Macroglobulinemia di Waldenström – Basi Biologiche

Dr. Aldo M. Roccaro, MD, PhD

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

ASST Spedali Civili di Brescia
S.C. Clinical Trial Center, Laboratorio di Ricerca C.R.E.A.

C.O.I. for Aldo M. Roccaro

Last two years

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca *(Provider Dynamicon)*					X		
Daiiki-Sankyo *(Provider Dynamicon)*					X		
Beigene *(Provider CTP)*					X		
Roche *(Provider CTP)*					X		
Abbvie *(Provider CTP)*					X		
Janssen *(Provider CTP)*					X		

The Importance of Translational Research in Defining Mechanisms Underlying Waldenström's Macroglobulinemia Biology

Tumor Clone

Bone Marrow Niche

Tumor Cell-to-Bone Marrow Niche Interaction

The Importance of Translational Research in Defining Mechanisms Underlying Waldenström's Macroglobulinemia Biology

Tumor Clone

Bone Marrow Niche

Tumor Cell-to-Bone Marrow Niche Interaction

Waldenström's Macroglobulinemia: Overview

- ✓Lymphoplasmacytic lymphoma (WHO)

Alaggio et al. Leukemia, 2022

Waldenström's Macroglobulinemia: Overview

- ✓Lymphoplasmacytic lymphoma (WHO)
- ✓1-2% of all hematologic neoplasms

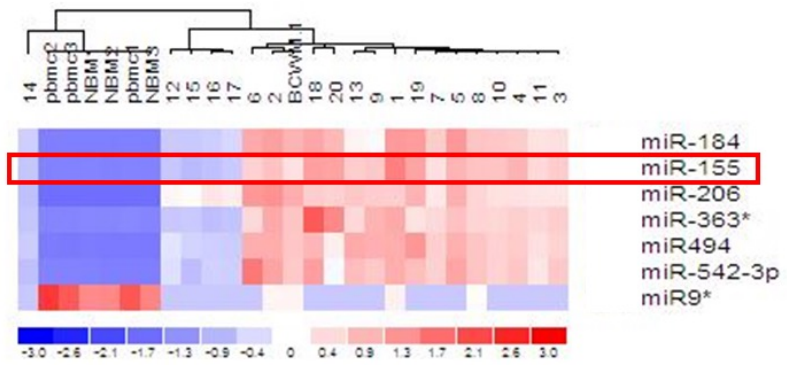
Alaggio et al. Leukemia, 2022
Ghobrial et al. Lancet Onc, 2010
Chen et al. Blood, 2006

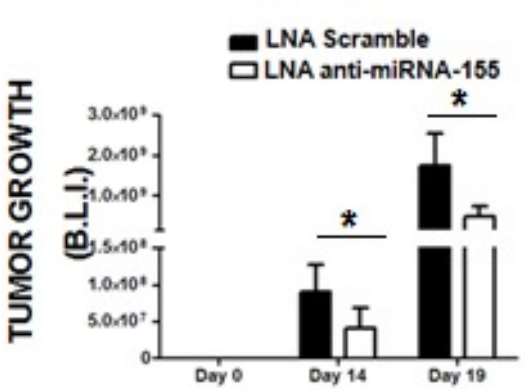
Waldenström's Macroglobulinemia: Overview

✓Lymphoplasmacytic lymphoma (WHO)

✓1-2% of all hematologic neoplasms

✓Specific miRNA signature

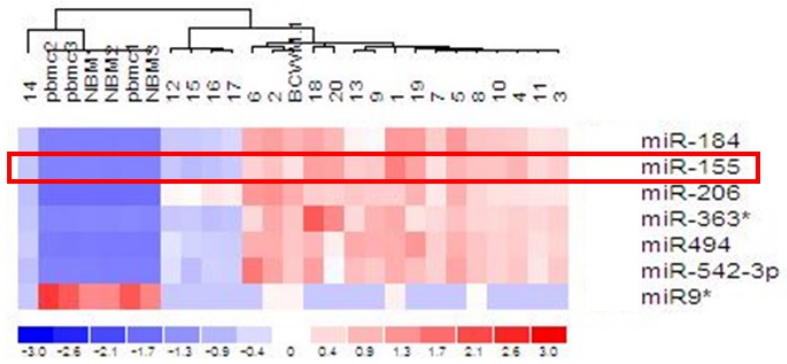


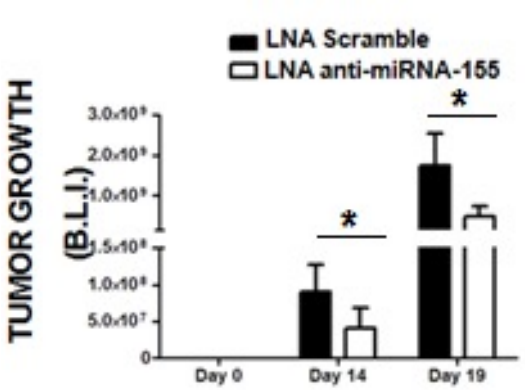


Alaggio et al. Leukemia, 2022
Ghobrial et al. Lancet Onc, 2010
Chen et al. Blood, 2006
Roccaro et al. Blood, 2009
Zhang et al. Blood, 2012

Waldenström's Macroglobulinemia: Overview

- ✓Lymphoplasmacytic lymphoma (WHO)
  - ✓1-2% of all hematologic neoplasms
- ✓Specific miRNA signature - 6q deletion





Alaggio et al. Leukemia, 2022
Ghobrial et al. Lancet Onc, 2010
Chen et al. Blood, 2006
Roccaro et al. Blood, 2009
Zhang et al. Blood, 2012 – Treon Ann. Oncol, 2006

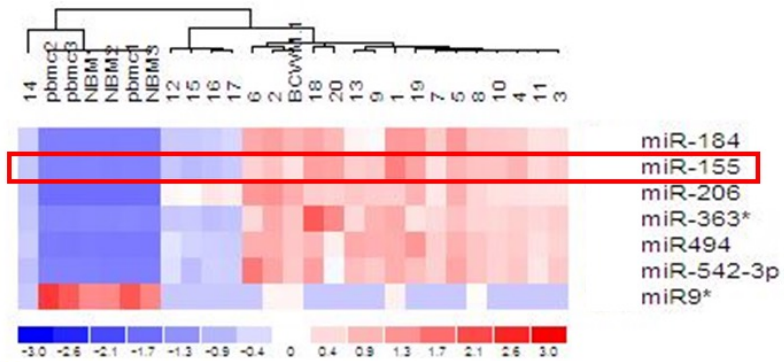
Waldenström's Macroglobulinemia: Overview

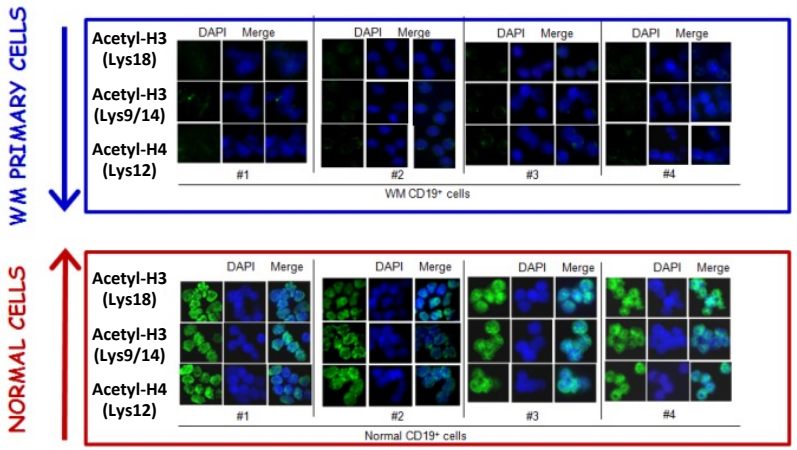
✓Lymphoplasmacytic lymphoma (WHO)

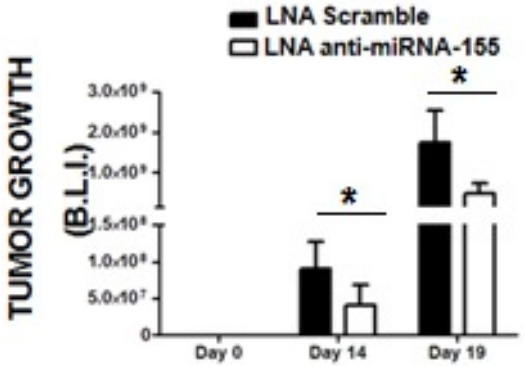
✓1-2% of all hematologic neoplasms

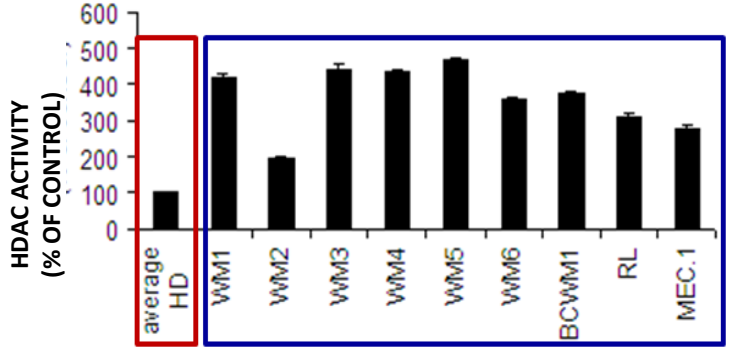
✓Specific miRNA signature - 6q deletion

✓ Reduced histone acetylation and increased HDAC activity









Alaggio et al. Leukemia, 2022
Ghobrial et al. Lancet Onc, 2010
Chen et al. Blood, 2006
Roccaro et al. Blood, 2009
Zhang et al. Blood, 2012 – Treon Ann Oncol, 2006
Roccaro et al. Blood, 2010

Waldenström's Macroglobulinemia: Overview

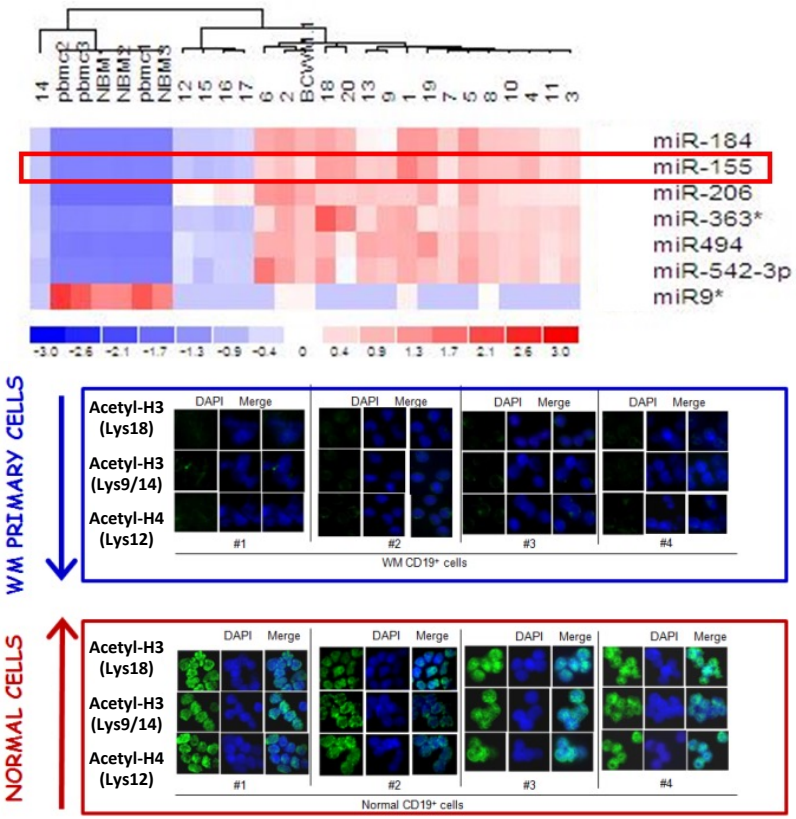
✓Lymphoplasmacytic lymphoma (WHO)

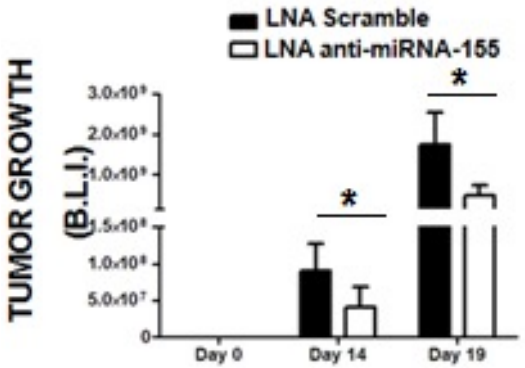
✓1-2% of all hematologic neoplasms

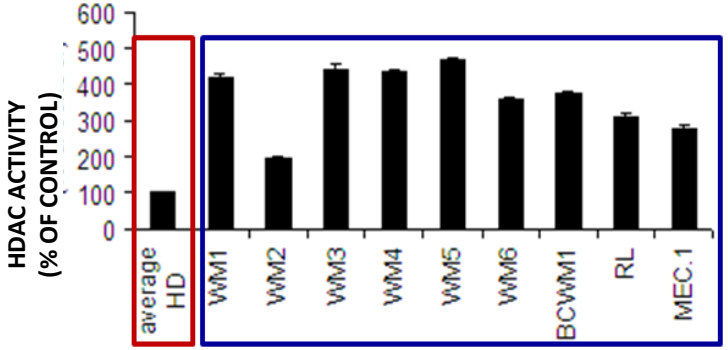
✓Specific miRNA signature - 6q deletion

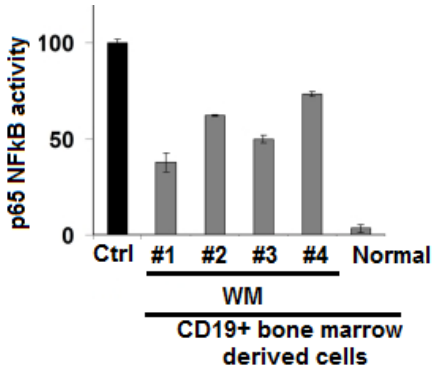
✓ Reduced histone acetylation and increased HDAC activity

✓ Constitutive PI3K/Akt and NFkB pathways









Alaggio et al. Leukemia, 2022
Ghobrial et al. Lancet Onc, 2010
Chen et al. Blood, 2006
Roccaro et al. Blood, 2009
Zhang et al. Blood, 2012 – Treon Ann Oncol 2006
Roccaro et al. Blood, 2010
Leleu et al. Blood, 2007
Roccaro et al. Blood, 2010

Waldenström's Macroglobulinemia: Focus on Somatic Mutations

✓Lymphoplasmacytic lymphoma (WHO)

✓1-2% of all hematologic neoplasms

✓Specific miRNA signature - 6q deletion

✓ Reduced histone acetylation and increased HDAC activity

✓ Constitutive PI3K/Akt and NFkB pathways

✓Recurrent somatic aberrations (90%: $MYD88^{L265P}$; 30%: $CXCR4^{C1013G}$)

Genomic scenario
(somatic mutations)

Waldenström's Macroglobulinemia: a Model for Studying lLymphoplasmacytic Transformation

high prevalence of *MYD88*^{L265P}

↓

Genetic marker of the disease

Waldenström's Macroglobulinemia: a Model for Studying lLymphoplasmacytic Transformation

high prevalence of *MYD88*^{L265P}

↓

Genetic marker of the disease

Bone marrow infiltration of mutated B-lymphocytes and plasma cells

↓

Characterization of intratumor diversity

Waldenström's Macroglobulinemia: a Model for Studying lLymphoplasmacytic Transformation

high prevalence of *MYD88*^{L265P}

↓

Genetic marker of the disease

Bone marrow infiltration of mutated B-lymphocytes and plasma cells

↓

Characterization of intratumor diversity

Existence of the IgM MGUS premalignant condition

↓

Observation of clonal evolution preceding full-blown disease status

Waldenström's Macroglobulinemia: a Model for Studying lLymphoplasmacytic Transformation

high prevalence of *MYD88*^{L265P}

↓

Genetic marker of the disease

Bone marrow infiltration of mutated B-lymphocytes and plasma cells

↓

Characterization of intratumor diversity

Existence of the IgM MGUS premalignant condition

↓

Observation of clonal evolution preceding full-blown disease status

WM provides a singular model for investigating lymphoplasmacytic transformation

MYD88^{L265P}: the Only Player?

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

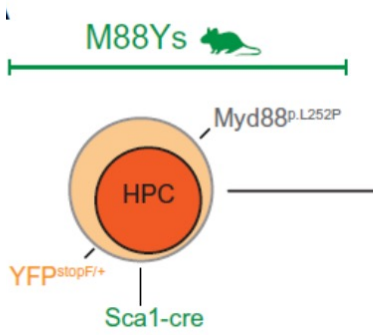
X

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre



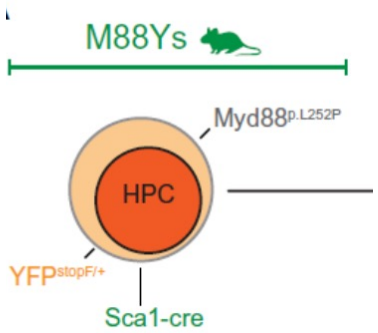
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre



MYD88^{L256P} activation in

HPCs

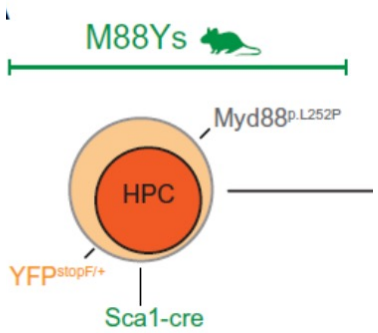
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre



MYD88^{L256P} activation in

HPCs

Spleen: myelomonocytic infiltration

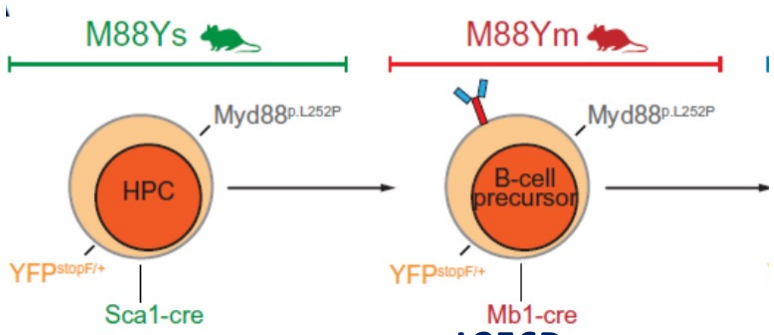
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre Mb1-cre



MYD88^{L256P} activation in

HPCs

B-cell precurors

Spleen: myelomonocytic infiltration

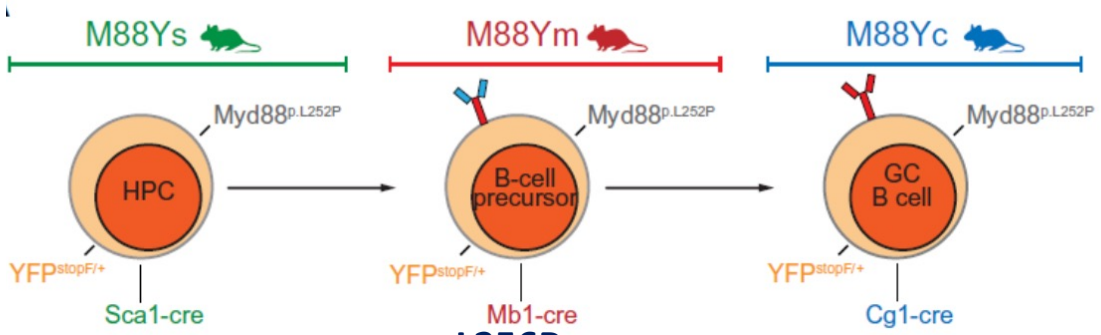
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre	Mb1-cre	Cγ1-cre



MYD88^{L256P} activation in

- **HPCs** → **Spleen: myelomonocytic infiltration**
- **B-cell precurors**
- **Germinal center B-cells**

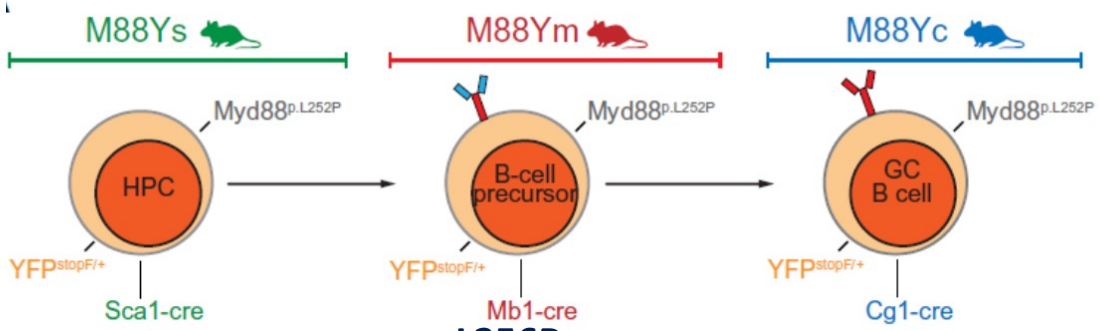
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre **Mb1-cre** **Cγ1-cre**

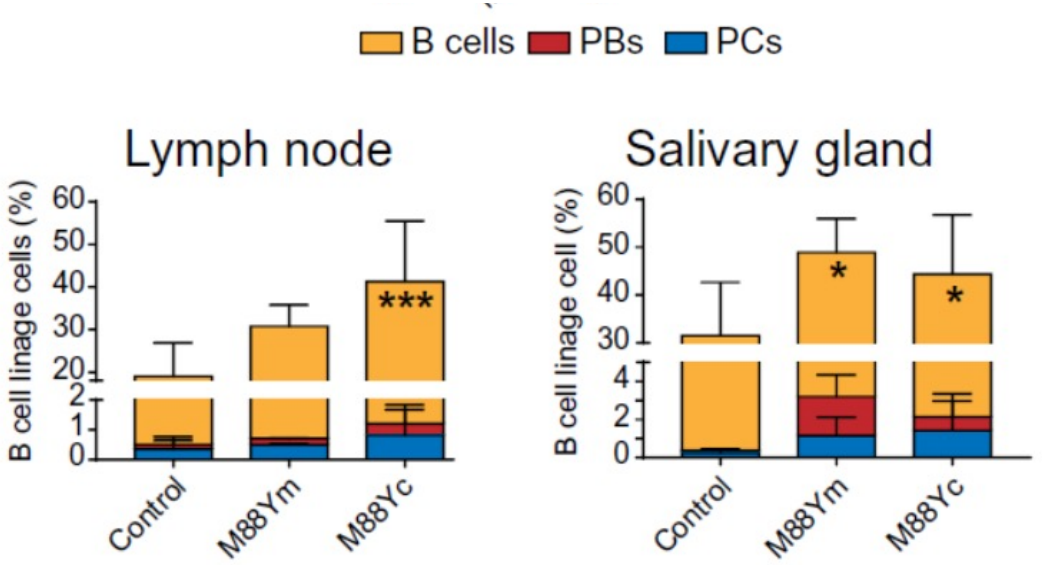


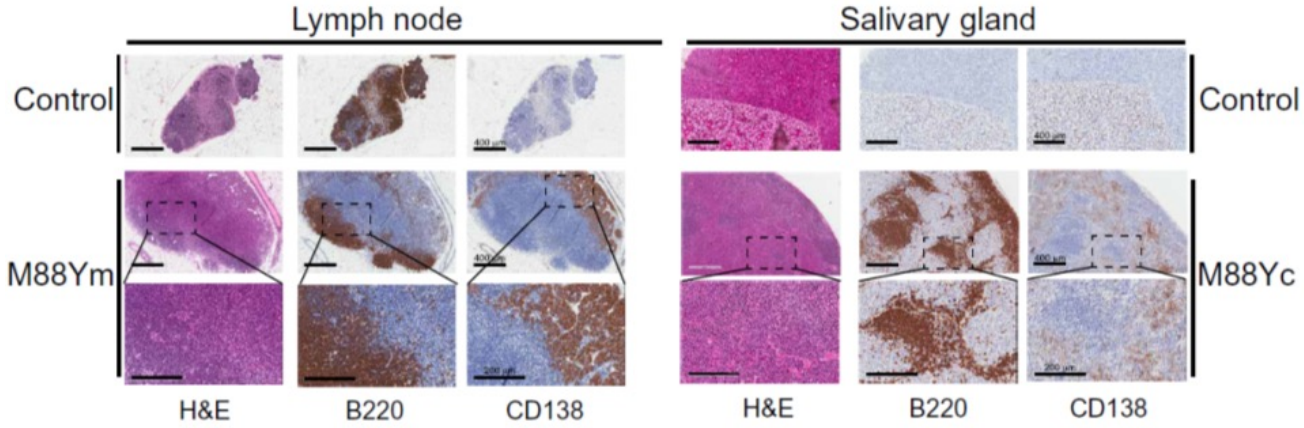
MYD88^{L256P} activation in

HPCs → **Spleen: myelomonocytic infiltration**

B-cell precurors

Germinal center B-cells





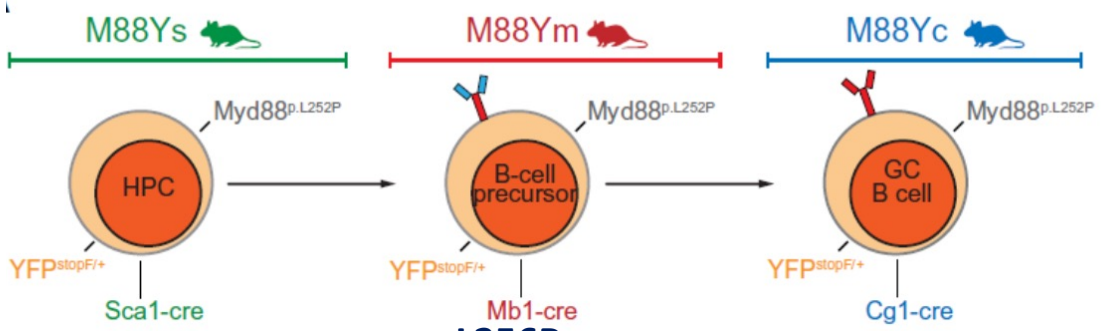
Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

MYD88^{L256P}

X

Sca1-cre **Mb1-cre** **Cγ1-cre**

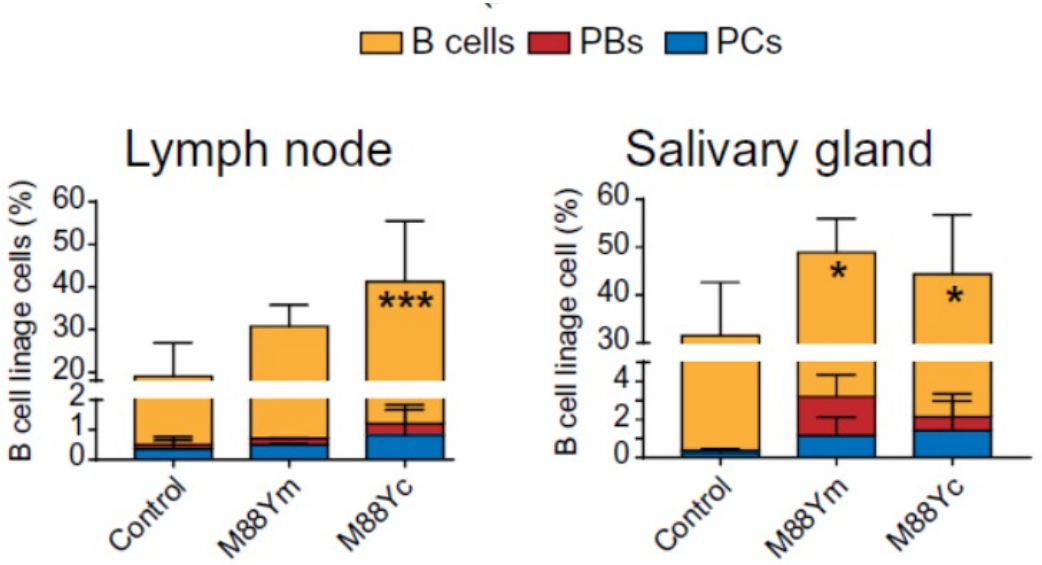


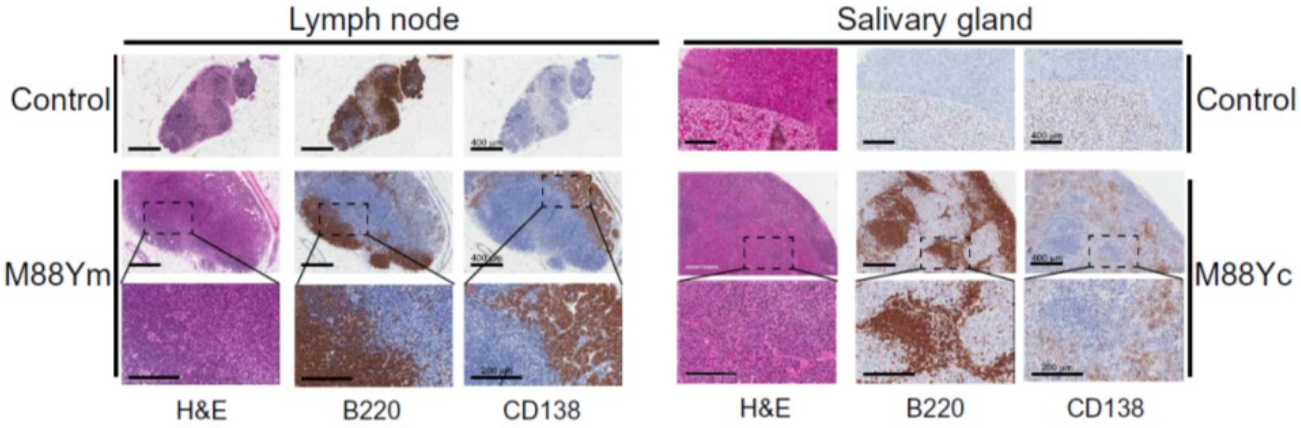
MYD88^{L256P} activation in

HPCs → **Spleen: myelomonocytic infiltration**

B-cell precurors

Germinal center B-cells





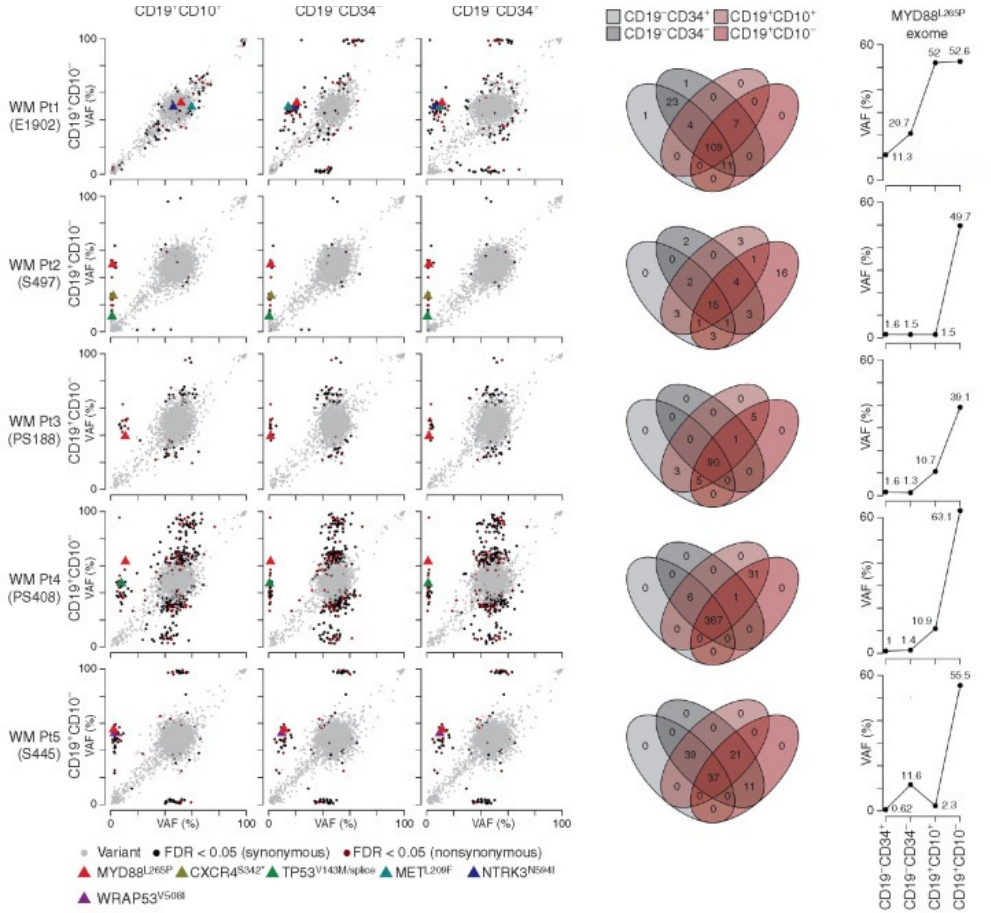
Lack of BM infiltration

Rodriguez S, et al. Sci Adv, 2022

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?

Mutated MYD88^{L256P} alone is insufficient to induce WM transformation in mice

Is MYD88^{L256P} Present in Progenitor and Mature B-cell Sufficient to Drive WM Transformation?



MYD88^{L265P} mutation could be detected in pre-B progenitor compartments and involved the entire mature B-cell clone (100% of pts).
Not detected in any fraction of HD marrow.

Mutated MYD88^{L256P} alone is insufficient to induce WM transformation in the human setting

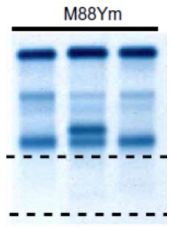
Kaushal et al. Blood Can Disc. 2021

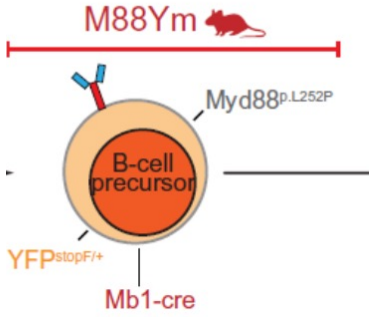
Are Other Molecular Aberrations Required for WM Transformation in Addition to MYD88^{L265P}?

MYD88^{L256P}

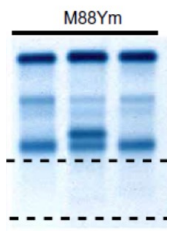
X

Mb1-cre





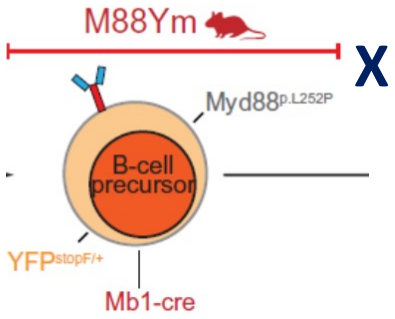
Are Other Molecular Aberrations Required for WM Transformation in Addition to MYD88^{L265P}?



MYD88^{L256P}

X

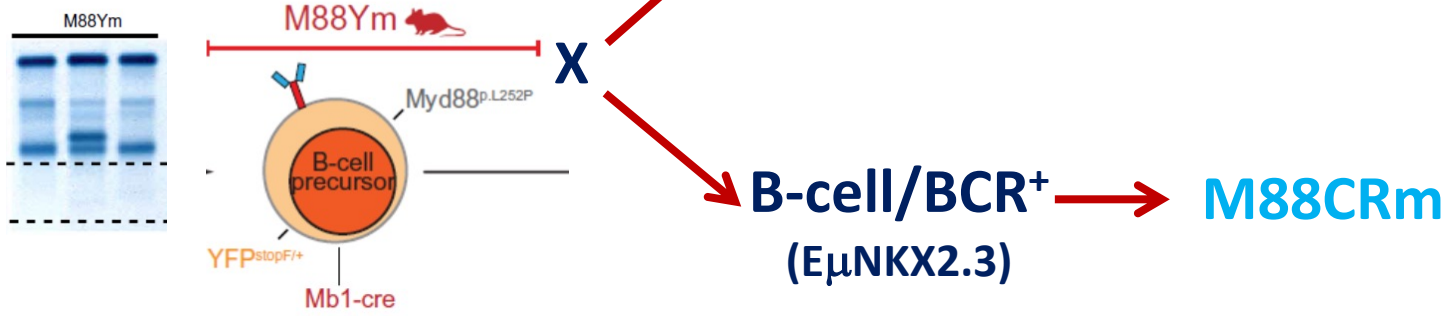
Mb1-cre



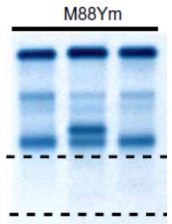
X

B-cell/BCL2^{+} → M88B2m

Are Other Molecular Aberrations Required for WM Transformation in Addition to MYD88^{L265P}?



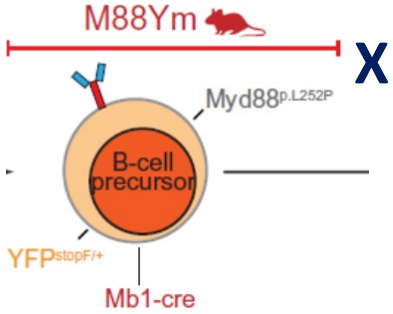
Are Other Molecular Aberrations Required for WM Transformation in Addition to MYD88^{L265P}?



MYD88^{L256P}

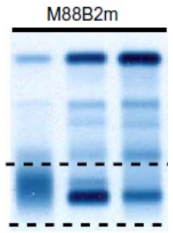
X

Mb1-cre



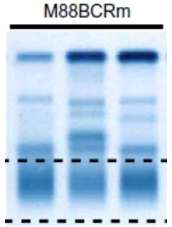
X

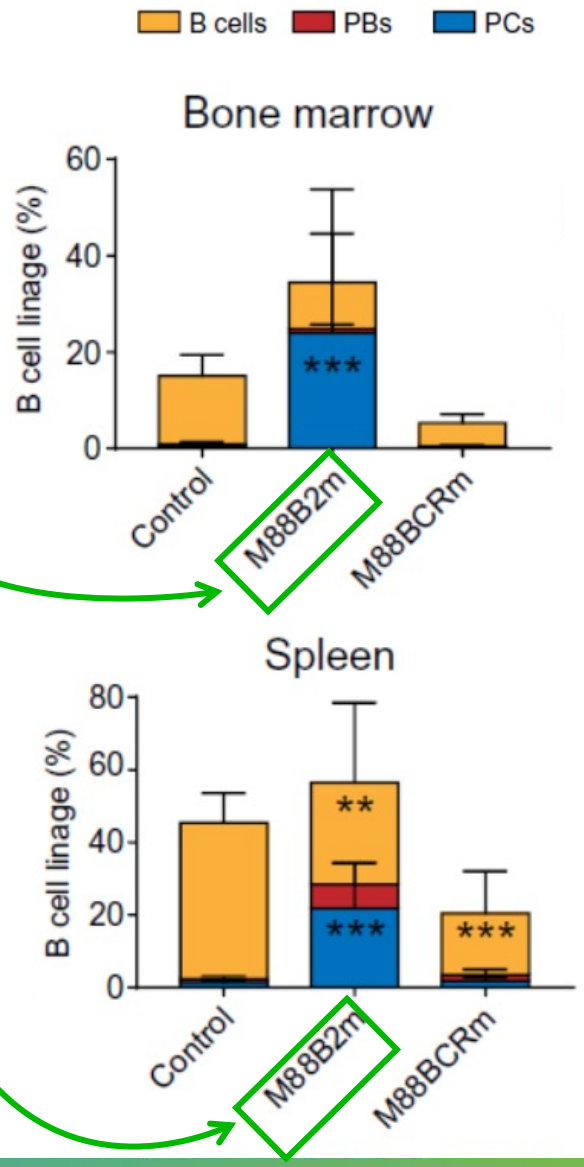
B-cell/BCL2^{+} → **M88B2m**



B-cell/BCR^{+} → **M88CRm**

(EμNKX2.3)





Are Other Molecular Aberrations Required for WM Transformation in Addition to MYD88^{L265P}?

Yes: co-occurrence of MYD88^{L265P} and BCL2 overexpression or constitutive BCR signaling accelerates LPL/WM development

Waldenström's Macroglobulinemia: a Model for Studying Lymphoplasmacytic Transformation

MYD88^{L265P} is detectable in most cases of IgM MGUS

after a median follow-up of 34 years, approximately 84% of individuals with IgM MGUS do not progress to WM

many patients with MYD88^{L265P} do not develop a B cell malignancy

Progression to WM is driven by both the cellular origin of the MYD88^{L265P} and the emergence of cooperating genetic alterations

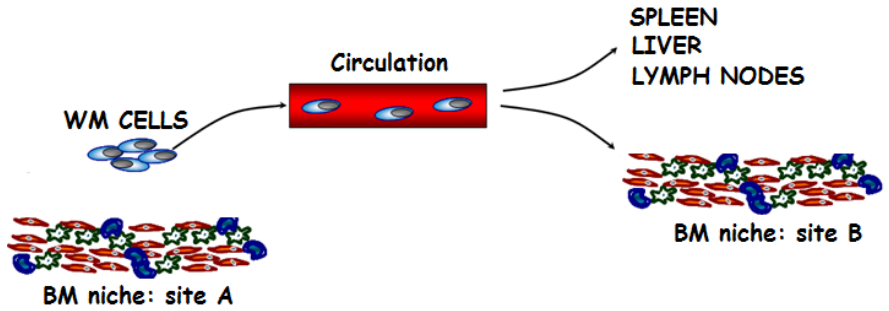
Xu L.e t al. Blood, 2013
Jimenez C, et al. Leukemia, 2013
Kyle RA, et al. NEJM, 2018

CXCR4-Genomic Aberrations: Role in WM Biology

Whole genome sequencing
WM patients

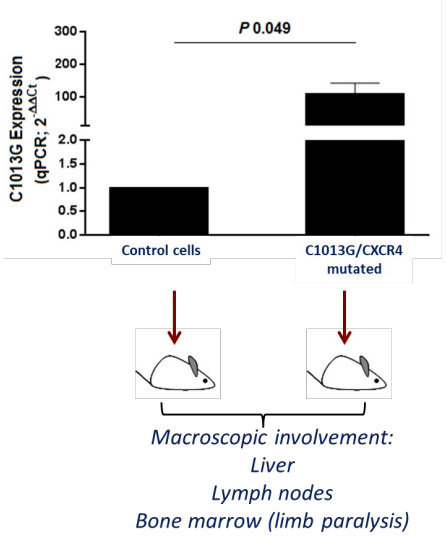
27% harboring aberrations within the carboxyl terminal domain of CXCR4

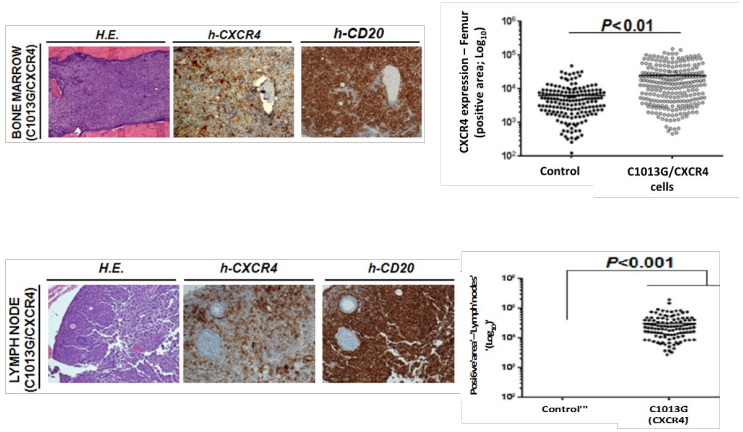
CXCR4-related somatic variant in primary WM cells may modulate WM biology

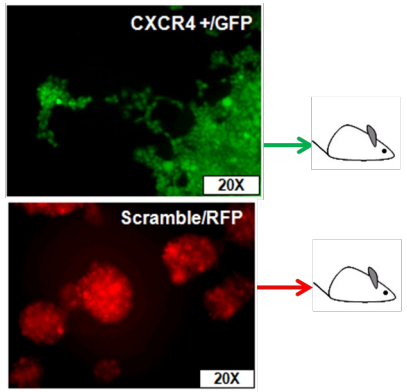


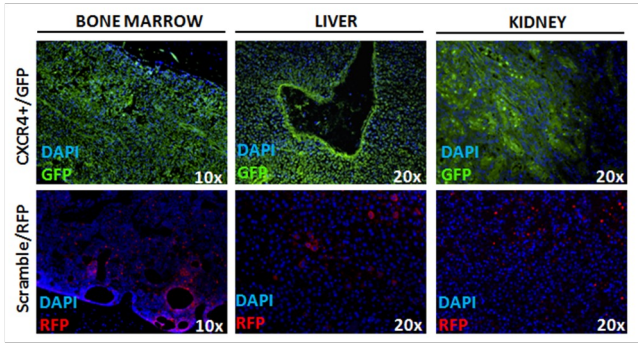
Hunter et al. Blood, 2013
Roccaro et al. Cell Reports, 2014
Roccaro et al. Cell Reports, 2015

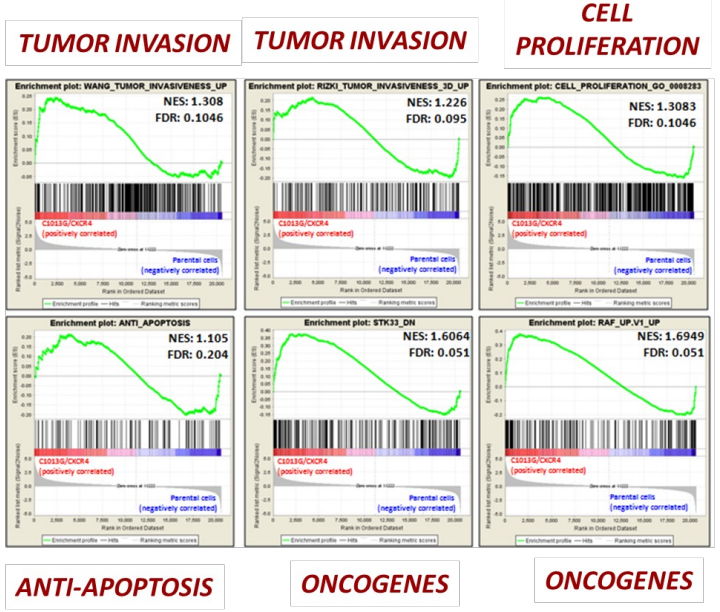
CXCR4^{C1013G}: *in Vivo* Functional Role in WM











Functional relevance of ***CXCR4^{C1013G}*** variant in WM:

- ***Oncogenic*** role

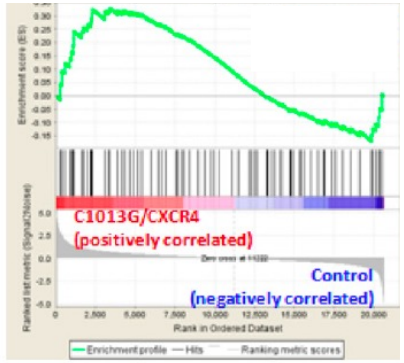
as shown both *in vivo* and at molecular level

Roccaro et a. Blood, 2014

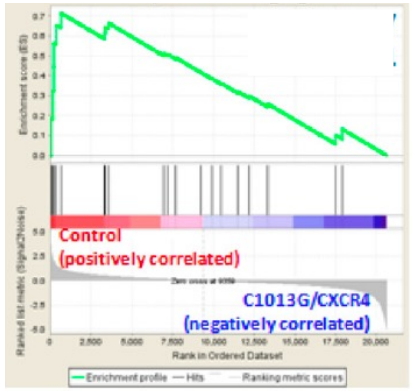
CXCR4^{C1013G} Confers Resistance to Ibrutinib Therapy: Pre-Clinical Setting

Transcriptome signature

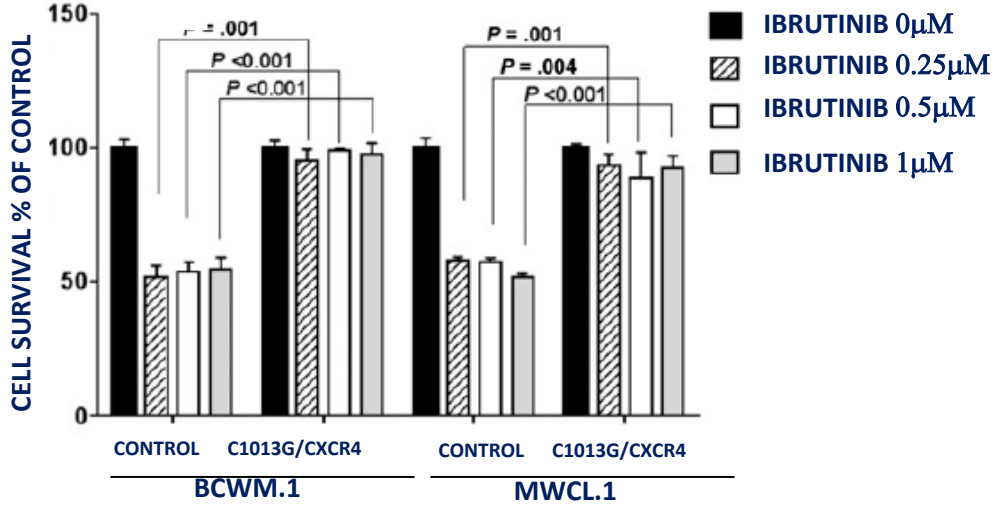
DRUG RESISTANCE
enriched in CXCR4 mutated cells



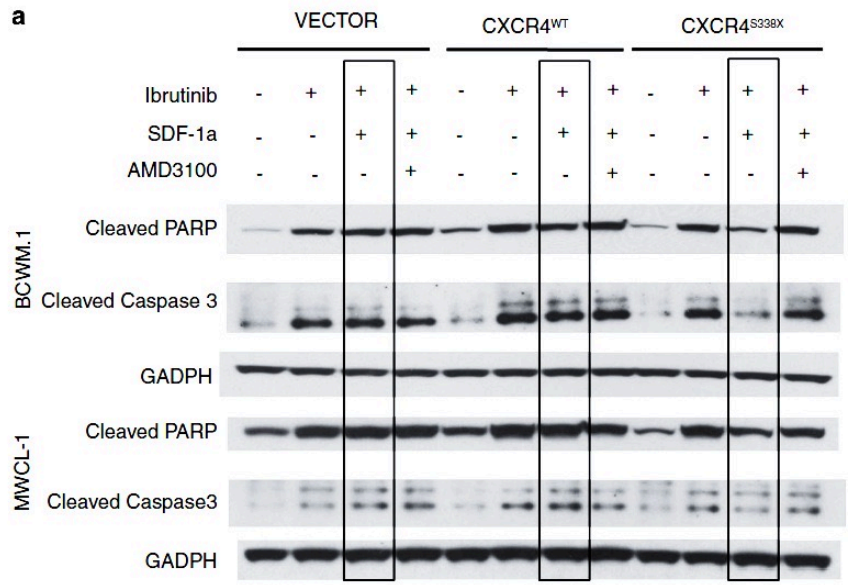
RESPONSE TO DRUGS
enriched in CXCR4 non-mutated cells



In vitro survival assay

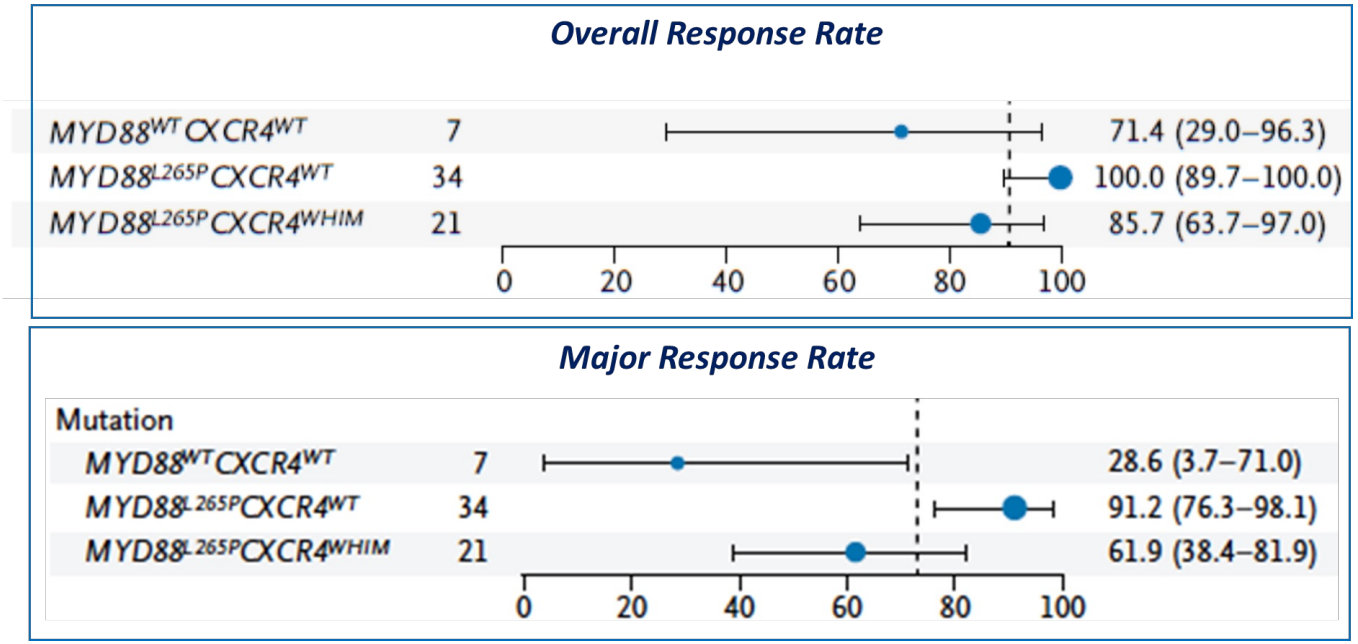


Protein signature



Roccaro et a. Blood, 2014
Cao et al. Leukemia, 2015
Treon et al. N Engl J Med, 2015

CXCR4^{C1013G} Confers Resistance to Ibrutinib Therapy: Clinical Setting



Treon et al. N Engl J Med, 2015

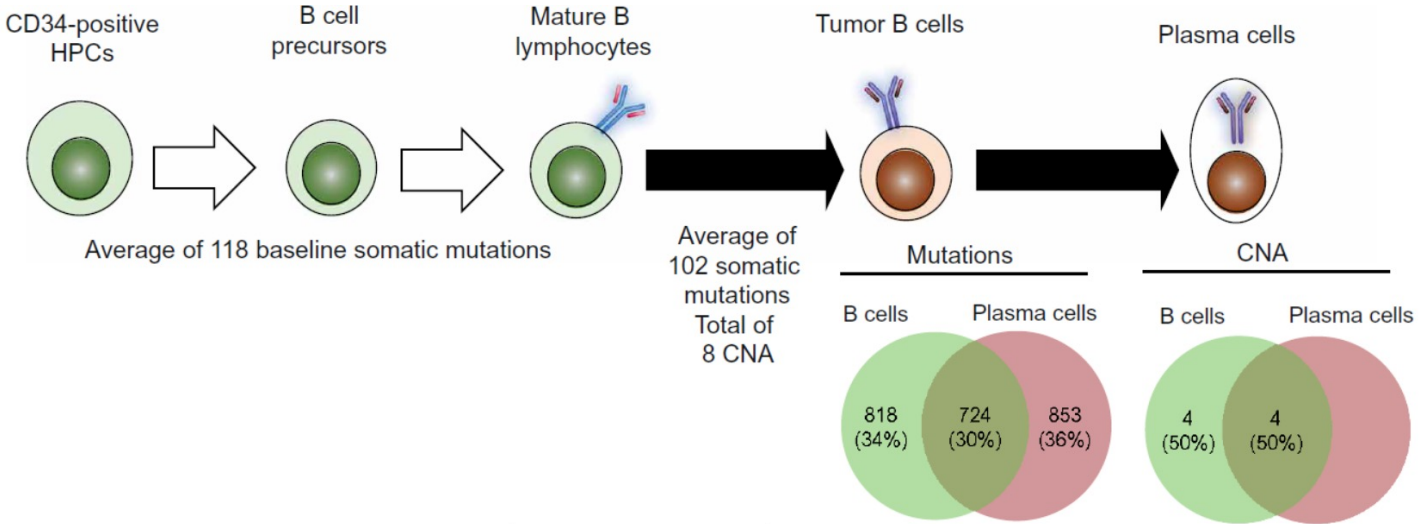
Subgroup	Response/patients: Ibrutinib	Response/patients: Zanubrutinib	Rate difference, % (95% CI)*
Baseline CXCR4 mutation status by central lab			
WHIM	1/8	1/11	-3.4 (-31.9, 25.1)
WT/UNKNOWN	18/91	28/91	11.0 (-1.5, 23.5)

Low proportion of CXCR4^{WHIM} mutated cases

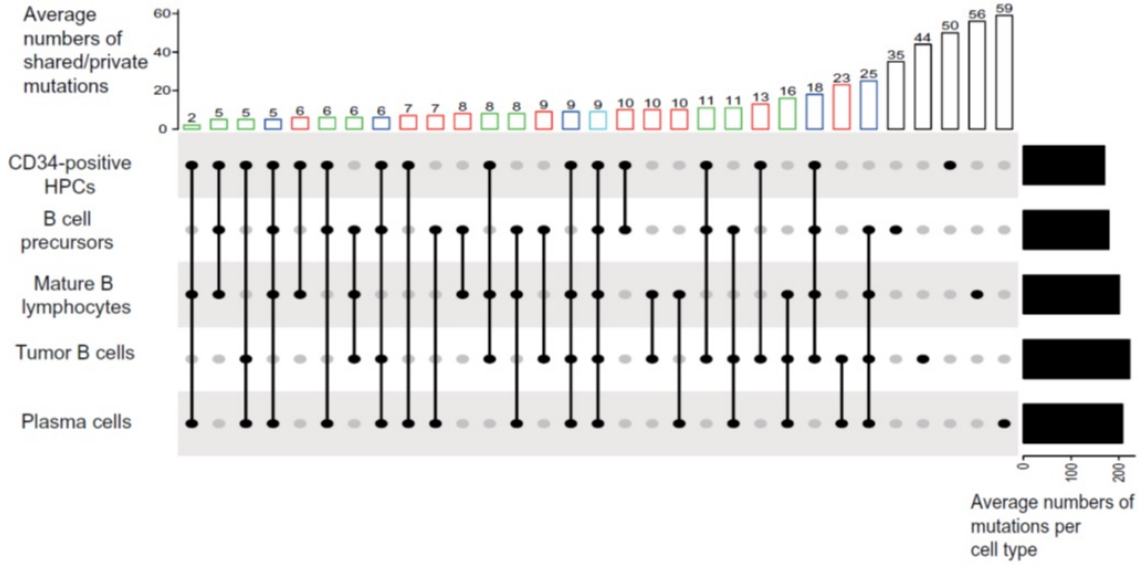
Higher VGPR rate in CXCR4^{WT} *vs* CXCR4^{WHIM}

Tam et al. Blood, 2020

Shared *vs* Unique Somatic Mutations Between Normal and Tumor Cells



shared somatic mutations between normal and tumor cells n. 156 (average)



somatic mutations unique to WM cells associated with progression

n. 44 (average)

↓

CXCR4, IGLL5, NADH3

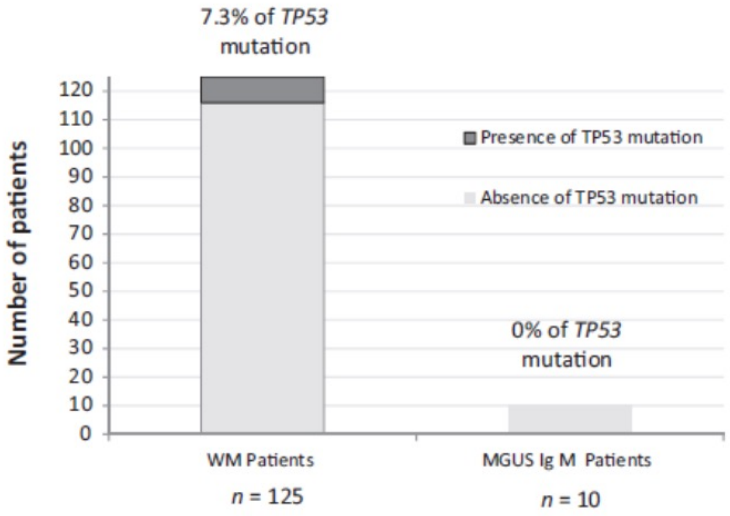
TP53, DICER1

Rodriguez S, et al. Sci Adv, 2022

TP53 and Its Prognostic Significance in WM

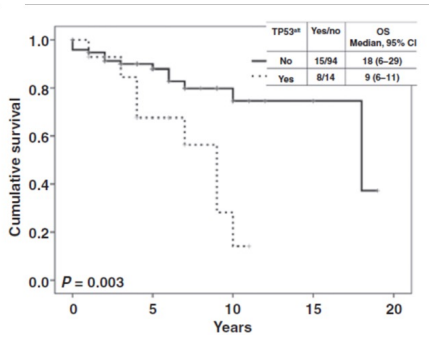
WM: n. 125
IgM MGUS: n. 10

Sanger sequencing
ultradeep-targeted sequencing

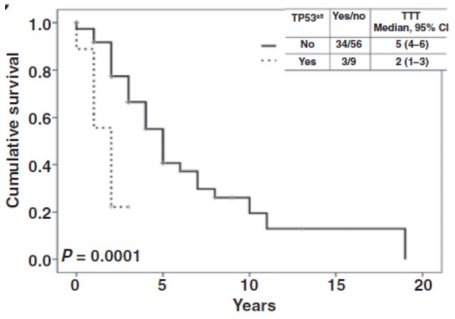


TP53 Mutation
7.3% WM
0% IgM MGUS

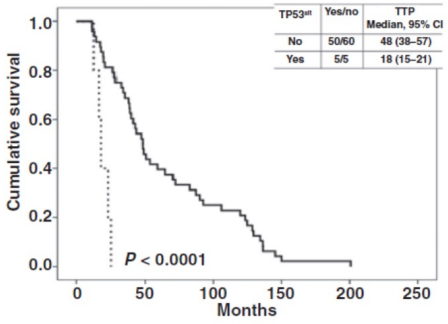
↓ Overall Survival



↓ Time To Treatment



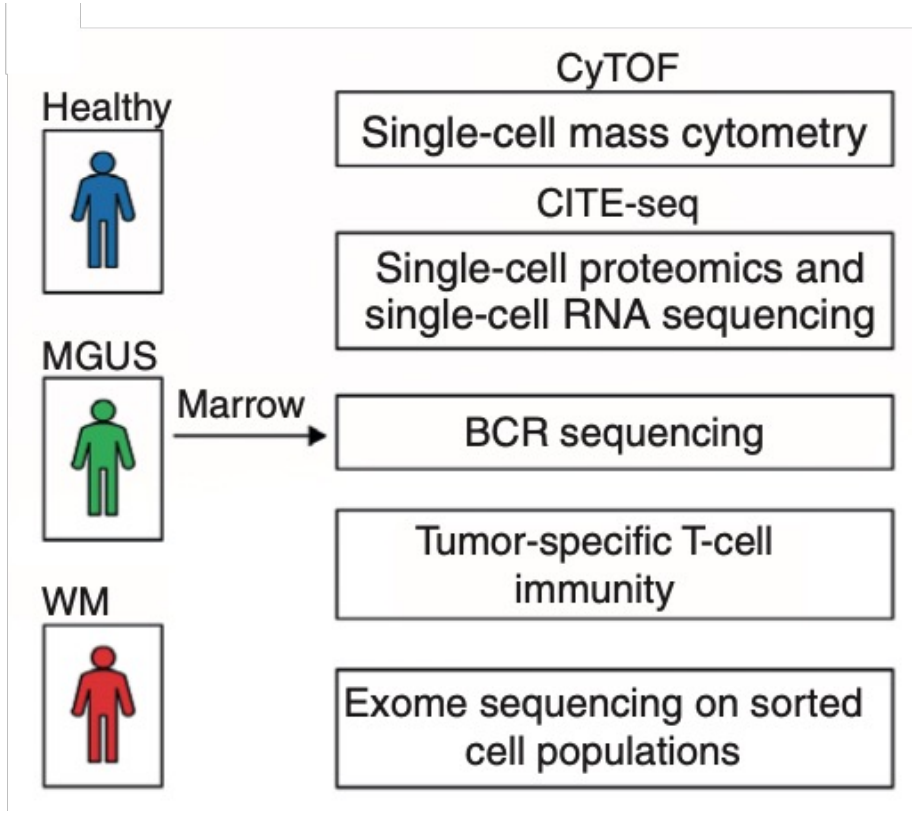
↓ Time To Progression



TP53: negative prognostic impact in WM

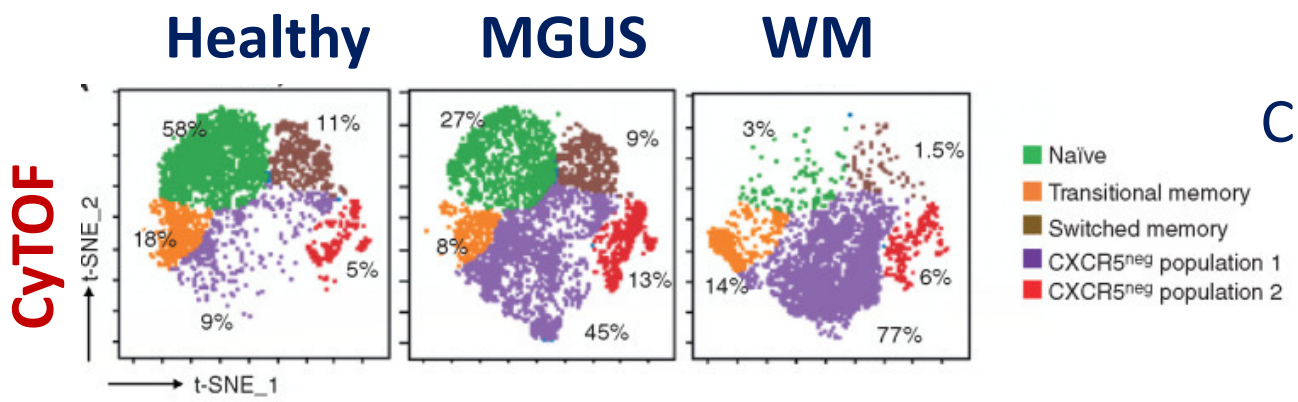
Poulain S, et al. Clin Cancer Res, 2017

How to Better Know and Investigate Potential Aberrations Going from IgM-MGUS Towards WM



Kaushal et al. Blood Can Disc. 2021

CD19^{+} B Cells: Changes Going from HD to MGUS to WM



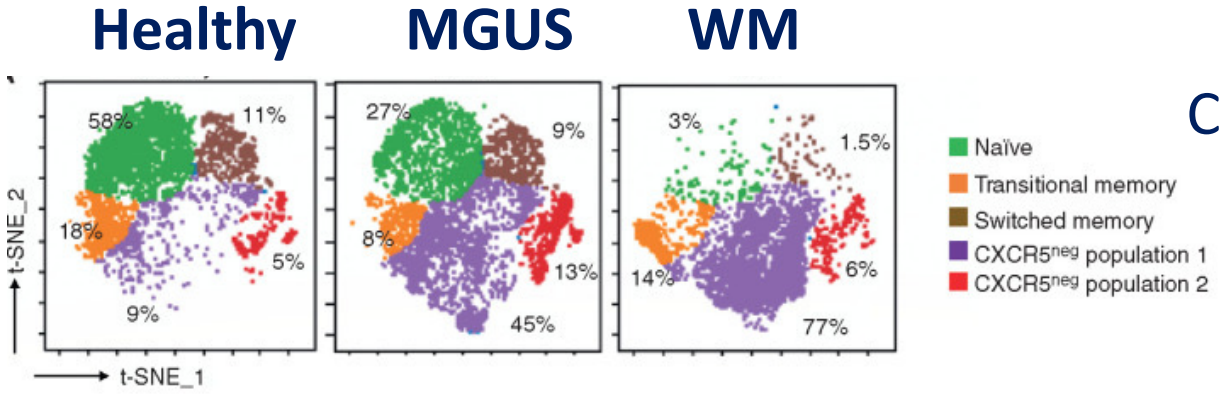
Changes in the B-cells evident as early as MGUS

- increase in CXCR5^{neg} B cells
- decline in naïve B cells

Kaushal et al. Blood Can Disc. 2021

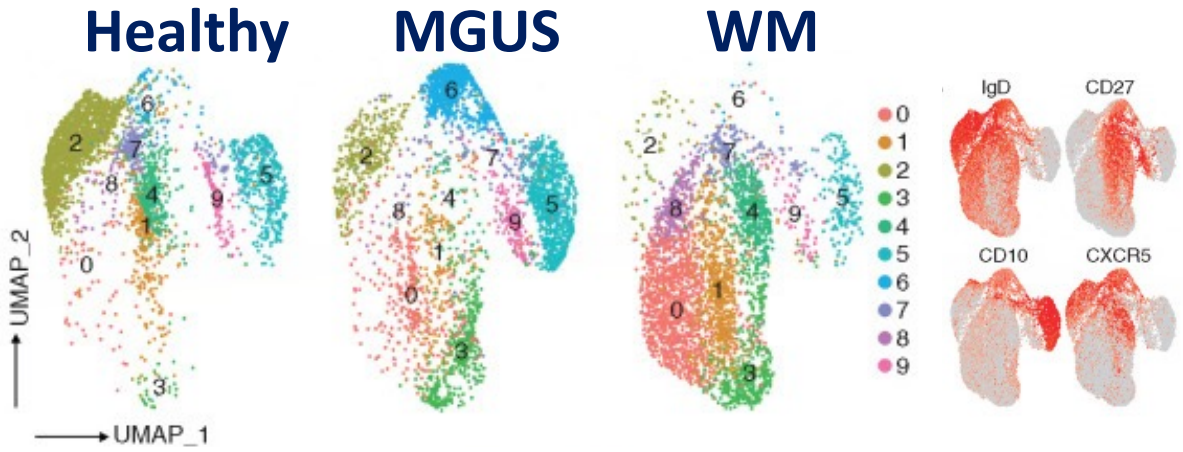
CD19^{+} B Cells: Changes Going from HD to MGUS to WM

CyTOF



Changes in the B-cells evident as early as MGUS
- increase in CXCR5^{neg} B cells
- decline in naïve B cells

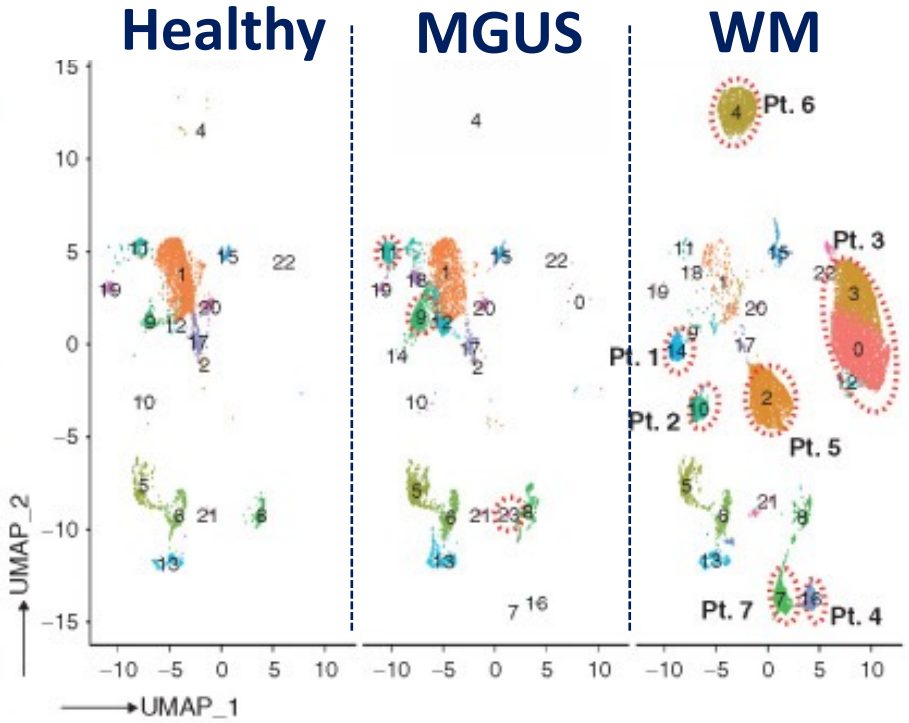
CITE-seq



CD19^{+} B cells: 10 distinct clusters
- progressive loss of IgD^{+}CD27^{-} naïve B cells
- increase CXCR5^{neg} B cells

Kaushal et al. Blood Can Disc. 2021

CD19⁺ B Cells: Changes Going from HD to MGUS to WM

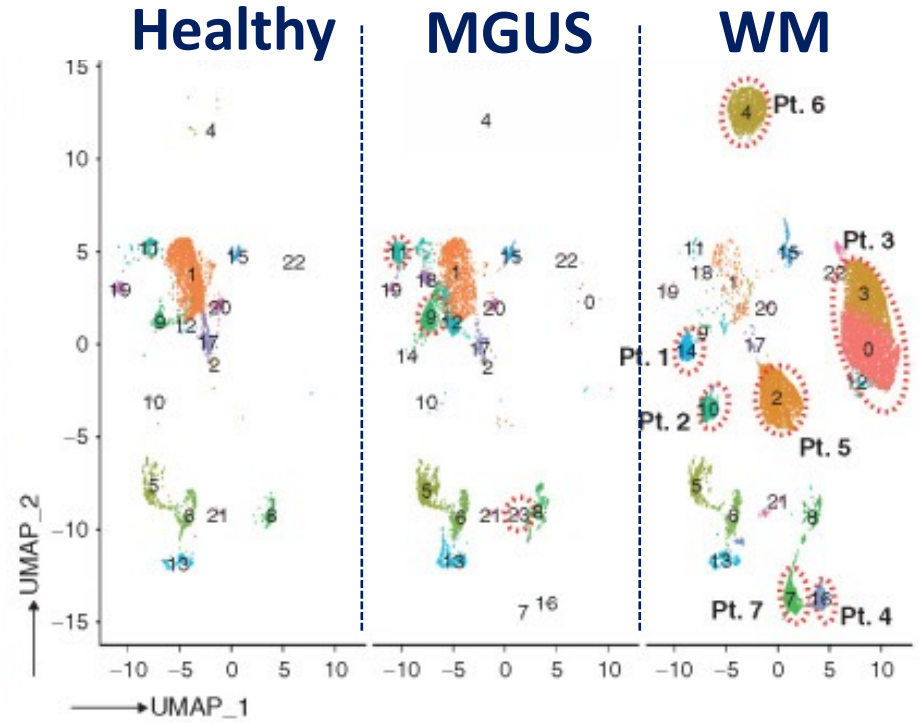


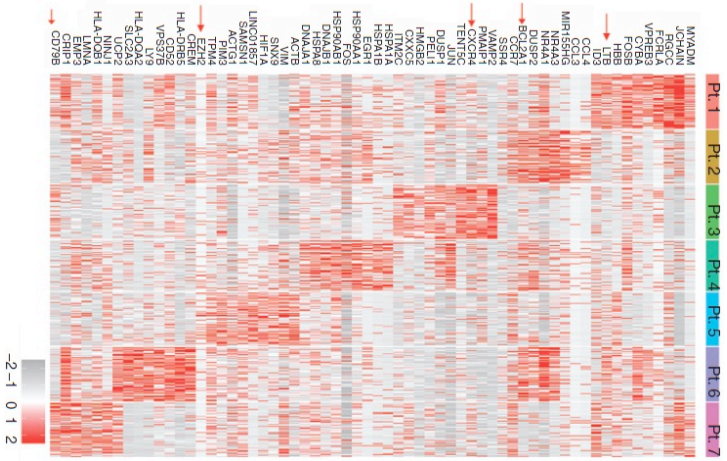
CD19⁺ B cell and transcriptome
- existence of distinct clusters
- each patient is transcriptionally distinct

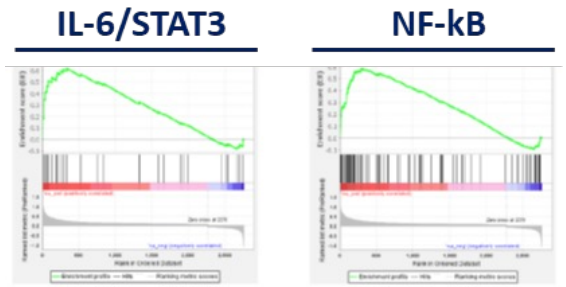
Top genes characterizing specific clones:
EZH2, CD79b, CXCR4, BCL2, and LT-β/TNF-c

Kaushal et al. Blood Can Disc. 2021

CD19⁺ B Cells: Changes Going from HD to MGUS to WM







CD19⁺ B cell and transcriptome
- existence of distinct clusters
- each patient is transcriptionally distinct

Top genes characterizing specific clones:
EZH2, CD79b, CXCR4, BCL2, and LT-β/TNF-c

Overall:
- B cells from WM and IgM MGUS patients transcriptionally distinct vs HDs

Top pathways
increased in WM and IgM MGUS B cells included NF-kB, IL6/STAT3

Kaushal et al. Blood Can Disc. 2021

Take-Home Points - I -

MYD88 mutation represents a pre-neoplastic event
Low frequency of MYD88 in HSCs: hard to think they act as Cancer-SCs

Progression to WM is driven by both the cellular origin of the $MYD88^{L265P}$ and the emergence of cooperating genetic alterations
(i.e.:BCL2; BCR; $CXCR4^{C1013G}$)

The Importance of Translational Research in Defining Mechanisms Underlying Waldenström's Macroglobulinemia Biology

Tumor Clone

Bone Marrow Niche

Tumor Cell-to-Bone Marrow Niche Interaction

The Importance of Translational Research in Defining Mechanisms Underlying Waldenström's Macroglobulinemia Biology

Tumor Clone

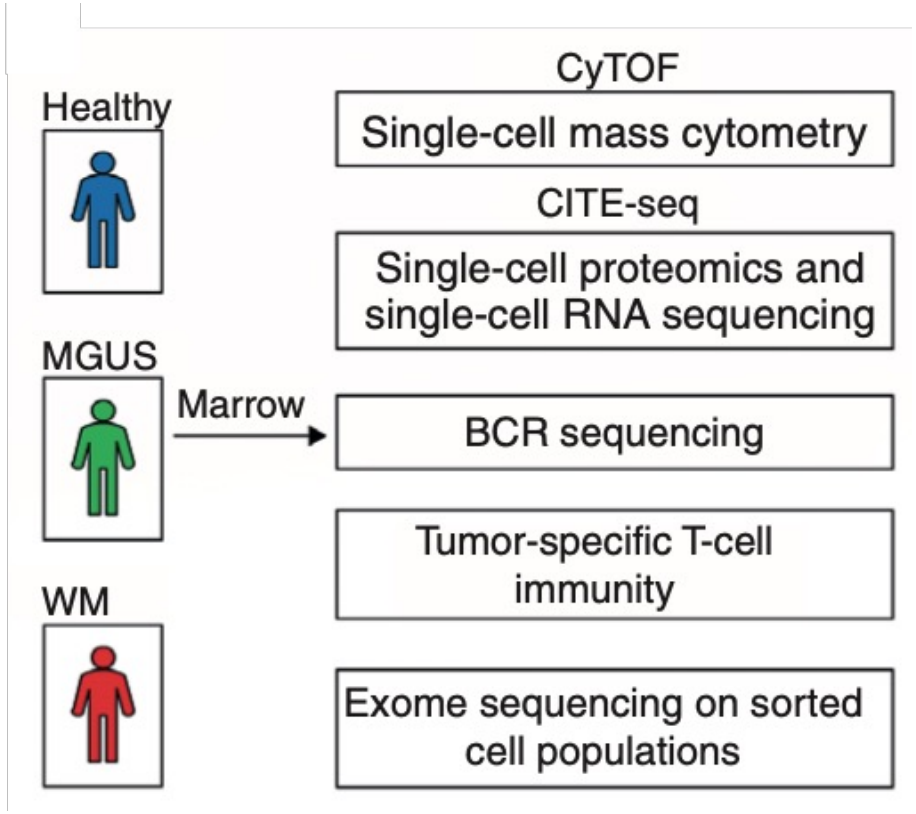
Bone Marrow Niche

Tumor Cell-to-Bone Marrow Niche Interaction

- ✓ *Bone marrow microenvironment*
- ✓ *Myeloid compartment*
- ✓ *Innate cells*
- ✓ *T-cells*

How to Better Know and Investigate the Bone Marrow Milieu Going from IgM-MGUS towards WM?

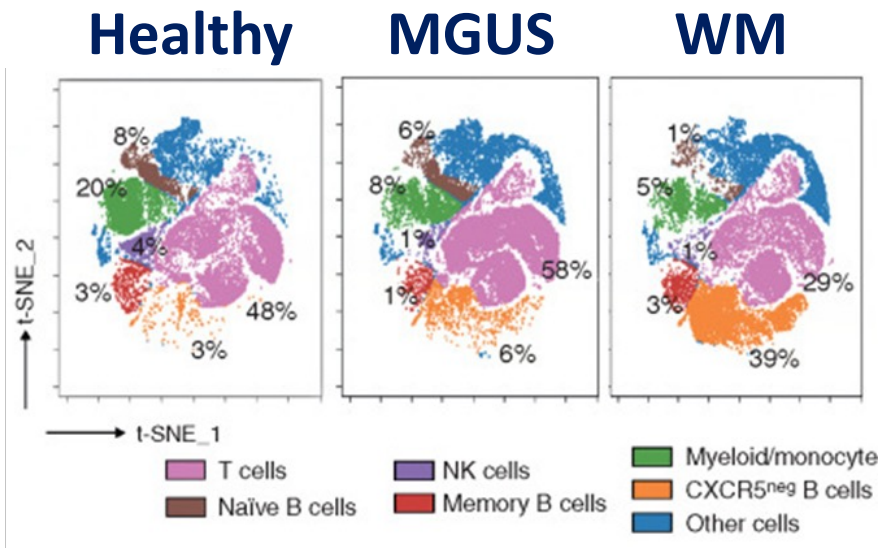
How to Better Know and Investigate the Bone Marrow Milieu Going from IgM-MGUS towards WM?



Kaushal et al. Blood Can Disc. 2021

Changes in the Bone Marrow Microenvironment Comparing HDs, IgM MGUS, and WM

CyTOF

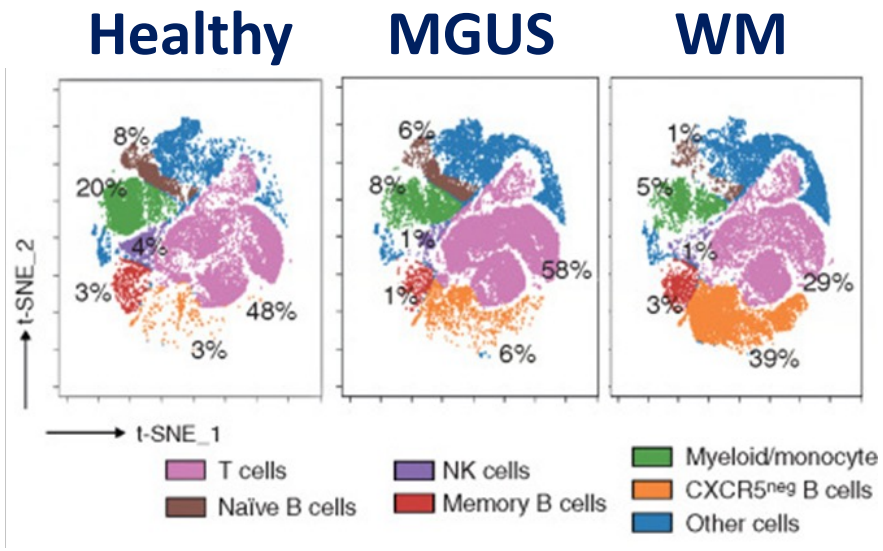


HD to IgM-MGUS to WM:
- increase in CXCR5^{NEG} B cells in WM
- decline in myeloid cells
- increase in BM-T cells in MGUS

Kaushal et al. Blood Can Disc. 2021

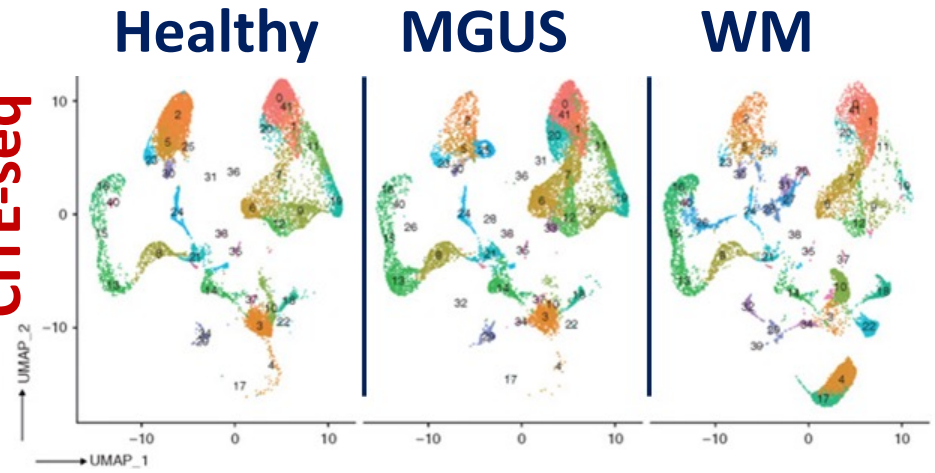
Changes in the Bone Marrow Microenvironment Comparing HDs, IgM MGUS, and WM

CyTOF



HD to IgM-MGUS to WM:
- increase in CXCR5^{NEG} B cells in WM
- decline in myeloid cells
- increase in BM-T cells in MGUS

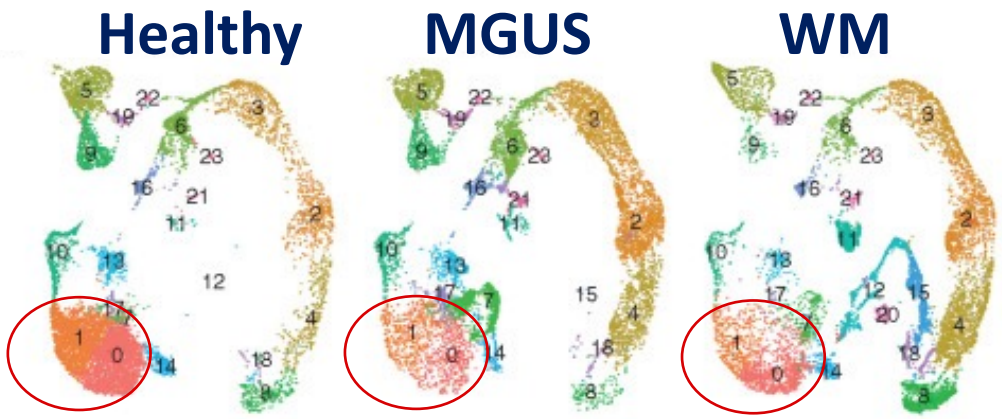
CITE-seq



Overall:
BM cells in WM and IgM-MGUS
are characterized by alterations
in several hematopoietic lineages vs HD

Kaushal et al. Blood Can Disc. 2021

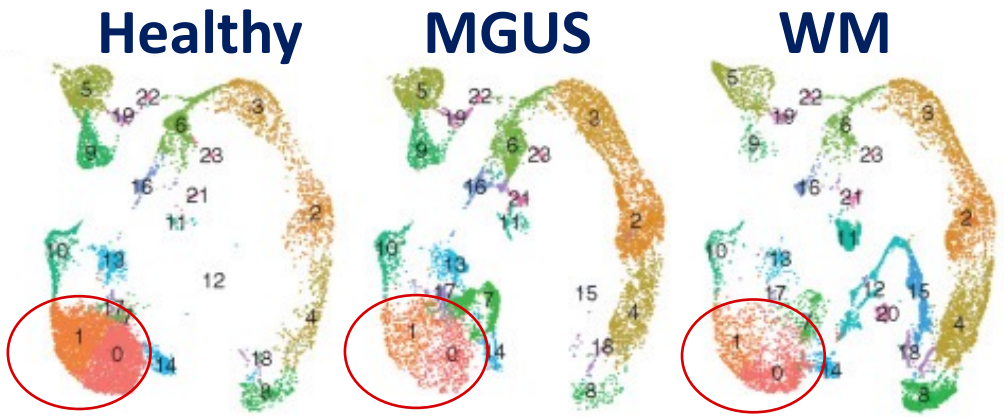
Changes in the Myeloid Compartment

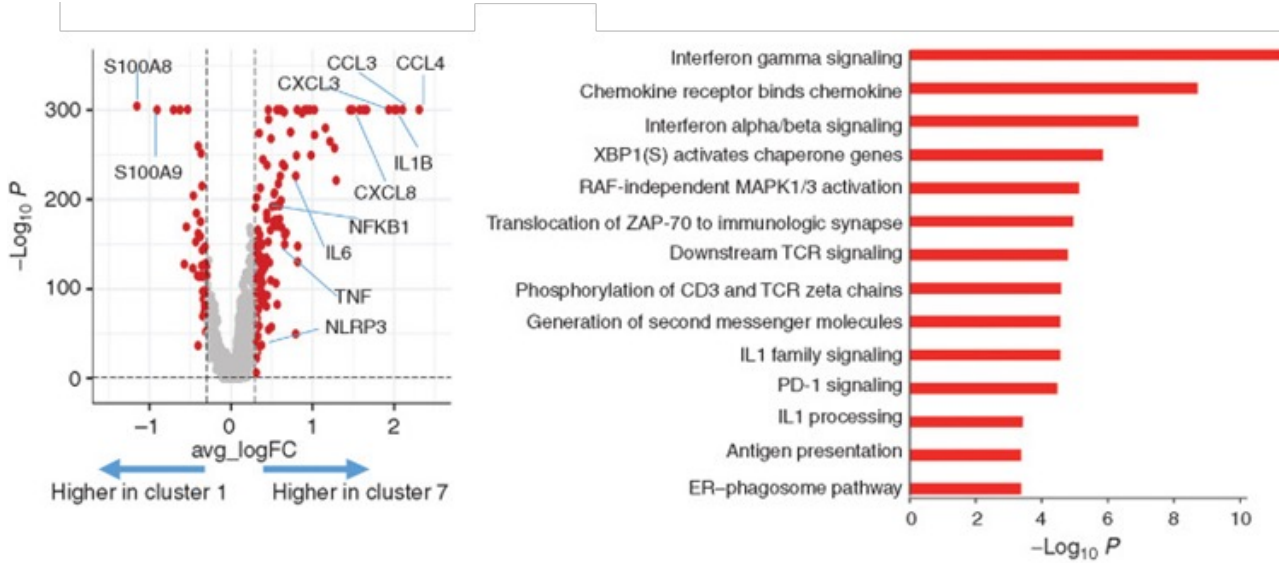


CD19-/CD3-depleted cells:
CD14+/CD11c+ cells
Both IgM-MGUS and WM showed
- decline in classic monocytes (cluster #1)

Kaushal et al. Blood Can Disc. 2021

Changes in the Myeloid Compartment



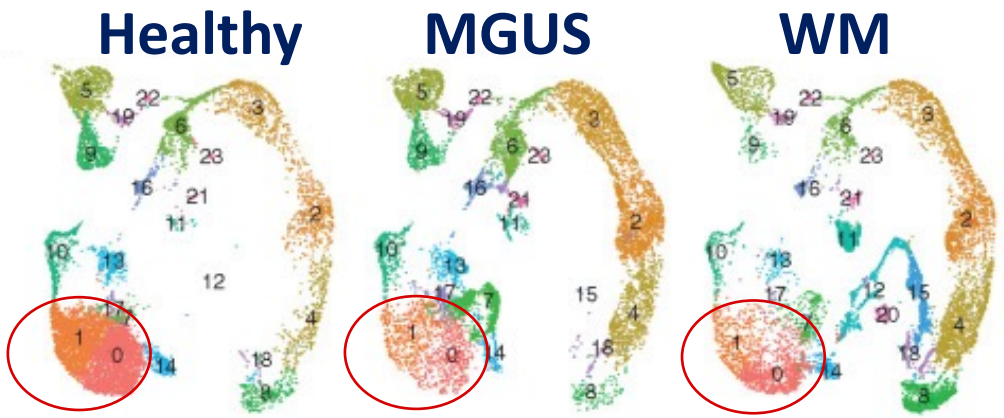


CD19-/CD3-depleted cells:
CD14+/CD11c+ cells
Both IgM-MGUS and WM showed
- decline in classic monocytes (cluster #1)

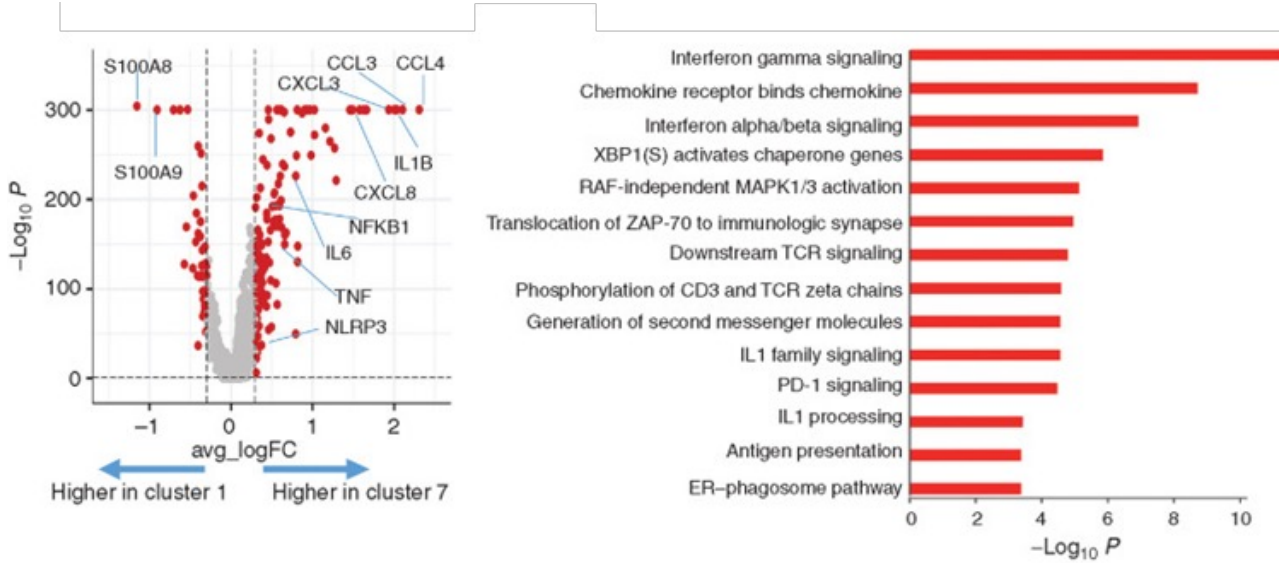
Myeloid population:
distinct genomic signature
of inflammation-associated genes (IL1β,
CCL4, CCL3, IL6, NLRP3, CXCL3) (> in MGUS)

Kaushal et al. Blood Can Disc. 2021

Changes in the Myeloid Compartment



CD19-/CD3-depleted cells:
CD14+/CD11c+ cells
Both IgM-MGUS and WM showed
- decline in classic monocytes (cluster #1)

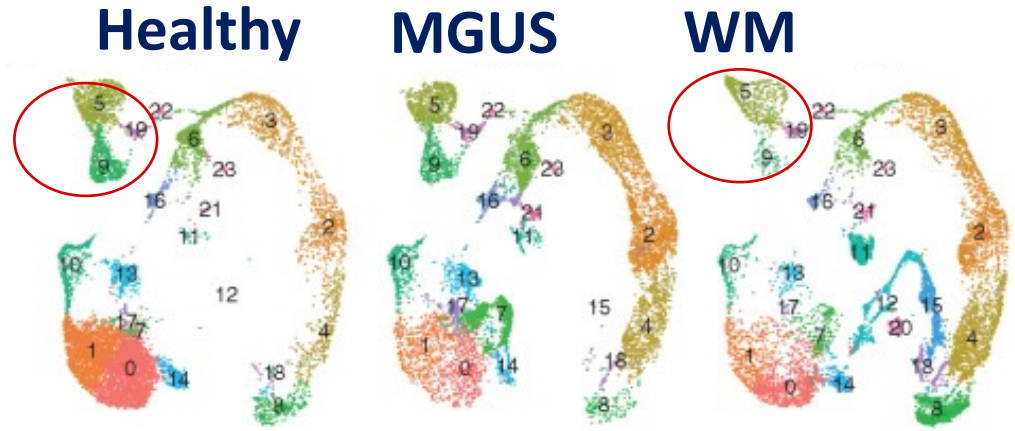


Myeloid population:
distinct genomic signature
of inflammation-associated genes (IL1β,
CCL4, CCL3, IL6, NLRP3, CXCL3) (> in MGUS)

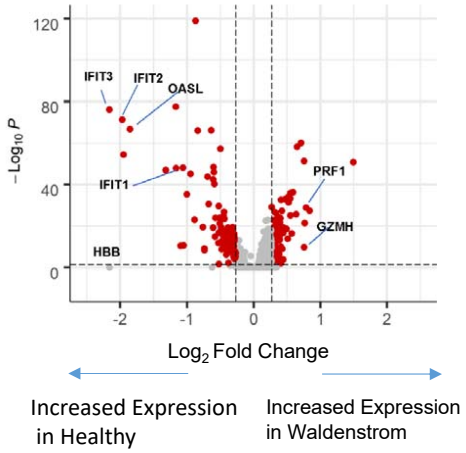
Together, these data suggest that activation of myeloid inflammation is an early feature of MGUS, occurring before the evolution of the malignant clone

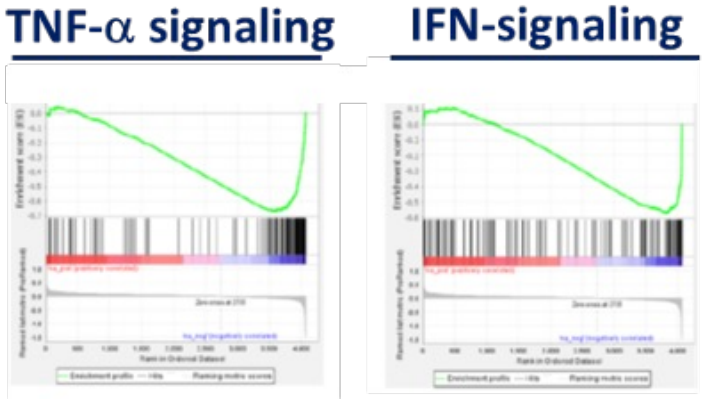
Kaushal et al. Blood Can Disc. 2021

Changes in Innate Cells



CD3-/CD56+ NK clusters:
- prominent alterations in WM
- greater expression of lytic/exhaustion markers
- loss of IFN-signature

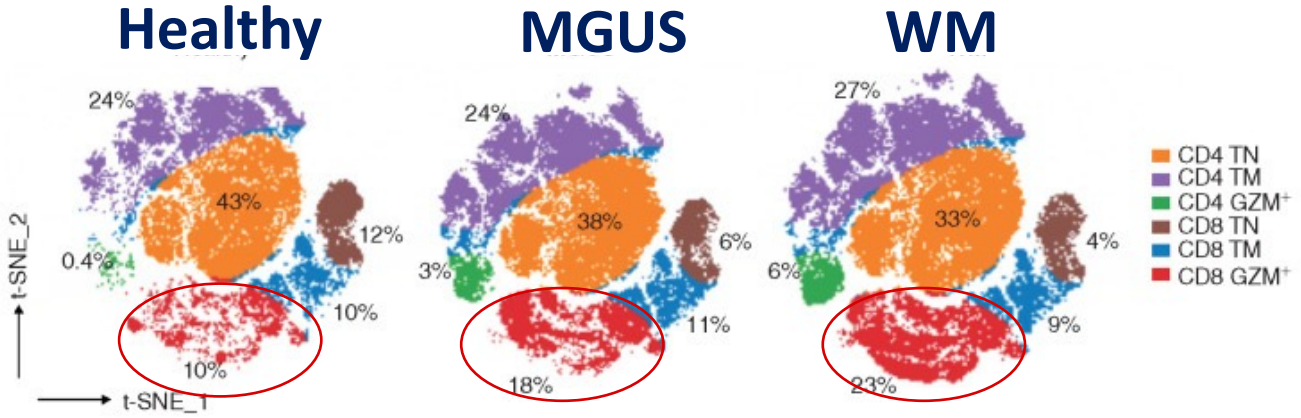




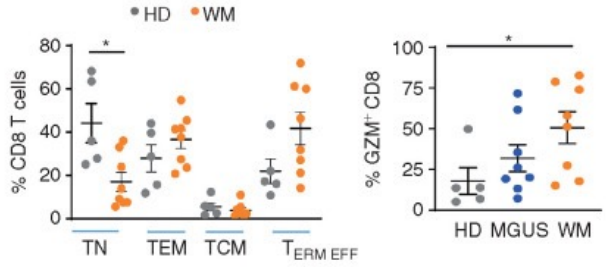
Immune exhaustion and dysfunction in NK cells with evolution of WM

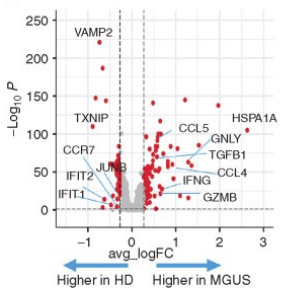
Kaushal et al. Blood Can Disc. 2021

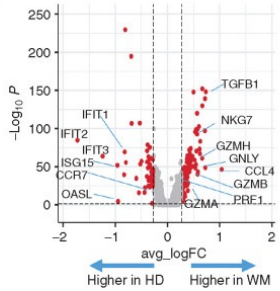
Changes in T Cells



T-cell niche:
- decrease in naïve CD8 T cells
- increase CD8+/Granzyme+ T cells







Most prominent transcriptome changes in CD8+T cells:
- increased lytic genes and markers associated with T-cell exhaustion in WM/MGUS
- loss of IFN-response genes

Changes in the T-cell compartment begin early in MGUS, before the establishment of progressive malignant clone, and are characterized by **progressive depletion of naïve T cells** and **enrichment of terminal effector T cells**

Take-Home Points - II -

Immune microenvironment

Several changes

- Increase in extrafollicular B cells
- Myeloid inflammation
- Alteration in immune function
- ***Treg deregulation***

Milieu favoring the emergence of the B-cell clone

↓

Acquisition further aberrations (Blc2; CXCR4)

Progressive growth and evolution to the **WM stage**

Host immune system
- mediates tumor-specific recognition of the clone
- undergoes immune exhaustion over time

↓

WM disease progression

The Importance of Translational Research in Defining Mechanisms Underlying Waldentröm's Macroglobulinemia Biology

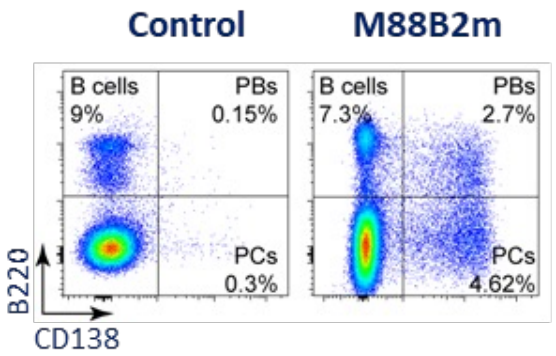
Tumor Clone

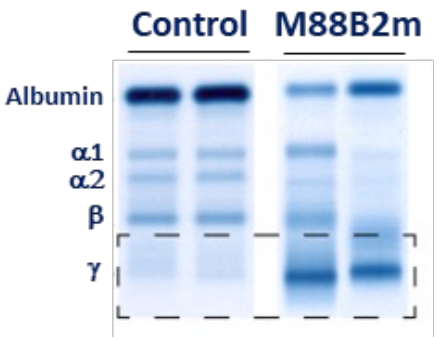
Bone Marrow Niche

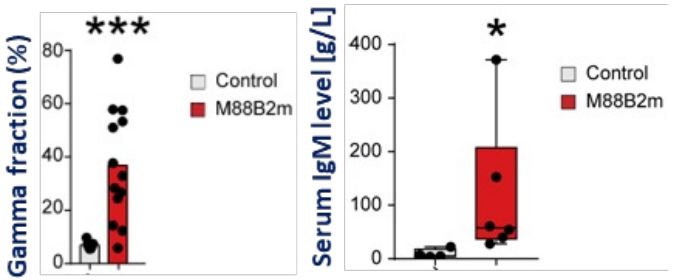
Tumor Cell-to-Bone Marrow Niche Interaction

WM Cell-to-TREG cell Interaction
Via
CD40-CD40 ligand

Transgenic Murine Lymphoplasmacytic/WM Model Points Towards a Role of Treg in Supporting WM Biology

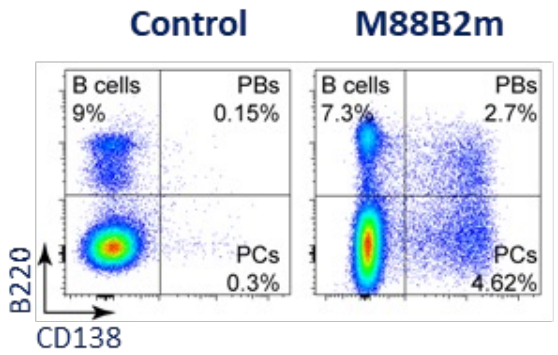


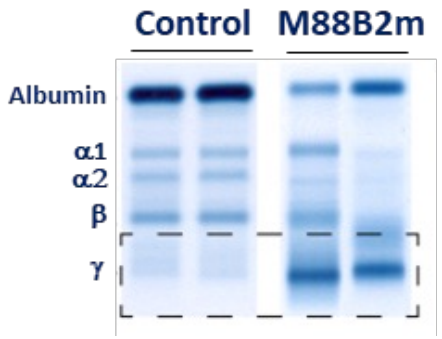


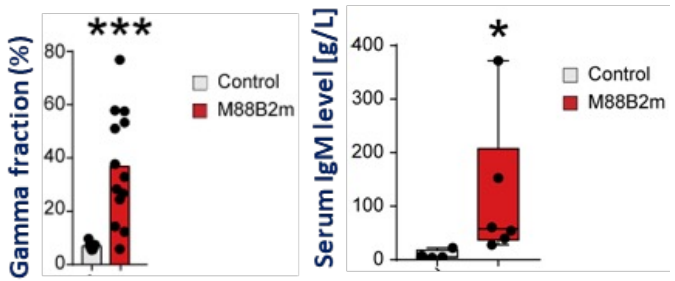


Sacco et al. Blood, 2023

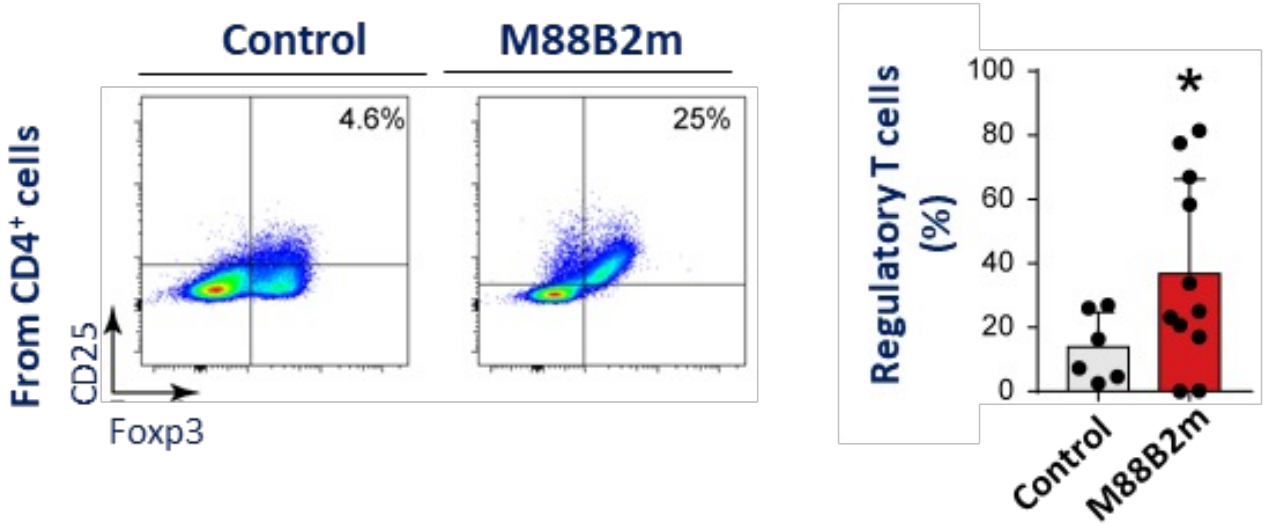
Transgenic Murine Lymphoplasmacytic/WM Model Points Towards a Role of Treg in Supporting WM Biology



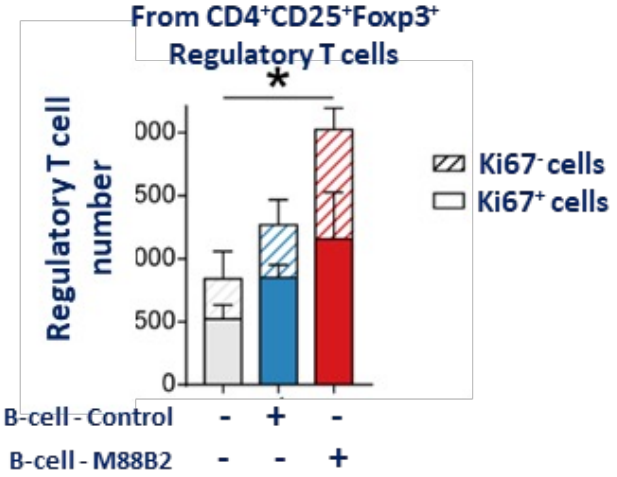




Higher levels of Treg cells in the M88B2m model vs control mice

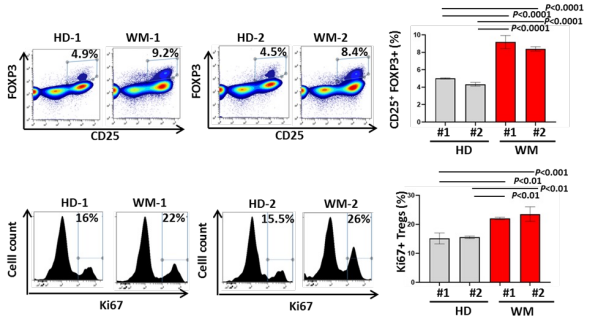


WM murine cells recruited a higher number of more abundant Ki67+ Treg cells



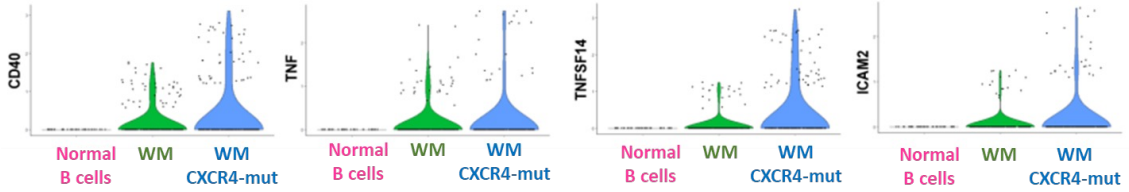
Sacco et al. Blood, 2023

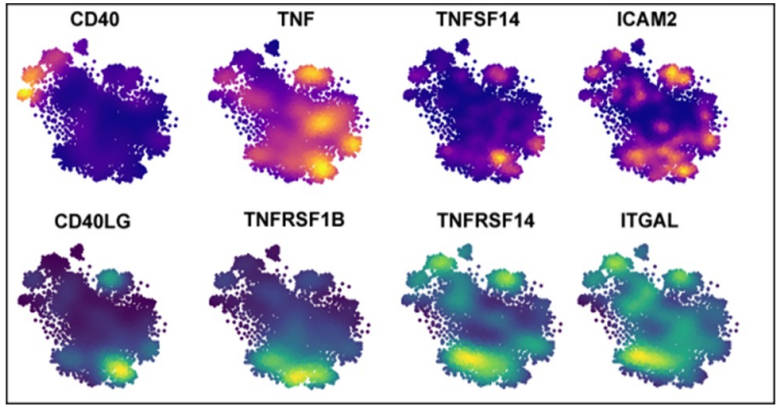
Primary WM Cells: Impact on Treg-Induction and Treg-Proliferation



Enhanced Treg-proliferation exerted by WM primary cells as compared to normal-B cells

Enrichment for MAPK- and PI3K/AKT-related genes in WM- versus HD-derived Tregs

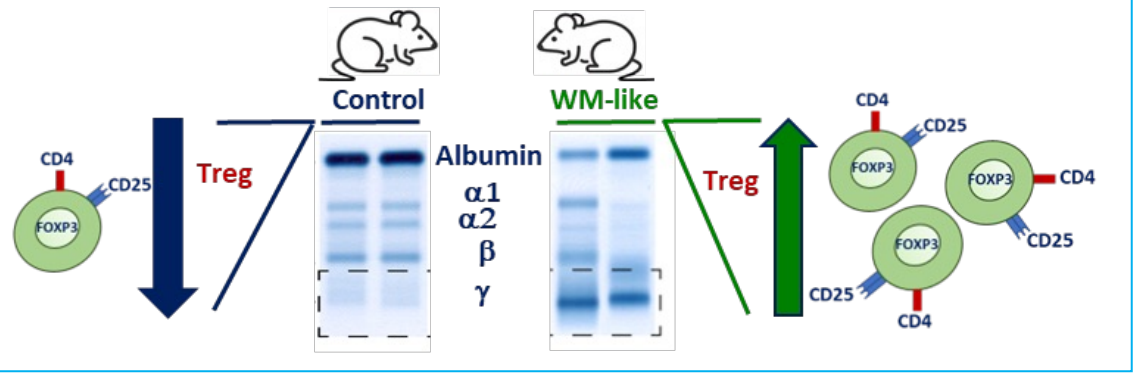


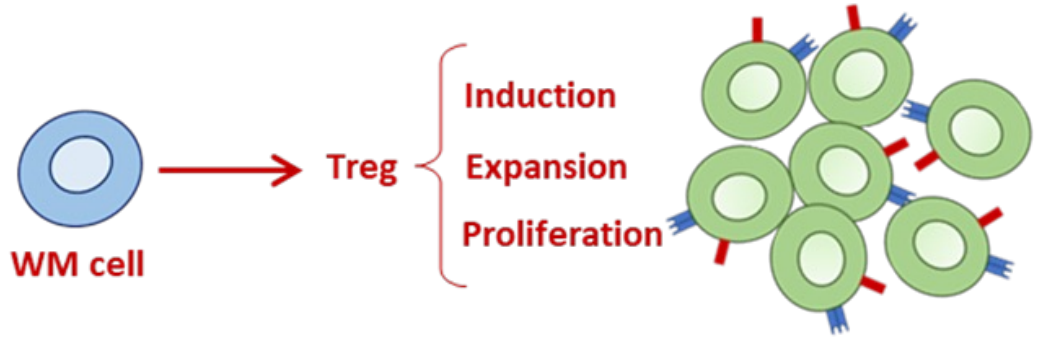


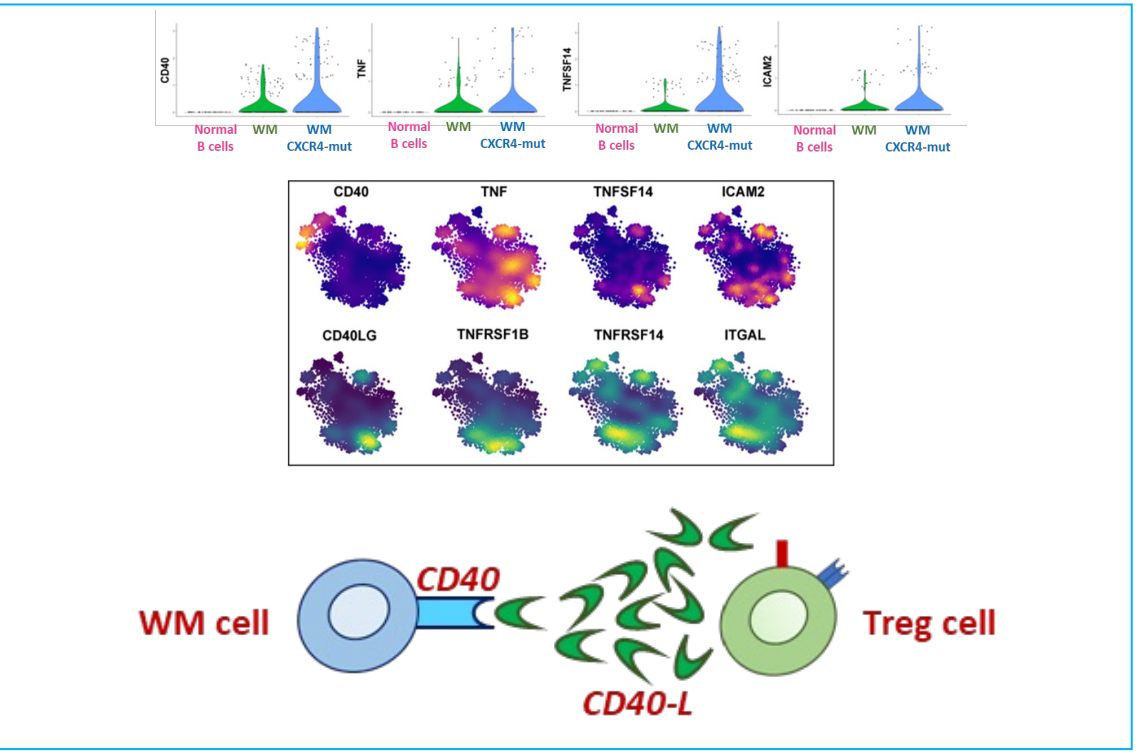
CD40: restricted on B-cells
CD40L: Treg-counterpart

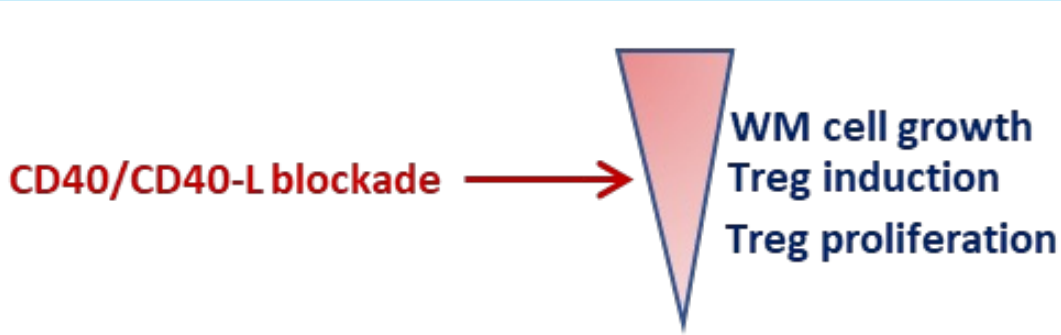
Sacco et al. Blood, 2023

Treg Cells Interact with WM Cells via CD40/CD40-Ligand Axis



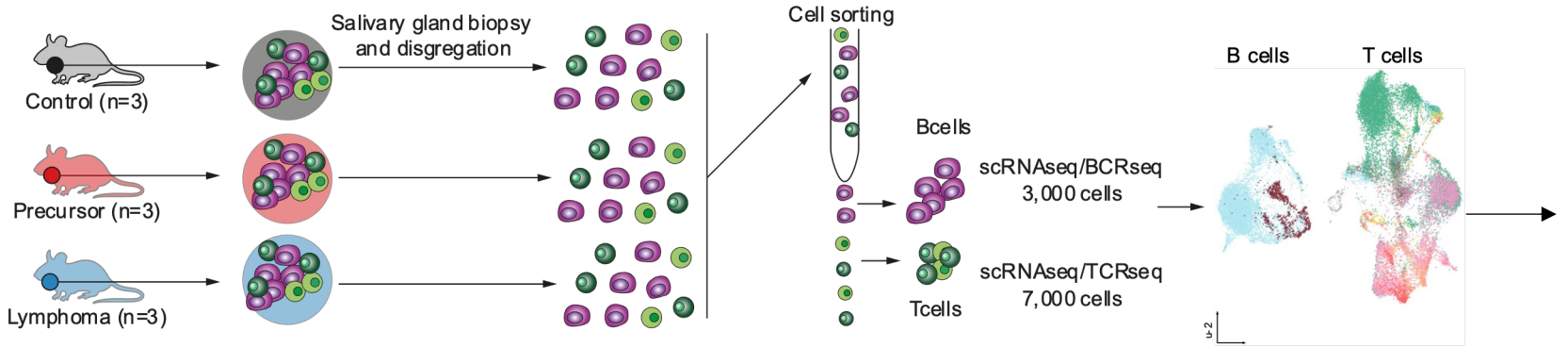


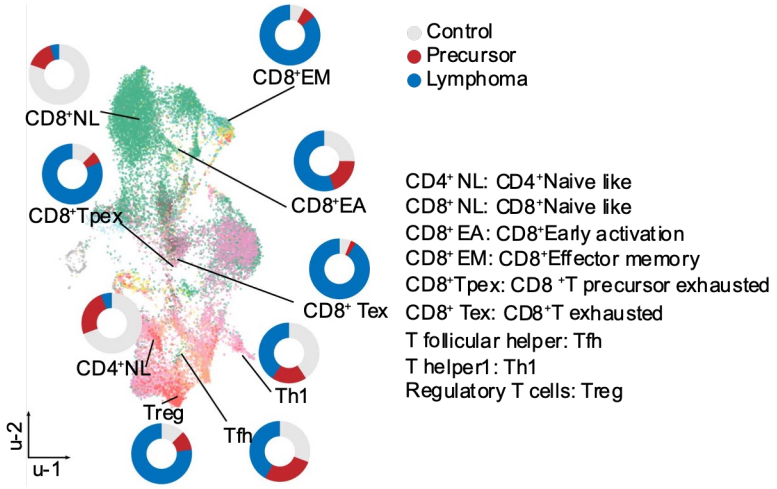




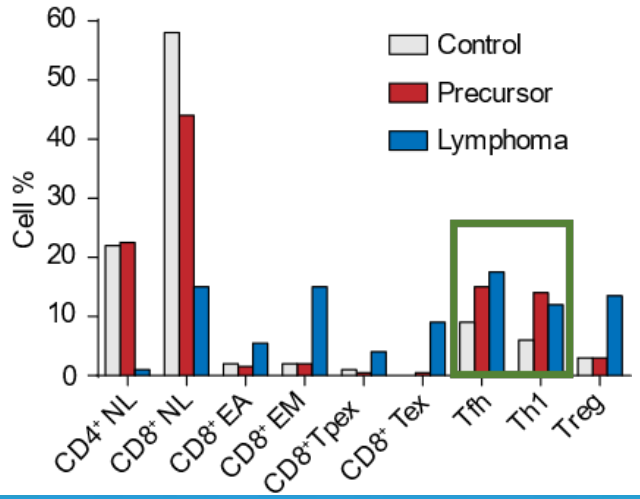
Sacco et a. Blood, 2023

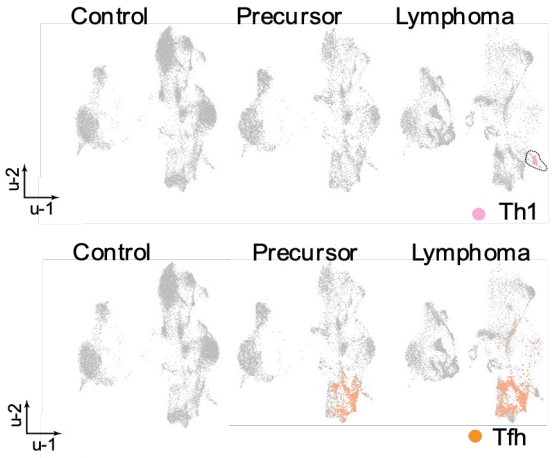
WM Cells Depend on CD4+ Th1 Cells for Survival via CD40:CD40L From Early Stages



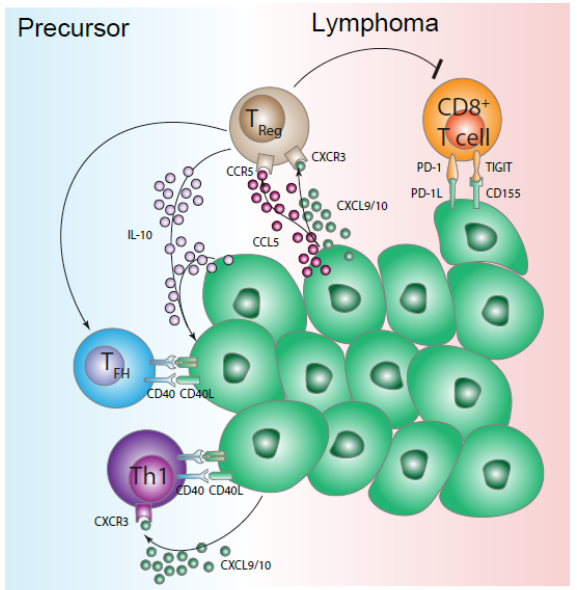


Mouse model of MYD88^{L252P} and BCL2 co-expression from inmature B cells (cd79a-cre)
Progressive Lymphoplasmacytic Lymphoma in extranodal locations including the BM
Mostly IgM, but some cases secrete IgG/IgA
Rodriguez et al, Science Adv 2022 - Sacco et al, Blood 2023
Celay et al, submited





20% of Th1 cells show clonal TCRs



Ion Celay, PhD
José A. Martinez-Climinet MD, PhD
Univ. Navarra, Pamplona, Spain

Take-Home Points - III -

Halting CD40/CD40-ligand interaction may represent a strategy to inhibit the Treg-mediated immunosuppressive in WM

Translational Research: Novel Drug Discovery

MOLECULES	→ PEER-REVIED PUBLICATION →	INITIATED CLINICAL TRIALS	PHASE
BMS936564 Anti-CXCR4 MoAb	**Roccaro AM, Sacco A, Jimenez C, et al.** **Blood, 2014**	**BMS936564+Len+Dex (MM)** **(Pending in WM)**	**I**
CARFILZOMIB proteasome inhibitor	**Sacco A, Aujay M, Morgan B…,** **Roccaro AM*, Ghobrial IM*** **(*Co-last Authors)** **Clin Cancer Res, 2012**	**Carfilzomib + Rituximab + Dexamethasone**	**II**
		Carfilzomib + Belinostat	**I**
		Carfilzomib	**II**
OPROZOMIB (ONX0912) proteasome inhibitor	**Roccaro AM, Sacco A, Aujay M, et al.** **Blood, 2010**	**Oprozomib**	**II**
PANOBINOSTAT (LBH589) HDAC inhibitor	**Roccaro AM, Sacco A, Jia X, et al.** **Blood, 2010**	**Panobinostat**	**II**
BORTEZOMIB proteasome inhibitor	**Roccaro AM, Hideshima T, Raje N, et al.** **Cancer Res, 2006**	**376 Bortezomib-based clinical trials - MM** **31 Bortezomib-based clinical trials - WM**	**II/III**

Translational Research: Novel Drug Discovery

MOLECULES →	PEER-REVIED PUBLICATION →	INITIATED CLINICAL TRIALS	PHASE
OLAPTESED PEGOL Oligonucleotide anti-SDF1	**Roccaro AM, Sacco A, et al. Cell Reports, 2014**	**ola-PEG + Dex + Bortezomib (MM)**	**II**
		ola-PEG + Rituximab + Bendamustine (CLL)	**II**
EVEROLIMUS (RAD001) mTOR inhibitor	**Roccaro AM, Sacco A, Jia X, et al Clin Cancer Res 2012**	**Everolims+Bortezomib+/-Rituximab**	**I/II**
		Everolimus +/- Bortezomib+Ritux+Dex	**I/II**
		Everolimus (first line)	**II**
		Everolimus + Lenalidomide	**I/II**
		Everolimus + Panobinostat	**I/II**
		Everolimus + Bortezomib	**I**
		Everolimus + Sorafenib	**I/II**

Overall Summary

Tumor clone

Bone marrow niche

Tumor cell-to-Bone marrow niche interaction

Novel insight into Waldenström's Macroglobulinemia biology

Identification of novel targets for novel therapeutical interventions

Acknowledgements

ASST Spedali Civili di Brescia
Clinical Trial Center, Translational Res. and Phase I Unit

Andrea Abate, Chiara Aquilina, Luisella Alessandrini, Gabriele Benini, Monica Boglioni, Giulia Campostrini, Greta Dasoli, Cristina Erconi, Francesca Filippini, Martina Gelmi, Cristina Gussago, Rossella Leopaldo, Raffaella Marcheselli, Nuzhat Noreen, Alessia Pantaleo, Matteo Regalzi, Fabio Rigali, Alessandra Rossi, Antonio Sacco, Anna Scalvini, Antonella Salvino, Margherita Sciumè, Sandra Sigala, Sara Taranto, Elena Tratta, Laura Zanotti

Hematology
Marina Motta, Antonella Anastasia, Alessandra Tucci

ASST Niguarda, Milan
Alessandra Tedeschi, Anna Maria Frustaci

University of Milan-Bicocca
Rocco Piazza, Deborah D'Aliberti, Silvia Spinelli, Daniele Ramazzotti

University of Bari
Detp. Of Biomedical Sciences and Human Oncology
Vanessa Desantis, Antonio G. Solimando

University of Genoa
Dept. of Hematology
Michele Cea, Antonia Cagnetta, Debora Soncini