

Strategic Research Roadmap:

Getting to a World Without WM

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Professor of Medicine

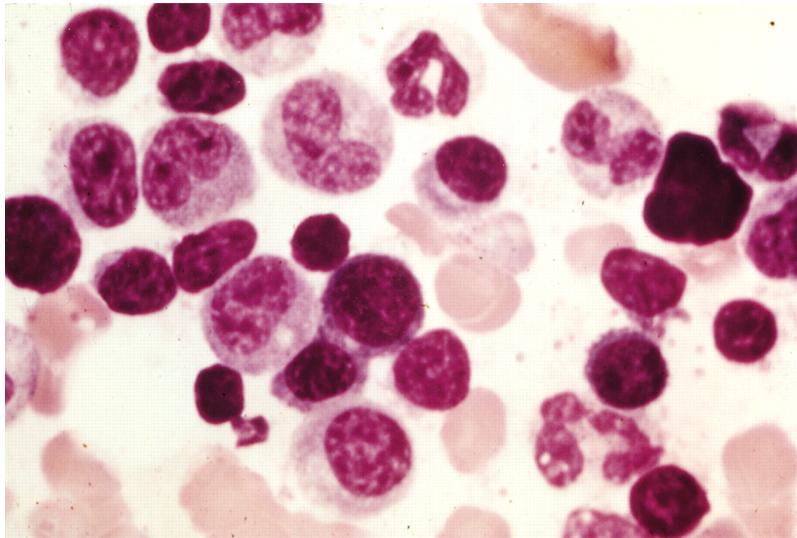
Mayo Clinic

Topics to be covered -

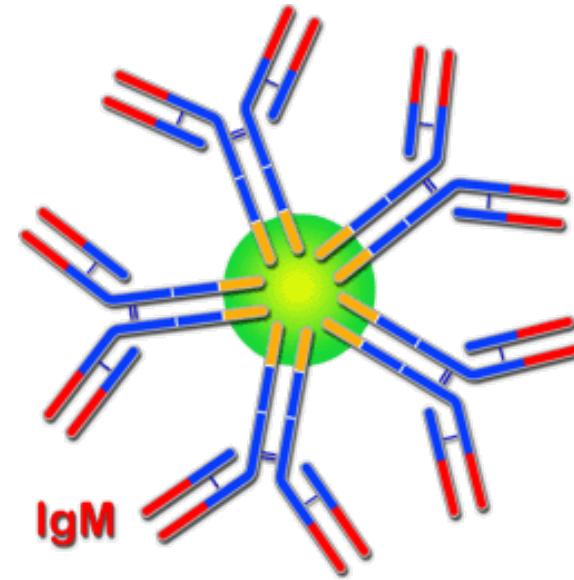
- What is unique about Waldenström macroglobulinemia?
 - What do we still need to know to get to a cure?
- What is the WM Strategic Roadmap Roadmap?
 - Why do we need one?
- How will supporting the Roadmap help?
 - Will it get us to a world without WM?

Waldenström macroglobulinemia

“A disease with two problems”



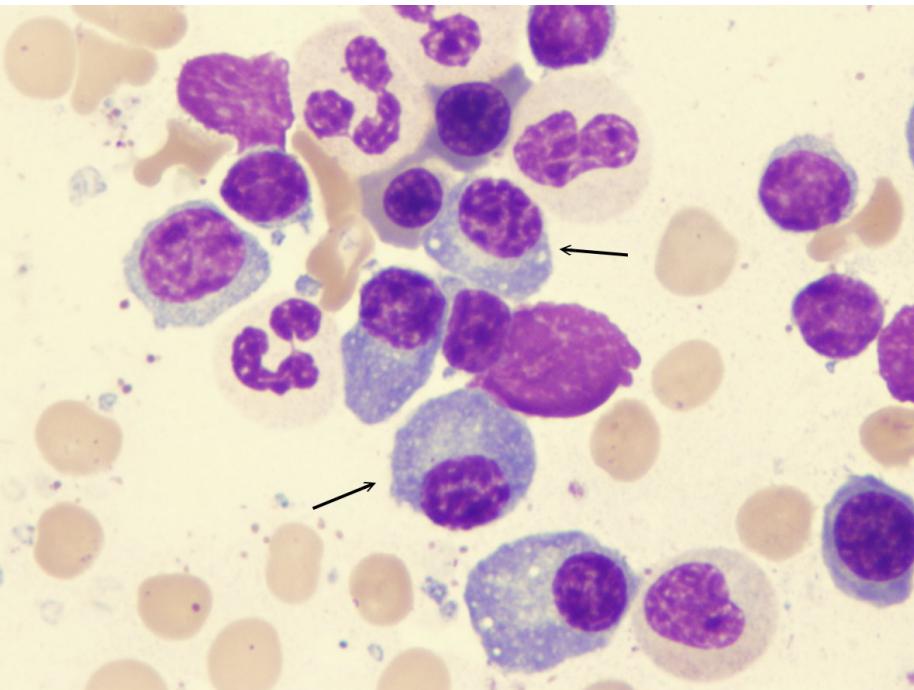
Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Waldenström macroglobulinemia

Morphology and Immunophenotype



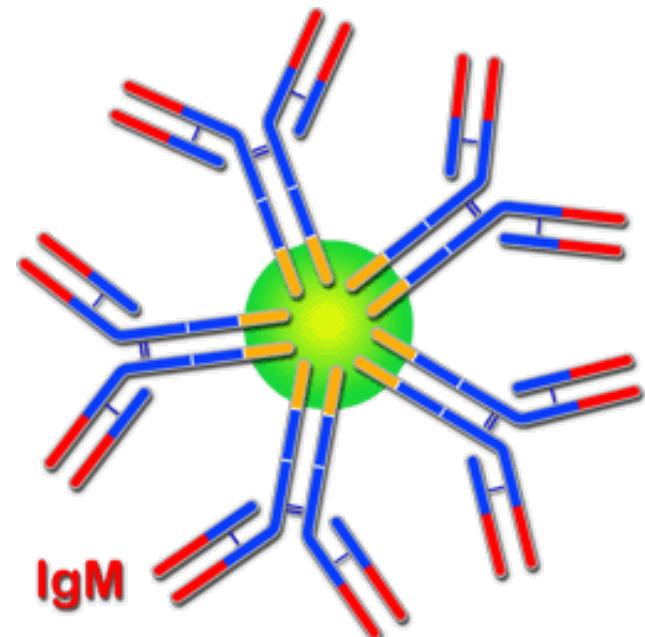
- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+.
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Waldenström macroglobulinemia

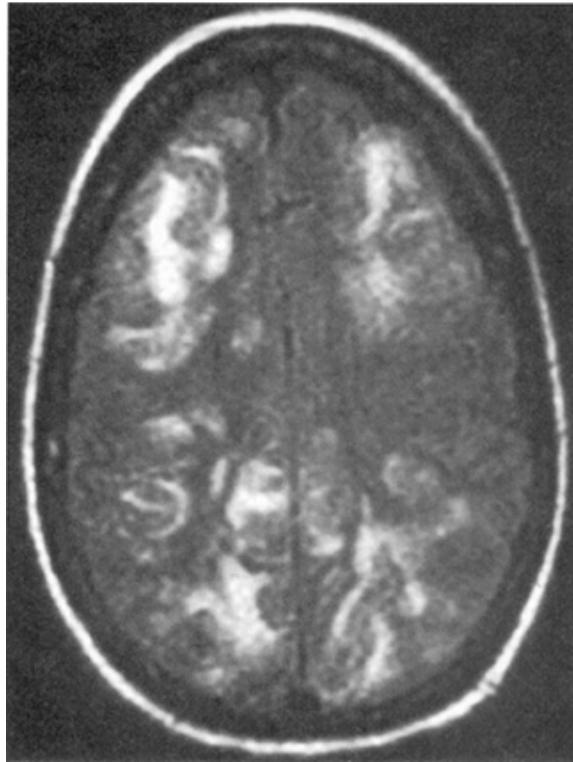
Monoclonal IgM

Symptoms related to the monoclonal IgM protein are attributable to -

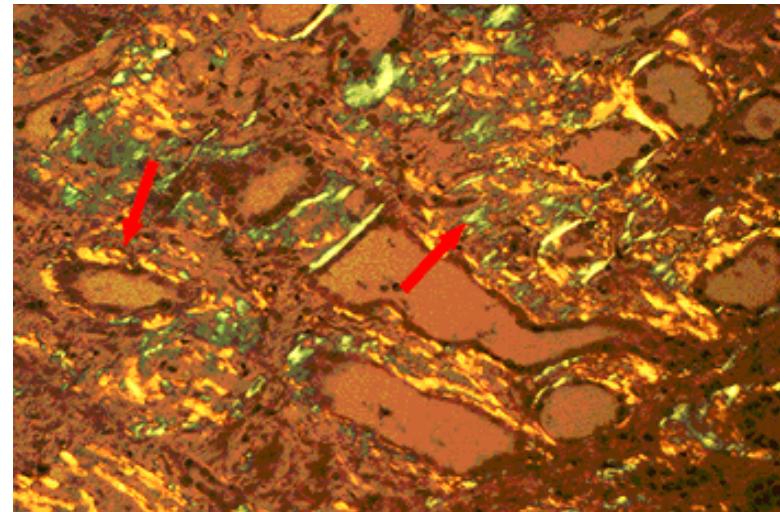
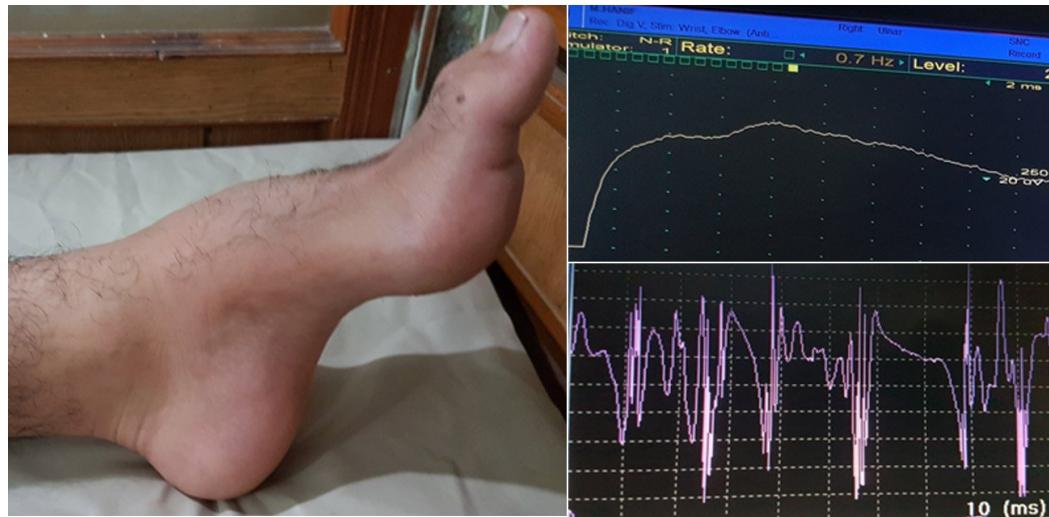
- its characteristics in the circulation,
- its interaction with various body tissues when deposited,
- and its autoantibody activity.



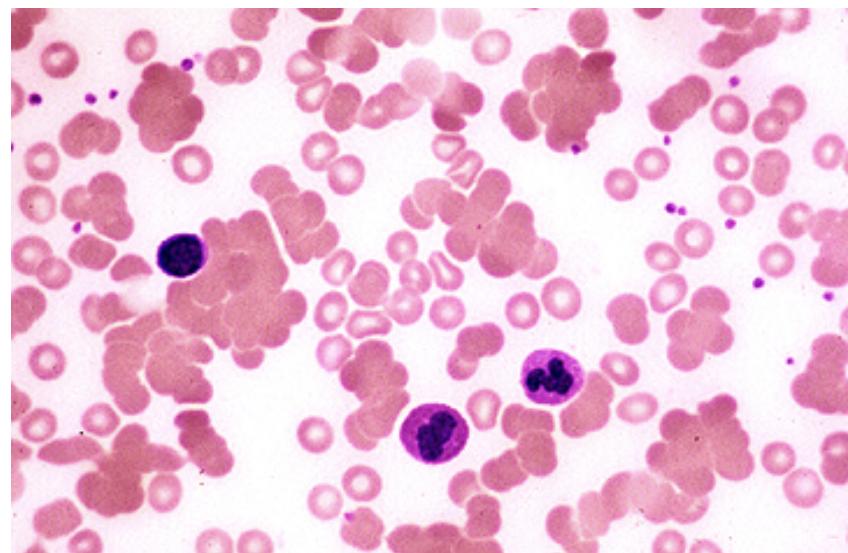
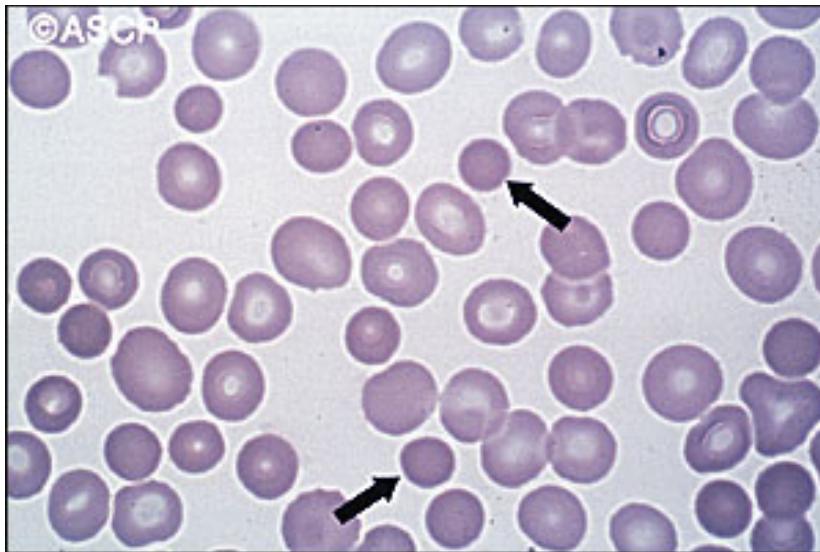
Hyperviscosity due to Waldenström macroglobulinemia



IgM deposition due to Waldenström macroglobulinemia



Autoimmune hemolysis and cold agglutinin disease secondary to Waldenström macroglobulinemia

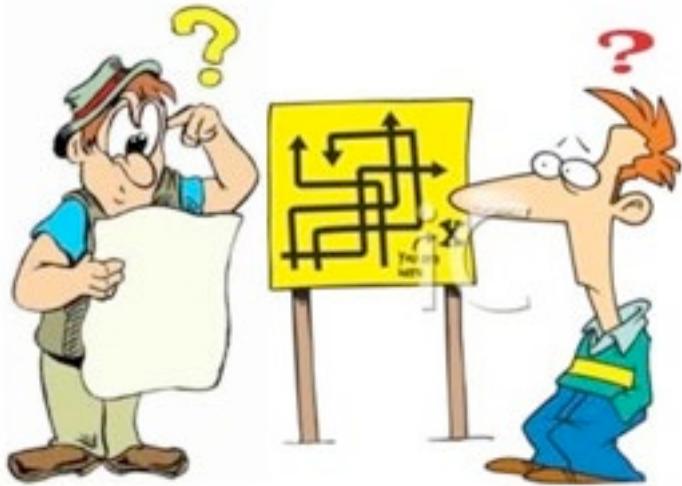


What are the Knowledge Gaps in Waldenström macroglobulinemia?



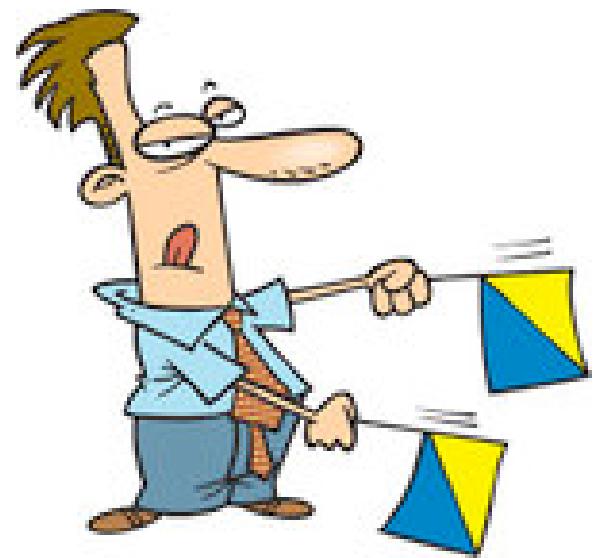
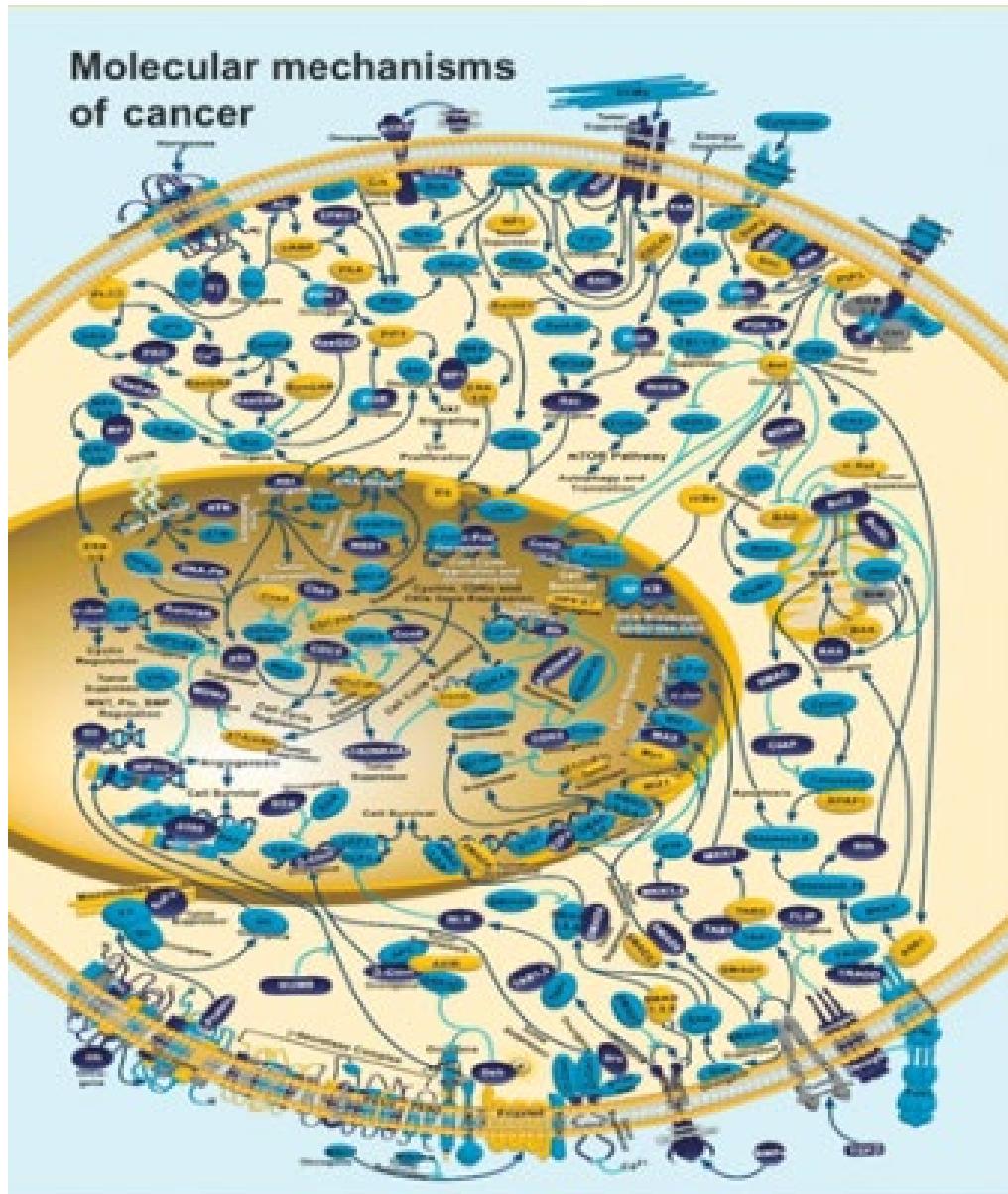
The WM Roadmap Identified 4

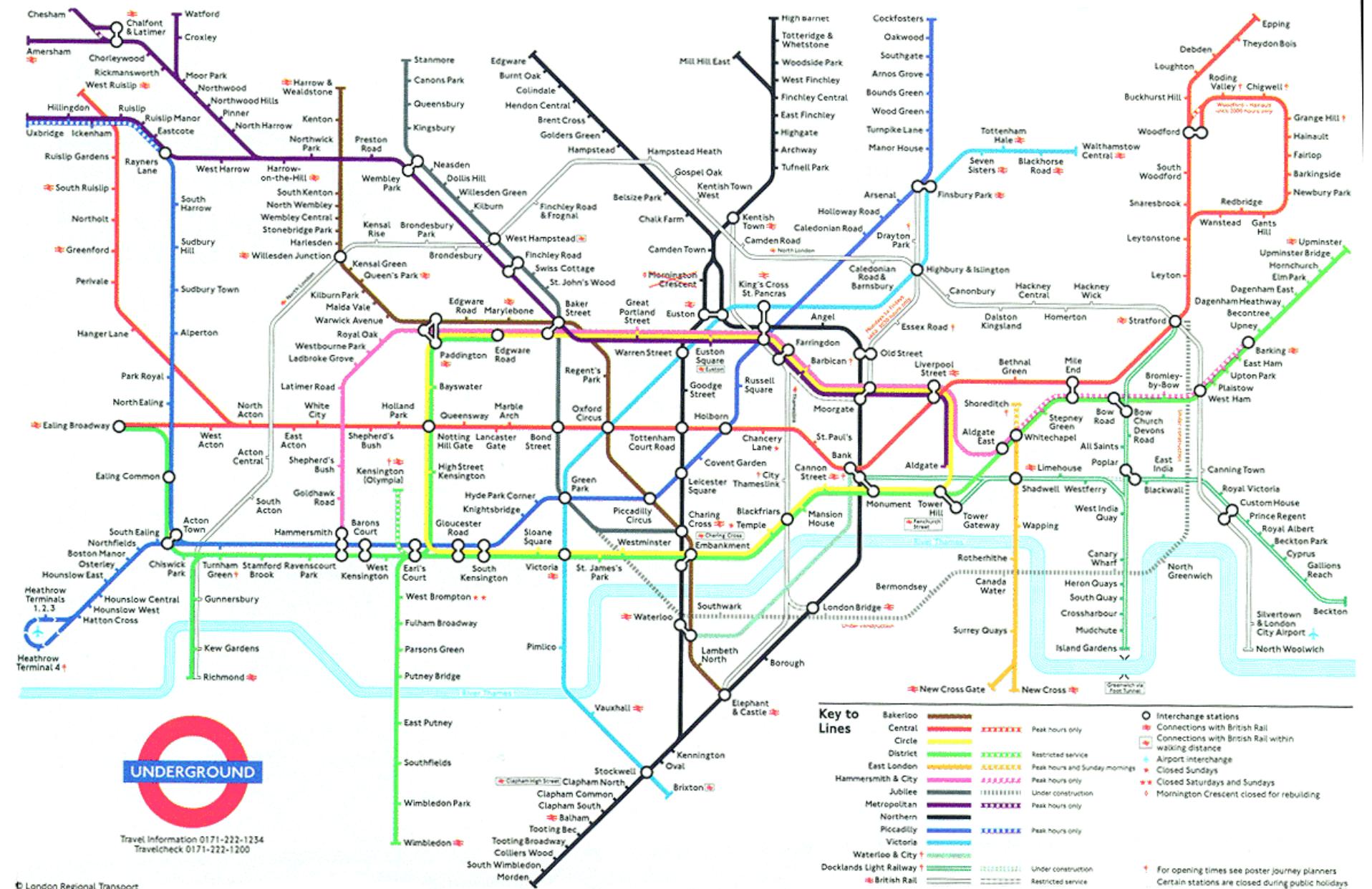
“Knowledge Gaps”



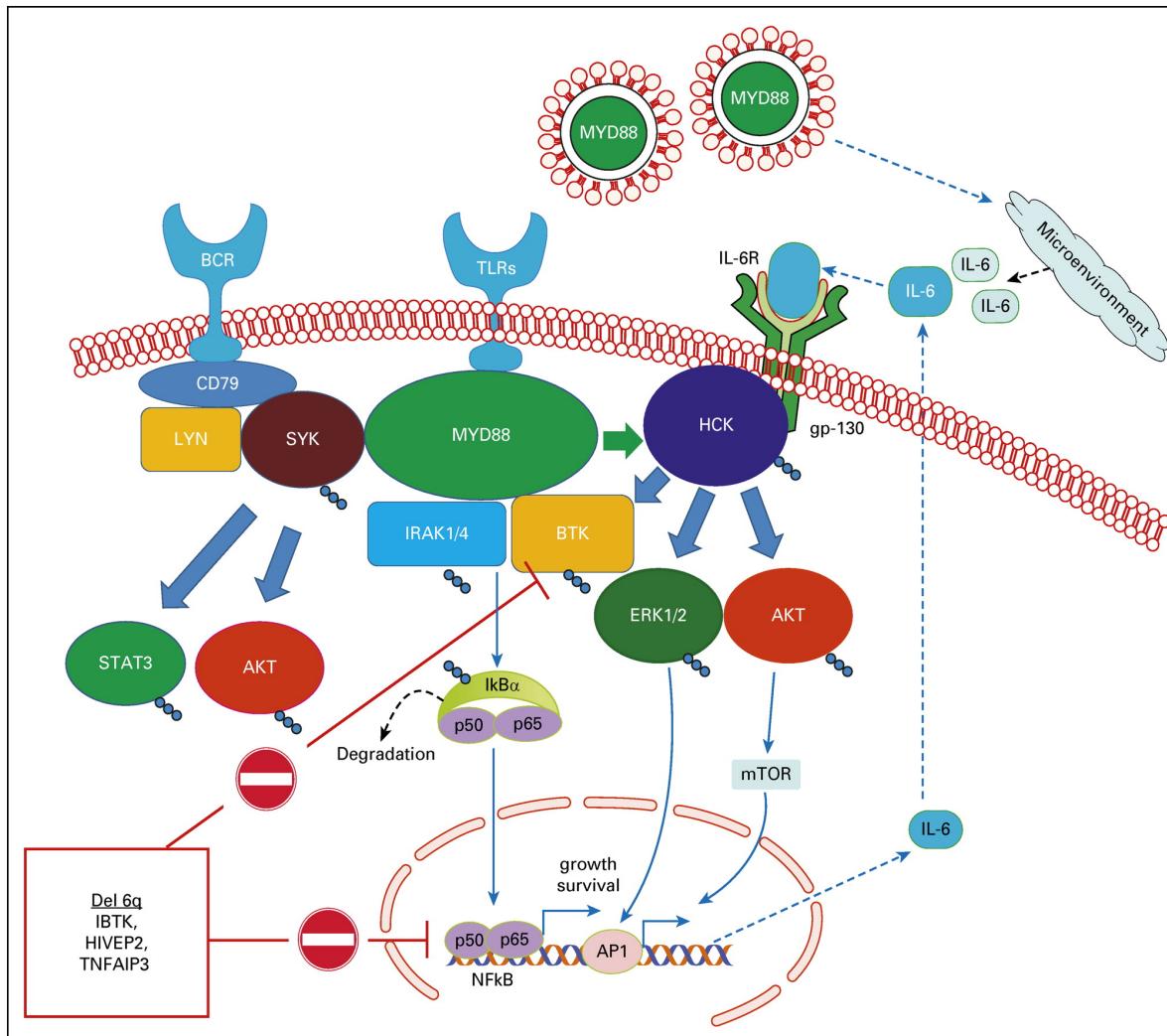
- Signaling
- ‘- omics’ – genomics, epigenomics, proteomics
- Immunology
- Bone marrow microenvironment

Signaling in WM and why it matters





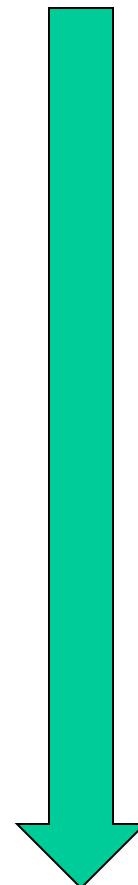
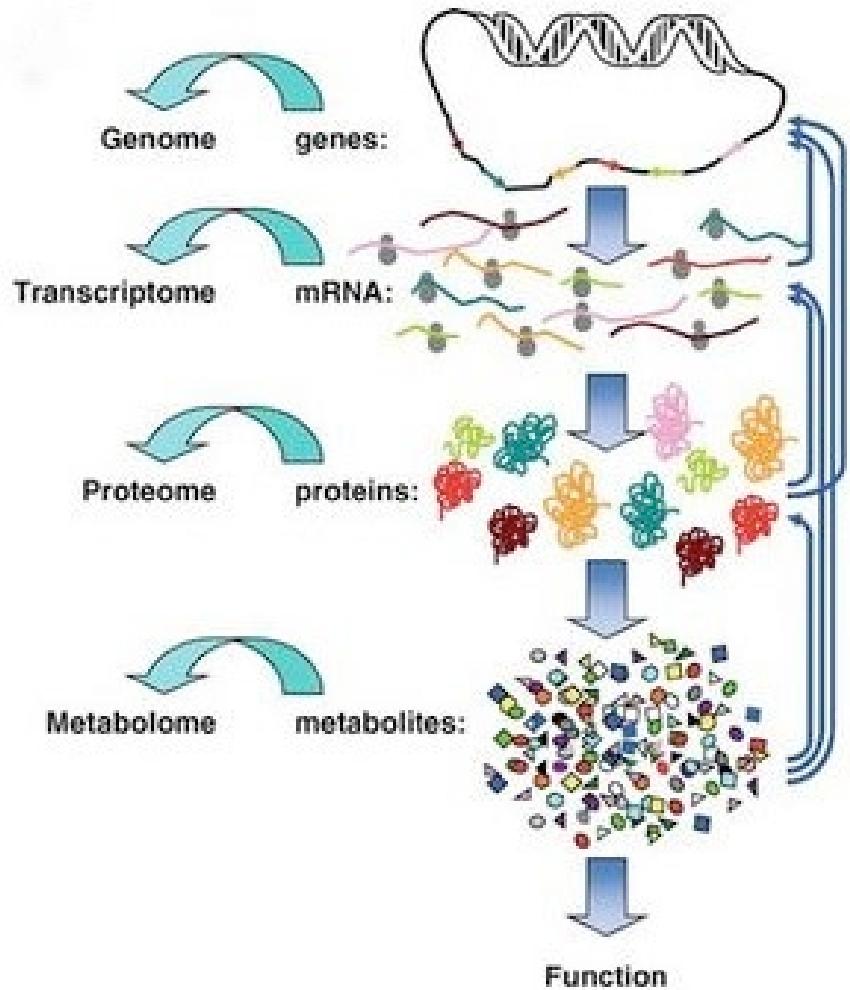
Pro-survival signaling mediated by mutated MYD88



Omics in WM and why it matters



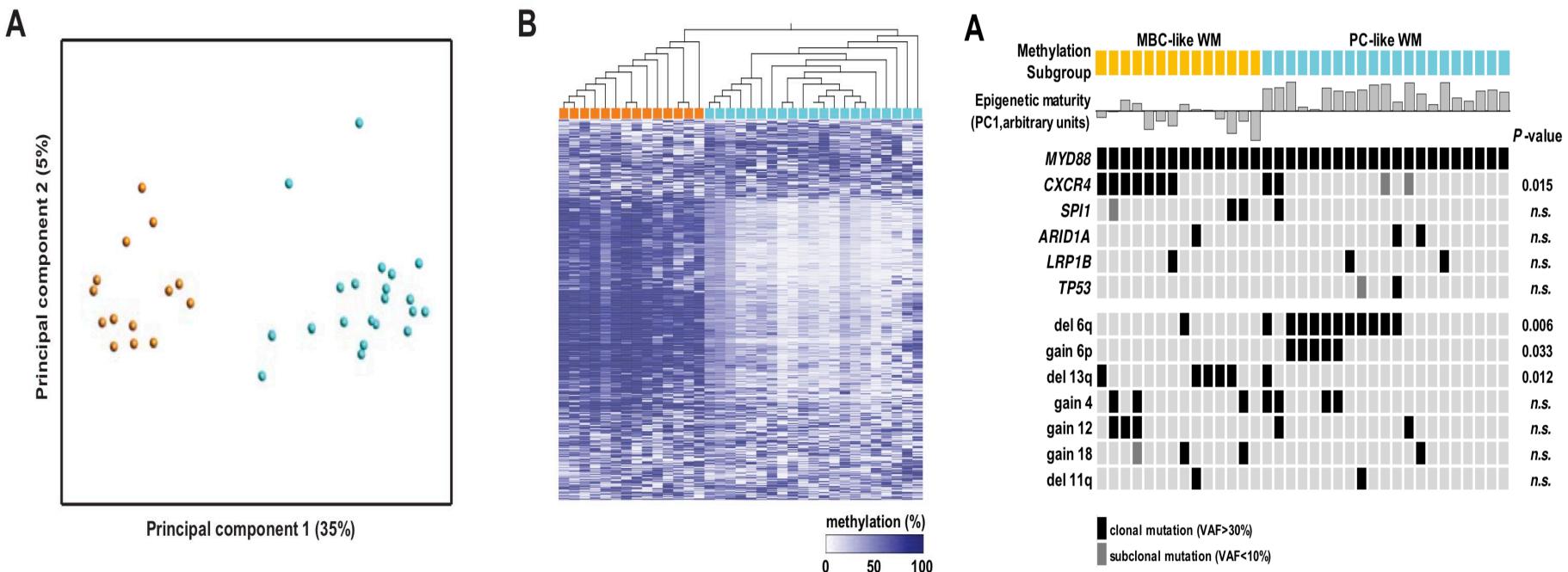
Genomics, Epigenomics, Proteomics, Metabolomics



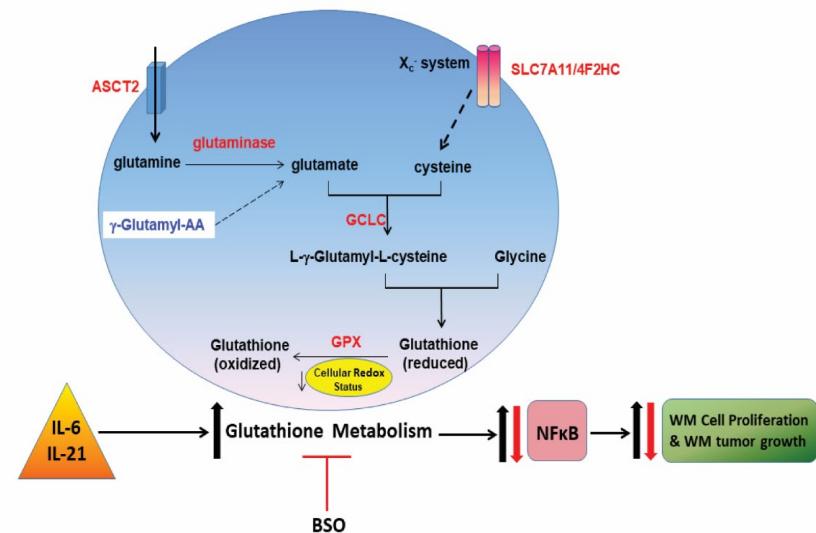
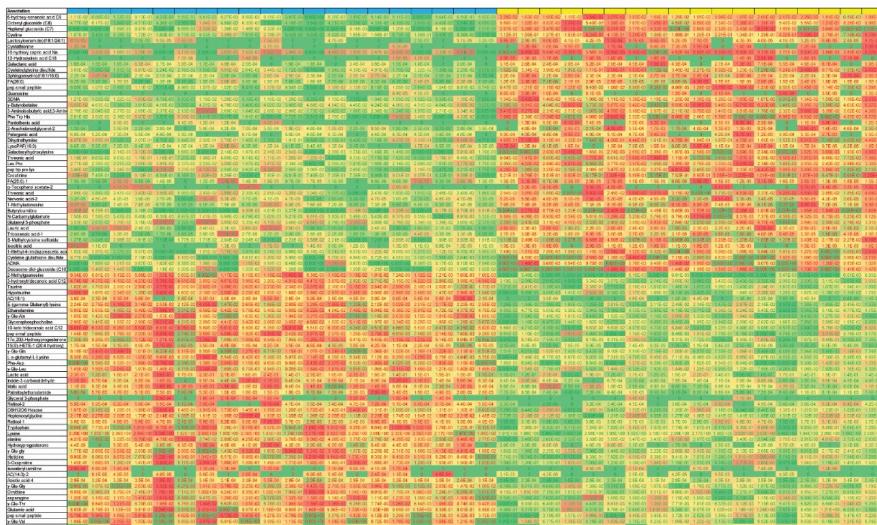
YouTube



Identification of two DNA methylation subtypes of Waldenström's macroglobulinemia with plasma and memory B cell features



Increased glutathione utilization augments tumor cell proliferation in Waldenstrom Macroglobulinemia



Immunology in WM and why it matters



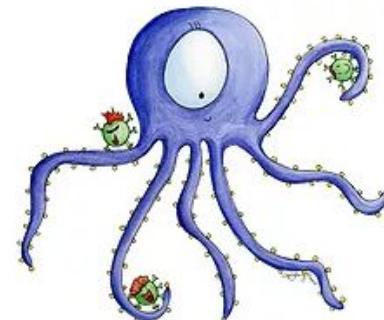
NK Cell



Cytotoxic T Cell



Helper T Cell



Follicular Dendritic Cell



Macrophage



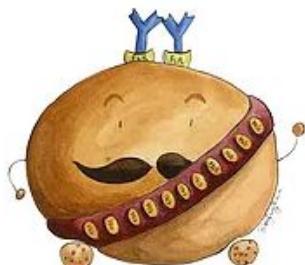
Treg



B Cell



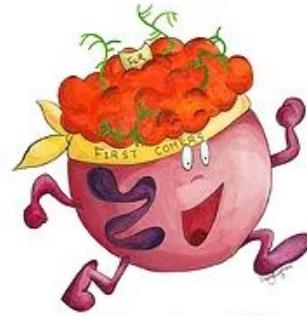
Plasma Cell



Mast Cell



Basophil

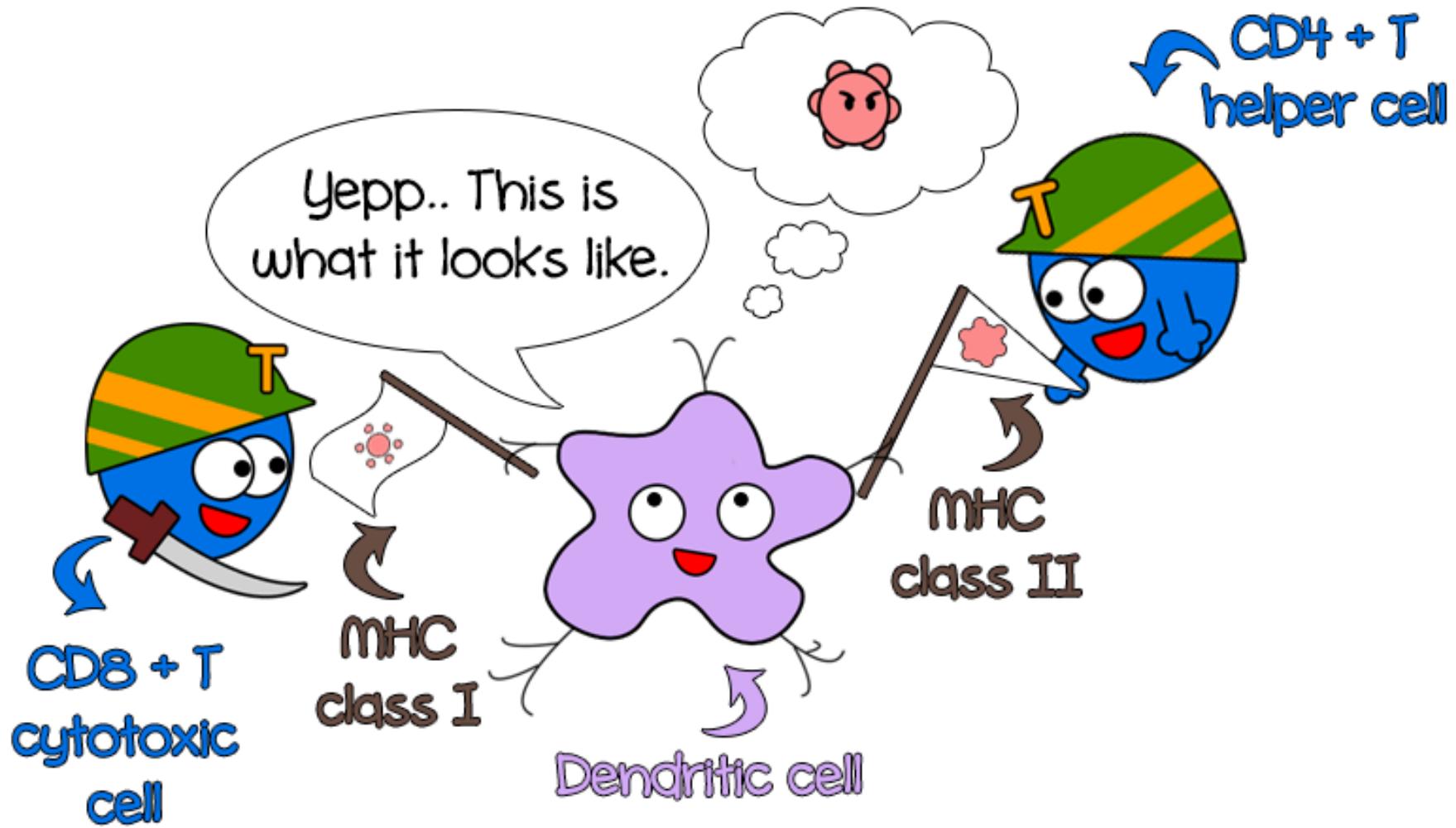


Neutrophil



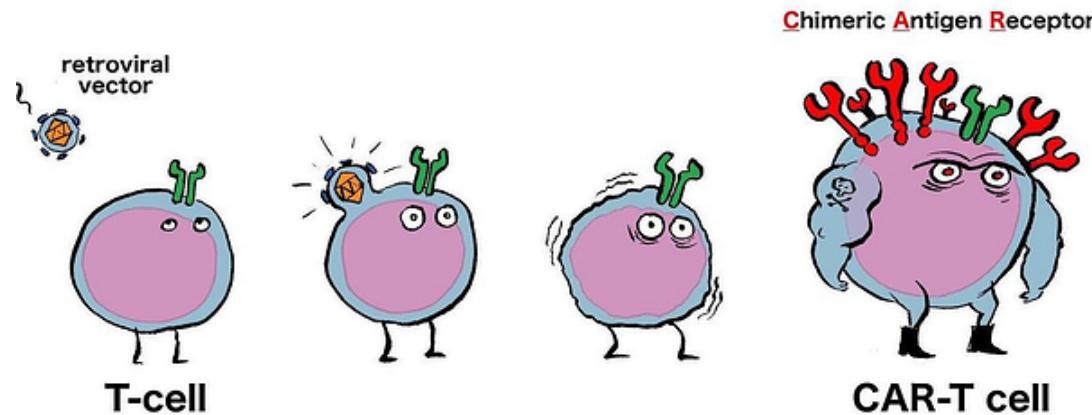
Eosinophil

Getting the Immune System to target WM



CAR T-cells - ZUMA-5: Efficacy endpoints in relapsed/refractory FL and MZL

| Endpoint | FL (n = 80) | MZL (n = 16) |
|-------------------|-------------|--------------|
| Overall response | 95% | 81% |
| Complete response | 81% | 75% |
| Partial response | 14% | 6% |
| Median DOR | 20.8 months | 10.6 months |
| Median PFS | 23.5 months | 11.8 months |
| 12-month OS | 93.4% | 100% |



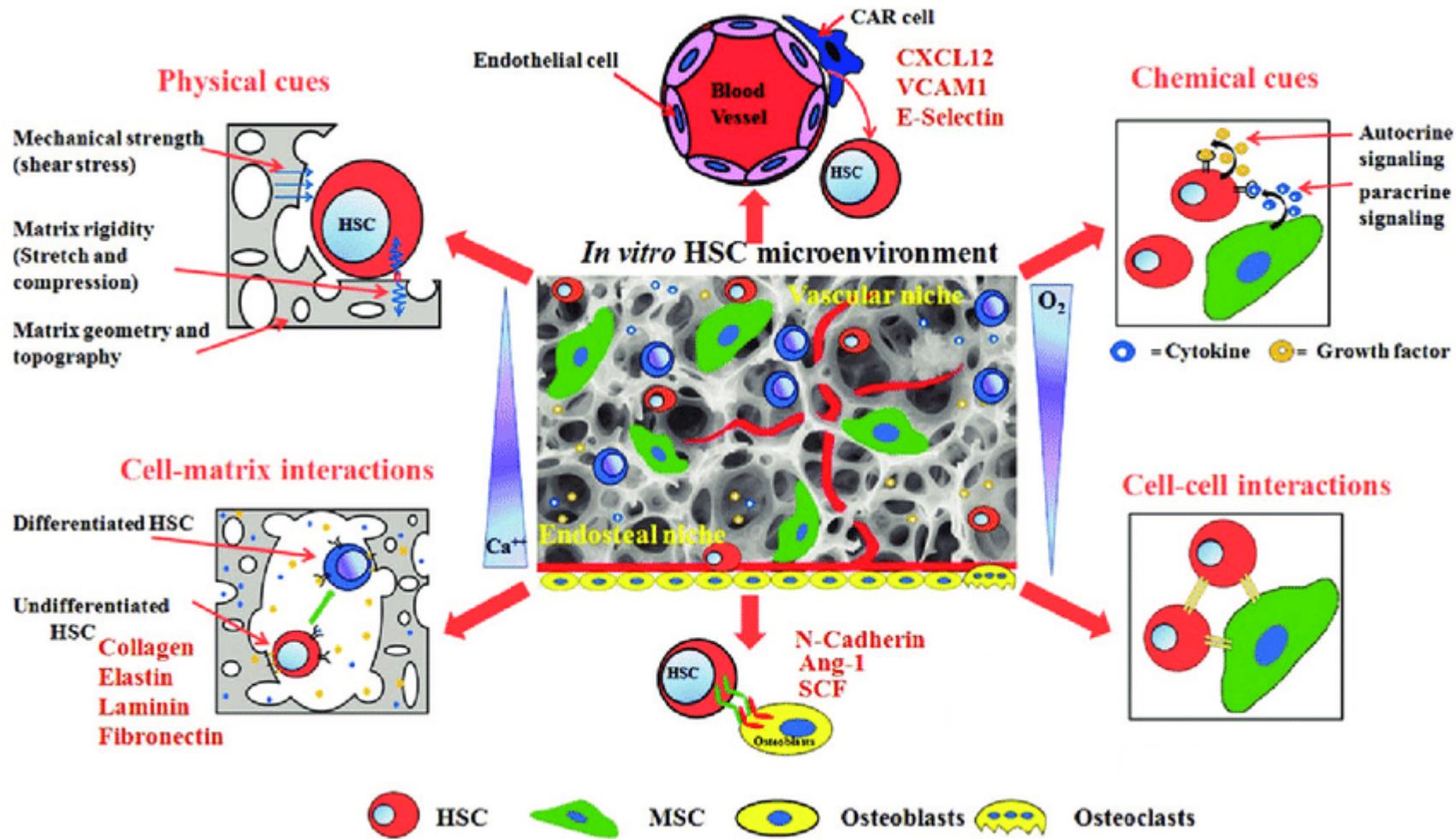
Bone marrow microenvironment and why it matters



Illustration: Dan Curtis

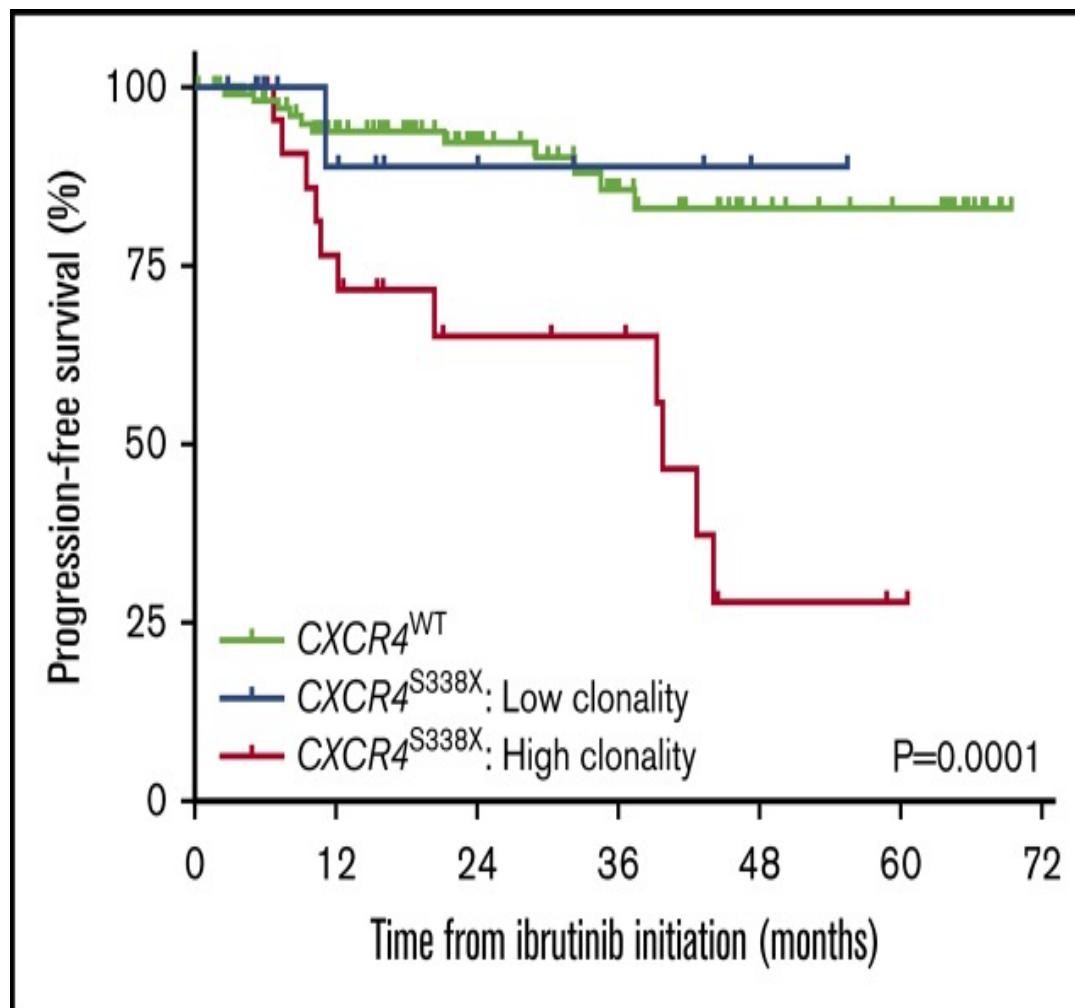
“A man is known by the company he keeps”
- Aesop

Bone Marrow supports WM growth but offers many Therapeutic Targets

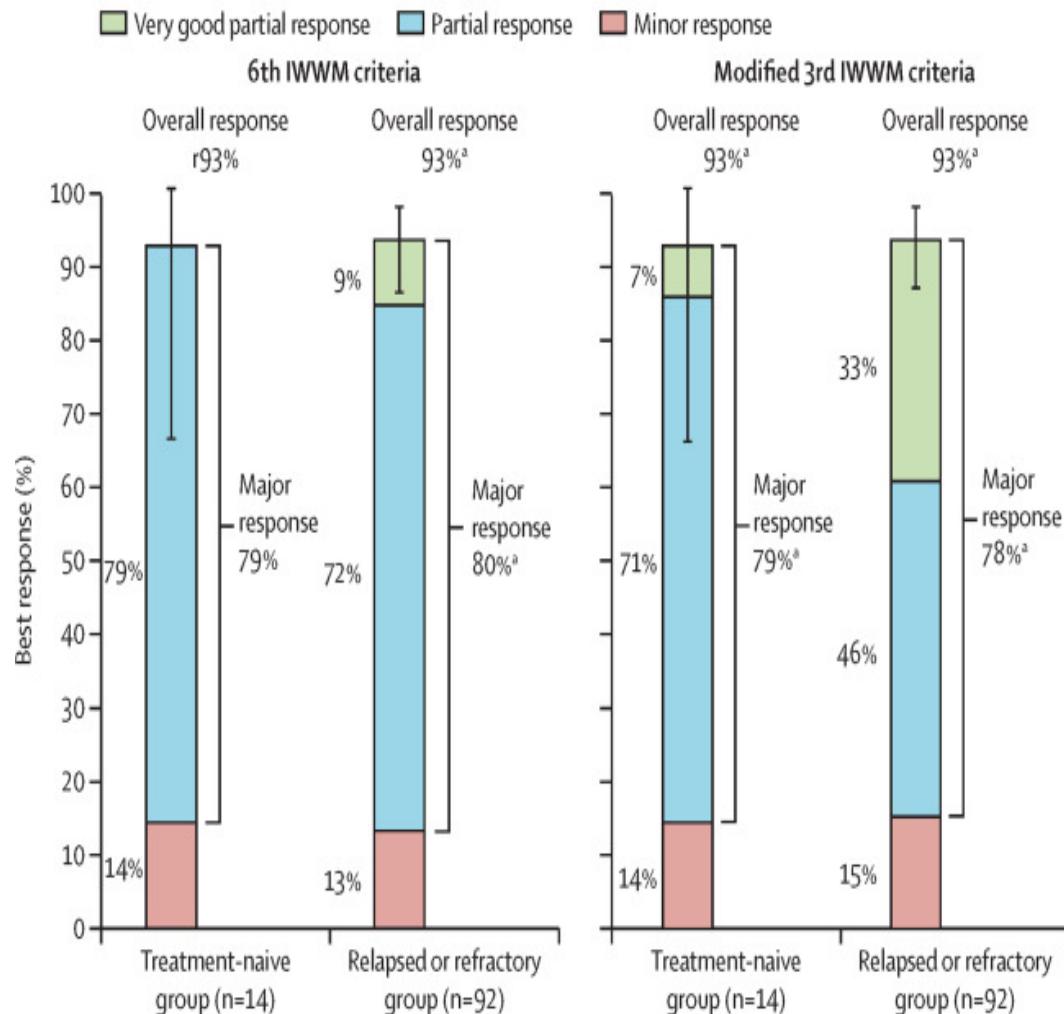


**How does this research and the
WM Roadmap affect me?**

$CXCR4^{S338X}$ clonality $\geq 25\%$ is associated with lower VGPR and shorter PFS to ibrutinib



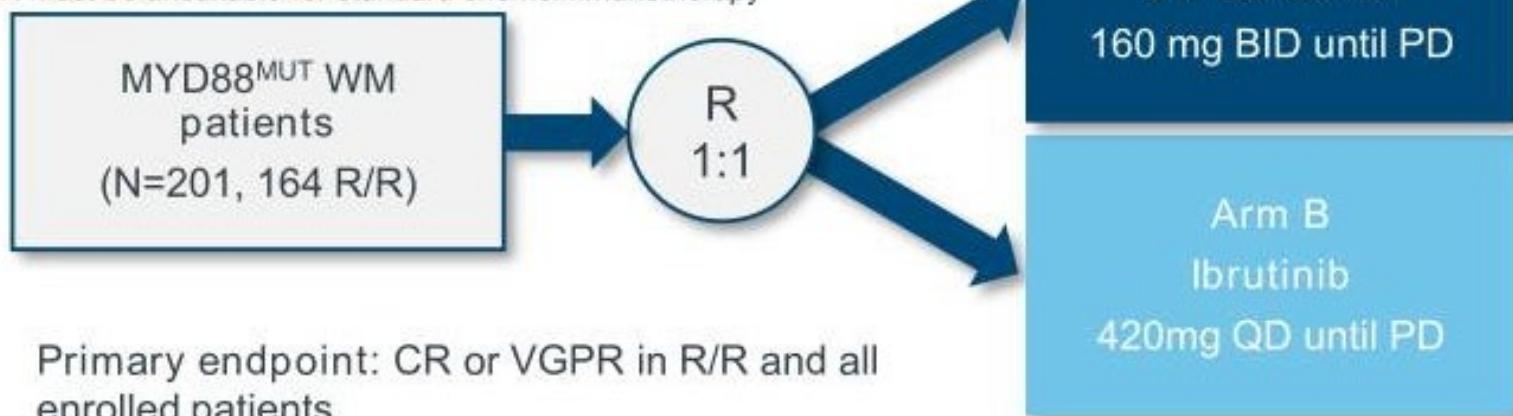
Acalabrutinib Monotherapy in Patients With Waldenström Macroglobulinemia



Zanubrutinib vs. Ibrutinib in WM

Cohort 1: R/R or TN* WM with MYD88^{L265P} mutation

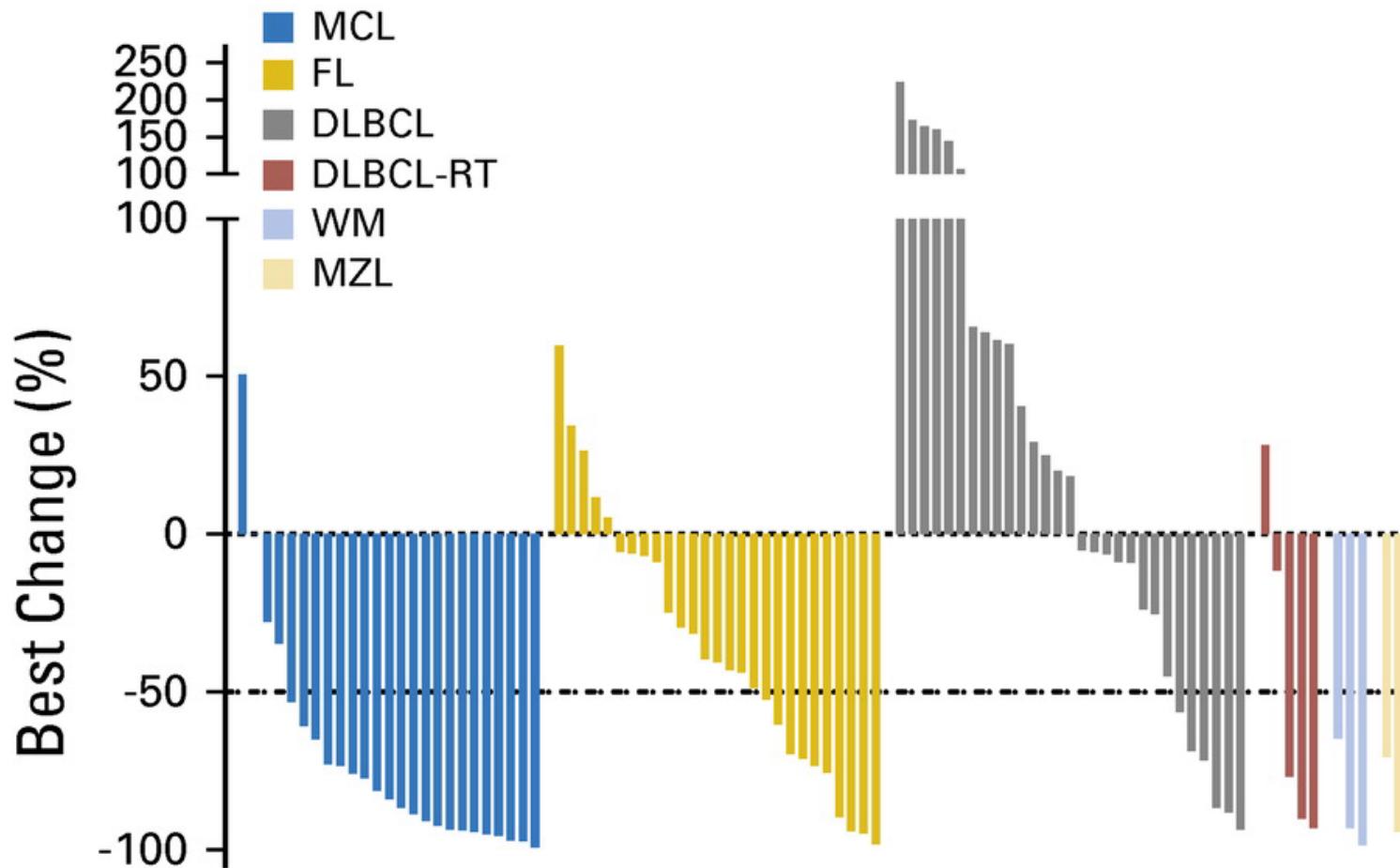
*TN must be unsuitable for standard chemoimmunotherapy



Cohort 2: WM with wild type MYD88



Venetoclax in WM Patients



**Thank you to all of you for supporting
WM research!**