliver peptides such as HVEM and restore tumor suppression.

In ongoing work, we engineer improved BTLA-/- CAR T cells to deliver BTLA agonists to Lymphomas.

The HVEM-BTLA checkpoint in lymphoma and CAR T cells

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Michael Boice
(now Biotech)

Non è possibile visualizzare l'immagine.

Ana Portelinha
(at MSK)

Non è possibile visualizzare l'immagine.

Darrin Salloum
(Sana Therapeutics)

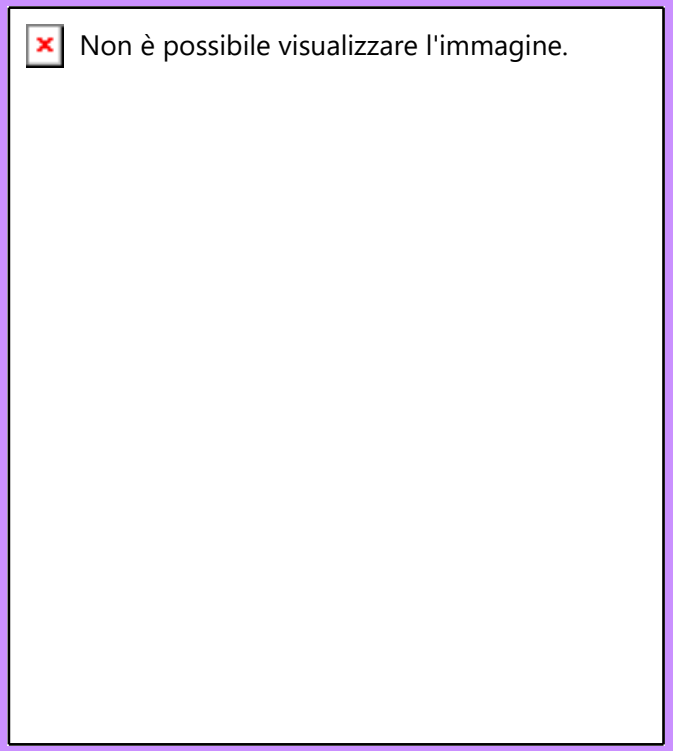
Collaborations with K. Tarte, J. Fitzgibbon, M. Rout, B. Chait (Rockefeller U.), and others.

The Hans-Guido Wendel Lab

Support from NIH, LRF, FLF/Cure Lymphoma, LLSA, Geoffrey Beene, P. Greenberg.

3. Oncogenic mRNA translation programs

Andy Wolfe, Kamini Singh, H. Guido Wendel
Memorial Sloan-Kettering



^{13}I-Puromycin PET-CT

Translation initiation is tightly regulated

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Abnormal growth signals in cancer converge on this complex (PI3K, MAPK, PIM, etc.)

Translation factors act as oncogenes

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How is it possible and what can we do about it?

Nature has identified the eIF4A RNA helicase as a target

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Are these compounds of any use in medicine?