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WM & Basic Terminology

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IWMF Educational Forum 2021

SARAH CANNON Cancer Institute at Presbyterian/St. Luke's Medical Center

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Objectives

- Make everything related to your WM diagnosis as understandable as possible.
- Develop fluency and be able to understand what on earth the doctor is saying during your visit!
- Develop a solid base for following the rest of the educational forum, especially when Dr. Castillo starts showing data.

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What is "Waldenstrom Macroglobulinemia" and why do we call it that?

- WM is a rare, very specific type of a blood cancer.
- It is a type of lymphoma, more precisely non-Hodgkin lymphoma (there is a Hodgkin lymphoma), called "lymphoplasmacytic lymphoma", often abbreviated "LPL".
- "Macroglobulinemia" refers to a very large type of protein, also called an immunoglobulin, made by the abnormal lymphoma cells called IgM.

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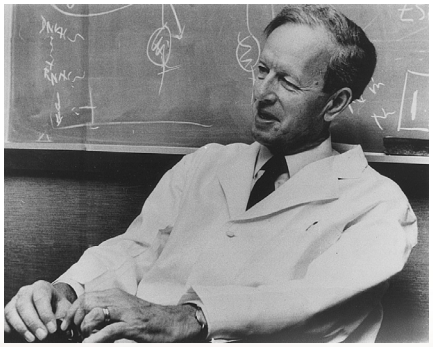
Jan Gosta Waldenstrom



- Swedish Physician 1906-1996
- He made many discoveries in medicine besides WM
- Described WM in 1944
- Described concept of monoclonal gammopathies in 1961

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There are dozens of different kinds of non Hodgkin Lymphoma (NHL)

Mature B-cell lymphomas (about 85%-90% of NHL cases)

Aggressive

- Diffuse large B-cell lymphoma (DLBCL) (31%)
- Mantle cell lymphoma (MCL) (can present as aggressive or indolent) (6%)
- Lymphoblastic lymphoma (2%)
- Burkitt lymphoma (BL) (2%)
- Primary mediastinal (thymic) large B-cell lymphoma (PMBCL) (2%)
- Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas
- High-grade B-cell lymphoma with double or triple hits (HBL)
- Primary cutaneous DLBCL, leg type
- Primary DLBCL of the central nervous system
- Primary central nervous system (CNS) lymphoma
- Acquired immunodeficiency syndrome (AIDS)-associated lymphoma

Indolent

- Follicular lymphoma (FL) (22%)
- Marginal zone lymphoma (MZL) (8%)
- Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL) (6%)
- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (5%)
- Lymphoplasmacytic lymphoma (1%)
- Waldenström macroglobulinemia (WM)
- Nodal marginal zone lymphoma (NMZL) (1%)
- Splenic marginal zone lymphoma (SMZL)

Mature T-cell and natural killer (NK)-cell lymphomas (about 10%-15% of NHL cases)

Aggressive

- Peripheral T-cell lymphoma (PTCL), not otherwise specified (6%)
- Systemic anaplastic large-cell lymphoma (ALCL) (2%)
- Lymphoblastic lymphoma (2%)
- Hepatosplenic gamma/delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
- Enteropathy-type intestinal T-cell lymphoma
- Primary cutaneous anaplastic large-cell lymphoma
- Angioimmunoblastic T-cell lymphoma (AITL)

Indolent

- Cutaneous T-cell lymphoma (CTCL) (4%)
- Mycosis fungoides (MF)
- Sézary syndrome (SS)
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma (ENK/TCL), nasal type

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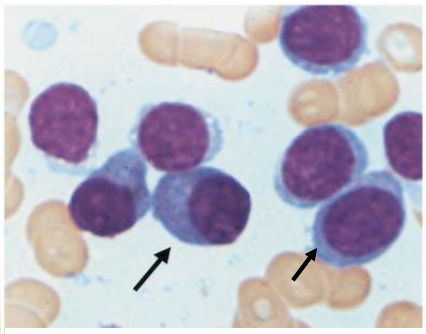
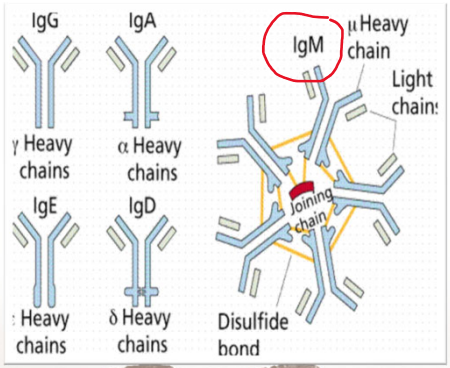
How is WM defined?

One needs to have BOTH abnormal cells in the bone marrow, found on the bone marrow biopsy, and the abnormal IgM macroglobulin in the blood.



Abnormal cells- both lymphocytes (R) and plasma cells (L)



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Let's talk about how we diagnose WM

- Some patients with WM were diagnosed as a complete surprise, without any symptoms.
- Others have symptoms of course.
- Normally, routine blood work can lead to clues that WM is present.
- For symptomatic patients, the blood test can lead to an accurate diagnosis and and assess in what manner the WM is affecting the patient.
- Let's learn about some of those important blood tests used to diagnose

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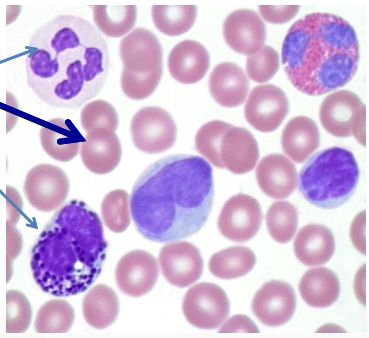
Complete blood count (CBC)

- Blood is made up of 3 kinds of cells suspended in a solution called plasma
- Red cells- carry oxygen
- White cells- fight infection
- Platelets- clot the blood

- Some special red cell tests help:
  - MCV (size of the cell)
  - Retic count (production rate of red cells)



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A CBC result

Ordered Items
CBC/Diff Ambiguous Default; Comp. Metabolic Panel (14); Protein Electro.,S; Immunoglobulins A/G/M, Qn, Ser; Ambig Abbrev CMP14 Default; Venipuncture

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC/Diff Ambiguous Default					
WBC	*2.3*	*Alert*	x10E3/uL	3.4 - 10.8	01
RBC	**3.67**	**Low**	x10E6/uL	3.77 - 5.28	01
Hemoglobin	**10.8**	**Low**	g/dL	11.1 - 15.9	01
Hematocrit	**33.0**	**Low**	%	34.0 - 46.6	01
MCV	90		fL	79 - 97	01
MCH	29.4		pg	26.6 - 33.0	01
MCHC	32.7		g/dL	31.5 - 35.7	01
RDW	**18.4**	**High**	%	12.3 - 15.4	01
Platelets	172		x10E3/uL	150 - 379	01
Neutrophils	54		%		01
Lymphs	32		%		01
Monocytes	12		%		01
Eos	2		%		01
Basos	0		%		01
Neutrophils (Absolute)	**1.2**	**Low**	x10E3/uL	1.4 - 7.0	01
Lymphs (Absolute)	0.7		x10E3/uL	0.7 - 3.1	01
Monocytes(Absolute)	0.3		x10E3/uL	0.1 - 0.9	01
Eos (Absolute)	0.1		x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.0		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%		01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01

These measure red blood cells

"ANC"

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Chemistry profile, a.k.a, "comp" or "CMP"

- Many bits of information available
- Kidney function (creatinine)
- Calcium level
- Liver blood tests
- Measurement of electrolytes such as potassium
- The basic chemistry test provides general information about WM
  - For more information, more specific tests must be ordered

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A real chemistry result

Ordered Items
CMP14+3AC+Mg; CBC With Differential/Platelet; Protein Electro.,S; Immunofixation, Serum; Free K+L Lt Chains,Qn,S; Venipuncture

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CMP14+3AC+Mg					
Glucose, Serum	95		mg/dL	65 - 99	01
BUN	17		mg/dL	8 - 27	01
Creatinine, Serum	**1.01**	**High**	mg/dL	0.57 - 1.00	01
eGFR If NonAfricn Am	60		mL/min/1.73	>59	
eGFR If Africn Am	69		mL/min/1.73	>59	
BUN/Creatinine Ratio	17			12 - 28	
Sodium, Serum	135		mmol/L	134 - 144	01
Potassium, Serum	4.4		mmol/L	3.5 - 5.2	01
Chloride, Serum	96		mmol/L	96 - 106	01
Carbon Dioxide, Total	21		mmol/L	18 - 28	01
Calcium, Serum	9.8		mg/dL	8.7 - 10.3	01
Phosphorus, Serum	2.7		mg/dL	2.5 - 4.5	01
Magnesium, Serum	1.8		mg/dL	1.6 - 2.3	01
Protein, Total, Serum	**9.0**	**High**	g/dL	6.0 - 8.5	01
Albumin, Serum	4.2		g/dL	3.6 - 4.8	01
Globulin, Total	**4.8**	**High**	g/dL	1.5 - 4.5	
A/G Ratio	**0.9**	**Low**		1.2 - 2.2	
Bilirubin, Total	0.6		mg/dL	0.0 - 1.2	01
Alkaline Phosphatase, S	46		IU/L	39 - 117	01
LDH	171		IU/L	119 - 226	01
AST (SGOT)	22		IU/L	0 - 40	01
ALT (SGPT)	7		IU/L	0 - 32	01
GGT	11		IU/L	0 - 60	01

IgM level is included in the total protein result

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Tests important for WM

- Measurement of the IgM protein
  - IgM level
  - M spike, SPEP (serum protein electrophoresis)
- Serum viscosity (how thick the blood is)
  - Have to order specifically
  - Higher level = thicker
  - Even if the test says the blood is too viscous, there may be NO symptoms!

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What is an “M” spike?

- Another way to measure the IgM.
- M = monoclonal, meaning all the IgM is produced by clones of the WM cells.
- Normal = 0.0
- We can follow the M spike and/or the IgM level to track the WM.
- *Usually* higher levels of IgM and/or the M spike mean there is more WM and lower levels mean less, but this is not always true and results can vary greatly between patients..

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WM labs- to track the disease

Ordered Items
Protein Electro.,S; Immunoglobulins A/G/M, Qn, Ser; Ca+PTH Intact; Free K+L Lt Chains,Qn,S; Viscosity, Serum; Vitamin D, 25-Hydroxy

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Protein Electro.,S					
Protein, Total	**9.0**	**High**	g/dL	6.0 - 8.5	01
Albumin	4.2		g/dL	2.9 - 4.4	02
Alpha-1-Globulin	0.3		g/dL	0.0 - 0.4	02
Alpha-2-Globulin	0.9		g/dL	0.4 - 1.0	02
Beta Globulin	1.2		g/dL	0.7 - 1.3	02
Gamma Globulin	**2.4**	**High**	g/dL	0.4 - 1.8	02
M-Spike	**1.8**	**High**	g/dL	Not Observed	02
Globulin, Total	**4.8**	**High**	g/dL	2.2 - 3.9	
A/G Ratio	0.9			0.7 - 1.7	
Please note: Protein electrophoresis scan will follow via computer, mail, or courier delivery.					02
PDF	.				02
Immunoglobulins A/G/M, Qn, Ser					
Immunoglobulin G, Qn, Serum	**666**	**Low**	mg/dL	700 - 1600	01
Immunoglobulin A, Qn, Serum Result confirmed on concentration.	**8**	**Low**	mg/dL	90 - 386	01
Immunoglobulin M, Qn, Serum Results confirmed on dilution.	**2849**	**High**	mg/dL	20 - 172	01

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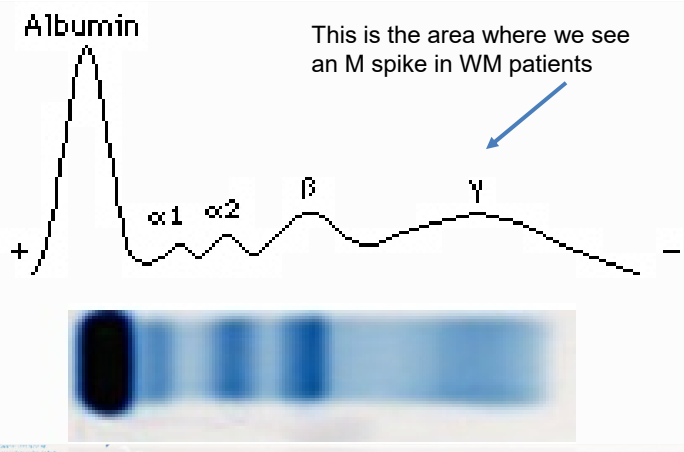
A real (normal) SPEP



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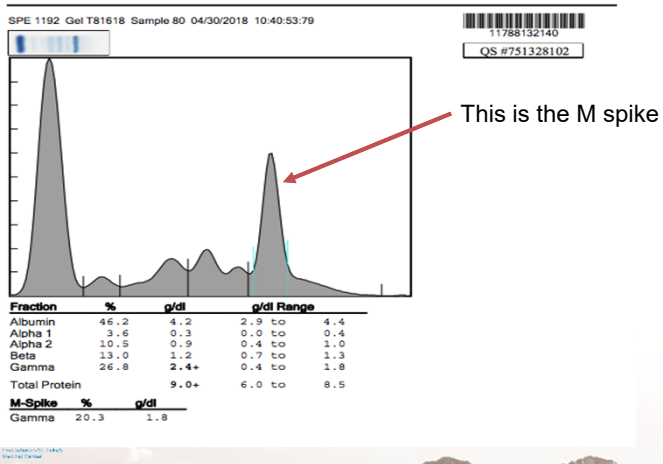
SPEP- abnormal with M spike



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Required to Properly diagnose WM

- A bone marrow biopsy MUST be done and show a type of non-Hodgkin lymphoma called LPL
- There MUST be monoclonal IgM in the blood
- Now in newly diagnosed patients testing for a mutation in the LPL cells called MYD88, and sometimes a less common one called CXCR4- we will talk more about this in a minute.

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Other important tests looking for more infrequent complications of WM

- **Cryoglobulins**- a condition where with cooler temperatures the blood flow to the kidneys or other tissues is reduced, causing damage.
- **Cold agglutinins-** an unusual complication of WM whereby the immune system reacts against red blood cells and destroys them (hemolysis) at cooler temperatures
- some tests to look for a rare complication known as **amyloid**, typically a biopsy of some kind is required (e.g., the kidney, fat around the belly button or even the heart)
- Special tests if there is too much bleeding (rare- a hemophiliac like condition known as von Willebrand's)
- **Neuropathy** tests- anti MAG or GM1

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WM occurs in phases

IgM MGUS

- MGUS = monoclonal gammopathy of undetermined significance
- IgM M spike < 3 g/dL
- Marrow with < 10% LPL
- no anemia, fevers, sweats, weight loss, or big lymph glands
- 2% chance per year of getting symptoms

Smoldering WM

- IgM M spike > 3 g/dL and/or,
- > 10% LPL in marrow
- no anemia, fevers, sweats, weight loss, or big lymph glands
- About 10% chance per year of getting symptoms

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Symptomatic WM

- Different patients have different symptoms
- By definition these patients need treatment
- What are some of the symptoms or problems?
  - Anemia or really low platelets
  - Fatigue
  - Fevers, drenching sweats, weight loss
  - Severe neuropathy
  - Hyperviscosity
  - Amyloidosis
  - Cold agglutinins or cryoglobulins
  - Enlarged lymph glands or spleen
  - Kidney damage from the WM

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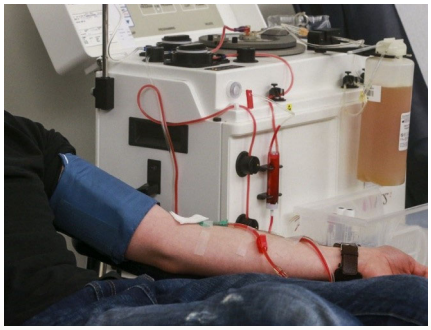
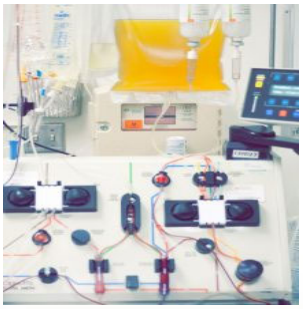
Plasmapheresis- a procedure to remove excess IgM when there are symptoms of hyperviscosity (blood too thick)





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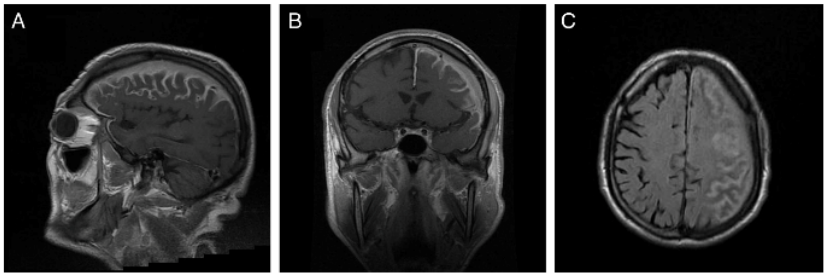
Bing Neel Syndrome- rare complication of WM where the lymphoma gets into the central nervous system (brain, spinal cord)



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Important WM Mutations

- We are talking about genetic mutations (changes in the DNA) inside some of the blood cells that are acquired- you were not born with them nor can you pass them on (SOMATIC).
- The 2 big ones in WM are MYD88 and CXCR4.
- We are learning that these mutations influence how the WM might behave clinically as well as respond to certain treatments.
- MYD88 is almost always one specific mutation (L265P)and is present in over 90% of WM patients- testing common.
- CXCR4- many different mutations present in about 40% of WM patients- tested less often- CXCR4 testing is more challenging technically and not all docs order it.

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Oncospeak- language used by hematology/oncology doctors - Mutations

- Wild type (WT)- UNMUTATED gene, applied to MYD88/CXCR4. This is the opposite of MUTATED (MUT)
- Mutated CXCR4 a.k.a. “WHIM”
- Mutated MYD88 a.k.a. “L265P”
- Mutations in CXCR4 can be “nonsense” or “frameshift” types

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Different genetic types of WM- you will hear a lot about this

What the DNA is

How it looks in the actual patient

Genotypic-Phenotypic Association in WM[a]

Clinical Characteristics	*MYD88*^{L265P} *CXCR4*^{WT}	*MYD88*^{L265P} *CXCR4*$^{WHIM/FS}$	*MYD88*^{L265P} *CXCR4*$^{WHIM/NS}$	*MYD88*^{WT} *CXCR4*^{WT}
IgM	↑↑	↑↑	↑↑↑↑	↑
BM infiltration	↑↑↑	↑↑	↑↑↑↑	↑
Sensitivity to BTK inhibitors	↑↑↑	↑↑	↑	↓
Incidence, %	~60	27-40[b]	27-40[b]	< 10
	MUT/WT	MUT/MUT	MUT/MUT	WT/WT

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Treatment of WM- we only treat patients with symptoms

- Many tools in the treatment tool box
  - Monoclonal antibodies, e.g., rituximab
  - BTK inhibitors (ibrutinib, zanubrutinib, acalabrutinib)
  - "old school" chemo like cyclophosphamide
  - Bendamustine, bortezomib
- Treatment can go on for a long time- "continuous therapy"
- Treatment can be for a set, defined period of time- "Fixed duration"

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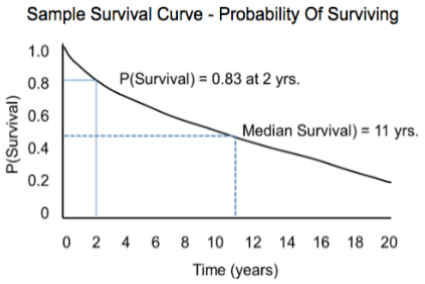
Oncospeak: Kaplan-Meier Curves: Doctors Always Show These. These represent probabilities and do NOT apply to individuals but to populations.



- Horizontal axis = time in years
- Vertical axis = probability of surviving or the proportion of people surviving
- At time zero everyone is alive
- The *probability* of survival is 83% at 2 yrs, 55% at 10 yrs, and the median survival is 11 yrs

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More oncospeak- you'll need to know this to be proficient in WM!

- RR- response rate (% of patients who had at least a 50% reduction in measurable WM, that is, the IgM level/M spike)- sometimes called "ORR" for overall response rate
- CR-complete response, we cannot detect the WM with the standard tests after treatment
- PR- partial response, between a 50-90% reduction in measurable WM
- VGPR- very good partial response, 90-99% reduction in measurable WM
- PFS- progression free survival- how long patients went before a relapse or dying, often reported as a median PFS (time point at which half of the patients had a relapse or died)
- OS- overall survival- just what it says

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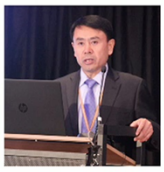
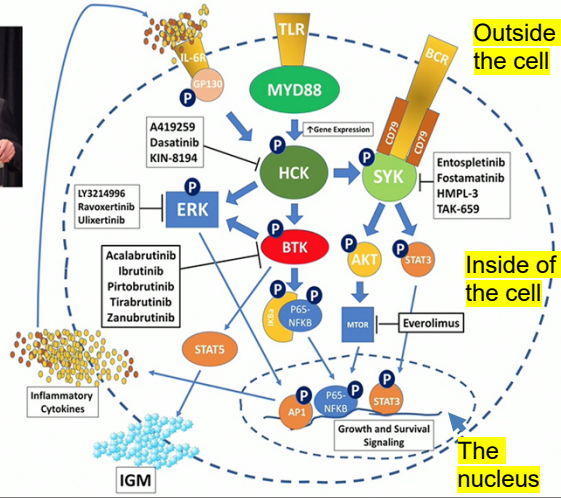
How WM cells misbehave-what goes on inside the cell. These are called intracellular signaling pathways.

MYD88 directed pro-survival signaling in WM





MYD88 mutations occur in 95-97% WM Patients

Treon et al, NEJM 2012
Yang et al, Blood 2013
Hodge et al, Blood 2014
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Chen et al, Blood 2018
Liu et al, Blood Adv 2020
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Munshi et al, Submitted.

Steve Treon
IMW 2021

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OK let's take some questions

And thank you!

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