

Overview of the IWMMF-LLS Strategic Research Roadmap – Our Track for the Future

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Professor of Medicine

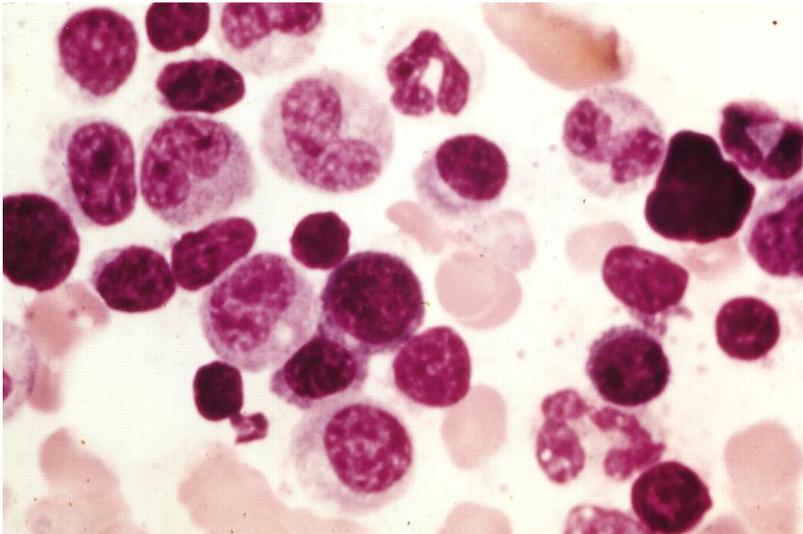
Mayo Clinic

Topics to be covered -

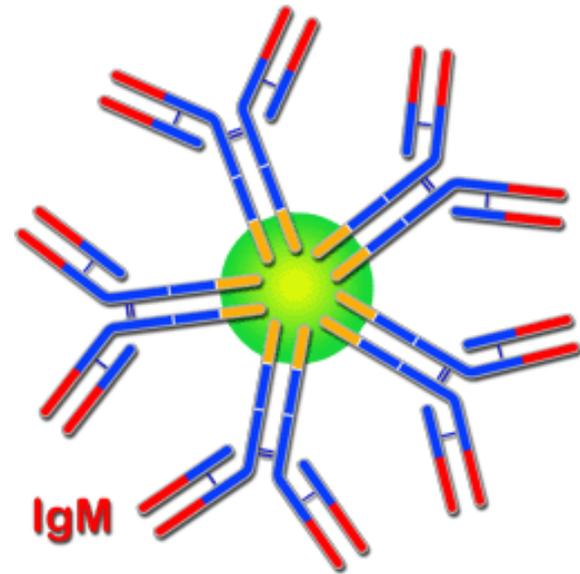
- What is unique about Waldenström macroglobulinemia?
 - What do we still need to know?
- What is the WM Roadmap?
 - Why do we need one?
- How will supporting the Roadmap help?
 - Will it improve the future?

Waldenström macroglobulinemia

“A disease with two problems”



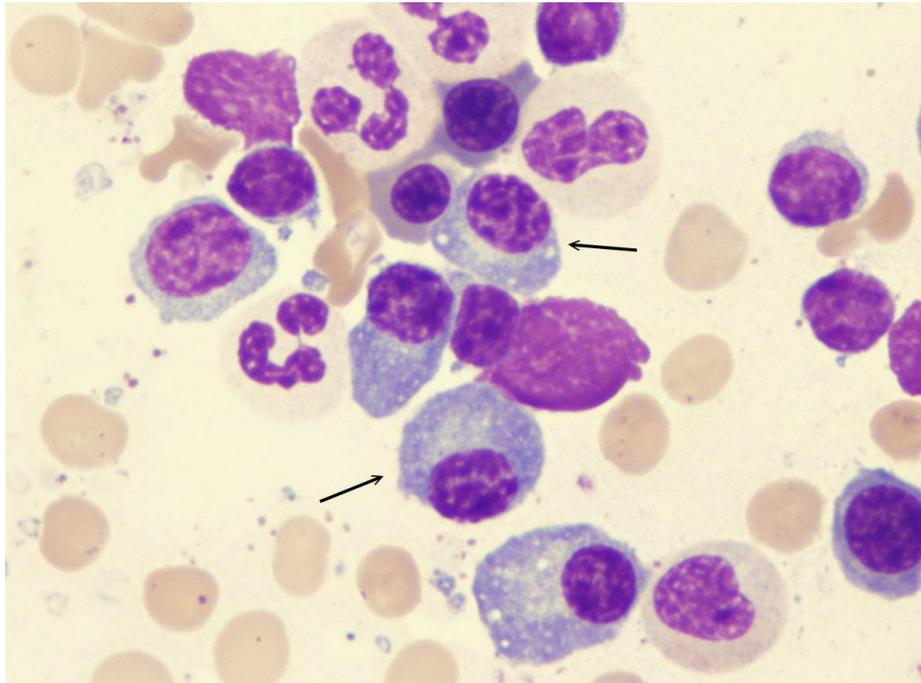
Lymphoplasmacytic infiltrate



Monoclonal IgM protein

Waldenström macroglobulinemia

Morphology and Immunophenotype



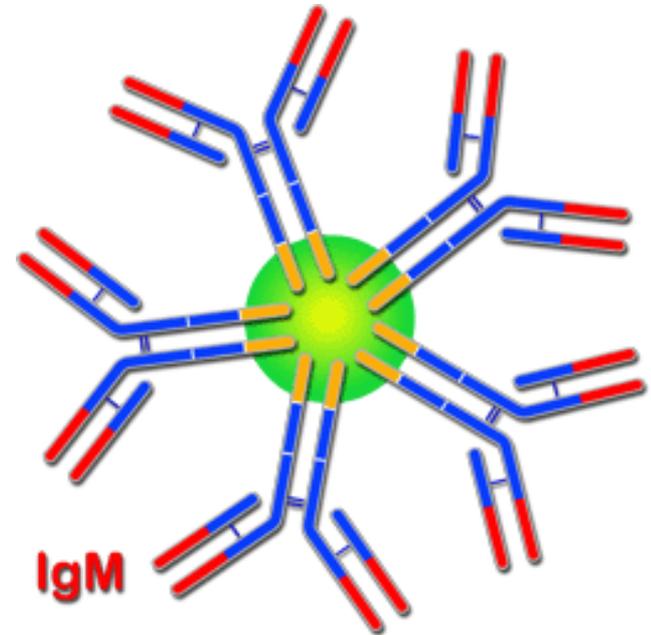
- Lymphoplasmacytic infiltrate (usually intertrabecular)
- Immunophenotype - surface IgM+, CD19+, CD20+, CD79a+ and PAX5+. CD5–, CD10–, CD23–.
- MYD88 L265P is the most common genetic abnormality seen
- del(6)(q21) and CXCR4 mutations are also seen

Waldenström macroglobulinemia

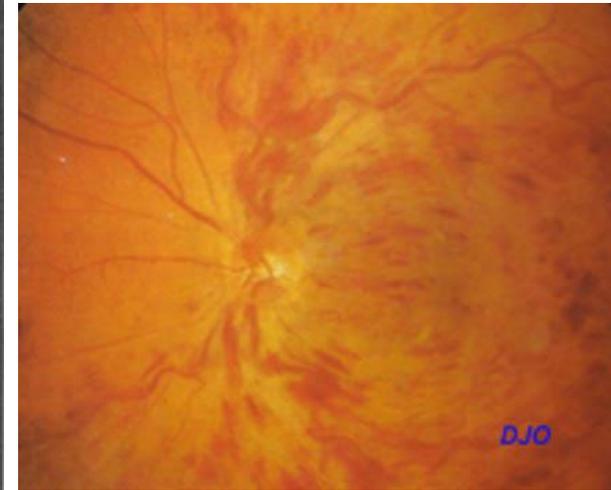
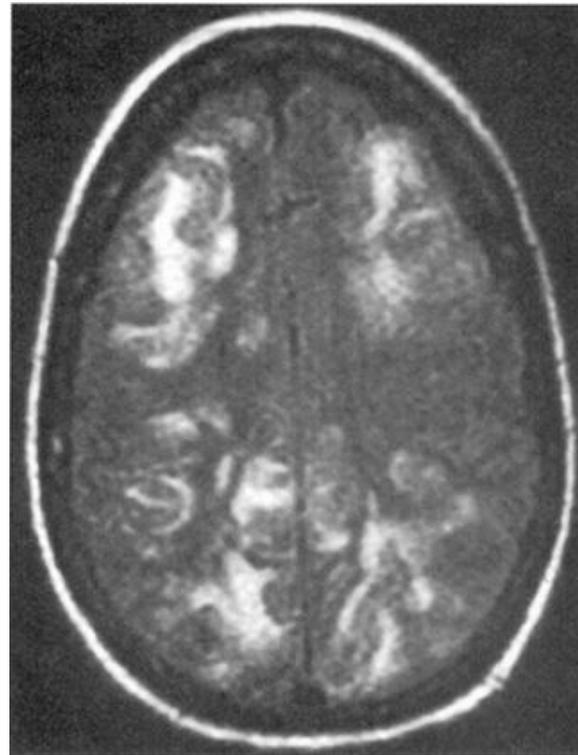
Monoclonal IgM

Symptoms related to the monoclonal IgM protein are attributable to -

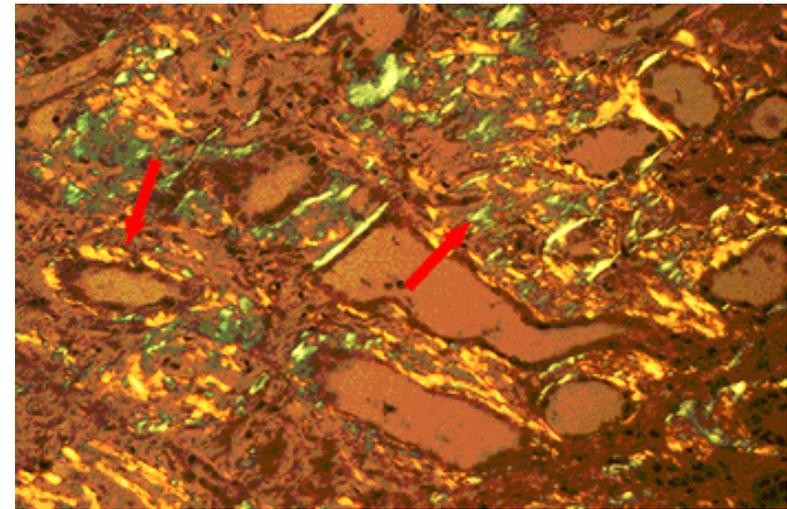
- its characteristics in the circulation,
- its interaction with various body tissues when deposited,
- and its autoantibody activity.



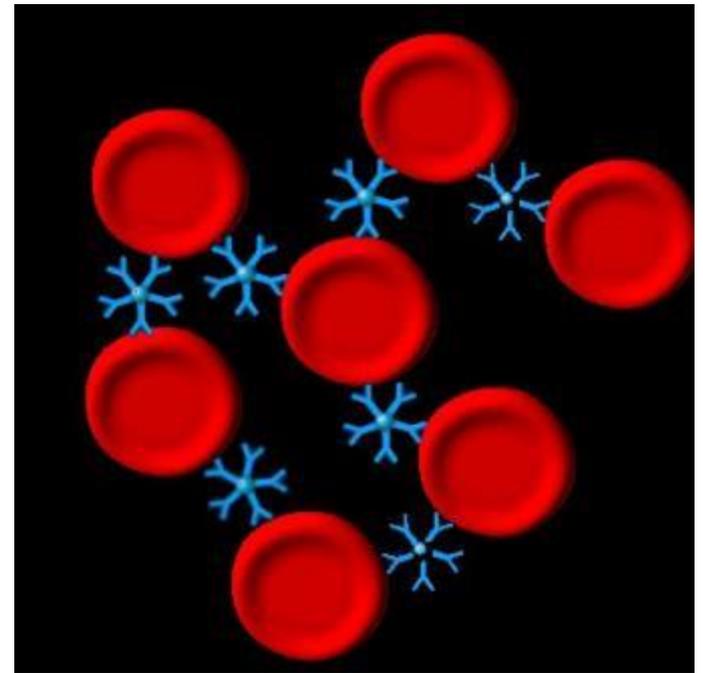
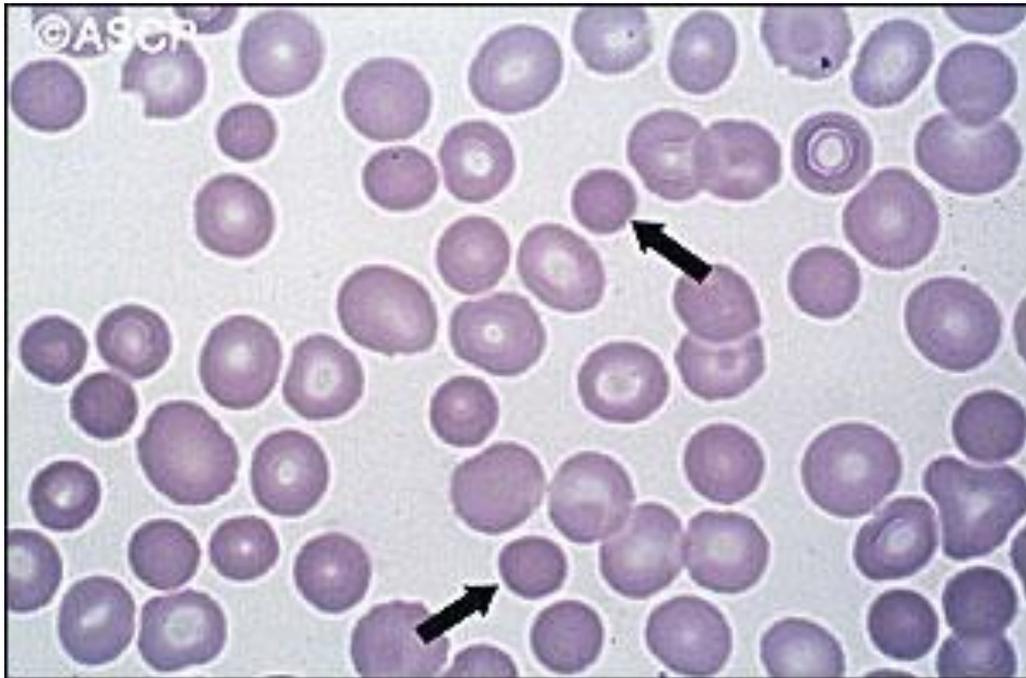
Hyperviscosity due to Waldenström macroglobulinemia



IgM deposition due to Waldenström macroglobulinemia



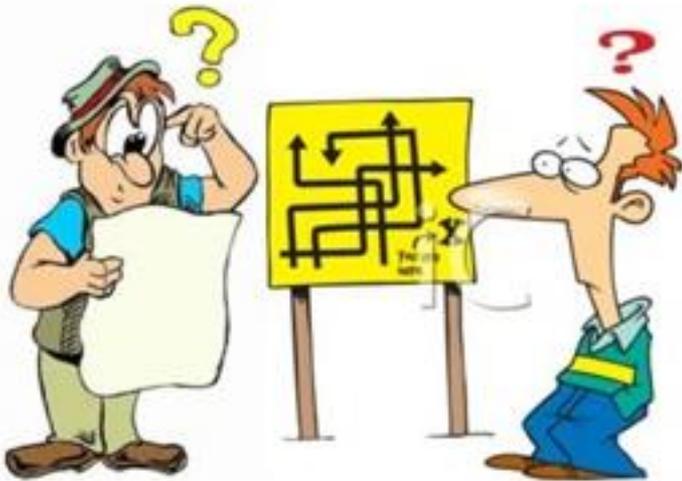
Autoimmune hemolysis secondary to Waldenström macroglobulinemia



What are the Knowledge Gaps in Waldenström macroglobulinemia?

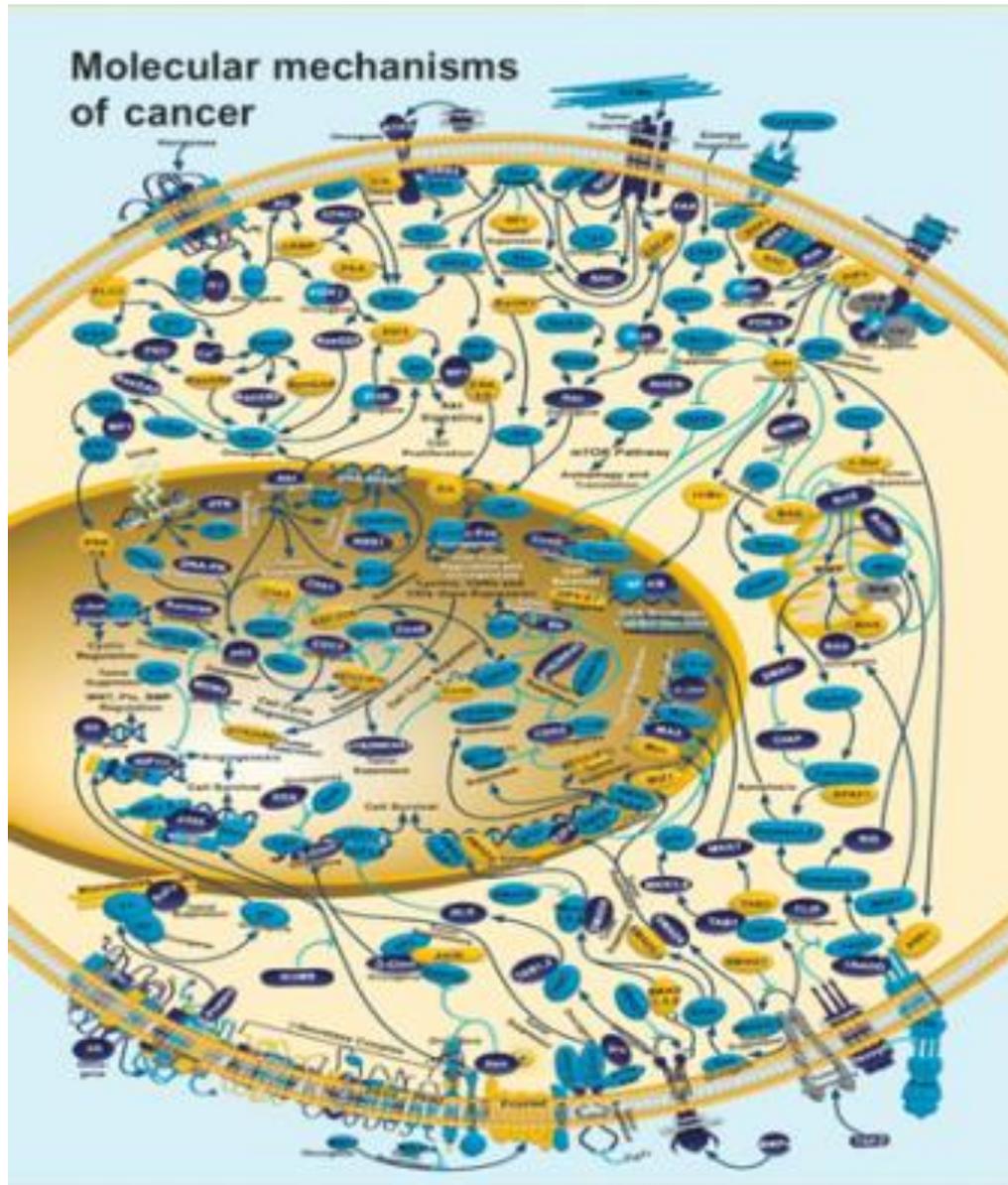


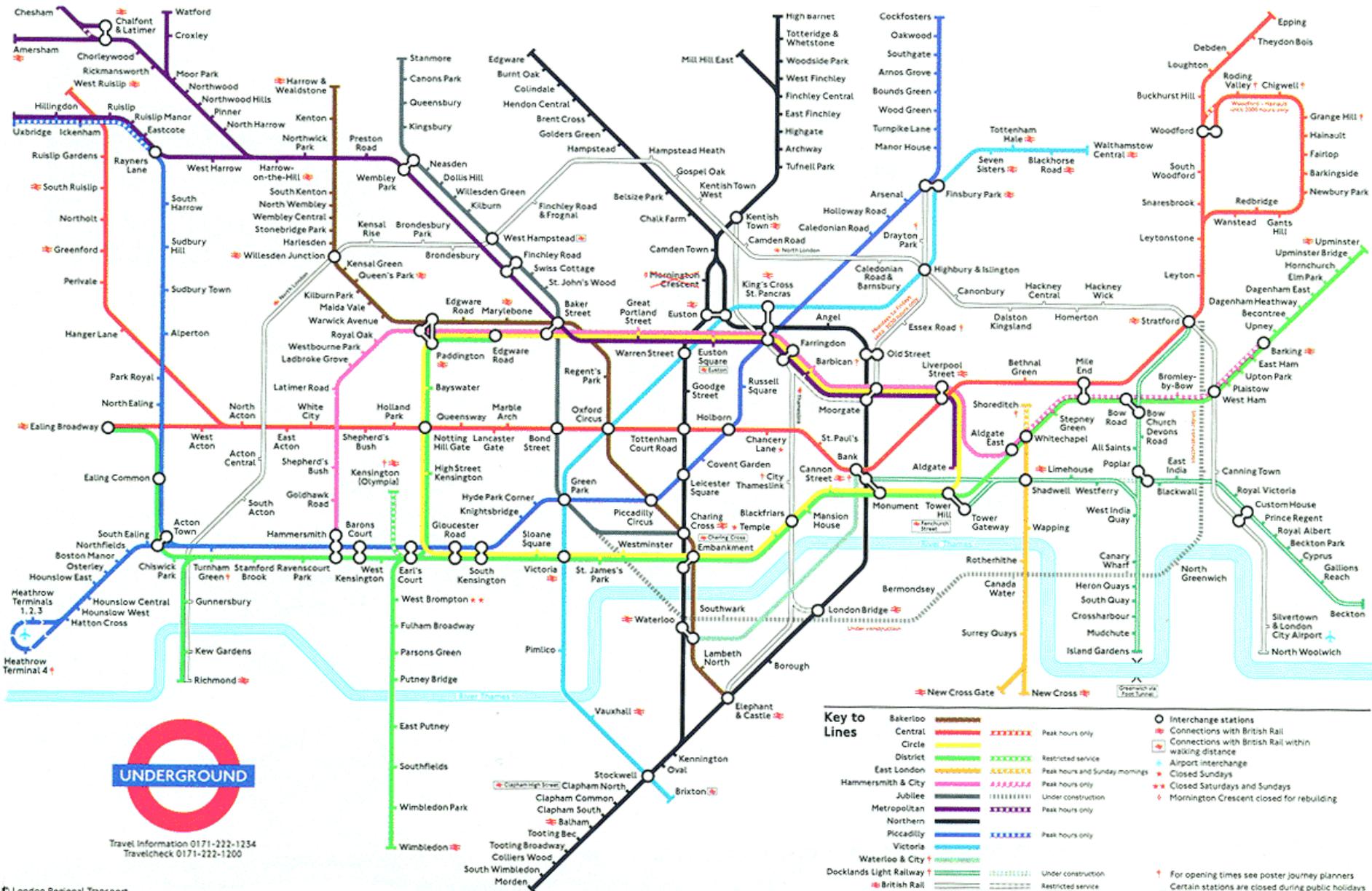
The WM Roadmap Identified 4 “Knowledge Gaps”



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

Signaling in WM and why it matters





Travel Information 0171-222-1234
Travelcheck 0171-222-1200

Key to Lines

Bakerloo			
Central			Peak hours only
District			
East London			Peak hours and Sunday mornings
Hammersmith & City			Peak hours only
Jubilee			Under construction
Metropolitan			Peak hours only
Northern			
Piccadilly			Peak hours only
Victoria			
Waterloo & City			
Docklands Light Railway			Under construction
British Rail			Restricted service

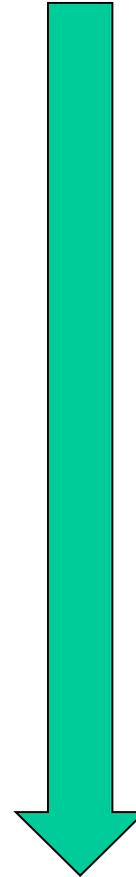
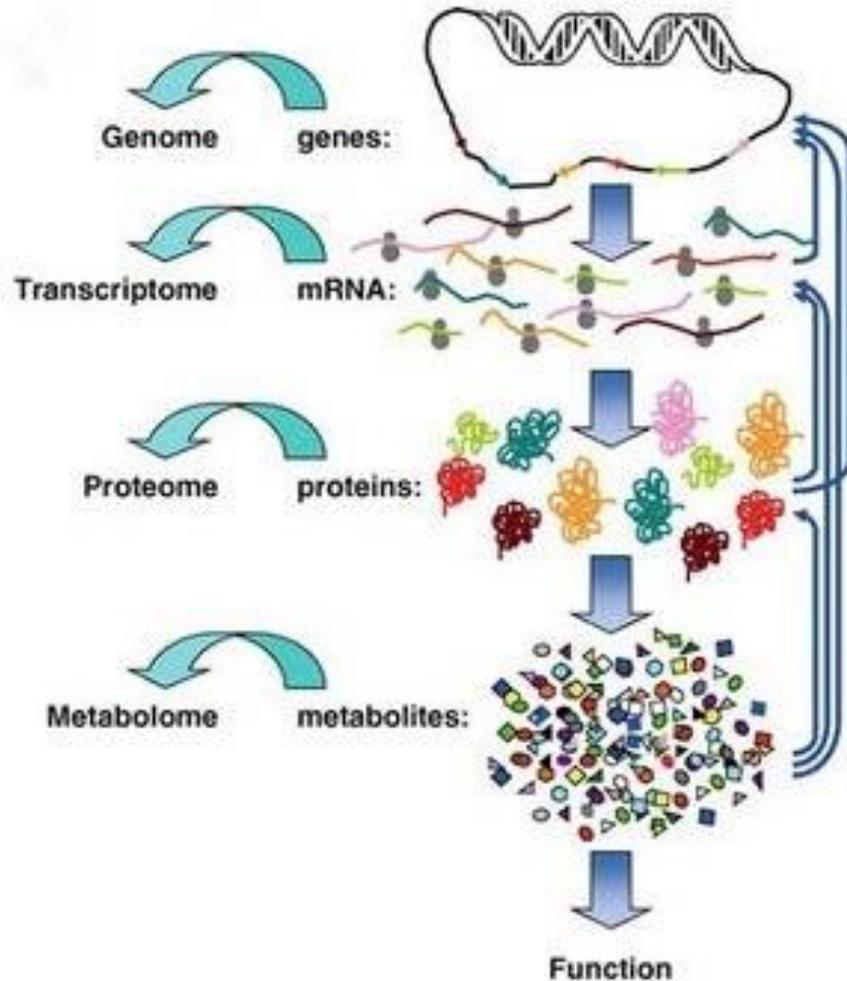
	Interchange stations
	Connections with British Rail
	Connections with British Rail within walking distance
	Airport interchange
	Closed Sundays
	Closed Saturdays and Sundays
	Mornington Crescent closed for rebuilding

† For opening times see poster journey planners
Certain stations are closed during public holidays
Diary IA 4-95

Omics in WM and why it matters



Genomics, Epigenomics, Proteomics, Metabolomics

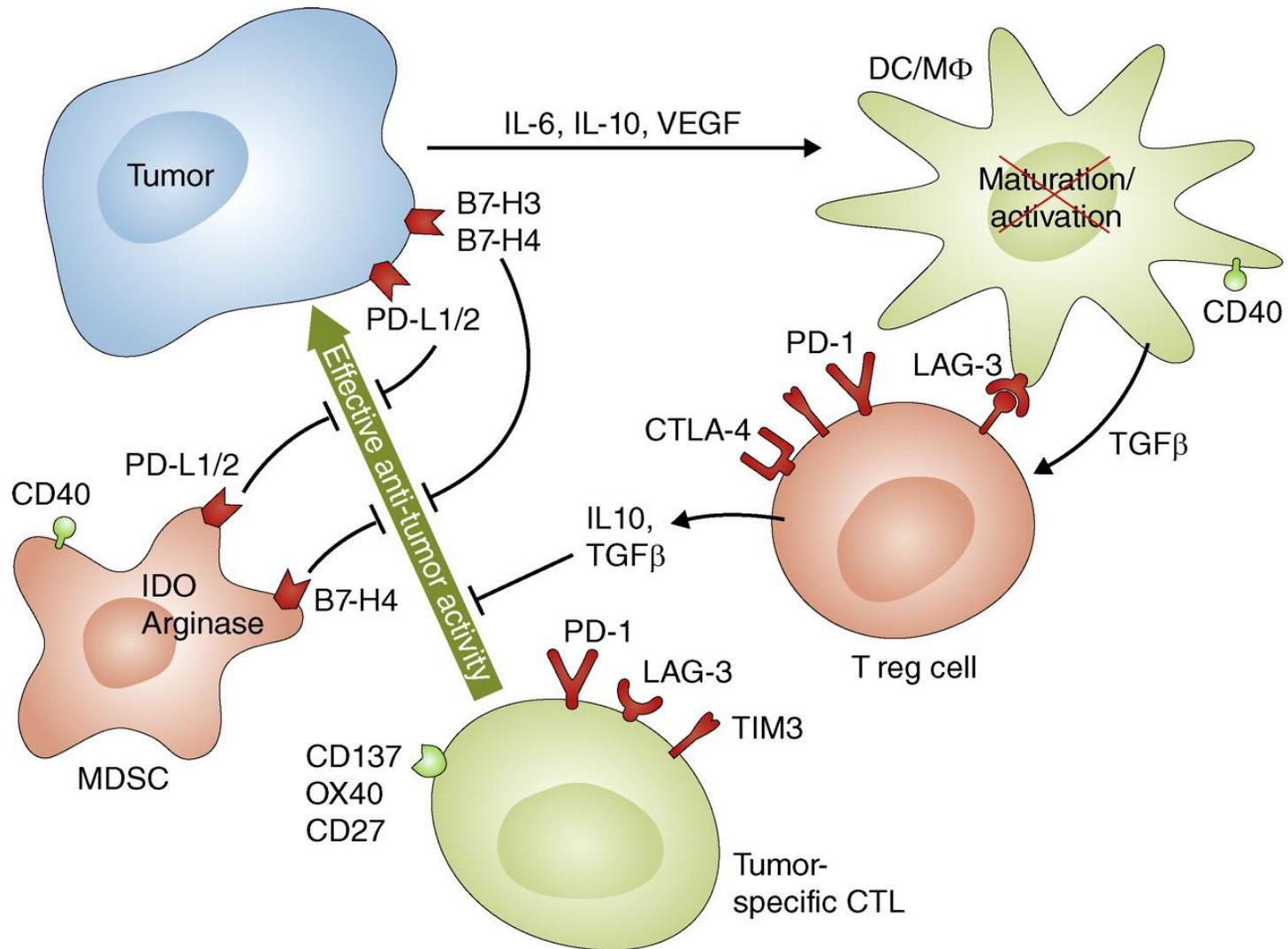


Immunology in WM and why it matters



"ACCORDING TO ALL OUR TESTS, YOUR IMMUNE SYSTEM IS 'OUT TO LUNCH.'"

Getting the Immune System to target WM



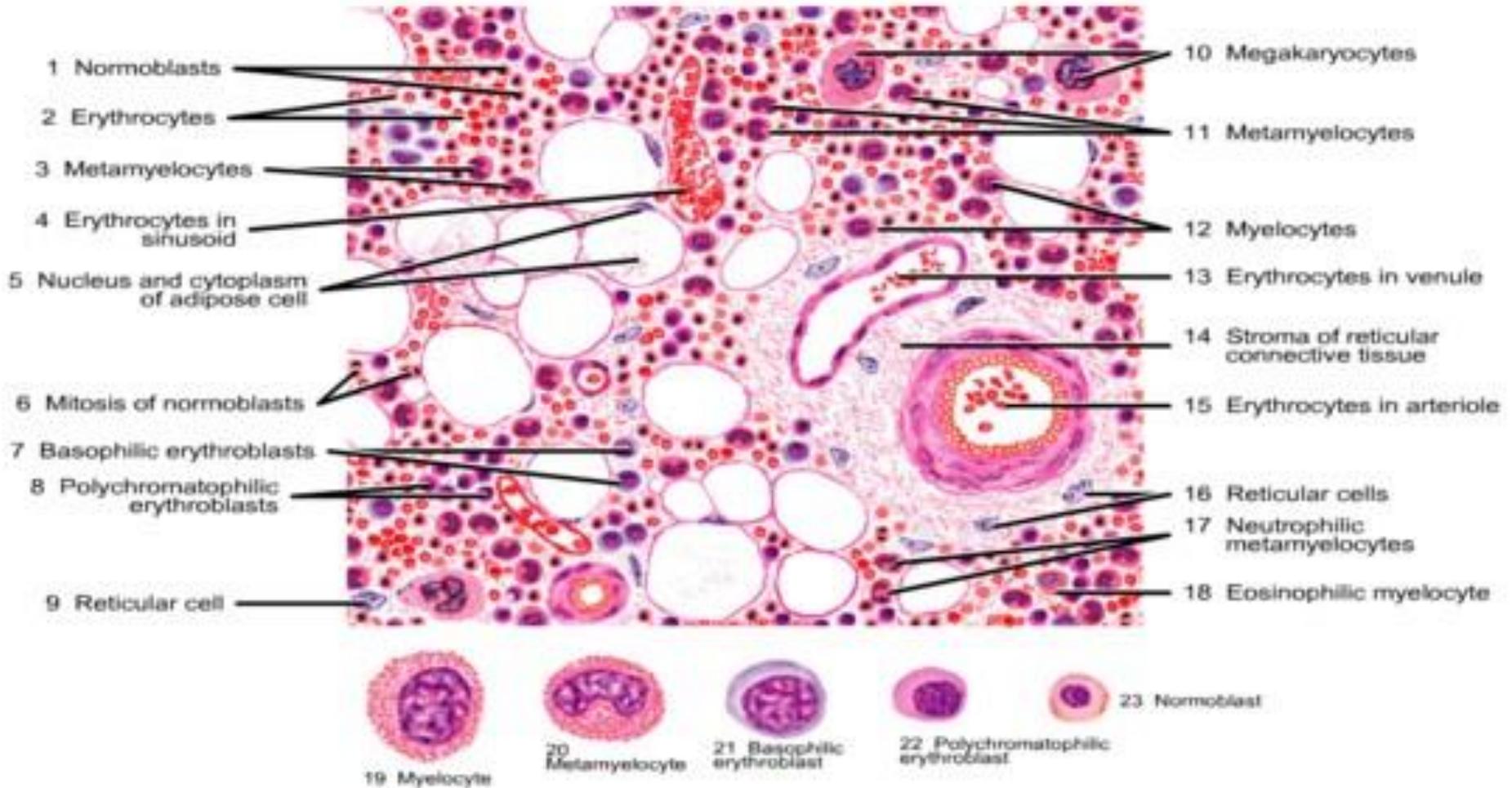
Bone marrow microenvironment and why it matters



“A man is known by the company he keeps”

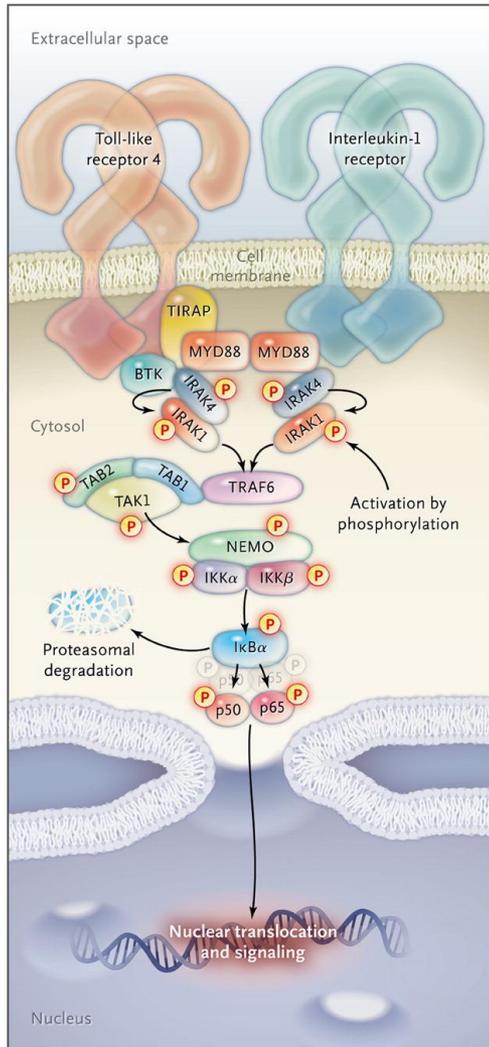
- Aesop

Bone Marrow supports WM growth but offers many Therapeutic Targets

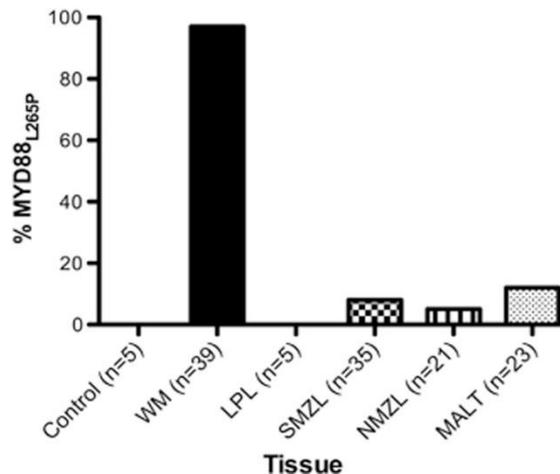


**How does this research and the
WM Roadmap affect me?**

MyD88 L265P mutations are almost universal in Waldenström macroglobulinemia



- Whole genome sequencing in 30 patients – MYD88 L265P mutation found in 27/30.
- High frequency confirmed in 49/54 additional cases (91%)
- Rarely expressed in myeloma, MZL, or IgM MGUS



Treon SP et al. *N Engl J Med* 2012;367:826-833.
 Ansell et al. *Blood Cancer J.* 2014 Feb 14;4:e183.

CXCR4 mutations in Waldenström macroglobulinemia in 40%

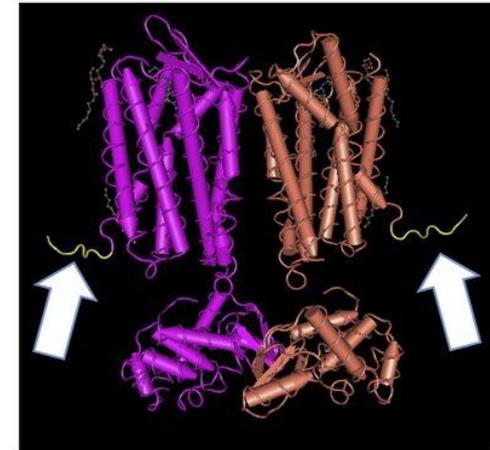
A

MEGISIYTS DNYTEEMGSGDYDSMKEPCFREANANFNKIFLPTI
 YSIIFLTGIVGNGLVILVMGYQKKLRSM TDKYRLHLSVADLLFVI
 TLPFWAVDAVANWYFGNFLCKAVHVIYTVNLYSSVLILAFISLD
 RYLAI VHATNSQRPRKLLAEKV VYVGVWIPALLTIPDFIFANVS
 EADDRYICDRFYPNDLWVVVFQFQHIMVGLILPGIVILSCYCIIS
 KLSHSHKGHQKRKALKTTVILILAFFACWLPYYIGISIDSFILLEIK
 QGCEFENTVHKWISITEALAFFHCCLNPILYAFLGAKFKTSAQH
 ALTSMSRGS SLKILSKCKRGCHSSVSTSESSSFHSS

LEGEND

A - Germline variant in WHIM syndrome **A** - Transmembrane helix
 □ - Somatic frame shift or nonsense WM variant

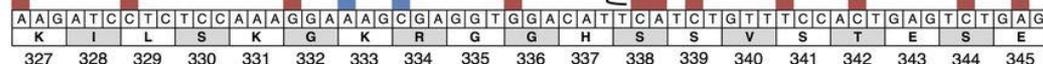
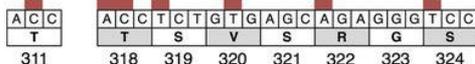
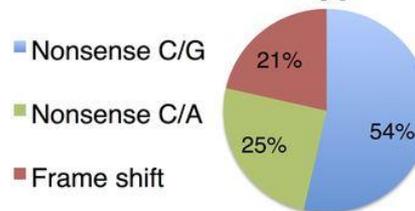
B



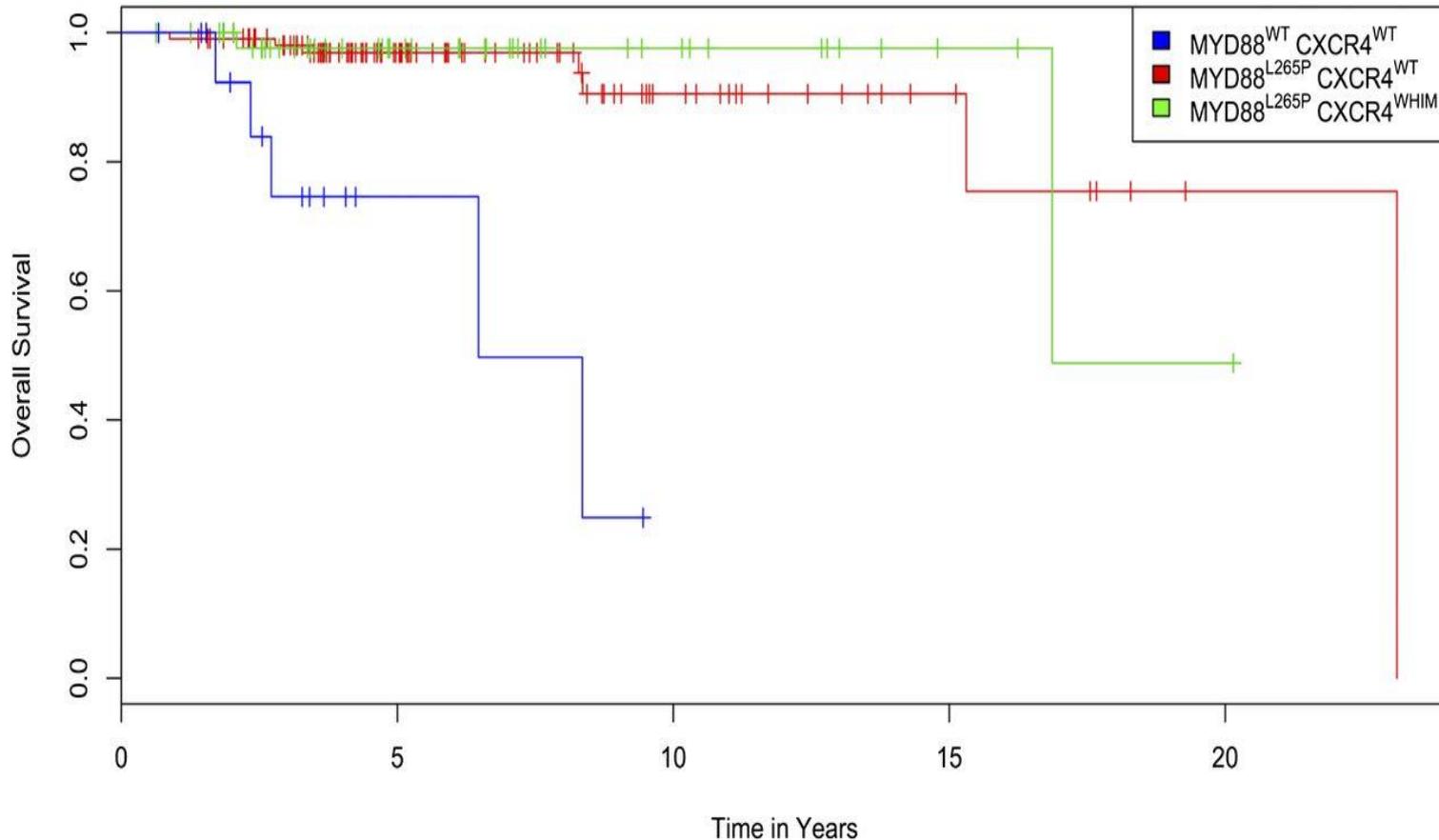
C

■ Frame shift mutation
 ■ Nonsense mutation

S338 Mutation Types



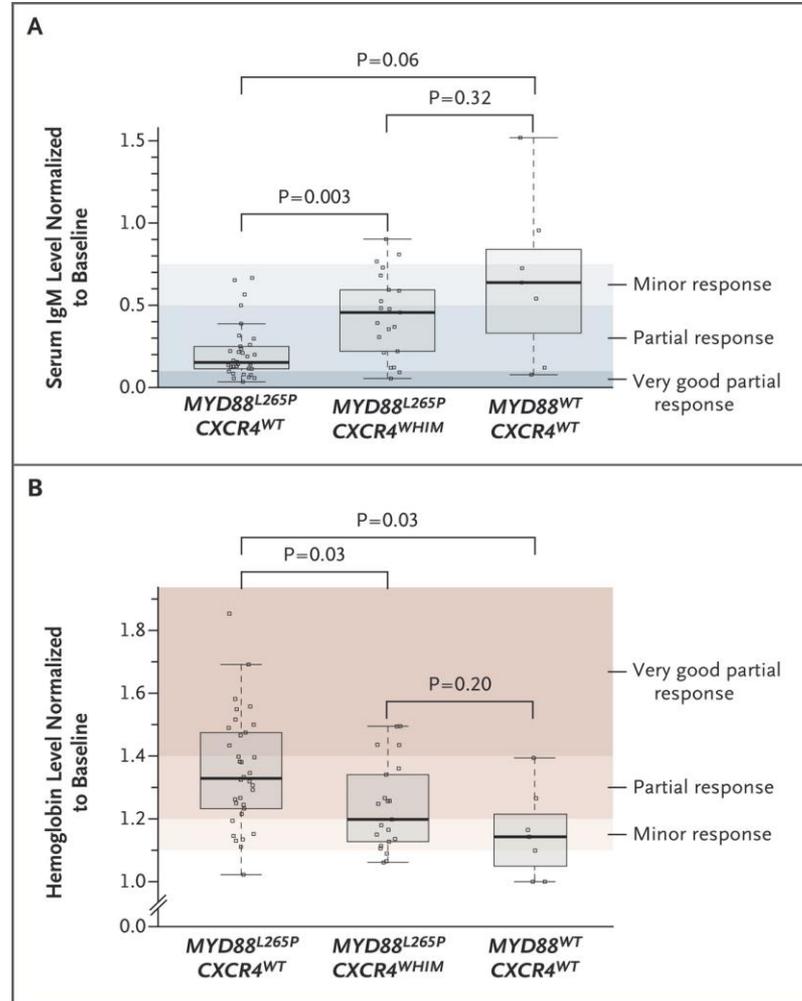
Overall survival of 175 WM patients stratified by MYD88 and CXCR4 mutation status



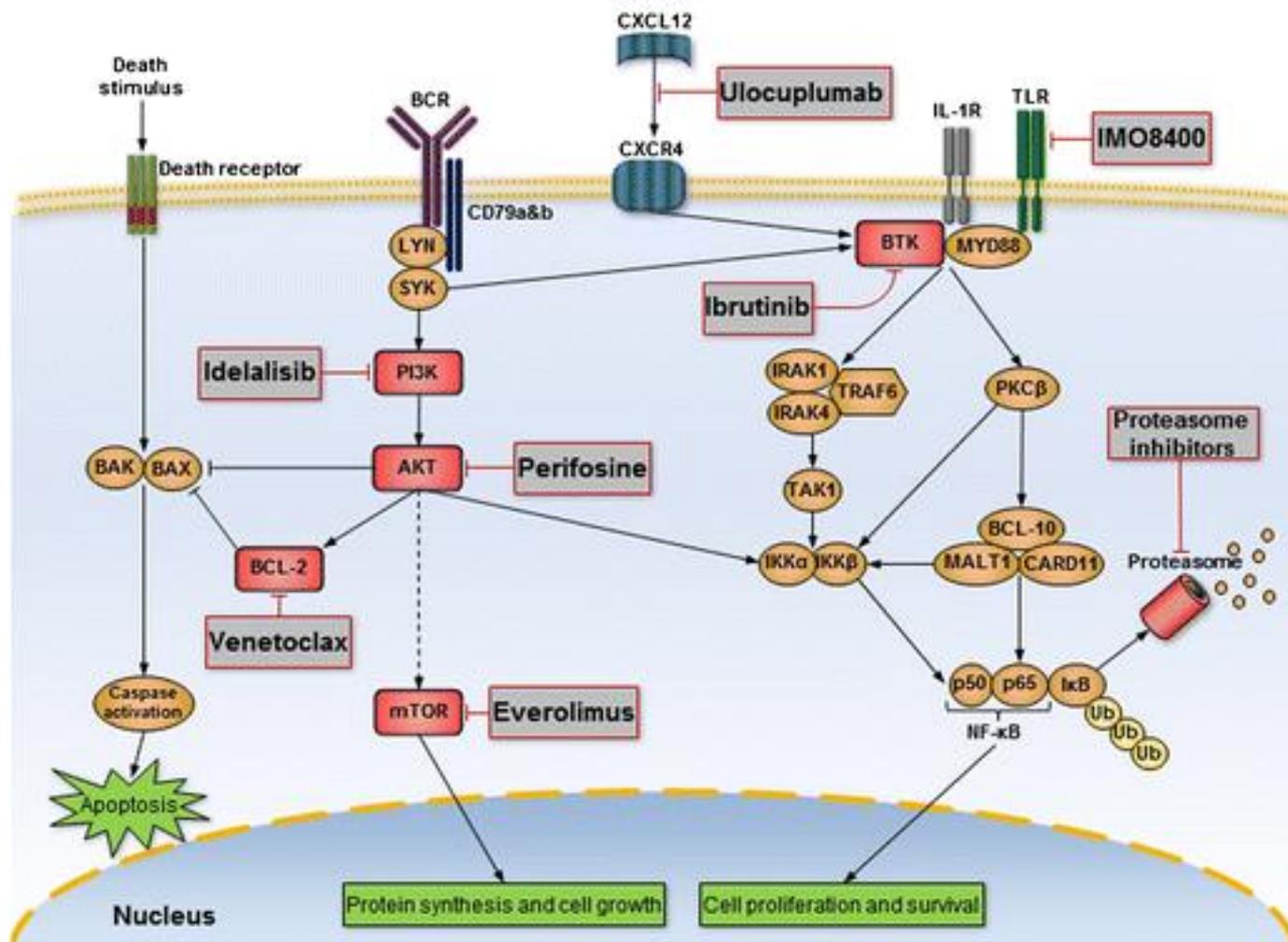
Ibrutinib in Waldenström macroglobulinemia

- 63 previously treated patients received 420 mg of oral ibrutinib daily for 2 years or until progression.
- ORR was 90.5%, with a major response rate (PR or better) of 73% and a median time to response of 4 weeks.
- 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively.
- Toxicities > grade 2 - thrombocytopenia; neutropenia; atrial fibrillation and epistaxis.

Effect of *MYD88* and *CXCR4* Mutation Status on Ibrutinib-Related Changes in Serum IgM and Hemoglobin Levels



Therapeutic opportunities afforded by the biology of Waldenström macroglobulinemia



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