

La **DIAGNOSTICA** **EMATOPATOLOGICA** nell'ERA della **MEDICINA** di **PRECISIONE**

Tracking the origin of high-grade B cell lymphomas with *MYC* and *BCL2* rearrangements

Stefano Casola, MD, PhD

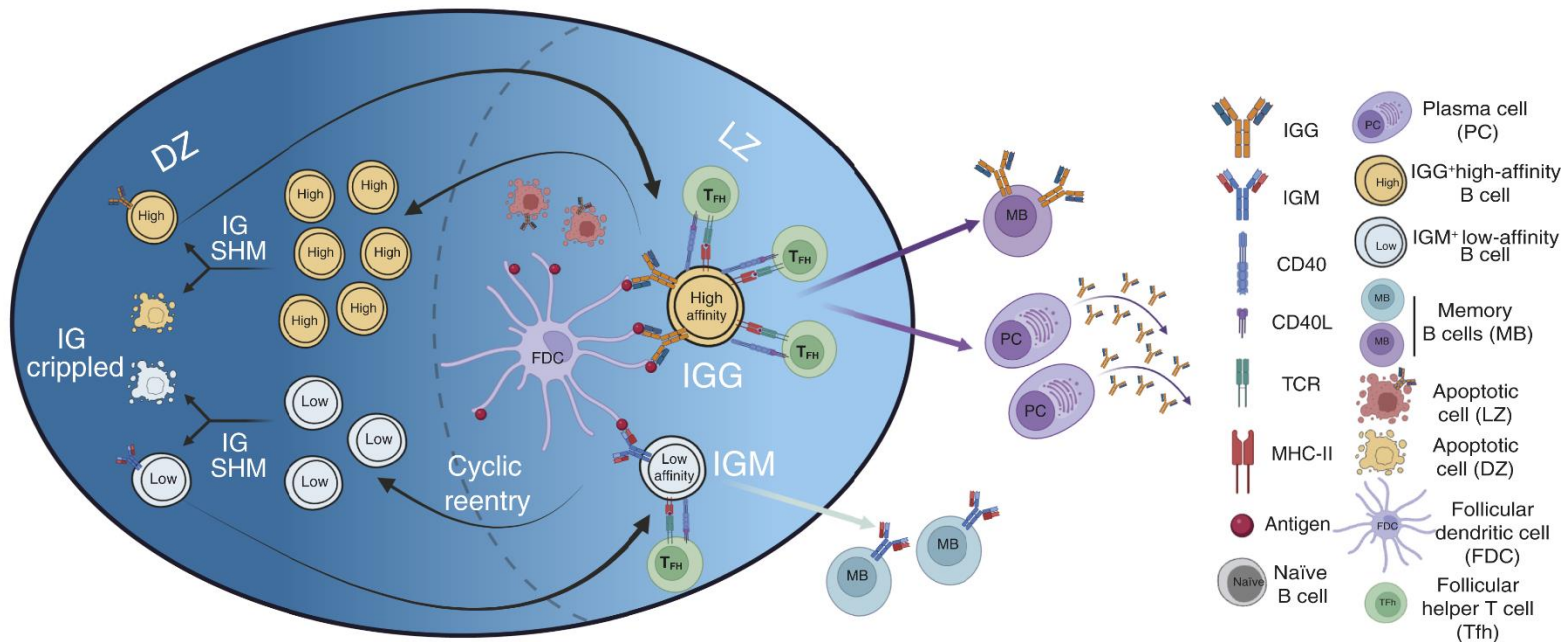


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University of Milan

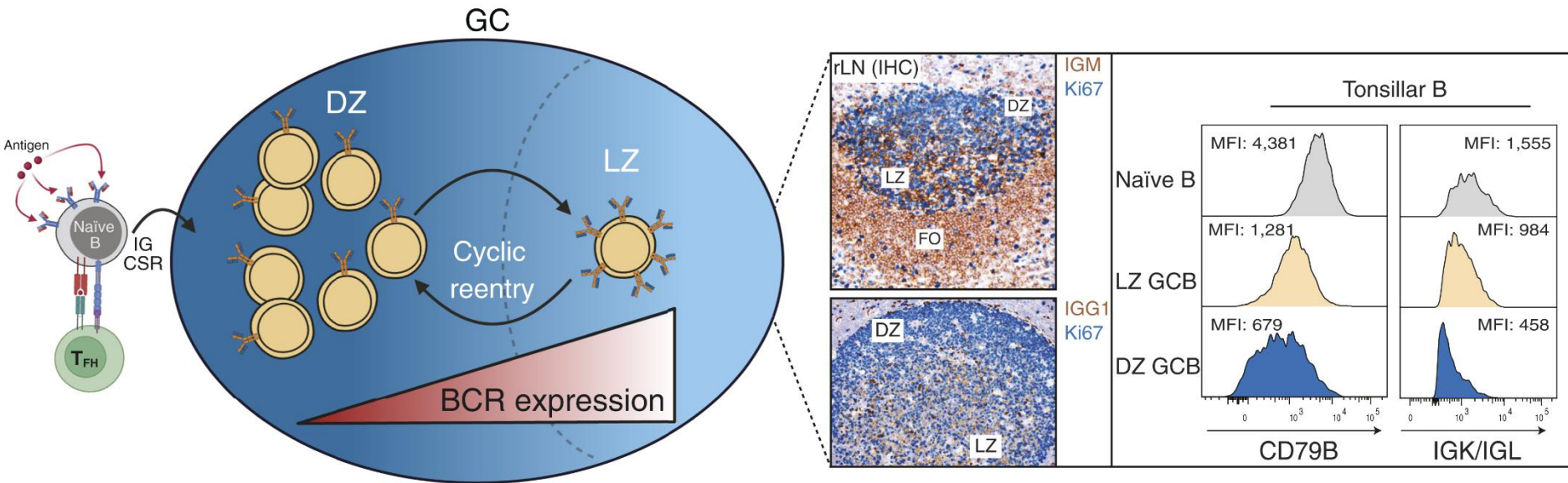
Nothing to disclose

The germinal center reaction: natural selection rules the game



Casola & Varano, *Blood Cancer Discov.* 2026

B cell receptor expression in the germinal center reaction



The BCR blueprint in mature B cell malignancies

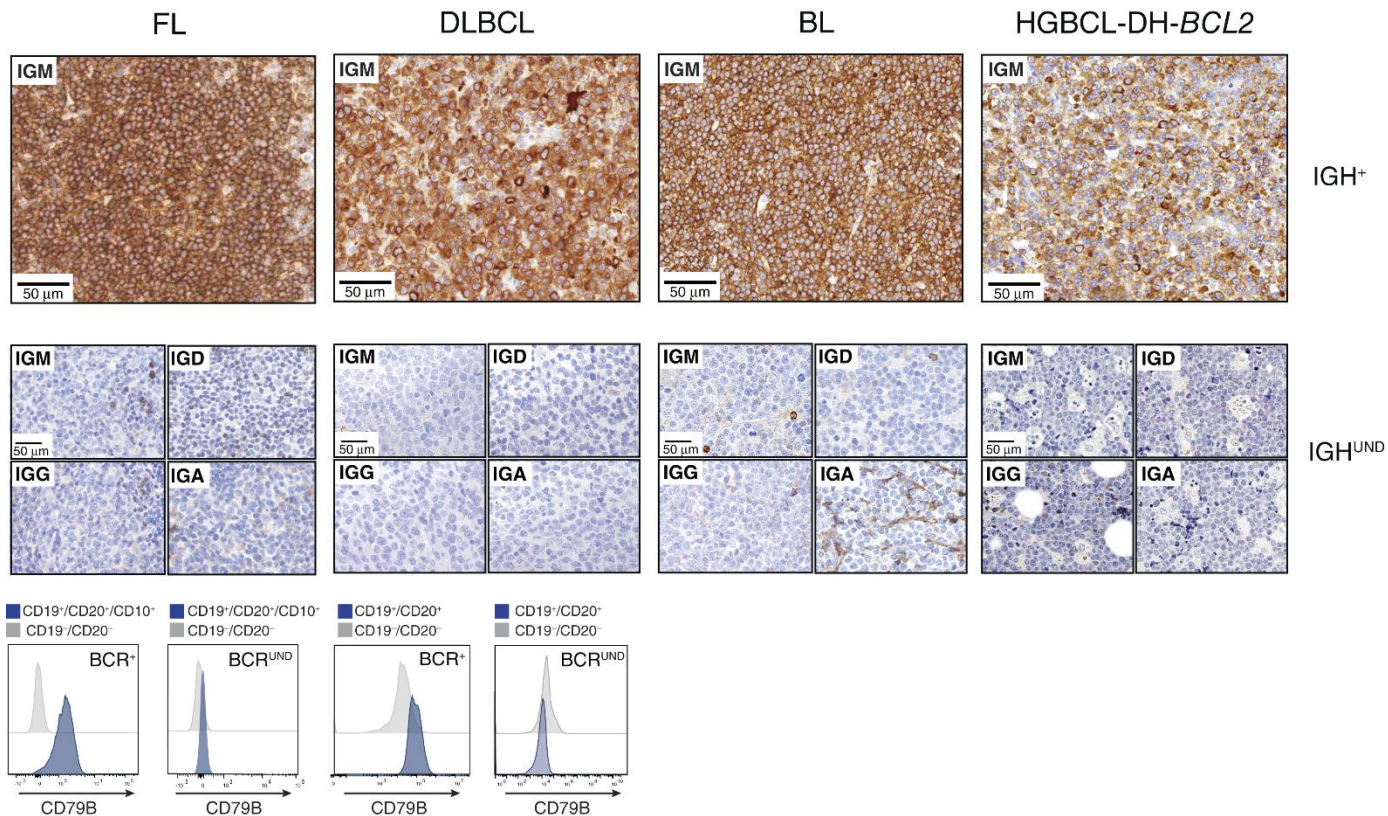
Mature B-cell neoplasm	CLL	MZL	MCL	BL	FL	DLBCL- EZB/C3 ST2/C4	HGBCL- DH-BCL2	DLBCL- MCD/C5 BN2/C1	WM	PTLD	PMBCL	cHL	NLPHL
Hallmarks													
Cell of origin	CD5 ⁺ B/Mem B	MZ/Mem B	FO/Mem B	GCB DZ	GCB	GCB	GCB DZ	GCB late LZ	Mem B/PB	GCB	GCB/post-GCB	GCB	GCB
BCR expression													
BCR signaling	CBM BTK/NF-κB PI3K/AKT mTOR RAS/MAPK	CBM BTK/NF-κB	PI3K/AKT mTOR BTK/NF-κB	PI3K/AKT mTOR	PI3K/AKT mTOR BTK/NF-κB RAS/MAPK	PI3K/AKT mTOR	PI3K/AKT mTOR	CBM BTK/NF-κB	CBM BTK/NF-κB	PI3K/AKT mTOR	NF-κB	NF-κB	CBM BTK/NF-κB PI3K/AKT
BCR class													
BCR enforcement/ bypass				<i>TCF3</i> <i>ID3</i> <i>NRAS</i>		<i>SGK1</i>	<i>MYC</i> <i>FBXW7</i> <i>BRAF</i> <i>SGK1</i>	<i>CARD11</i> <i>CD79A</i> <i>CD79B</i> <i>TCF4</i>	<i>CXCR4</i> <i>CD79B</i>	<i>EBV-LMP2A</i>	<i>JAK2</i> <i>SOCS1</i> <i>STAT6</i> <i>TNFAIP3</i> <i>PTPN1</i>	<i>EBV-LMP2A</i> <i>REL</i> <i>TNFAIP3</i> <i>SOCS1</i>	

Casola & Varano, Blood Cancer Discov. 2026

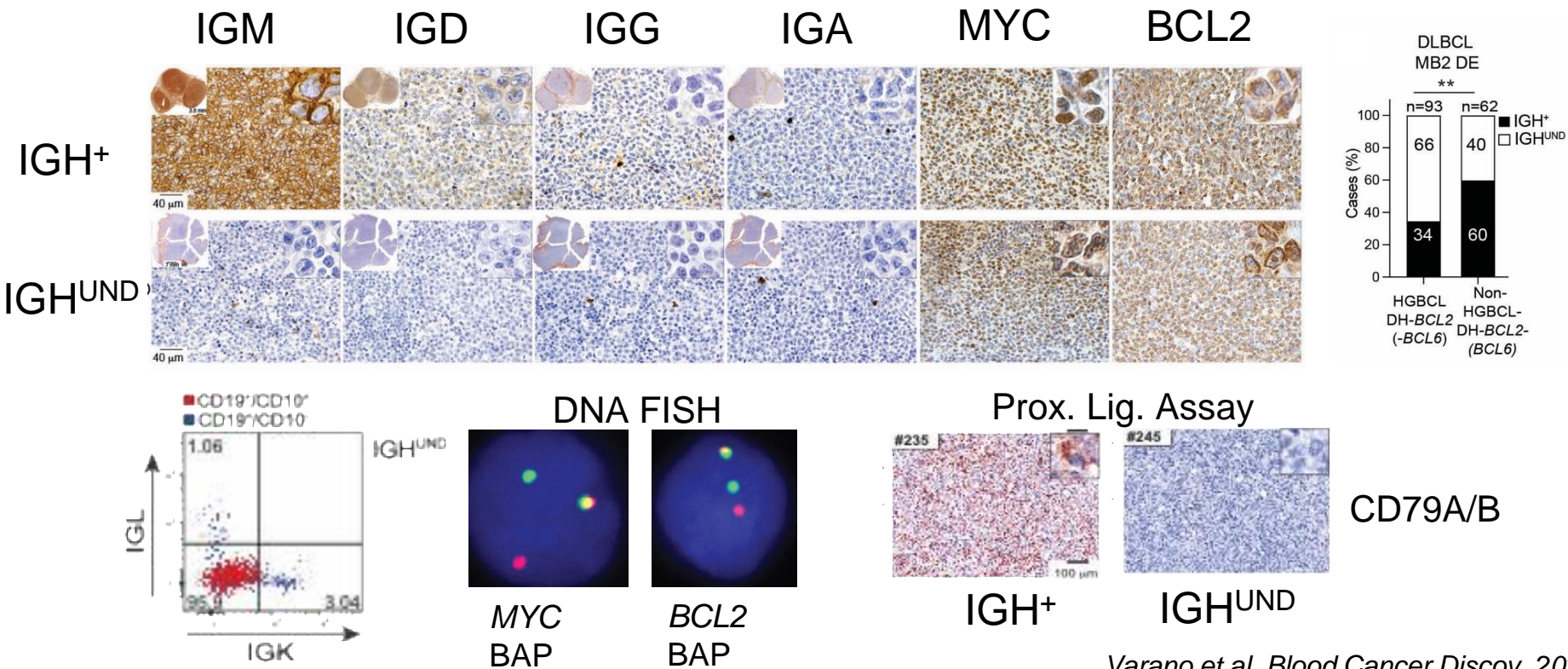
The BCR blueprint in mature B cell malignancies

Mature B-cell neoplasm	CLL	MZL	MCL	BL	FL	DLBCL- EZB/C3 ST2/C4	HGBCL- DH-BCL2	DLBCL- MCD/C5 BN2/C1	WM	PTLD	PMBCL	cHL	NLPHL
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BCR expression in GC-derived B cell malignancies



BCR silencing in MYC/BCL2 rearr.high-grade B cell lymphomas



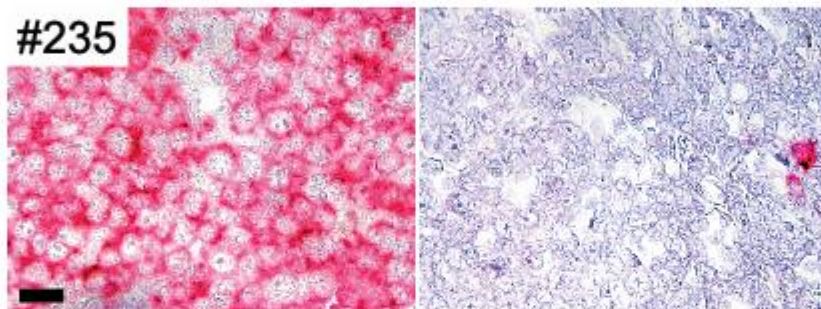
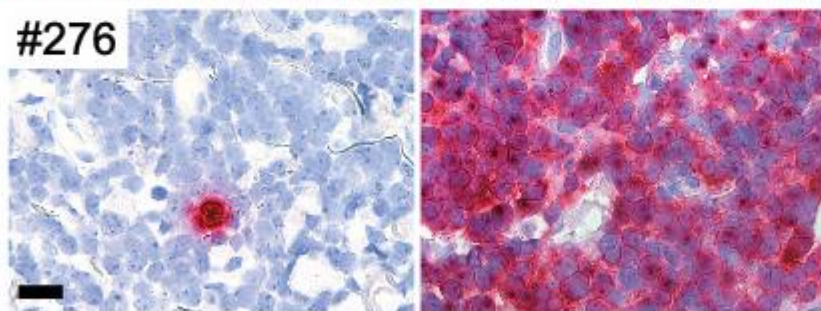
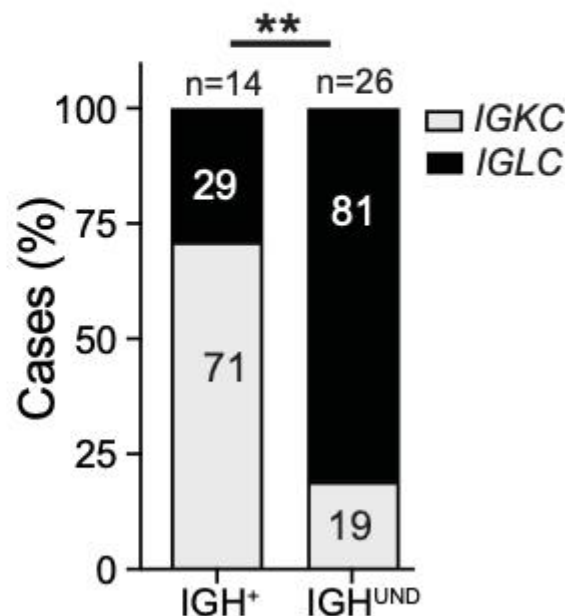
Varano et al. Blood Cancer Discov, 2025

IGL chain skewing in IGH^{UND} HGBCL-DH-*BCL2* (*BCL6*)

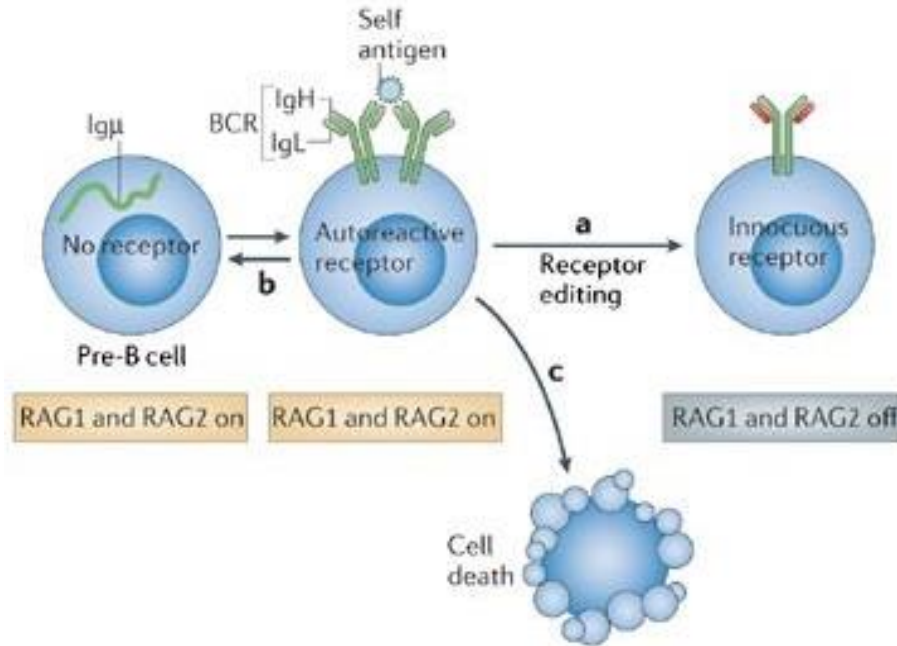
RNA scope

IGKC

IGLC

IGH⁺
HGBCL-DH-
BCL2-BCL6IGH^{UND}
HGBCL-DH-
BCL2HGBCL-DH-*BCL2* (-*BCL6*)

IG light chain revision in rescue of autoreactive B cells

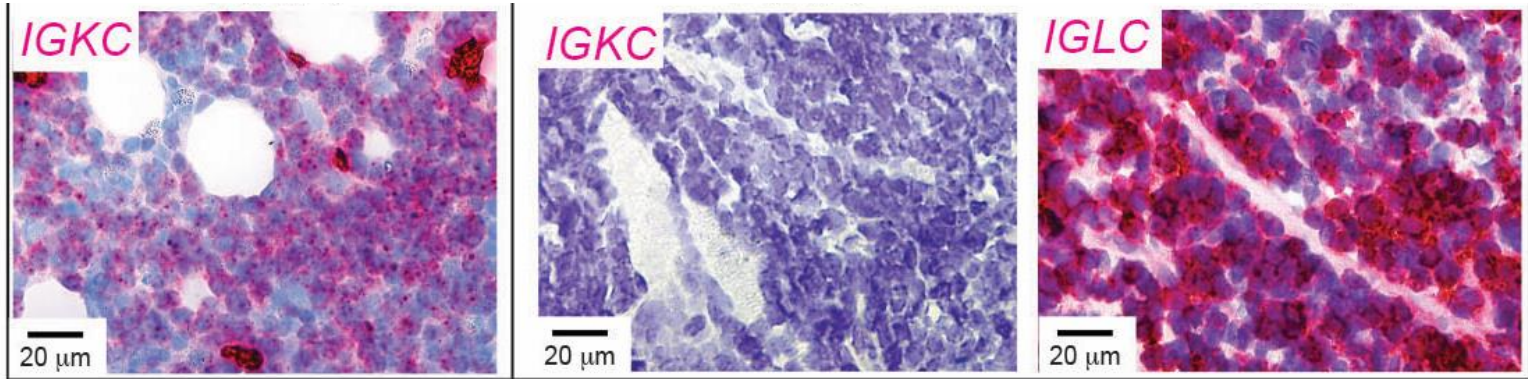


Ig-Kappa to Ig-lambda switch is a marker of receptor editing

IGK-to-IGL switch during HGBCL-DH-*BCL2-BCL6* progression

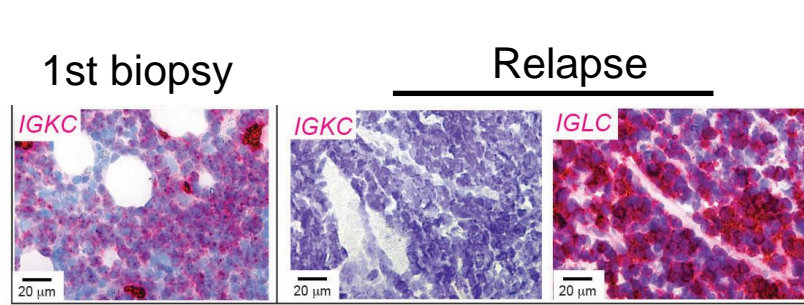
1st biopsy

Relapse

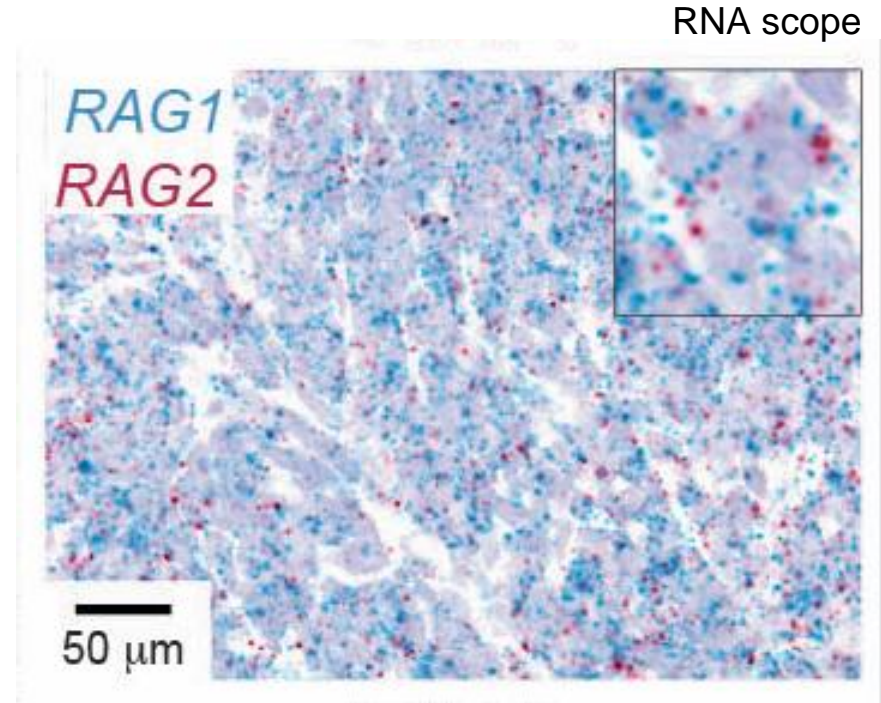


RNA scope

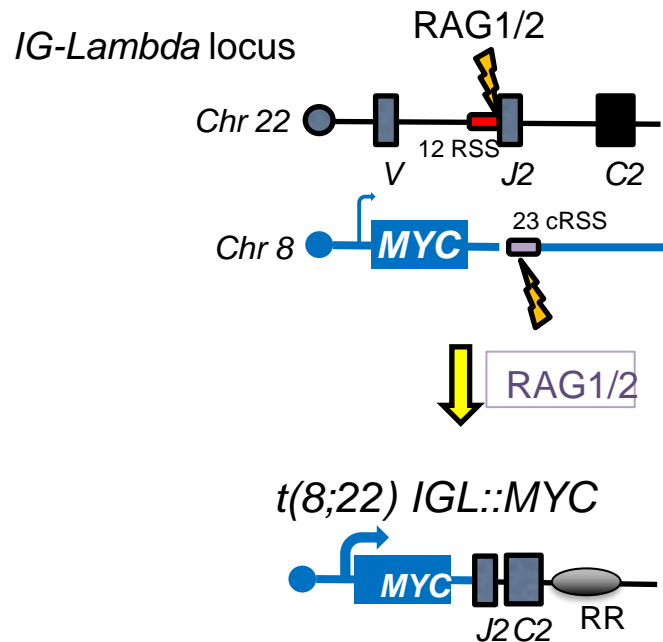
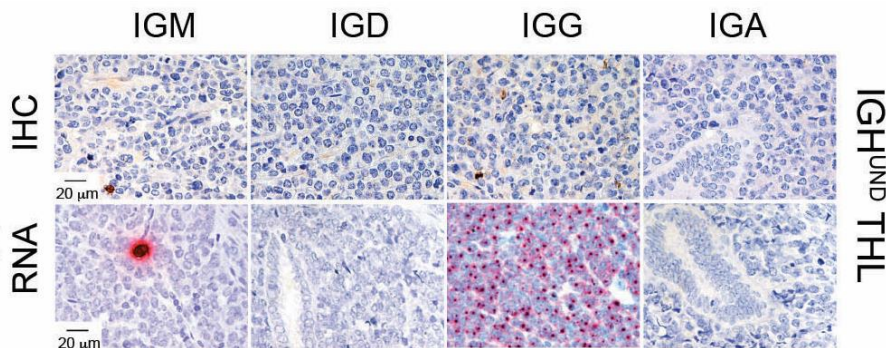
Ongoing IG light chain editing in lymphomas is linked to *RAG1/2* expression



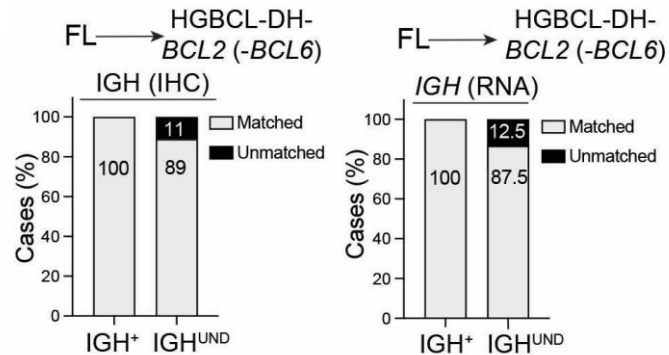
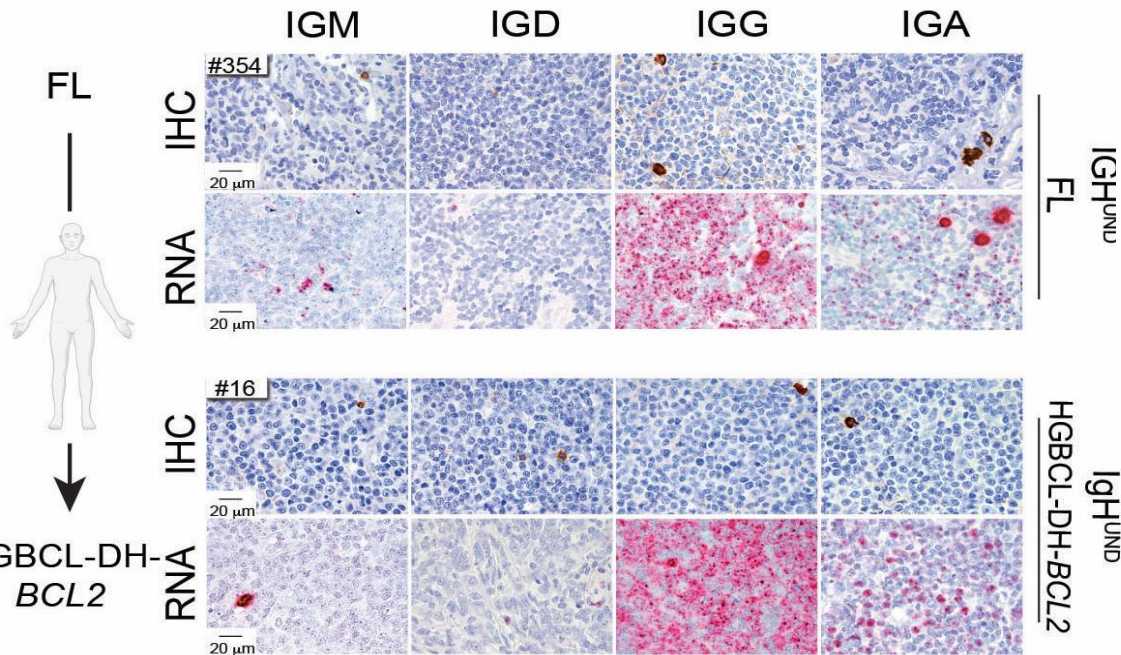
HGBCL-DH-*BCL2*



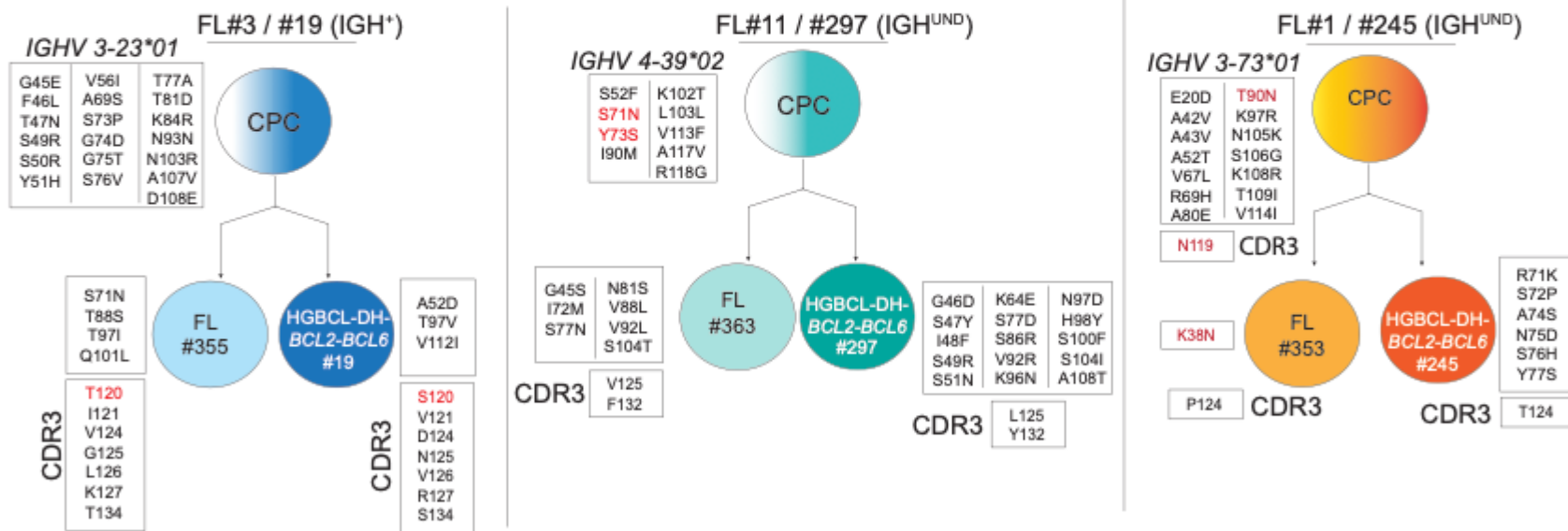
RAG-induced t(8;22) in IGH^{UND} HGBCL-DH-*BCL2*



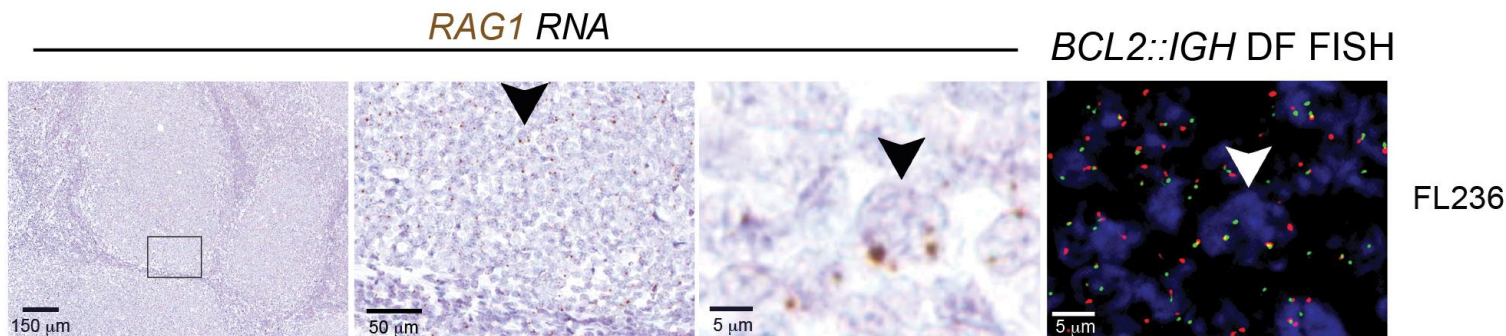
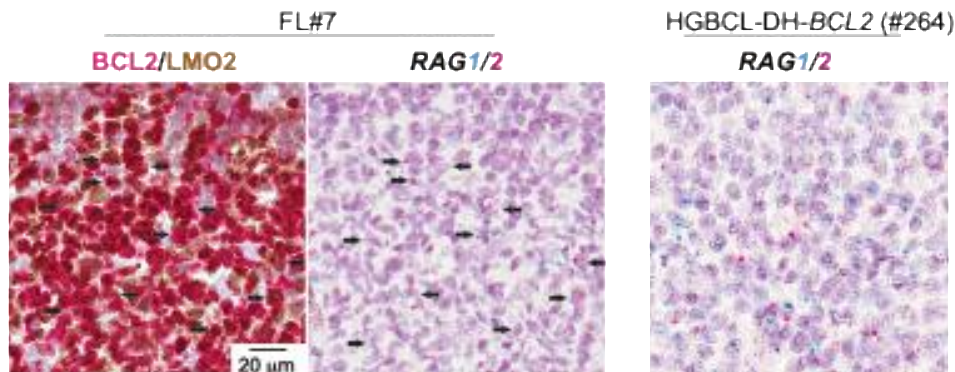
IG silencing is set in FL preceding HGBCL-DH-*BCL2*



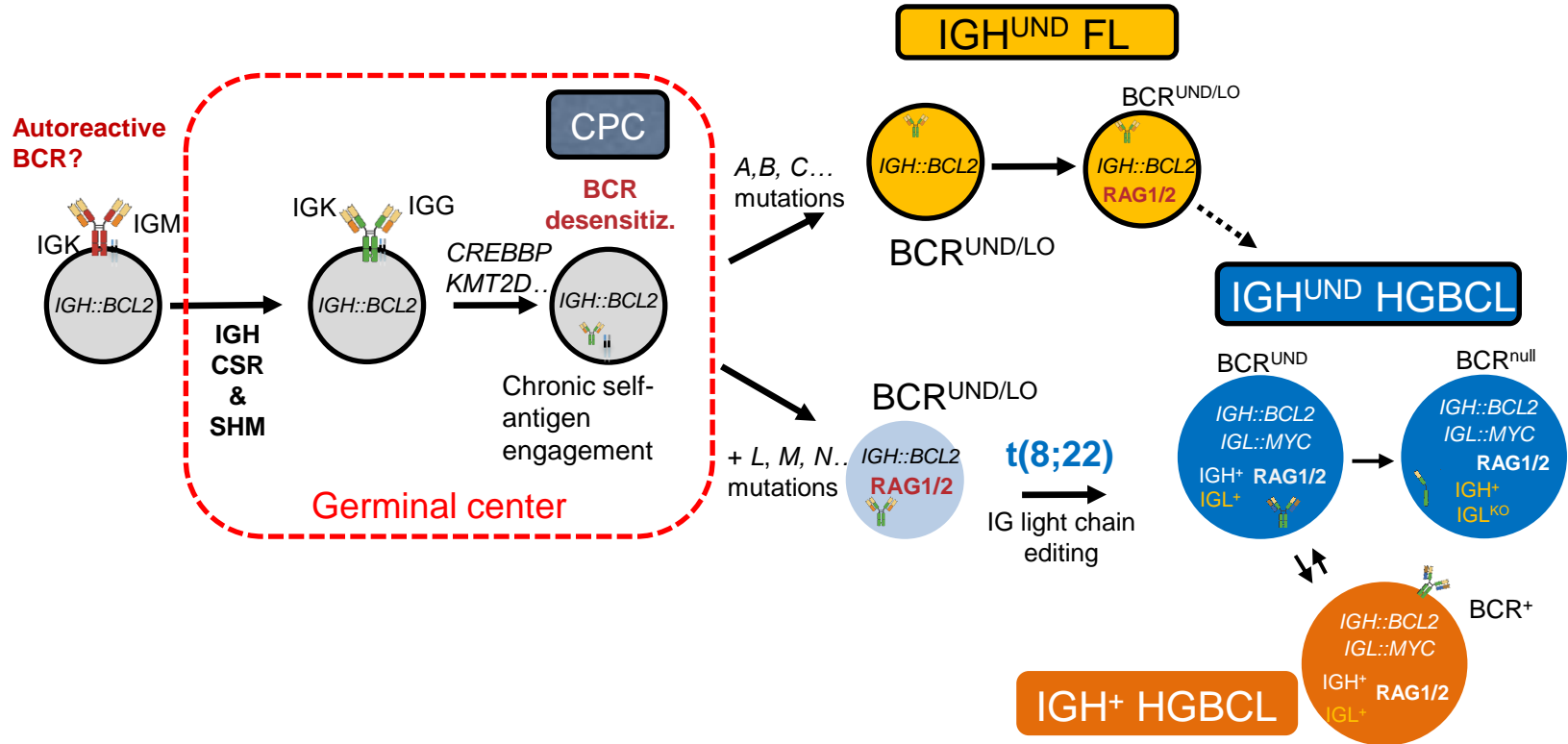
FL and HGBCL-DH-*BCL2* originate from a common precursor cell



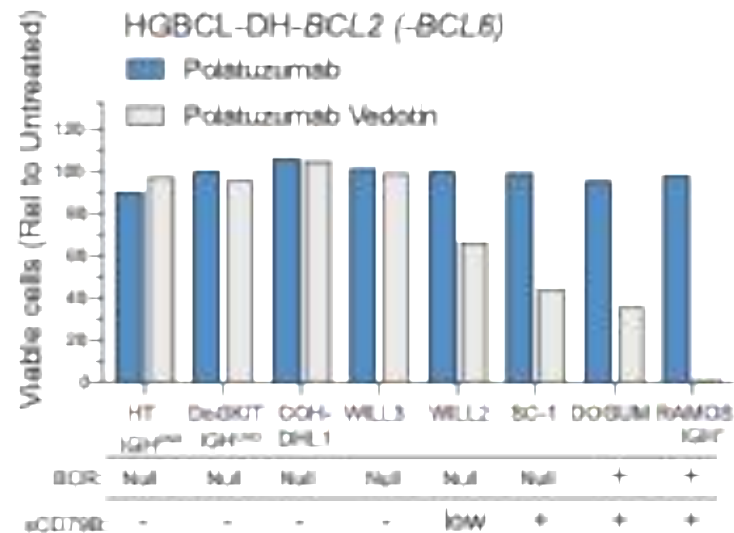
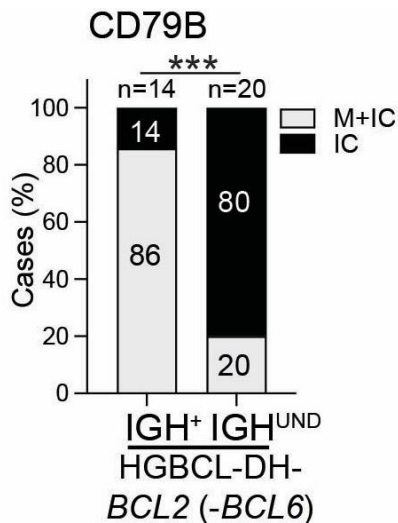
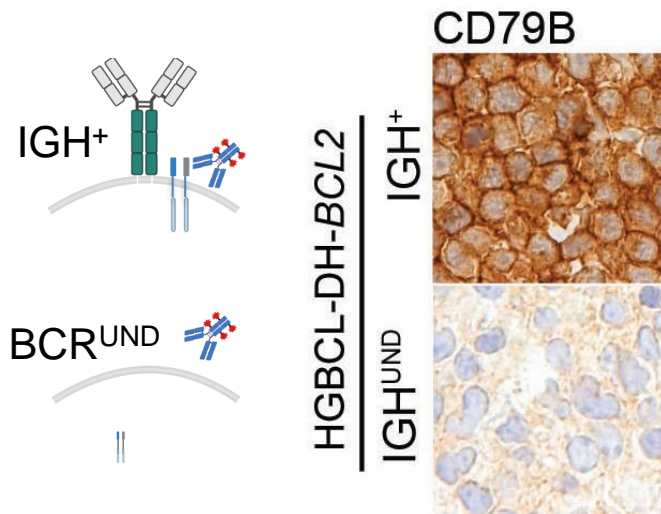
Is RAG expression defining the FL/HGBCL-DH-BCL2 CPC?



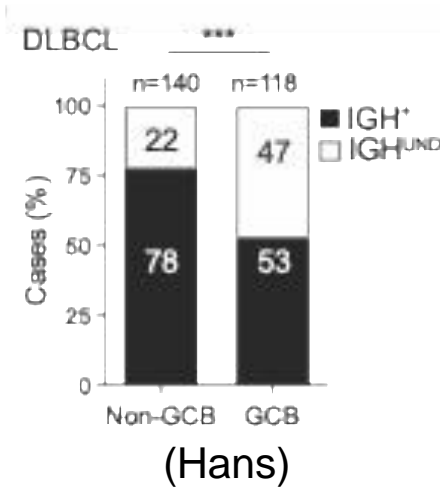
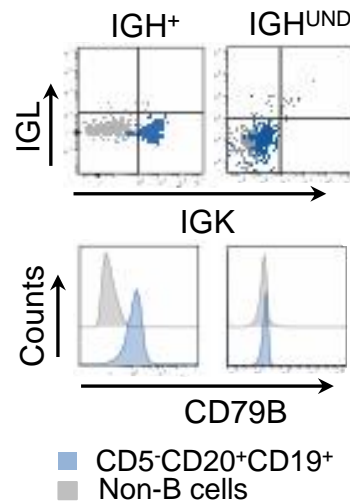
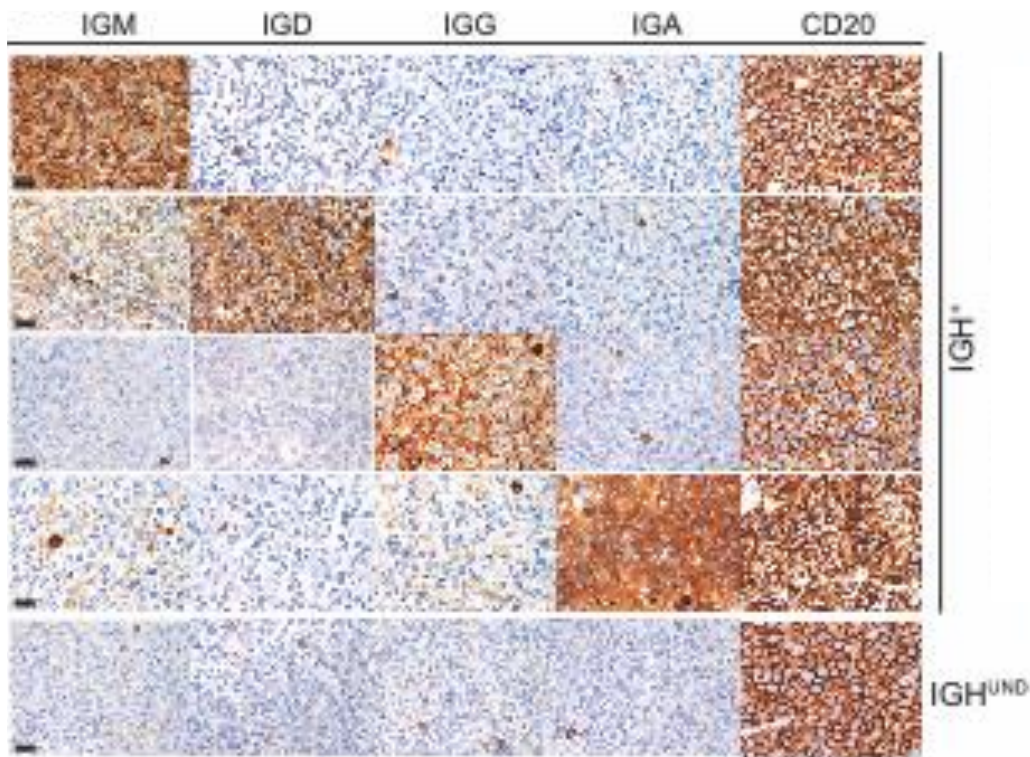
Reconstructing the origins of HGBCL-DH-*BCL2*



IGH silencing in the era of CD79B-targeting therapies



Recurrent BCR silencing in GCB-type DLBCL



THANK YOU



Fabio Facchetti
Claudio Tripodo
Maurilio Ponzoni



Luisa Lorenzi

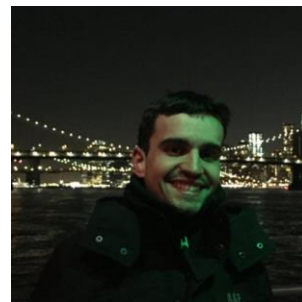


Piera Balzarini

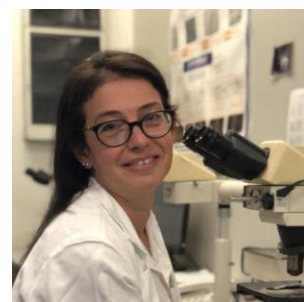


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Patients and families

