B cell Lymphoma as a Cancer Model

Cellular and Molecular Biology of Cancer

PATH G4500

December 3th, 2025

Columbia University

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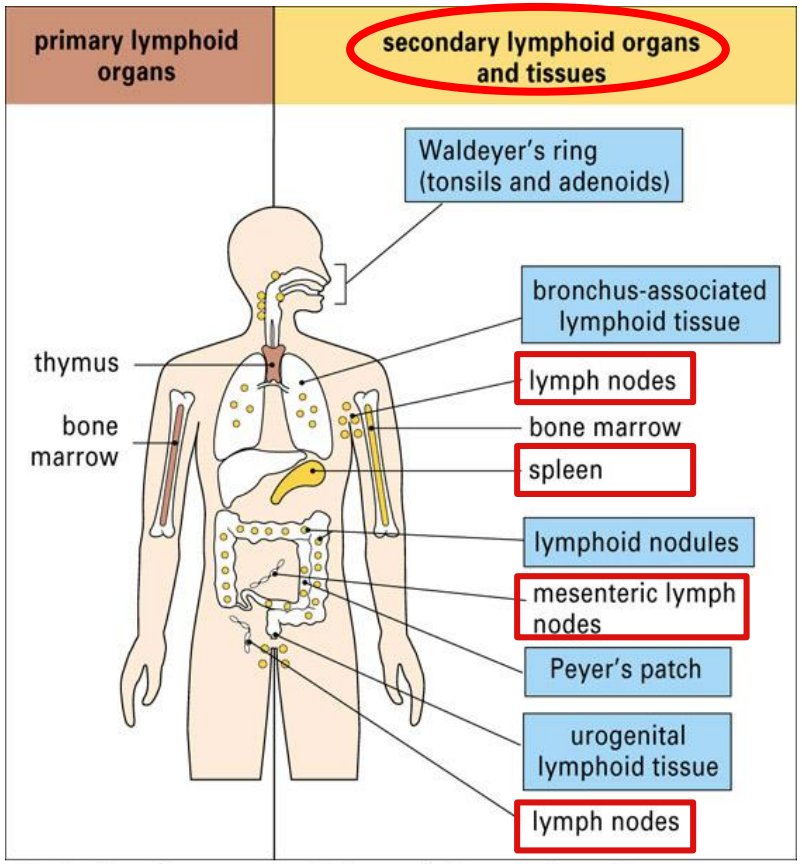
Lymphomas

- Tumors of the lymphoid organs
- 6th most common cancer
- 89,070 new cases in the US for 2025
  20,540 cancer-related deaths
- Not a single disease: over 70 distinct types recognized by the WHO classification (different origin, oncogenic mechanisms, incidence and cure rates)



What we'll be covering today

- The double-edged sword of the germinal center reaction
- BCL6: the Germinal Center Master Switch
- Mechanisms of Genetic Lesion in lymphoma (and role of AID)
- Lymphoma Classification
- Diffuse Large B cell Lymphoma (DLBCL) as a model
- Therapeutic Implications

Lymphoma classification (historical)

LYMPHOMA

NON-HODGKIN

HODGKIN

B cells (85%)

T cells (15%)

B-NHL

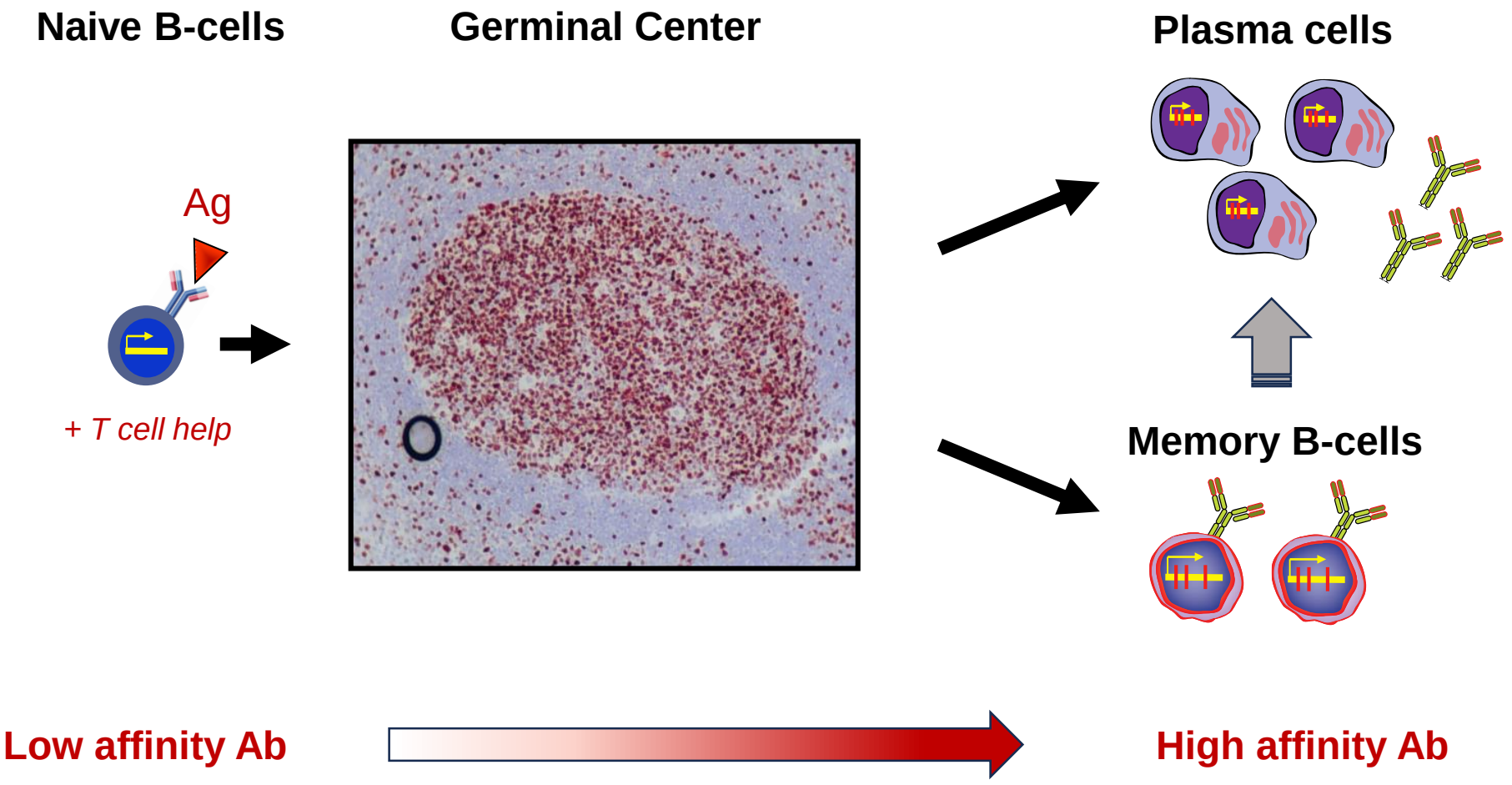
T-NHL

Ratio between non-Hodgkin and Hodgkin's lymphomas ~4:1

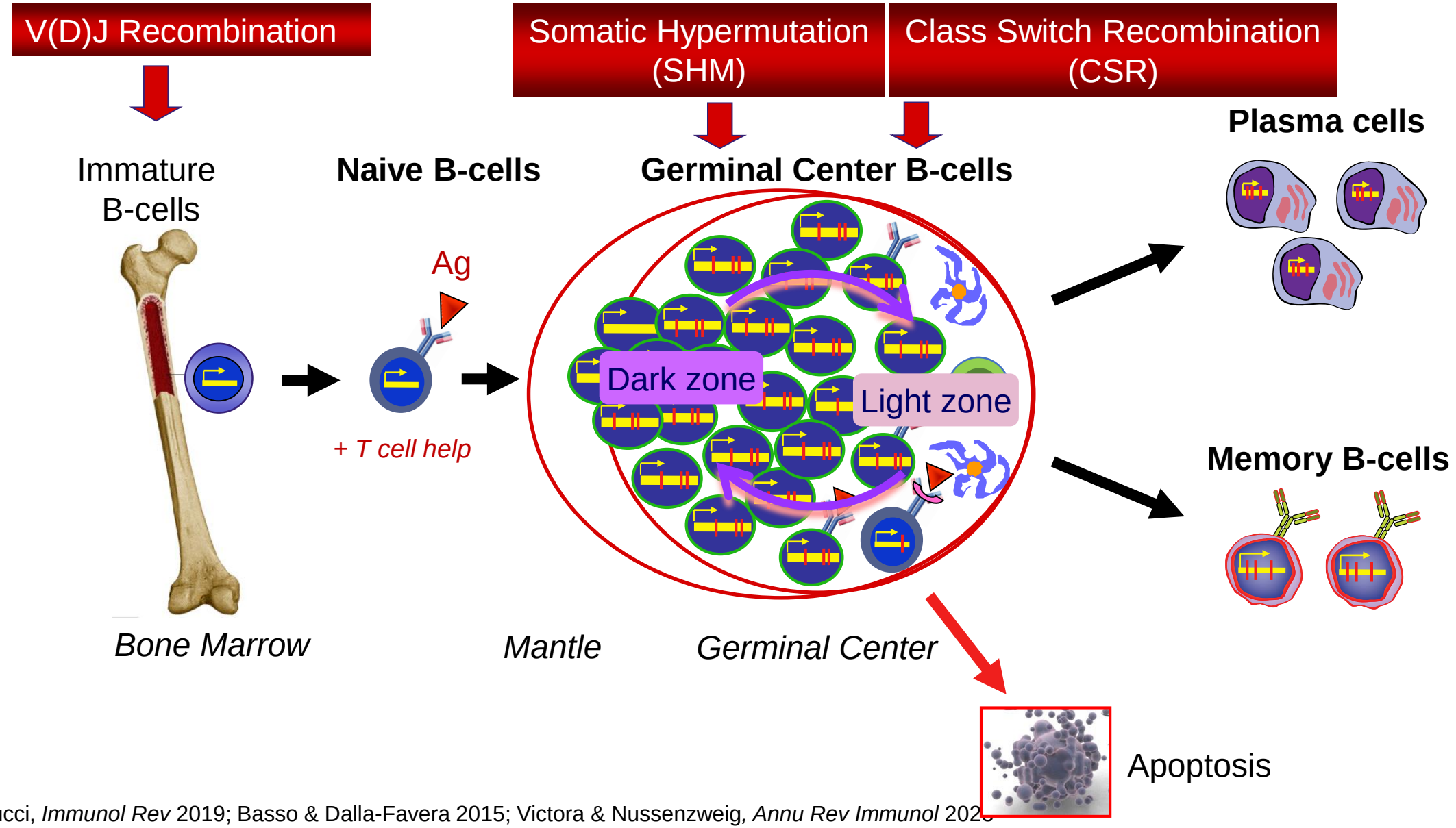
Thomas Hodgkin (1798-1866)

B cell origin

Germinal Centers are critical for protective immunity

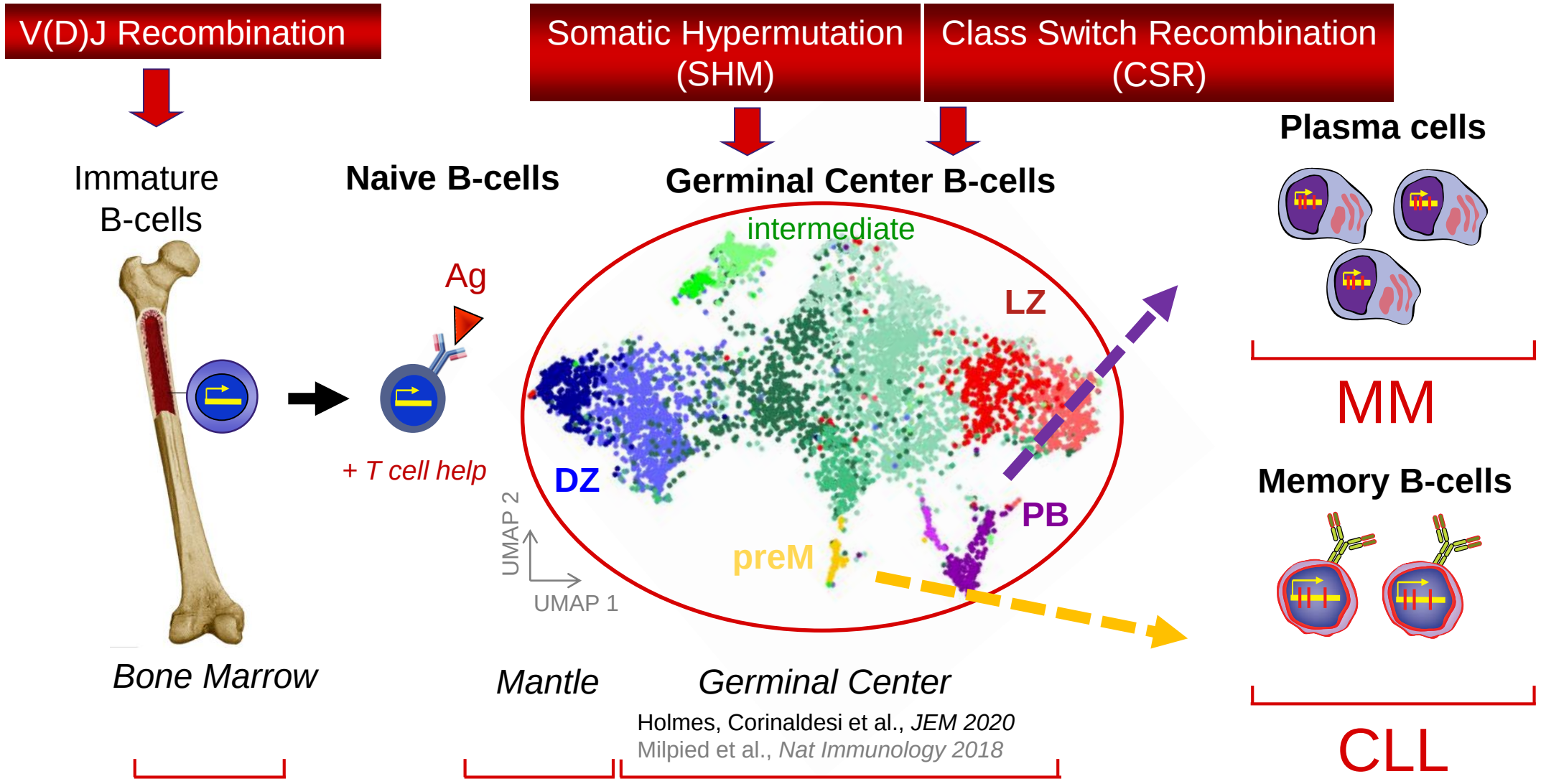


The double-edged sword of the Germinal Center reaction



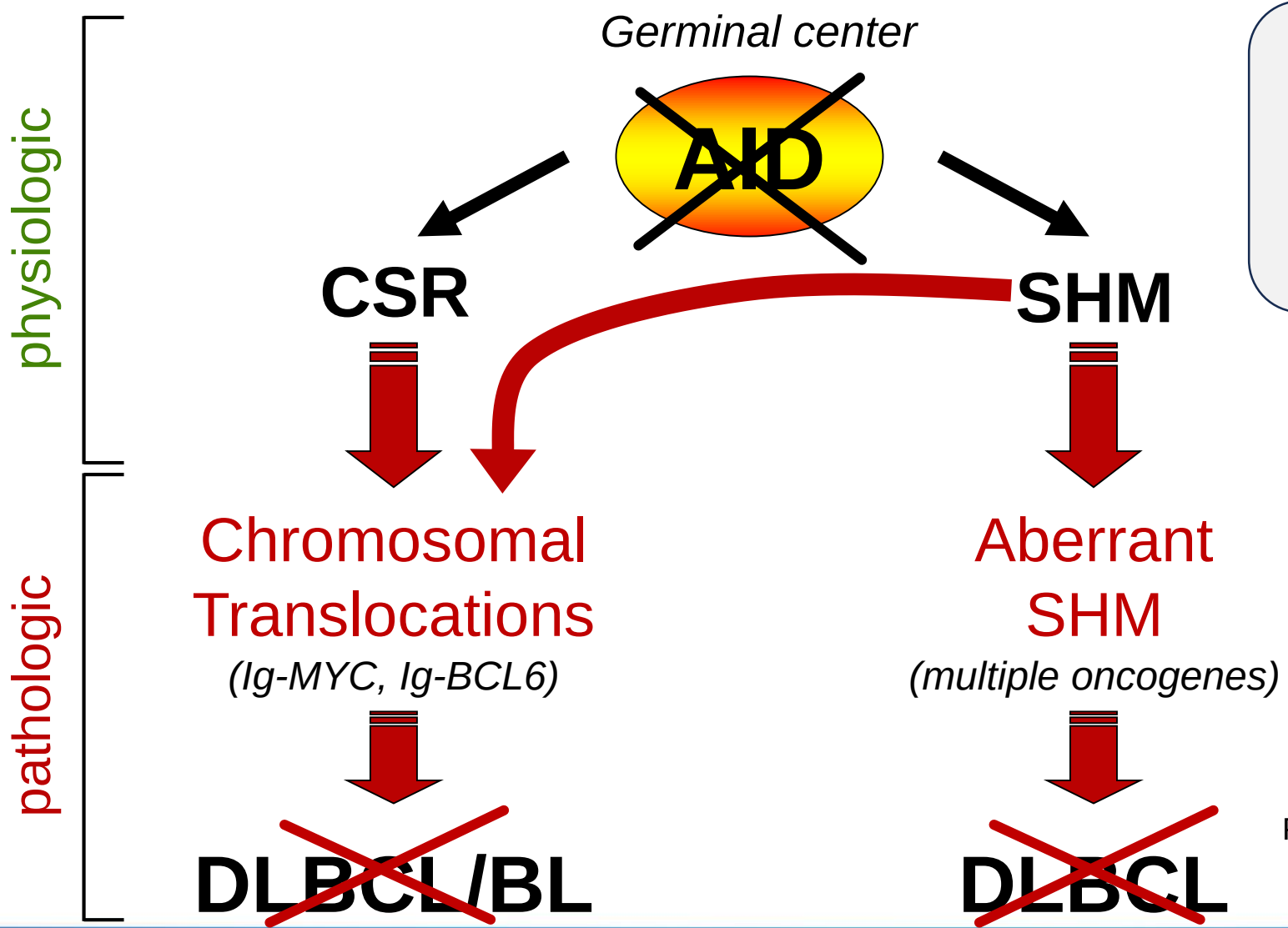
Pasqualucci, *Immunol Rev* 2019; Basso & Dalla-Favera 2015; Victora & Nussenzweig, *Annu Rev Immunol* 2020

The double-edged sword of the Germinal Center reaction

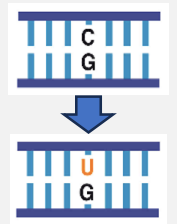


Holmes, Corinaldesi et al., *JEM 2020*
Milpied et al., *Nat Immunology 2018*

AID is required for GC-derived lymphomagenesis



- DNA Cytidine deaminase
- APOBEC family member

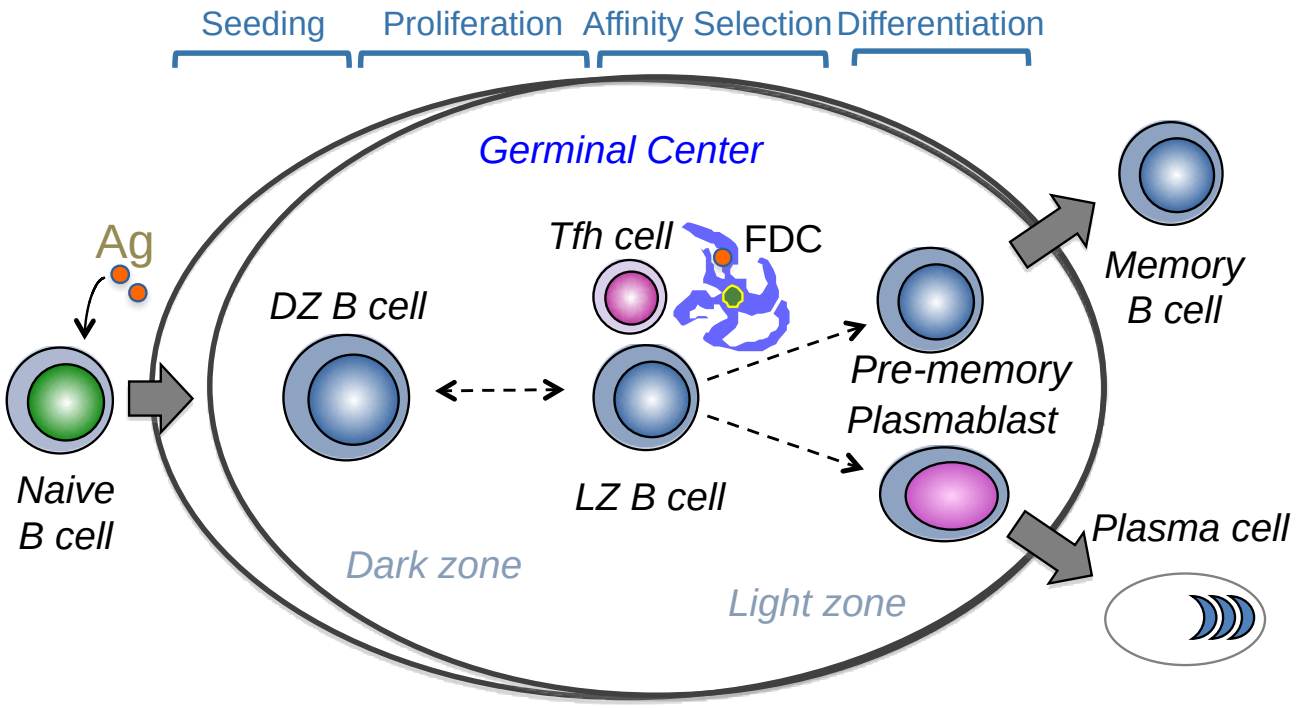


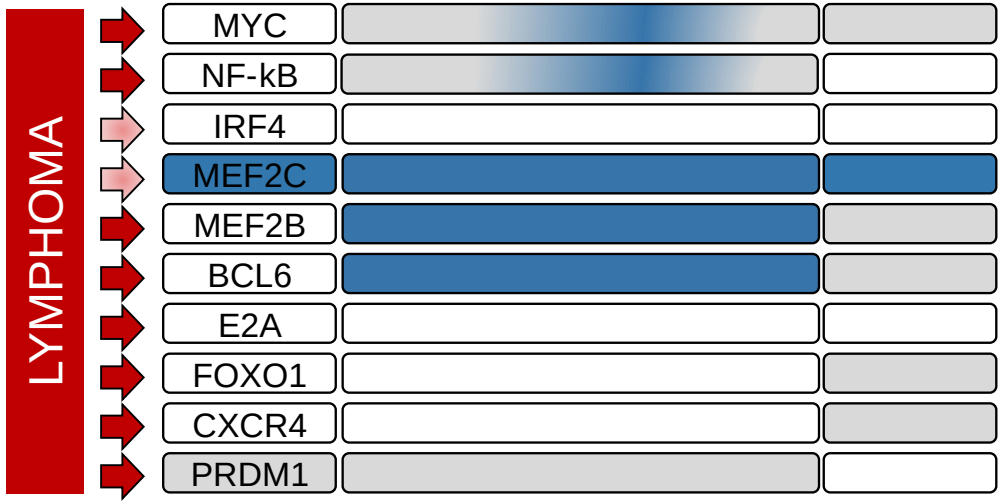
abasic site breaks

Muramatsu et al., *Cell* 2000
Di Noia et al., *Nature* 2002

Pasqualucci et al., *Nature* 2001
Pasqualucci et al., *Nature Genetics* 2008
Ramiro et al., *Cell* 2004
Robbiani et al., *Cell* 2008

Transcription factor networks regulating the GC reaction





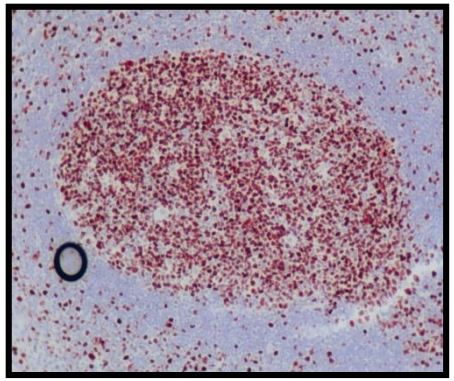
Not expressed

Expressed/nuclear localization

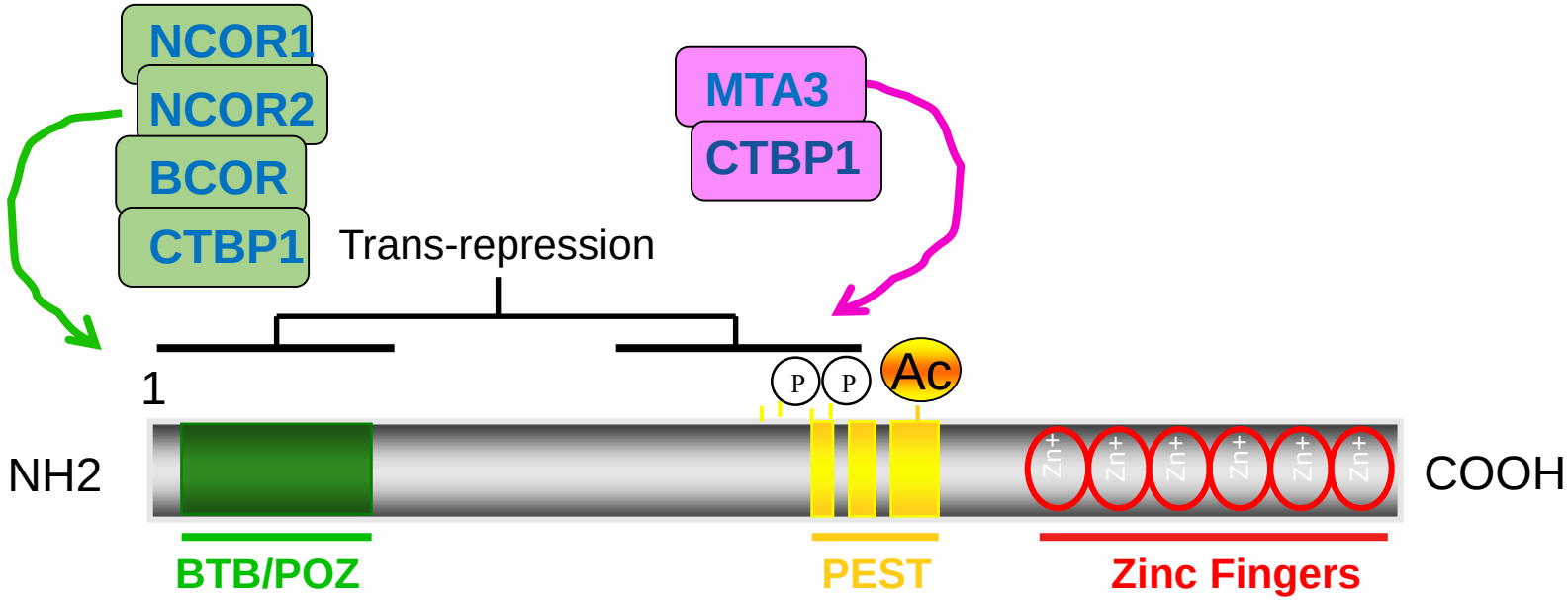
Ye et al., *Nature Genetics* 1997
Cattoretti et al., *J Pathol* 2005
Cattoretti,et al., *Cancer Cell* 2005
Klein et al., *Nature Immunol* 2006
Saito et al., *Cancer Cell* 2007
Ying et al., *Nature Immunol* 2013
Brescia et al., *Cancer Cell* 2018
Phan et al., *Nature Immunol* 2005, 2007
Dominguez-Sola et al., *Immunity* 2015
Basso et al., *Blood* 2004
Basso, Saito et al., *Blood* 2010
Dominguez Sola et al., *Nature Immunol* 2012
Mandelbaum et al., *Cancer Cell* 2010
Roberto, Varano et al., *Immunity* 2021
Pasqualucci L, *Immunological Reviews* 2019

Shaffer et al., *Annu Rev Immunol* 2012
Victora & Nussenzweig, *Annu Rev Immunol* 2022
De Silva & Klein, *Nature Reviews Immunol* 2015
Mesin et al., *Immunity* 2016
Bannard & Cyster, *Curr Opin Immunol* 2017
Nakagawa & Calado, *Front Immunol* 2021

BCL6:
the Germinal Center Master Regulator

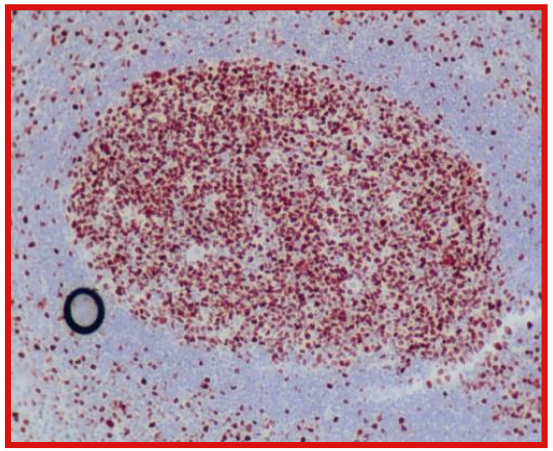


The BCL6 protein

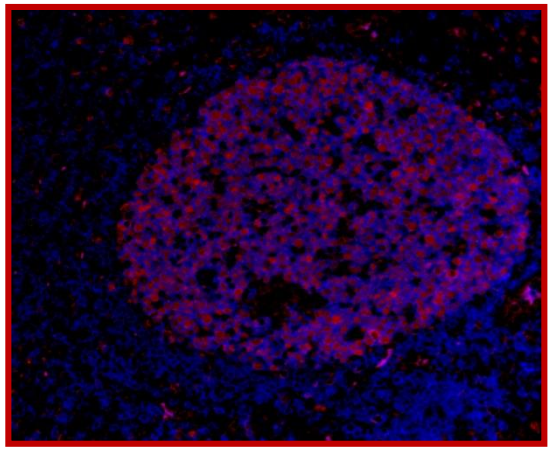


DNA binding motifs
@ promoters/enhancers

BCL6 is specifically expressed in the GC

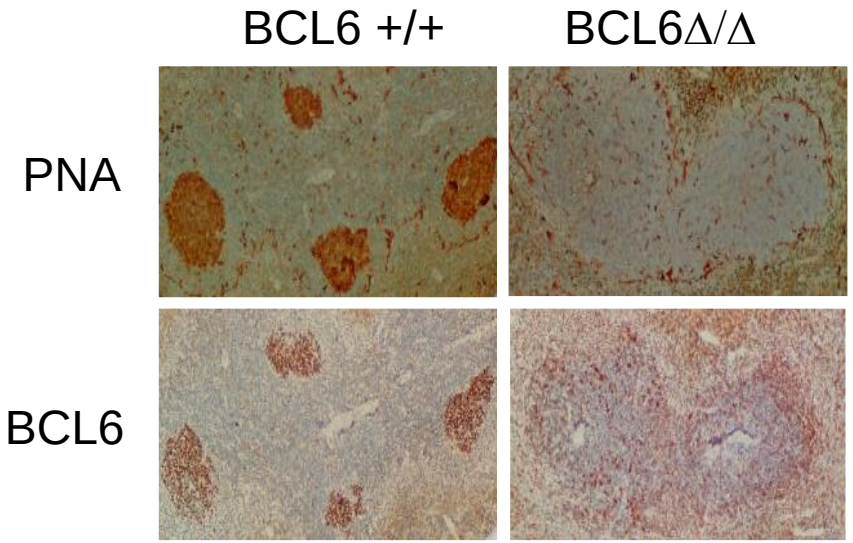


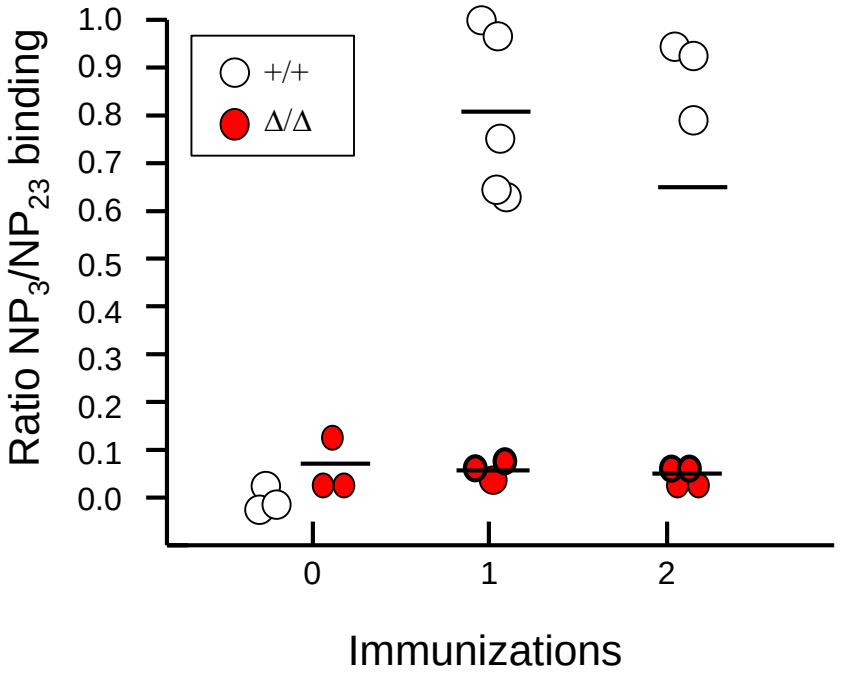
BCL6



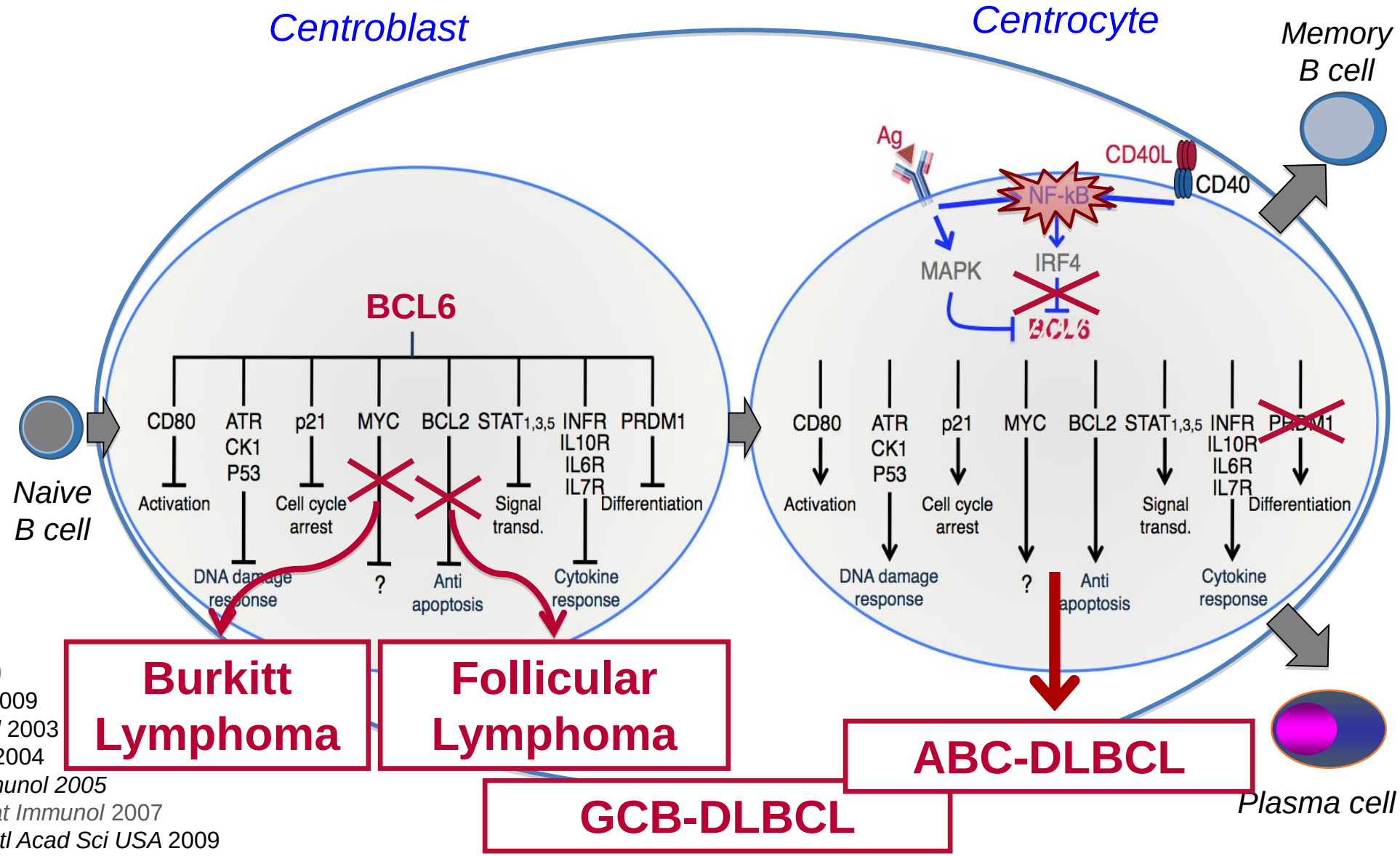
BCL6 CD20

BCL6 is required for GC formation





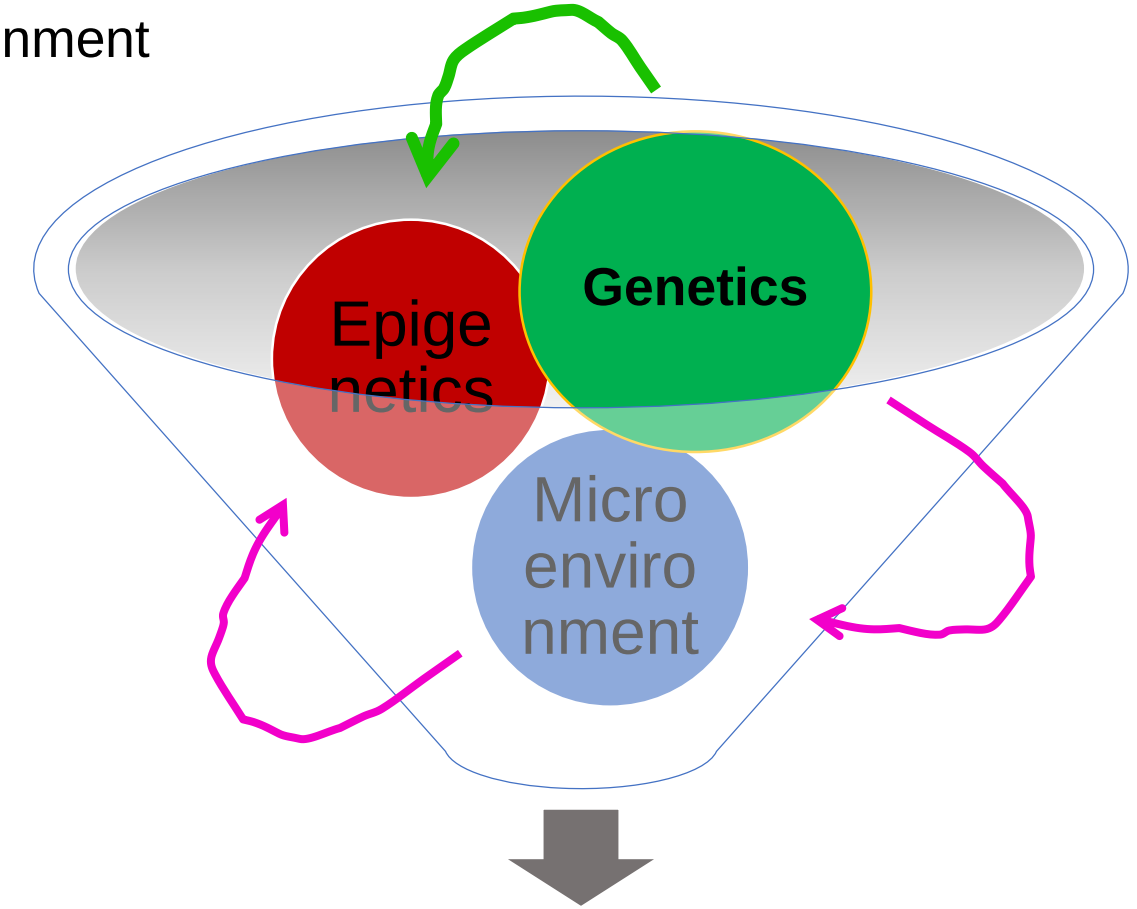
Biological function of BCL6 in the Germinal Center



Ci et al., *Blood* 2009
Basso et al, *Blood* 2009
Niu et al, *J Exp Med* 2003
Phan et al., *Nature* 2004
Phan et al., *Nat Immunol 2005*
Ranuncolo et al., *Nat Immunol* 2007
Saito et al., *Proc Natl Acad Sci USA* 2009

The pathogenesis of B cell lymphomas involves multiple layers of complexity

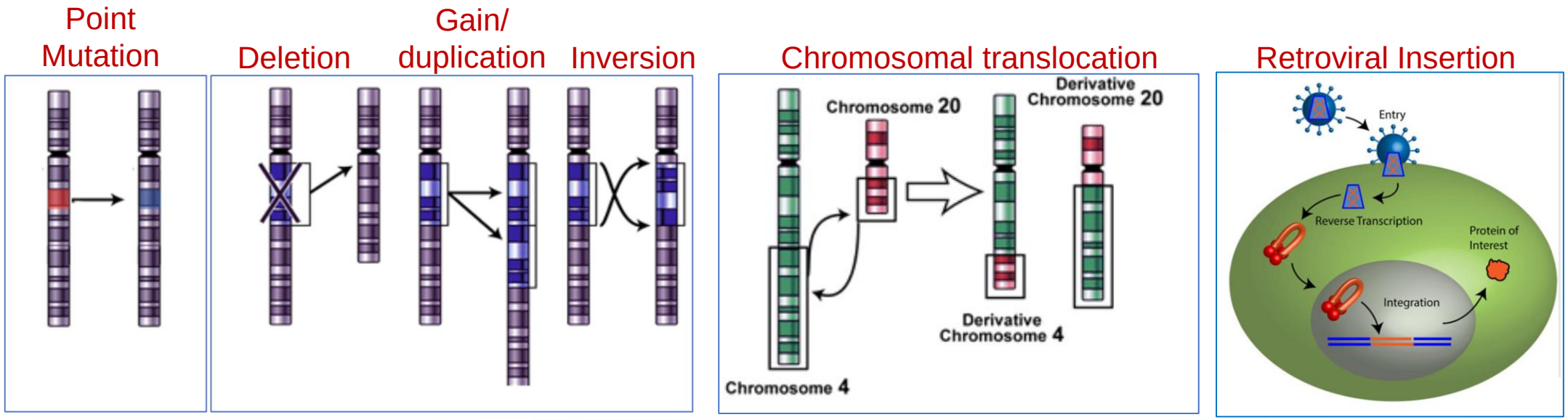
Tumor microenvironment



Mechanisms of genetic lesion in B cell Lymphomas

Types of genetic alterations associated with lymphoma

- Mutations
- Copy number aberrations: deletions and gains (low CN gains, duplications, amplifications)
- Gene rearrangements/chromosomal translocations
- Retroviral insertion



Mechanisms of genetic lesion in B cell lymphomas

- non-random chromosomal translocations

..due to aberrant resolution of DNA breaks during

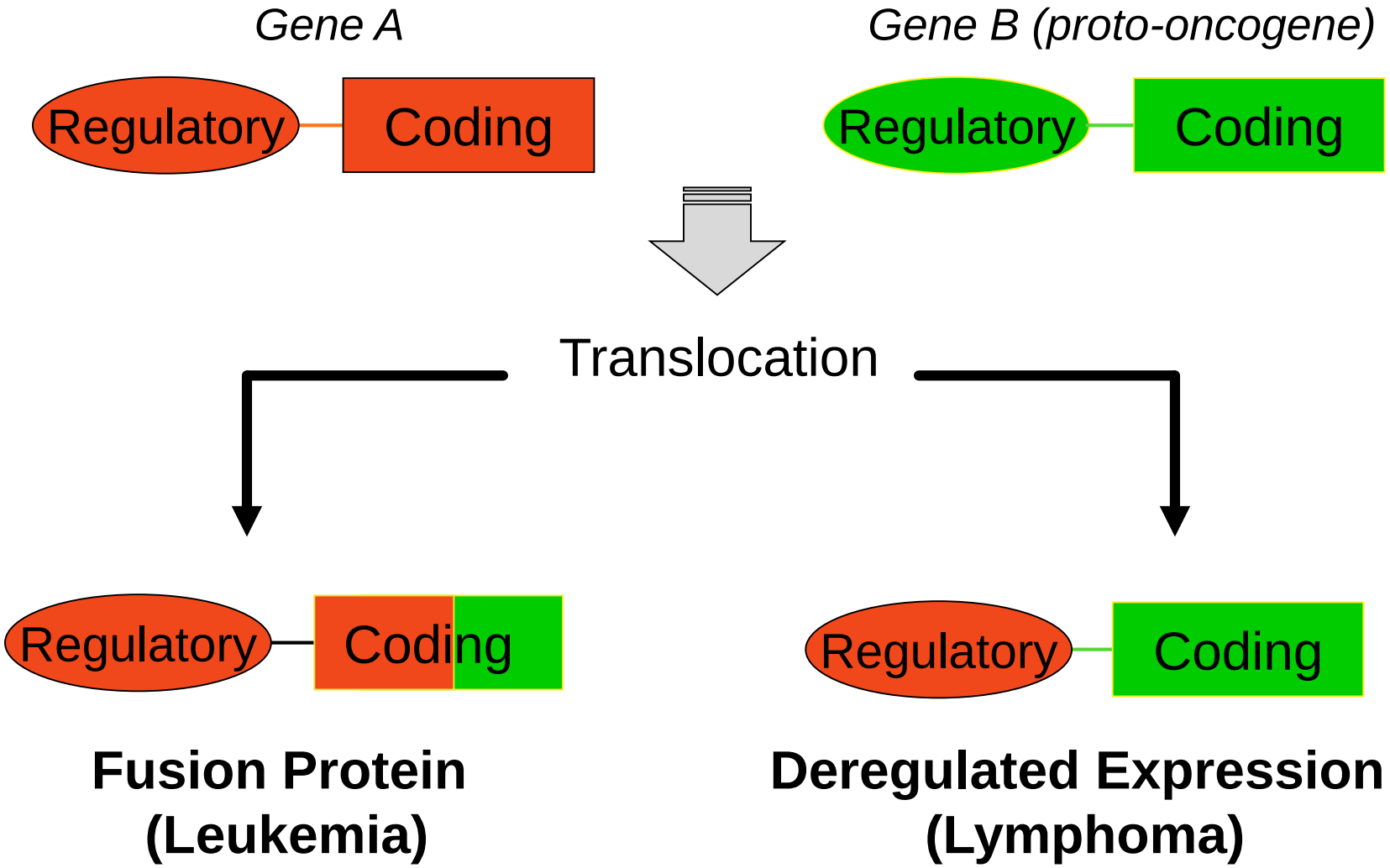
- **V(D)J recombination**
- **Class Switch Recombination**
- **Somatic Hypermutation**

- aberrant somatic hypermutation (in DLBCL)

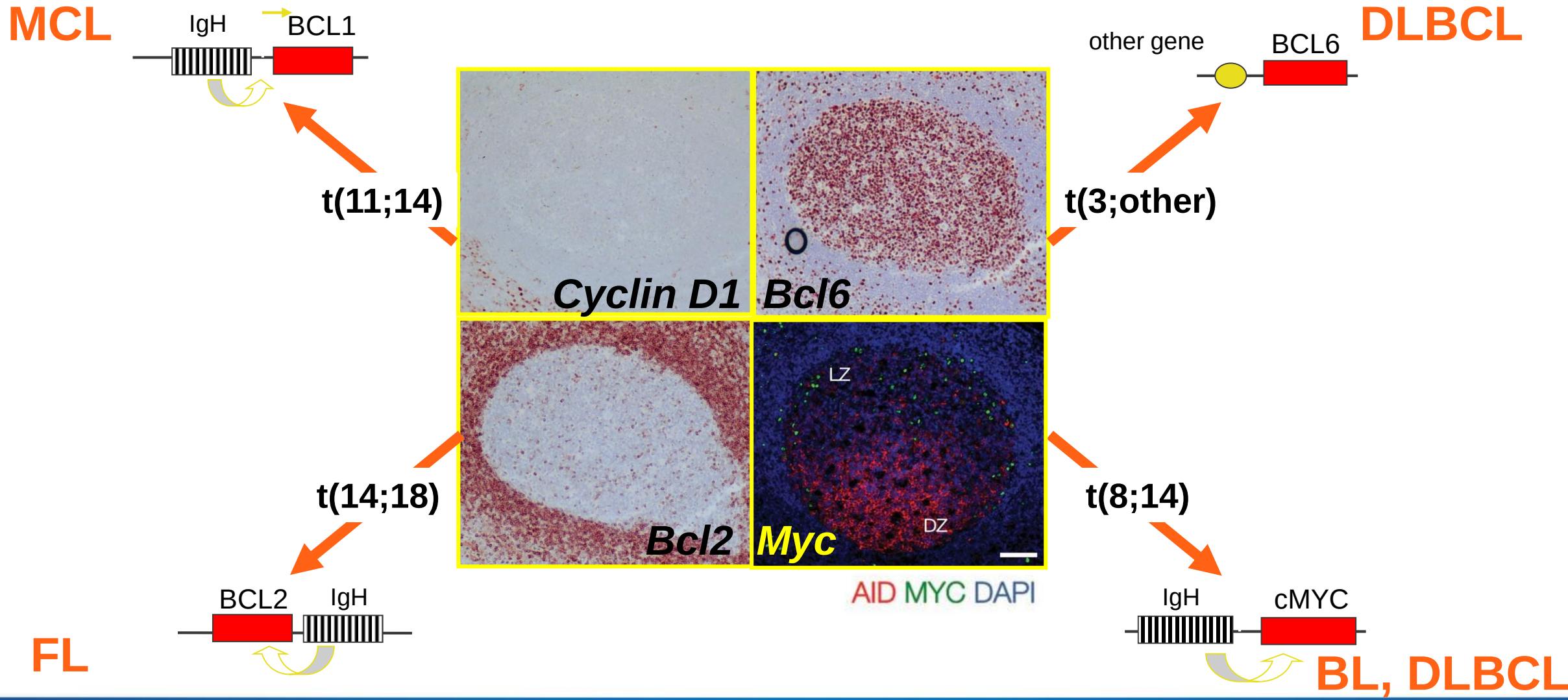
Lymphoma associated chromosomal translocations: genetic features

- **Balanced**
- **Reciprocal**
- **Clonal**
- **Recurrent**

Consequences of Chromosomal Translocations



Oncogene deregulation in the Germinal Center



Mechanisms of genetic lesion in B cell lymphomas

- non-random chromosomal translocations

..due to aberrant resolution of DNA breaks during

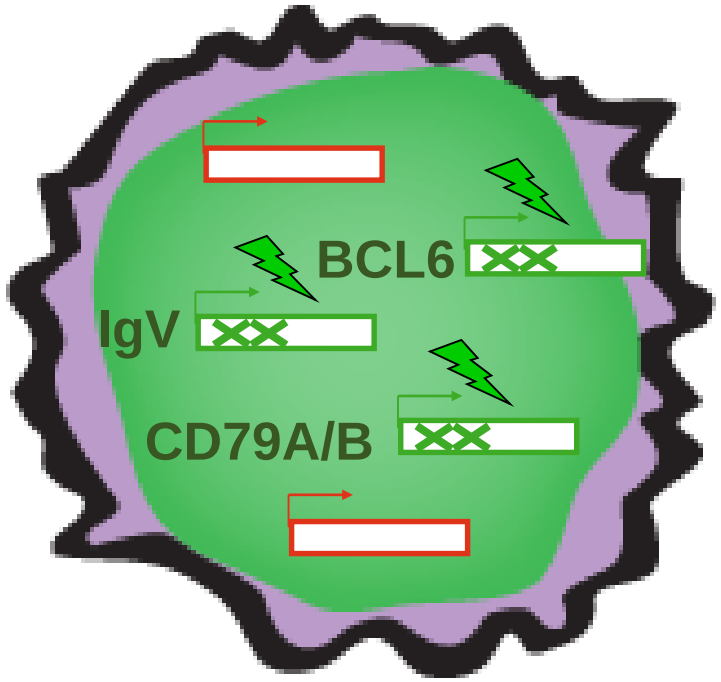
- V(D)J recombination
- Class Switch Recombination
- Somatic Hypermutation

- aberrant somatic hypermutation (noncoding regions) (in DLBCL)

..due to a malfunction of SOMATIC HYPERMUTATION

Physiology and Pathology of Somatic Hypermutation

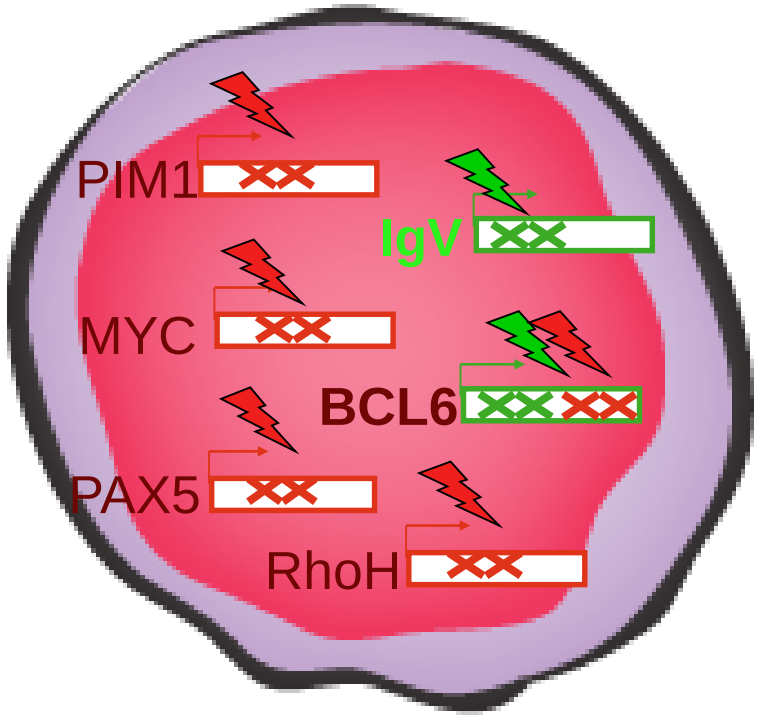
physiological



GC B cells

Shen et al., *Science* 1998; Pasqualucci et al, *PNAS* 1998

aberrant

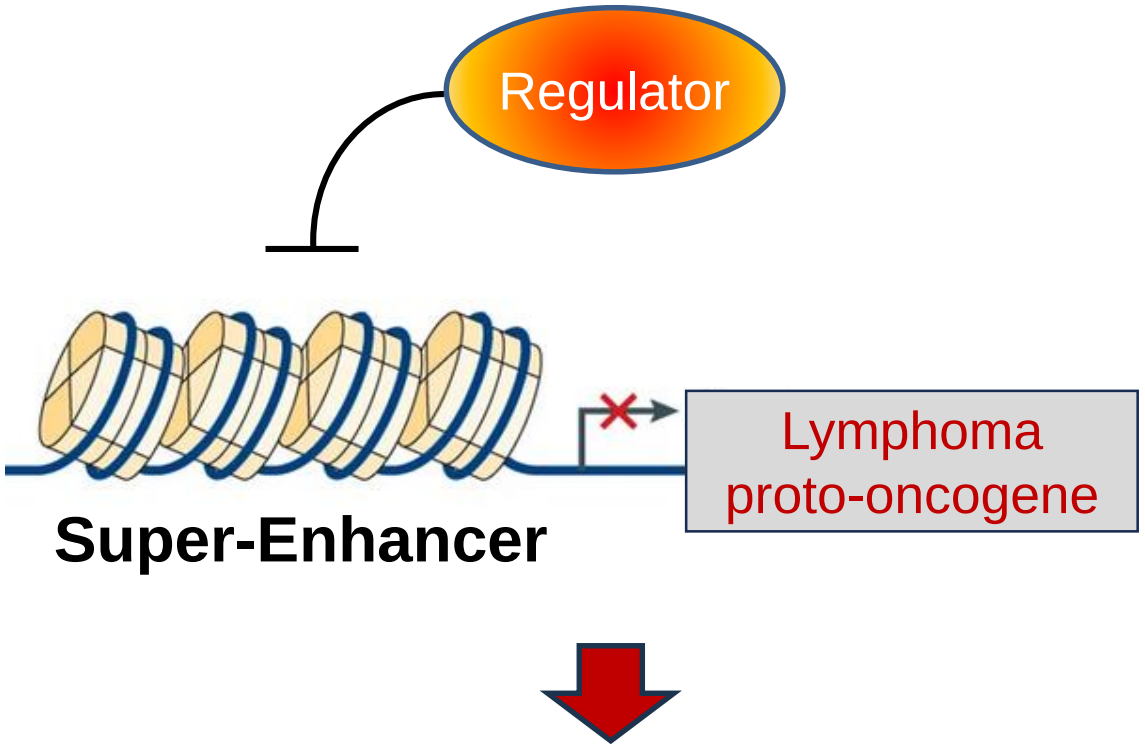


DLBCL

Pasqualucci et al., *Nature* 2001

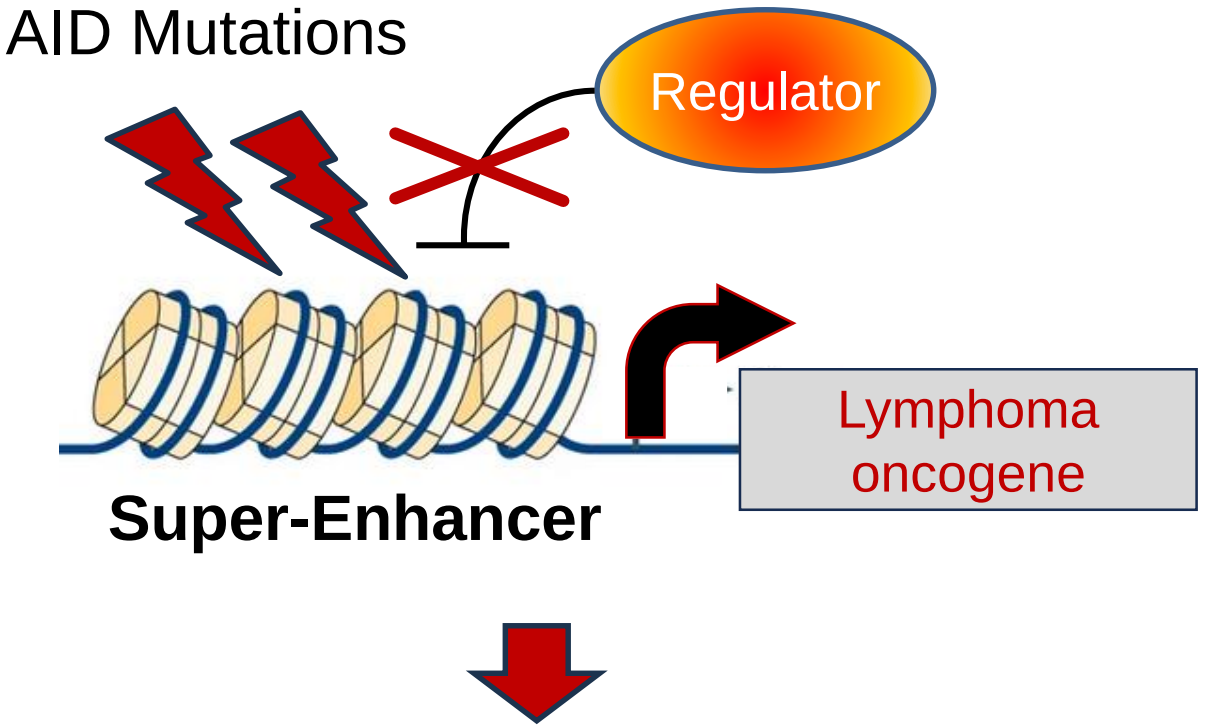
Aberrant hypermutation of noncoding regulatory domains (super-enhancers) deregulate expression of multiple oncogenes

Normal GC B cell



Controlled gene expression

DLBCL (>90% of cases)



Deregulated gene expression

Shen et al., *Science* 1998; Pasqualucci et al, *PNAS* 1998

Bal et al., *Nature*, 2022

Lymphoma Classification

Historical background of lymphoma classification

Classification	*Year*	*Criteria*
Rappaport	‘60	morphology
Kiel, Lukes & Collins	‘70	morphology, phenotype
Working Formulation	‘80	morphology, phenotype, clinical
REAL	‘90	morphology, phenotype, clinical, genetics
WHO	2001, 2008, 2016, 2022	*Refinement, nomenclature, provisional entities*
ICC	2022	

Two new classification systems for B cell lymphoid neoplasms in 2022

- WHO 5th edition (WHO HAEM5) (Leukemia 2022;36:1720)
- International Consensus Classification (ICC) (Blood 2022;140:1229)

•Reflect advancements in genomic profiling and evidence based clinical data

•Updates include
  - •newly defined subtypes
  - •more encompassing umbrella terms
  - •deletion of old entities
  - •modified nomenclature
  - •putative new entities with limited data are designated as provisional in WHO HAEM4 and ICC but no provisional designation exists in WHO HAEM5

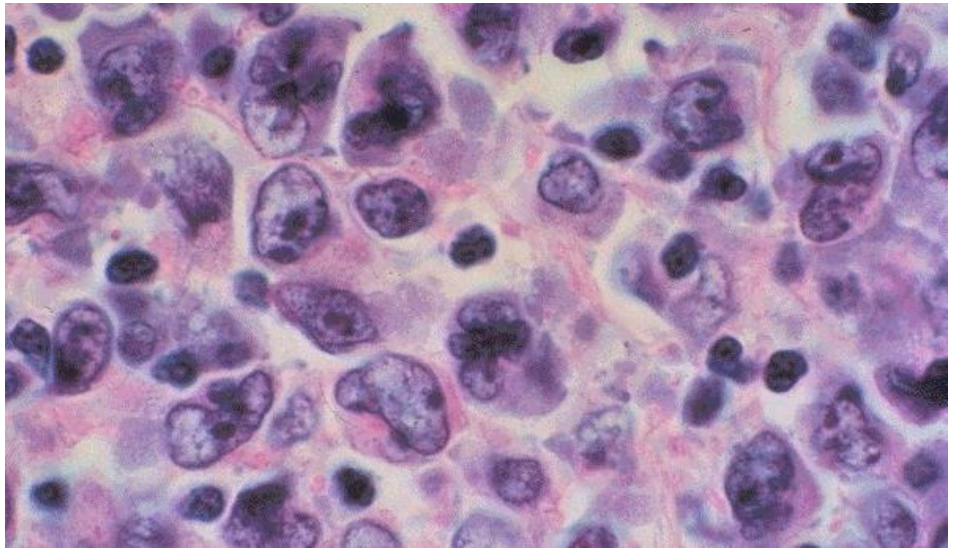
Two new classification systems for B cell lymphoid neoplasms in 2022

WHO HAEM4R	WHO HAEM5	ICC
Large B cell lymphoma		
Diffuse large B cell lymphoma (DLBCL), NOS	Diffuse large B cell lymphoma, NOS	Diffuse large B cell lymphoma, NOS
EBV positive mucocutaneous ulcer*	EBV positive mucocutaneous ulcer	EBV positive mucocutaneous ulcer
EBV positive diffuse large B cell lymphoma, NOS	EBV positive diffuse large B cell lymphoma	EBV positive diffuse large B cell lymphoma, NOS
Diffuse large B cell lymphoma associated with chronic inflammation	Diffuse large B cell lymphoma associated with chronic inflammation	Diffuse large B cell lymphoma associated with chronic inflammation
Primary large B cell lymphoma of the central nervous system	Primary large B cell lymphoma of immune privileged sites (new umbrella term for DLBCL arising in the CNS, vitreoretina and testis)	Primary diffuse large B cell lymphoma of central nervous system
Not included		Primary diffuse large B cell lymphoma of testis
Primary cutaneous diffuse large B cell lymphoma, leg type	Primary cutaneous diffuse large B cell lymphoma, leg type	Primary cutaneous diffuse large B cell lymphoma, leg type
Intravascular large B cell lymphoma	Intravascular large B cell lymphoma	Intravascular large B cell lymphoma
ALK positive large B cell lymphoma	ALK positive large B cell lymphoma	ALK positive large B cell lymphoma
Plasmablastic lymphoma	Plasmablastic lymphoma	Plasmablastic lymphoma
Large B cell lymphoma with *IRF4* rearrangement	Large B cell lymphoma with *IRF4* rearrangement	Large B cell lymphoma with *IRF4* rearrangement
Primary mediastinal large B cell lymphoma	Primary mediastinal large B cell lymphoma	Primary mediastinal large B cell lymphoma
B cell lymphoma, unclassified with features intermediate between DLBCL and classic Hodgkin lymphoma	Mediastinal gray zone lymphoma (cases without mediastinal involvement are classified as DLBCL, NOS)	Mediastinal gray zone lymphoma

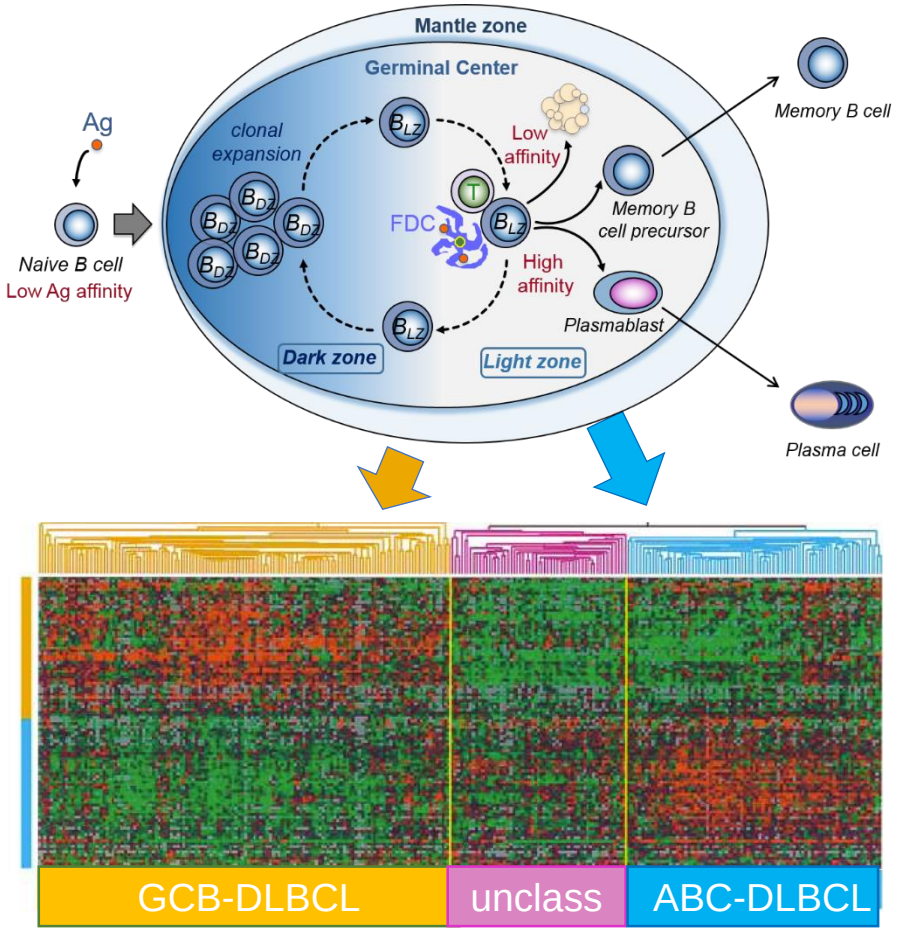
What are the genes/pathways that must be disrupted in order to make a DLBCL?

Diffuse Large B cell Lymphoma

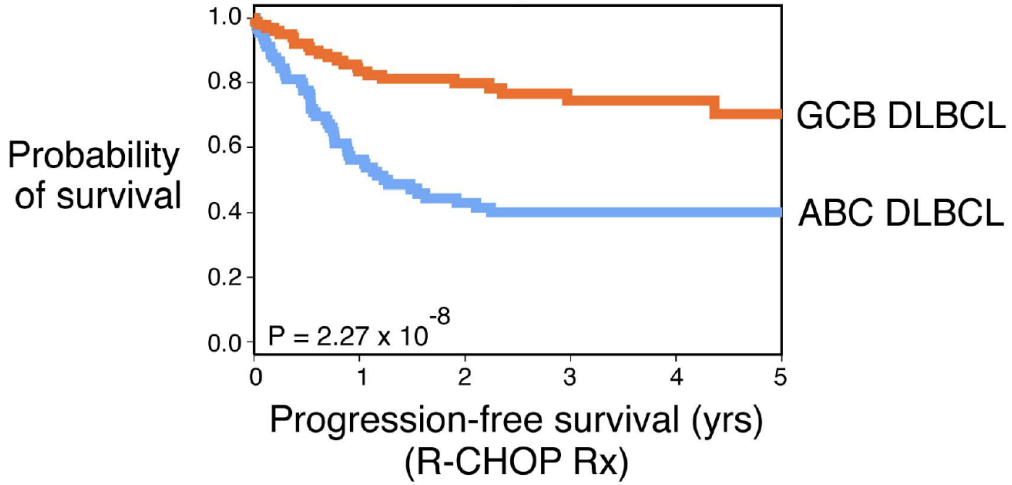
- Most common lymphoma diagnosis
- Incurable in ~30% of patients
- Biologically and clinically heterogeneous
- Multiple transcriptionally defined subtypes
- Distinct clinical outcome



Cell of Origin Classification of DLBCL

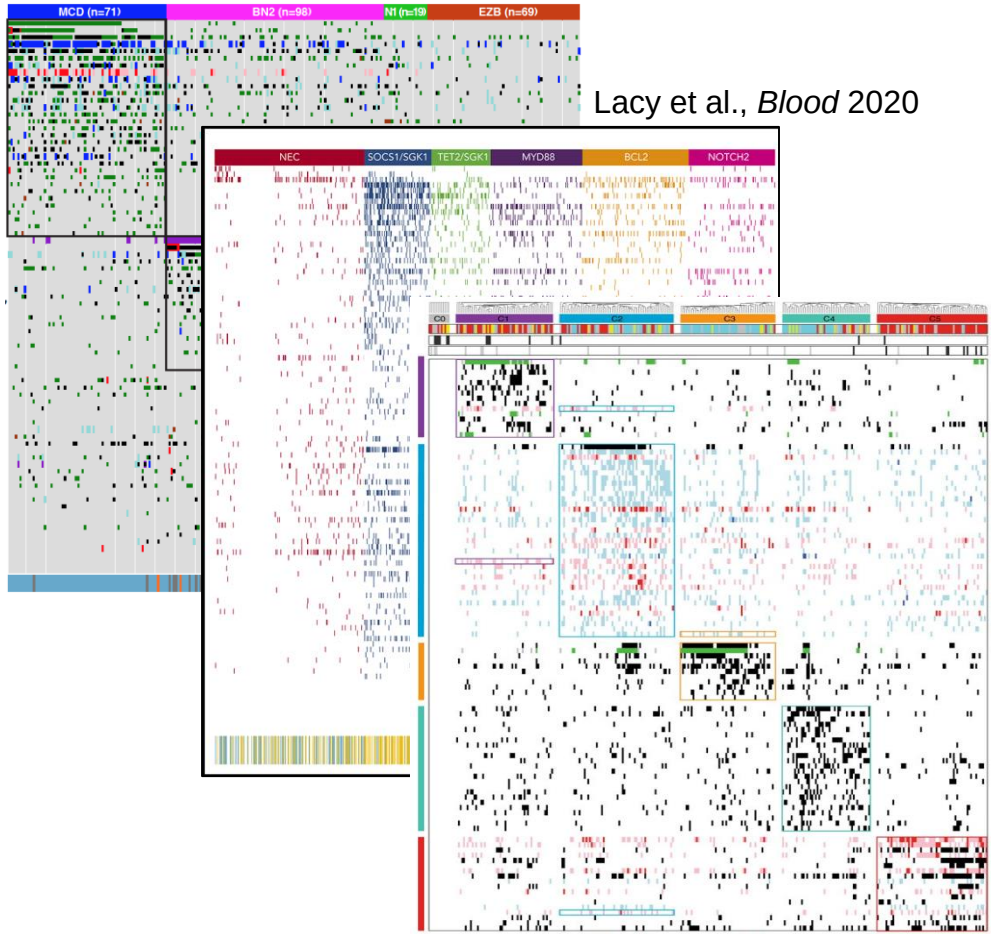


Alizadeh et al, *Nature* 2000; Rosenwald et al, *NEJM* 2002



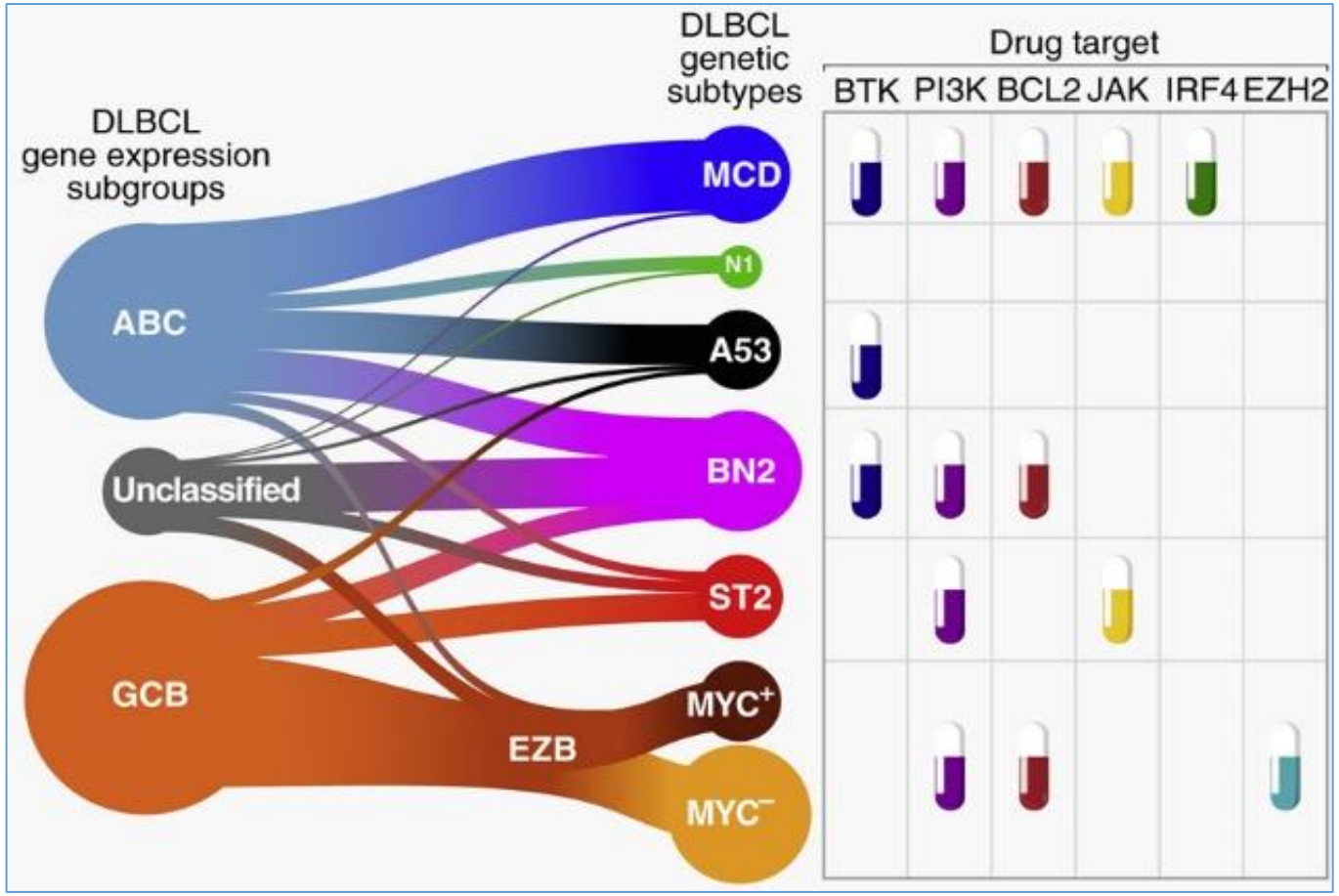
Genetic Classifications of DLBCL based on the pattern of concurrent mutations

Schmitz et al, *NEJM 2018*



Lacy et al., *Blood* 2020

Chapuy et al, *Nature Med 2018*



Wright et al, *Cancer Cell 2020*

DLBCL subtypes are addicted to distinct oncogenic lesions

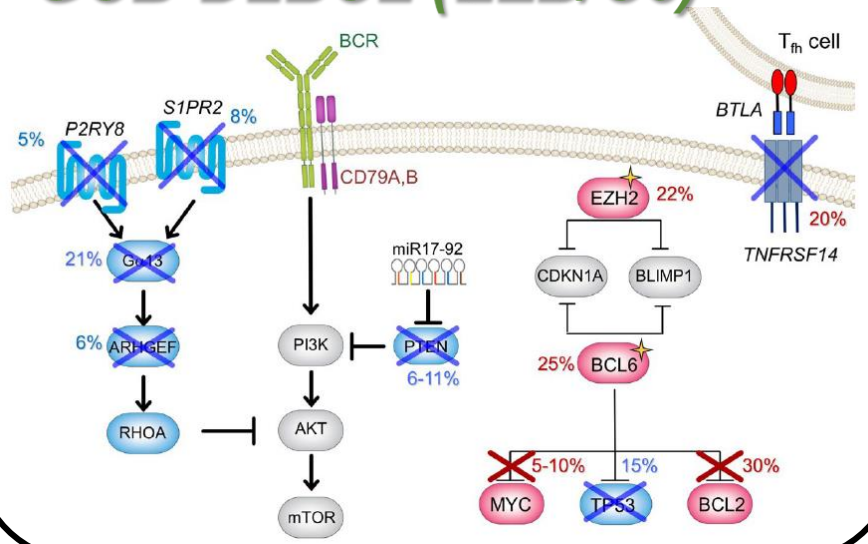
Epigenetic Remodeling
(*KMT2D M, CREBBP M, Histone H1 M, TET2 M – in different subtypes*)

Deregulation of BCL6 activity
(*BCL6 Tx, FBXO11 M, MEF2B M*)

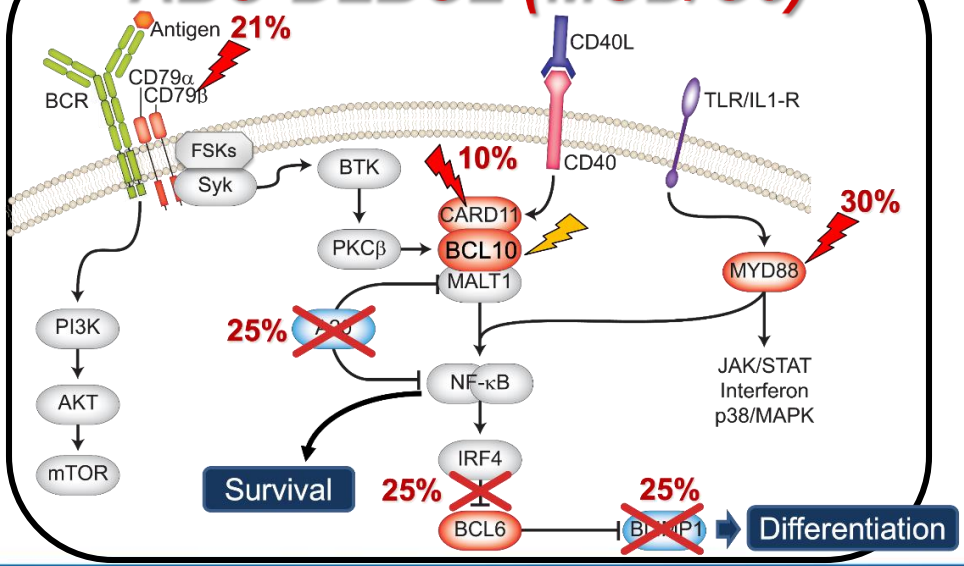
Escape from immune surveillance (CTL + NK)
(*B2M* M, *HLA-I* M, *CD58*M)

Shared

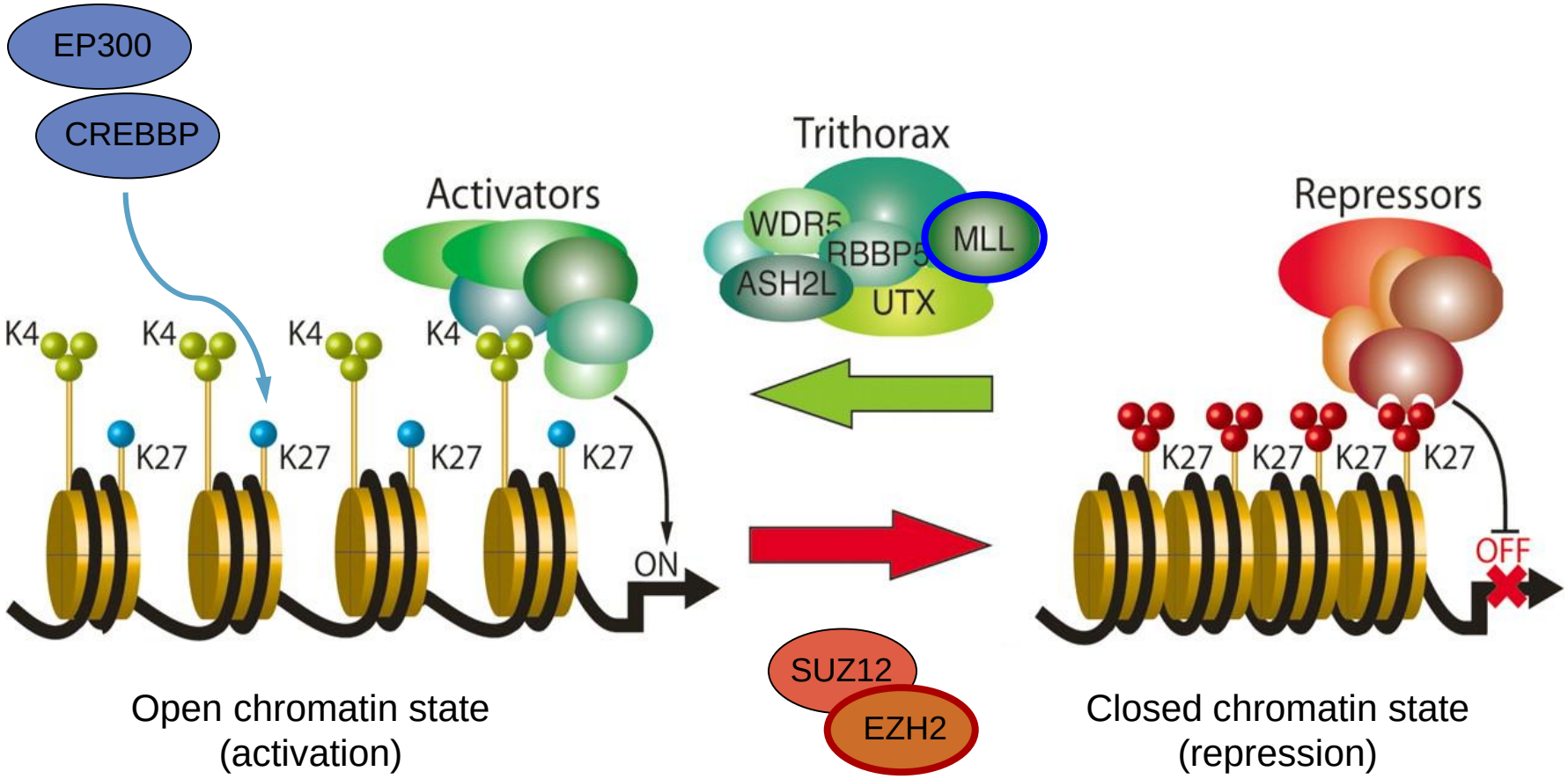
GCB-DLBCL (EZB/C3)



ABC-DLBCL (MCD/C5)

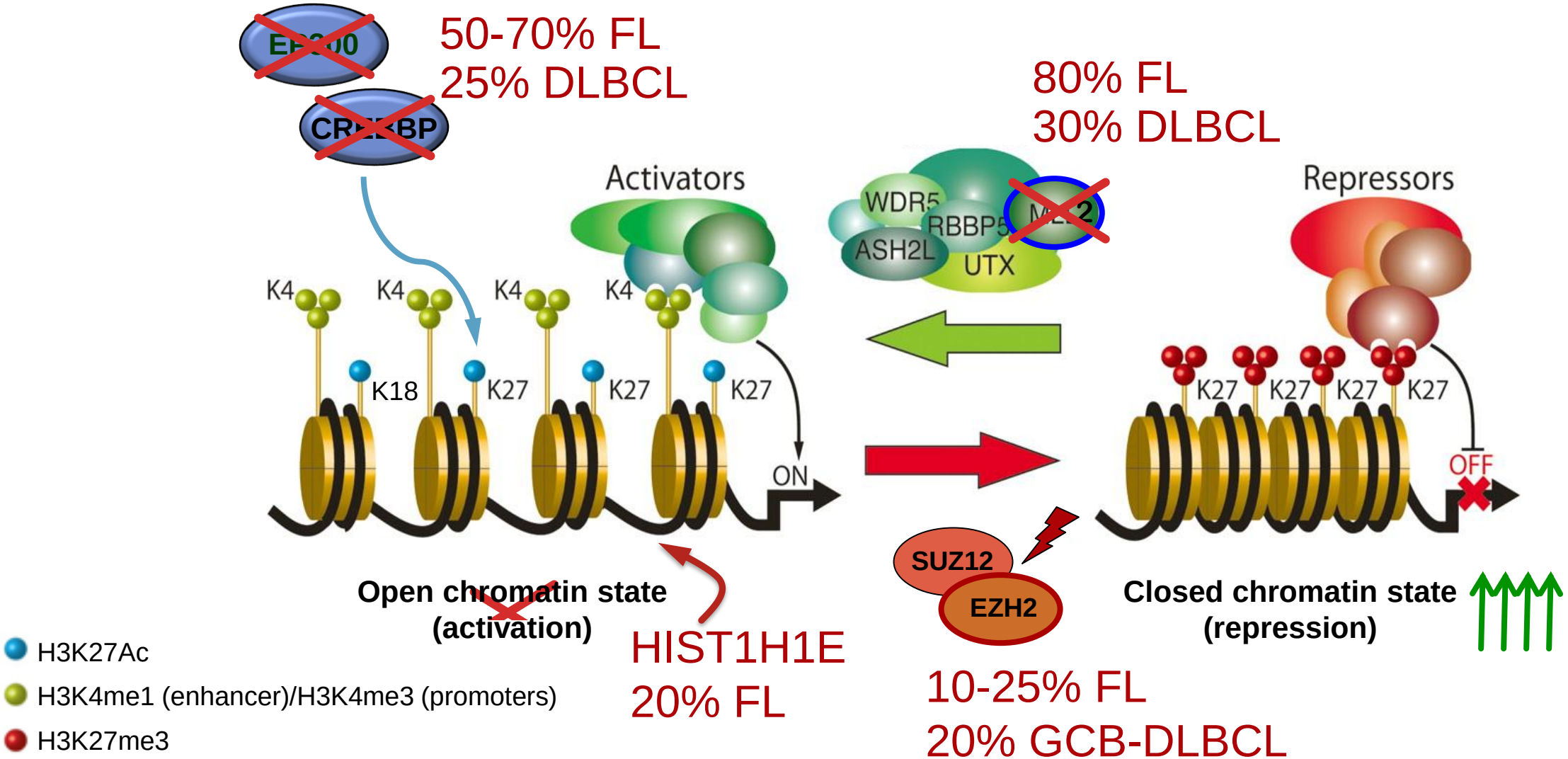


Epigenetic mechanisms and transcriptional regulation



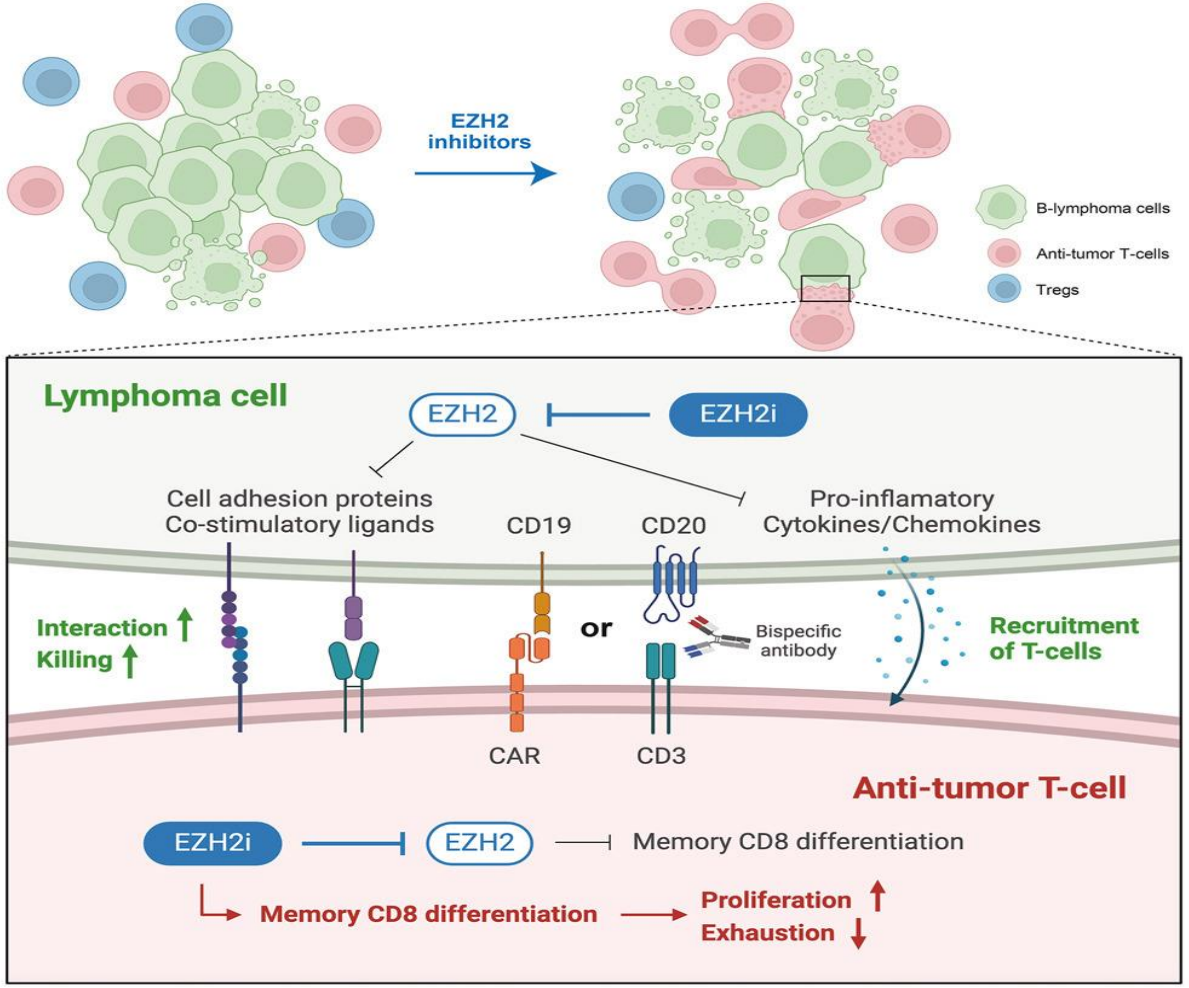
- H3K27Ac
- H3K4me1 (enhancer)/H3K4me3 (promoters)
- H3K27me3

Mutations in histone/chromatin modifier genes are a hallmark of GC-derived lymphomas



“Epigenetic” therapies (EZH2 inhibition) may prime T cells and the microenvironment for immunotherapy

- EZH2 inhibition increases immunogenicity of lymphoma cells and T cell interaction
- EZH2 inhibition sensitizes lymphoma to T cell immunotherapies
- EZH2 inhibition prevents T cell exhaustion by promoting a memory phenotype



Isshiki and Béguelin, Cancer Cell 2024

DLBCL subtypes are addicted to distinct oncogenic lesions

Epigenetic Remodeling

(*KMT2D M, CREBBP M, Histone H1 M, TET2 M – in different subtypes*)

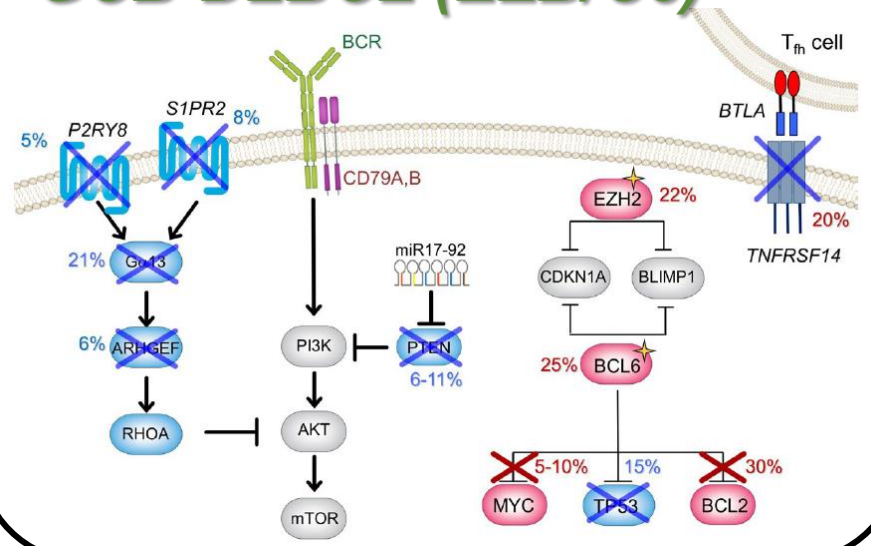
Deregulation of BCL6 activity

(*BCL6 Tx, FBXO11 M, MEF2B M*)

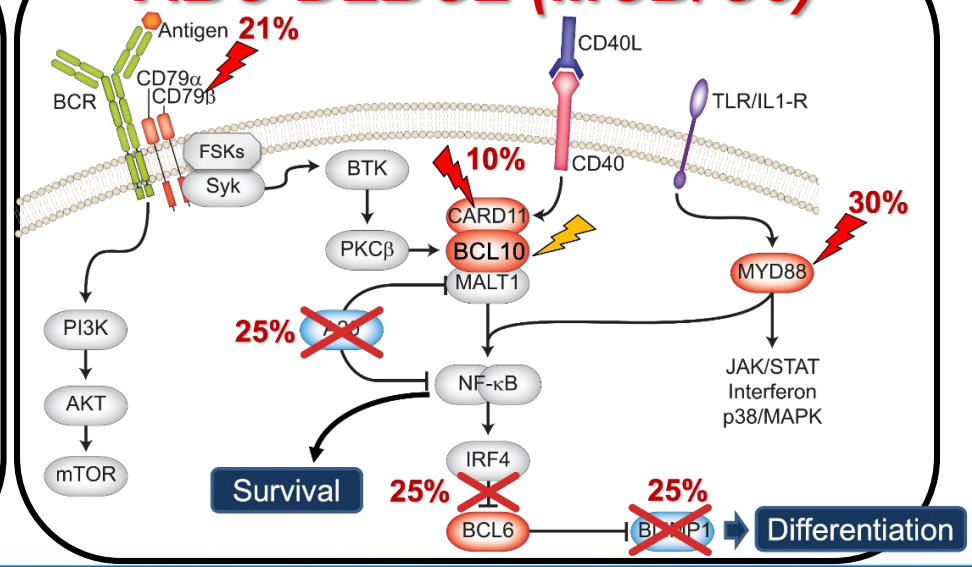
Escape from immune surveillance (CTL + NK)

(*B2M* M, *HLA-I* M, *CD58*M)

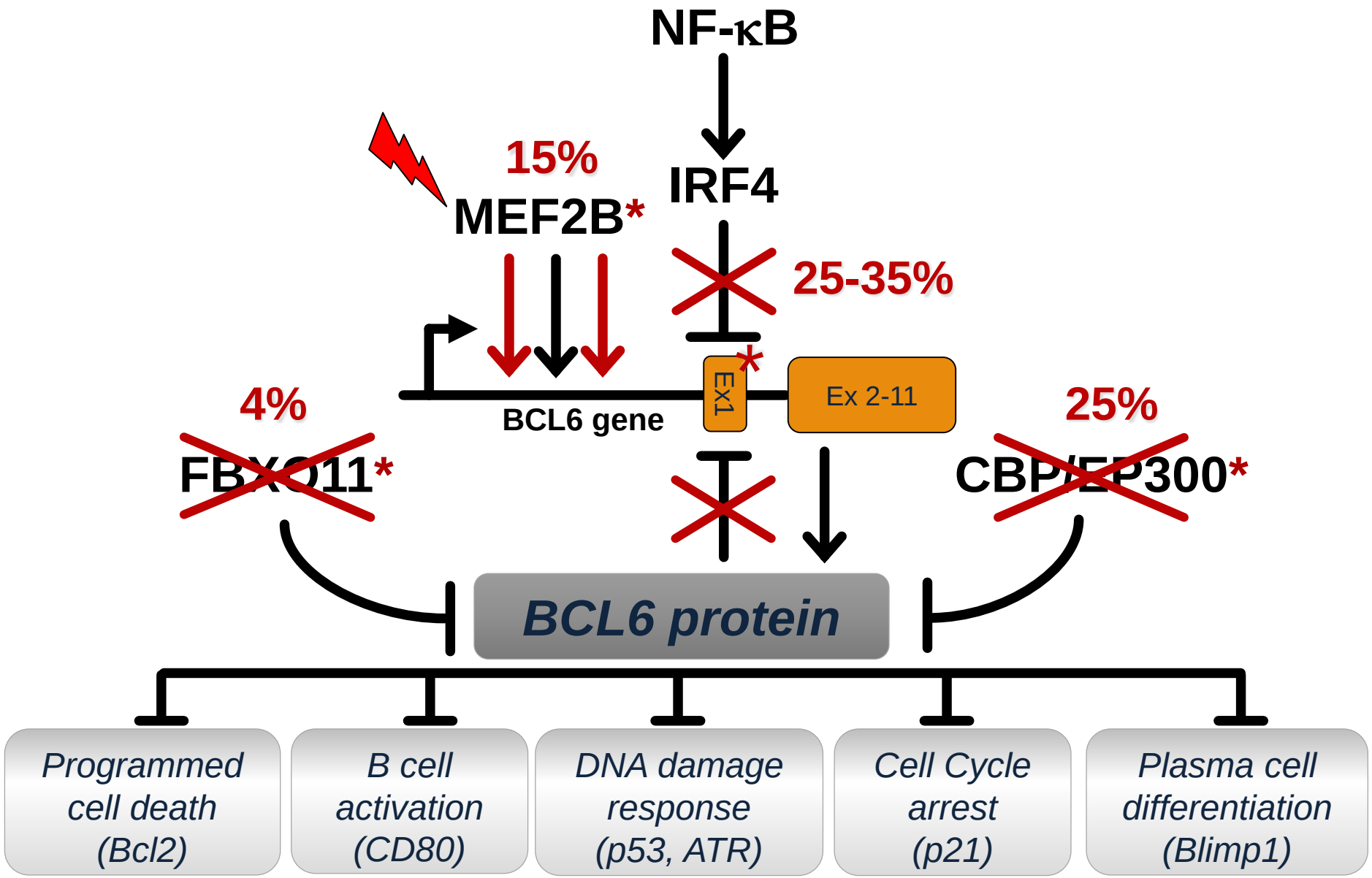
GCB-DLBCL (EZB/C3)



ABC-DLBCL (MCD/C5)



Multiple genetic alterations deregulate BCL6 activity in DLBCL



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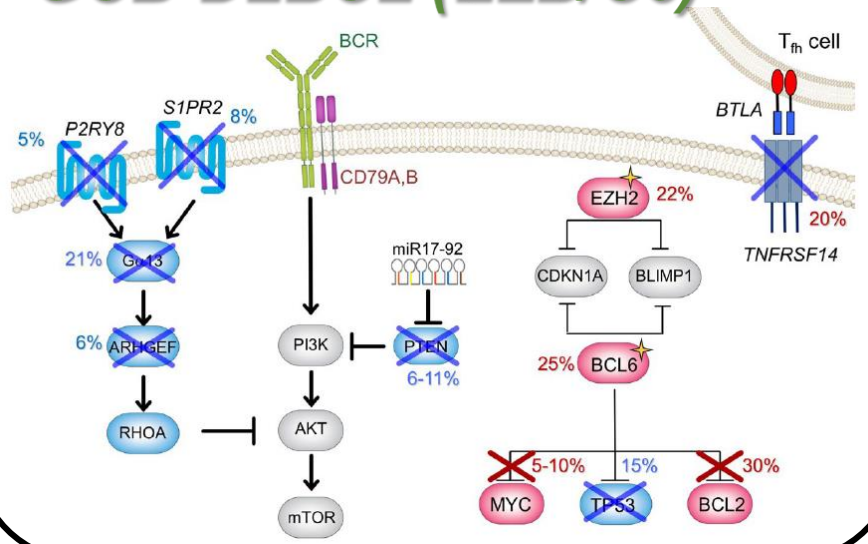
Deregulation of BCL6 activity
(*BCL6 Tx, FBXO11 M, MEF2B M*)

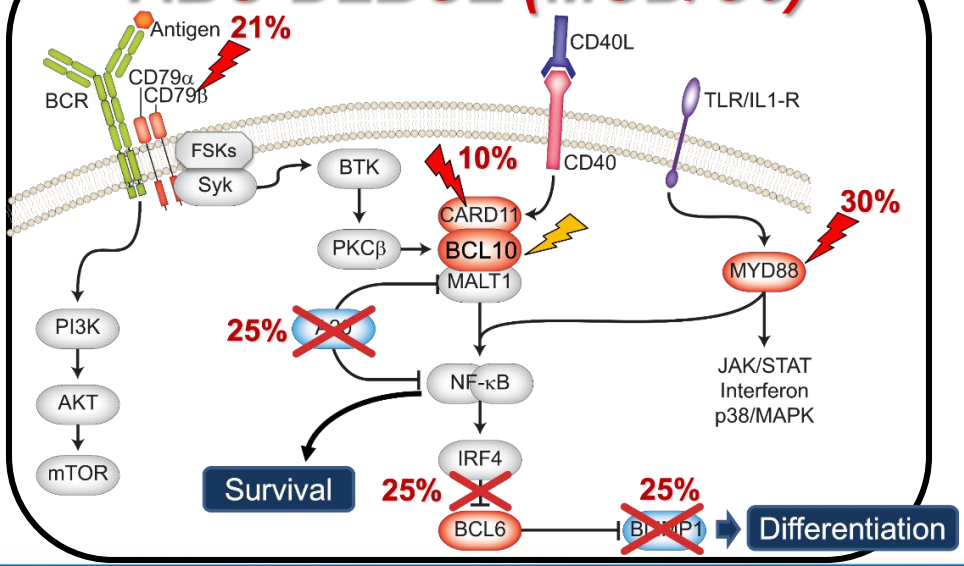
Escape from immune surveillance (CTL + NK)
(*B2M* M, *HLA-I* M, *CD58* M, *CD70* M)

Enriched in C1/BN2-DLBCL

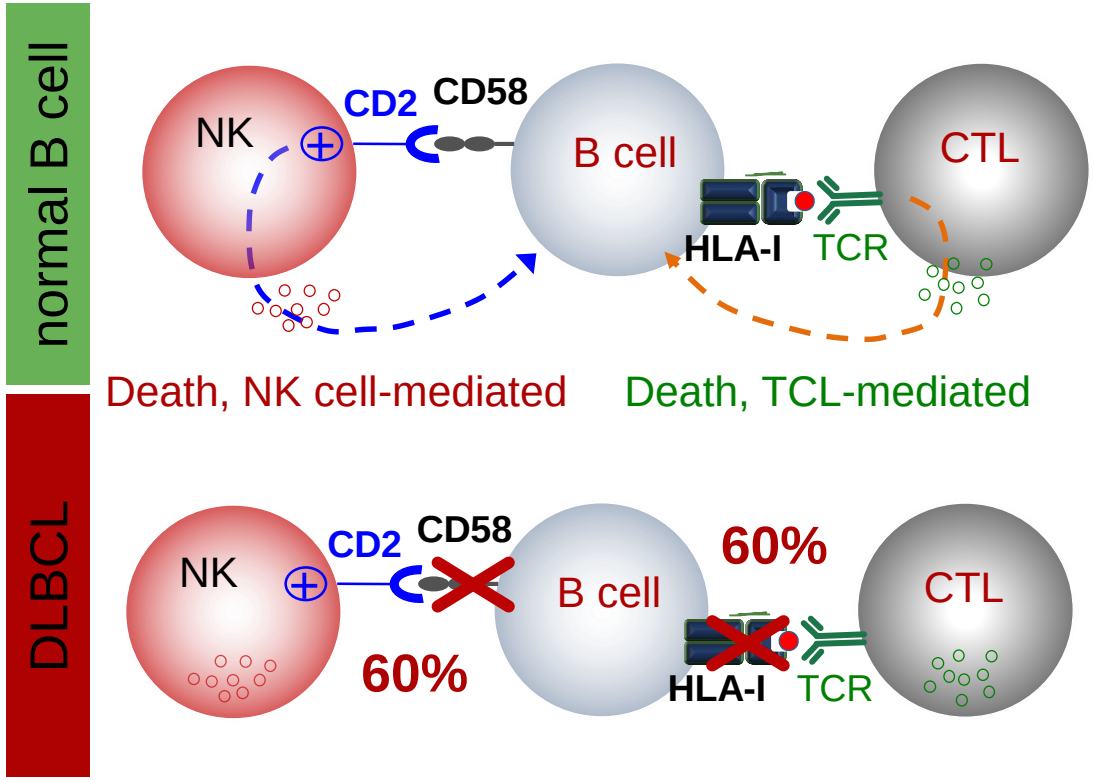
GCB-DLBCL (EZB/C3)

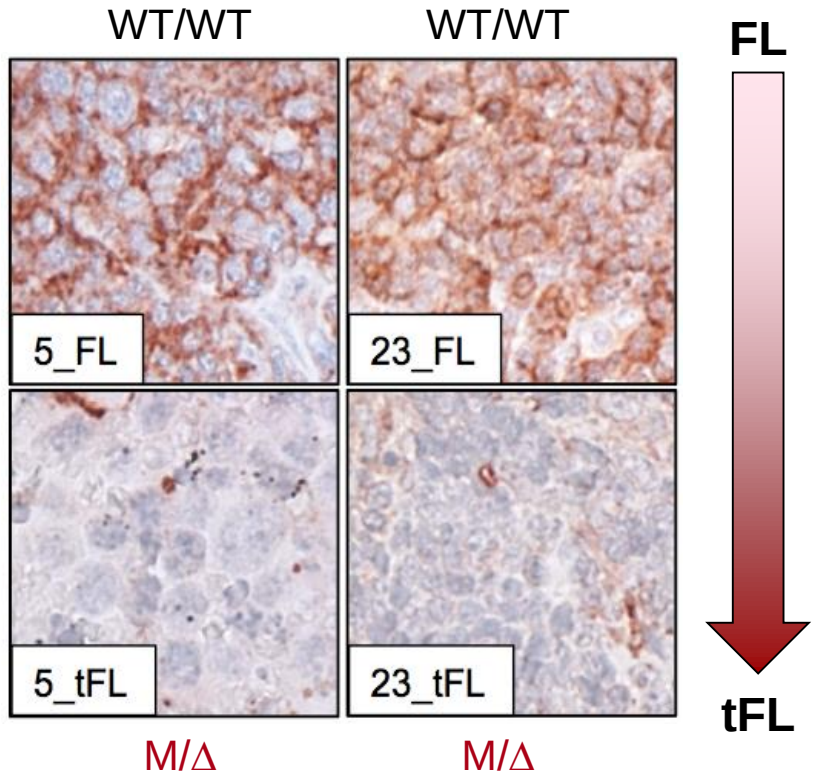


ABC-DLBCL (MCD/C5)



Concurrent loss of HLA-I and CD58 allows escape from CD8+ and NK-cell mediated immune surveillance



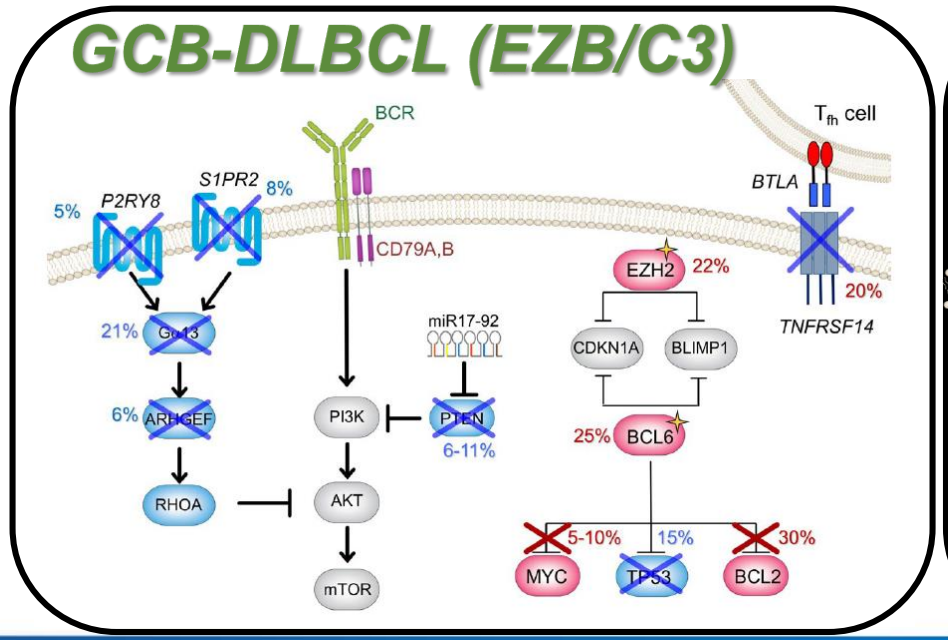


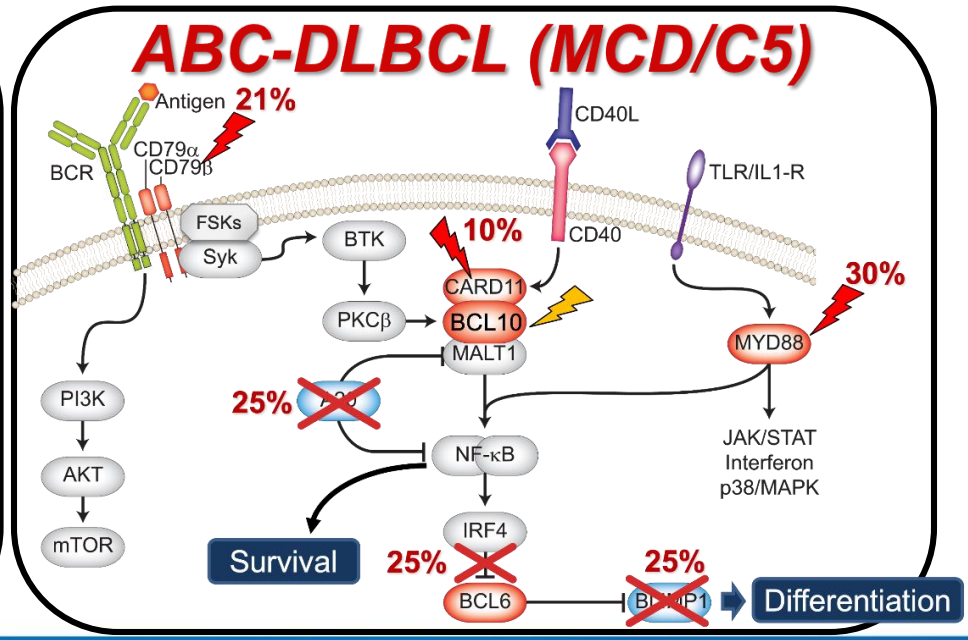
DLBCL subtypes are addicted to distinct oncogenic lesions

Epigenetic Remodeling
(*KMT2D M, CREBBP M, Histone H1 M, TET2 M – in different subtypes*)

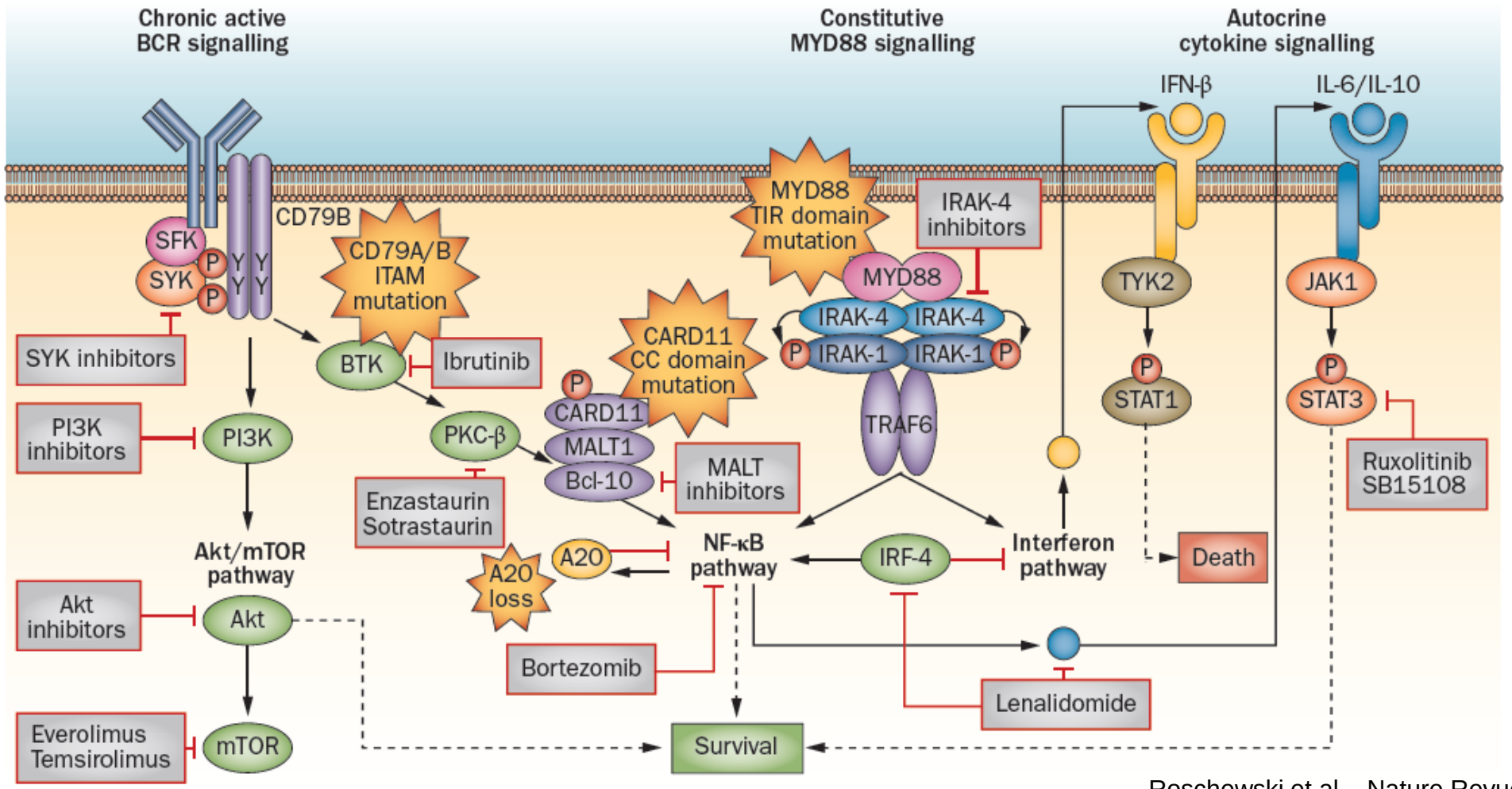
Deregulation of BCL6 activity
(*BCL6 Tx, FBXO11 M, MEF2B M*)

Escape from immune surveillance (CTL + NK)
(*B2M* M, *HLA-I* M, *CD58*M)



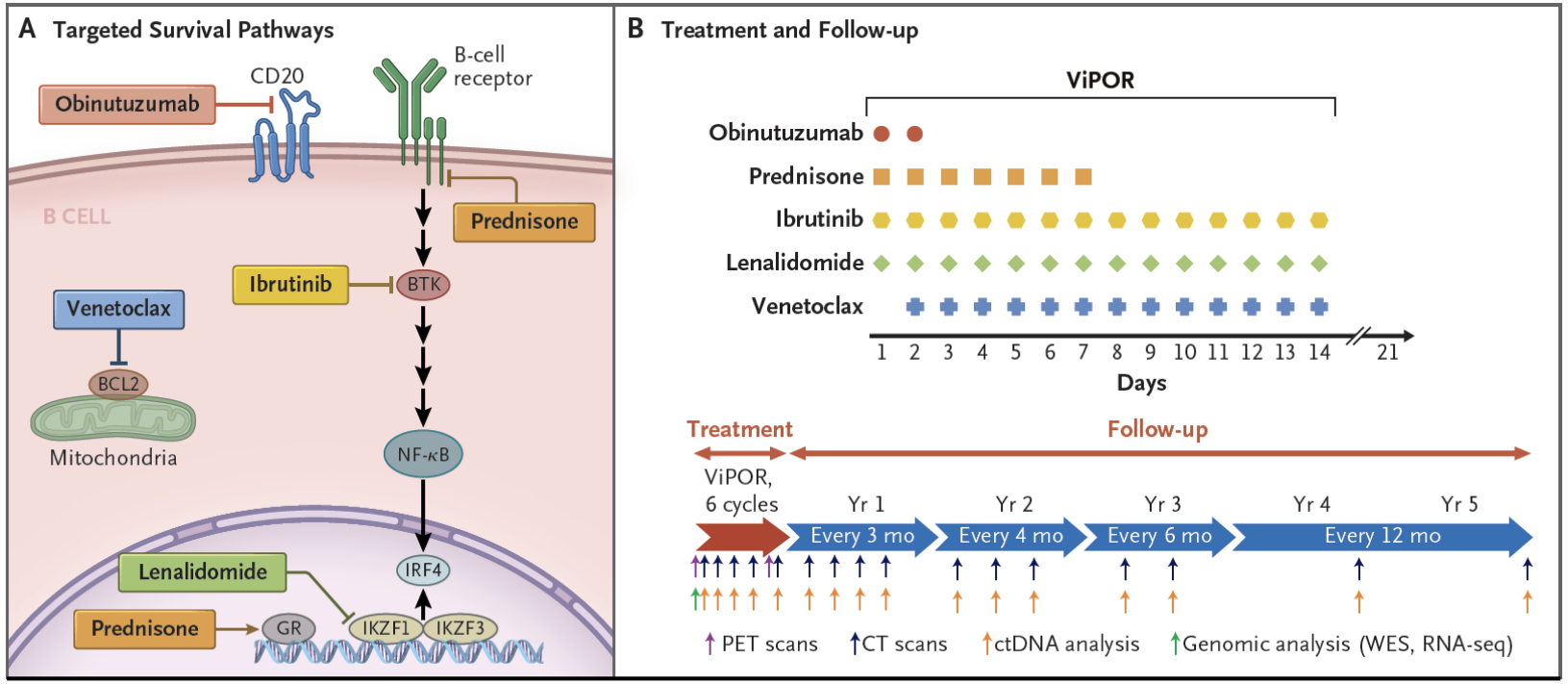


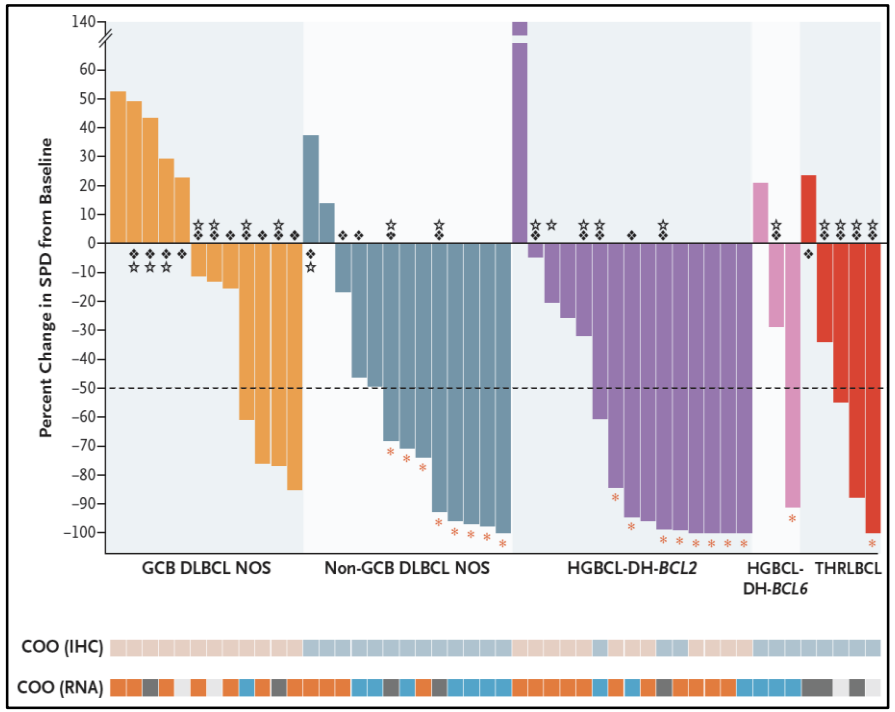
Targeting genetic addictions in ABC-DLBCL



Roschewski et al., Nature Revuews Clin Oncol 2014

ViPER: Combination Targeted Therapy in Relapsed DLBCL





Single-center, phase 1b–2 study in relapsed or refractory DLBCL.

Melani et al., *NEJM* 2024

Key Take-aways

- The pathogenesis of B cell lymphoma is tightly linked to the biology of the germinal center reaction
- Two main mechanisms of genetic alteration resulting for the malfunction of GC-associated physiological processes
- Recurrent genetic alterations in lymphoma have revealed new biology central to both the physiology and pathology of the germinal center
- Genetically-defined subtypes may benefit from specific combination targeted therapies >> *Understanding the mechanisms of tumor transformation and tumor heterogeneity is essential to advance cure rates*
- Pathogenic mutations in non-coding regulatory regions uncover a new layer in the genetics of DLBCL (and other tumors?) >> implications for precision diagnosis, classification, and targeted therapeutics

Learning Objectives

After attending this class, participants should be able to:

-Describe the relationship between B cell lymphomas and normal B cell developmental stages

-Illustrate the major mechanisms of genetic lesion that are associated with mature B cell non-Hodgkin lymphomas

-Define the most common targets of structural alterations in major lymphoma subtypes

-Explain how these lesions can favor malignant transformation

-Identify ways to utilize this information for diagnostic and therapeutic purposes