

M-protein diagnostics of Multiple Myeloma patients treated with biologics

EFLM webinar March 27th 2018

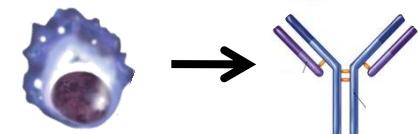
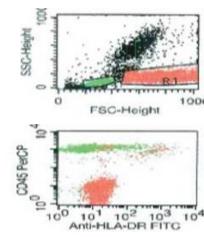
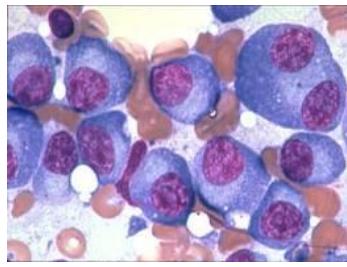
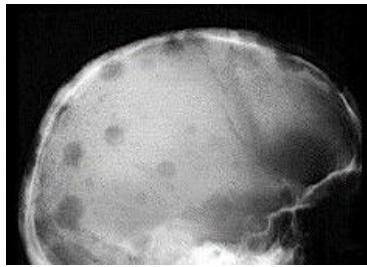
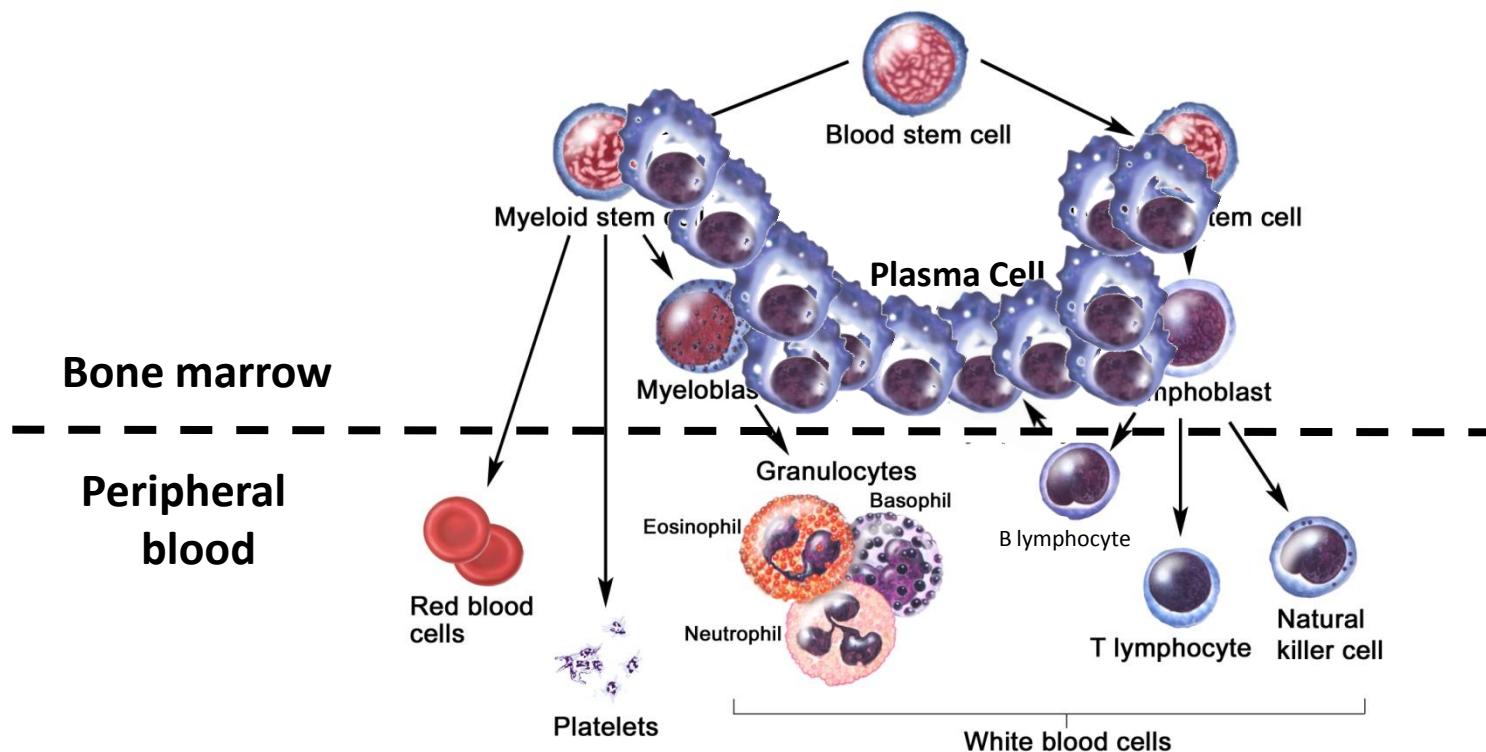
JFM (Hans) Jacobs

Radboud university medical center (The Netherlands)

Laboratory Specialist Medical Immunology (H.Jacobs@Radboudumc.nl)

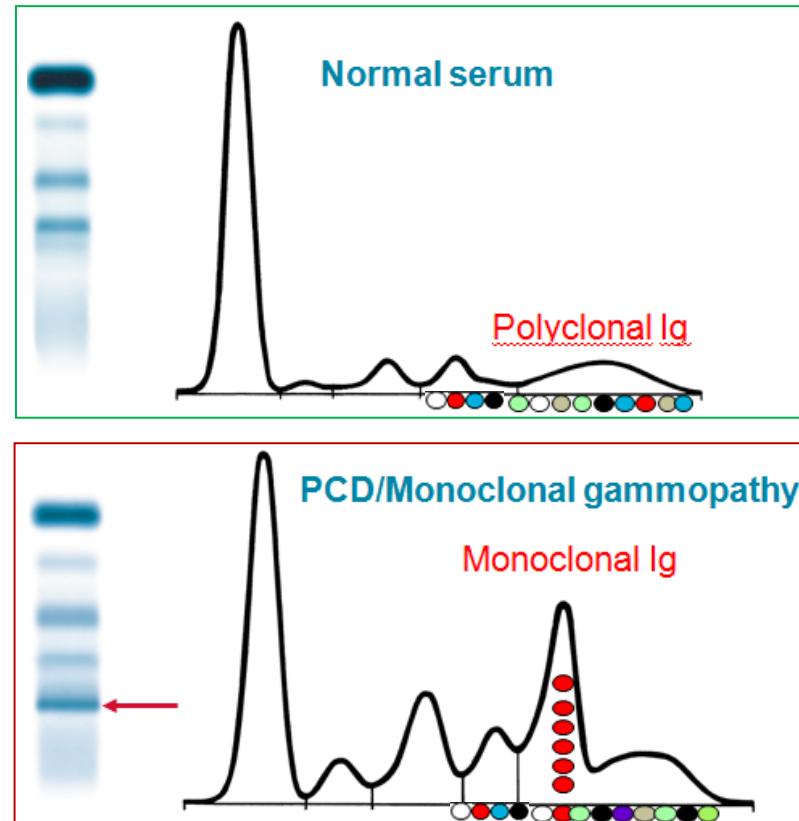
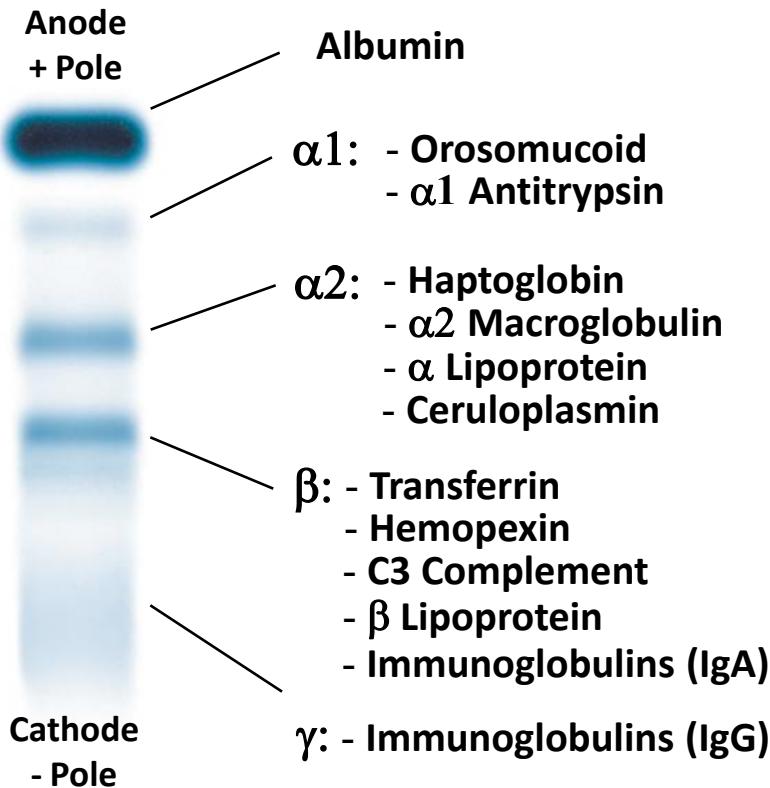
Moderated by Christopher McCudden (Ottawa, Canada)

Monoclonal gammopathy/plasma cell dyscrasia (e.g. multiple myeloma)



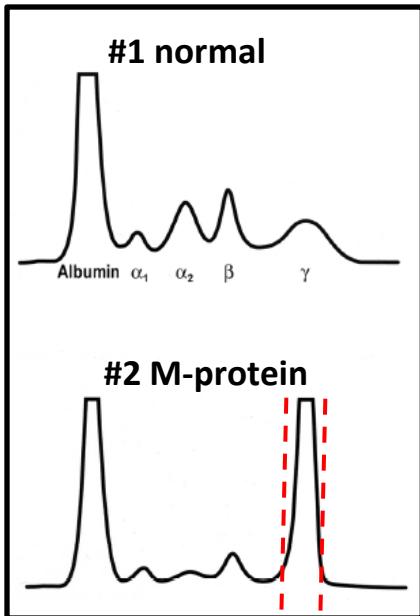
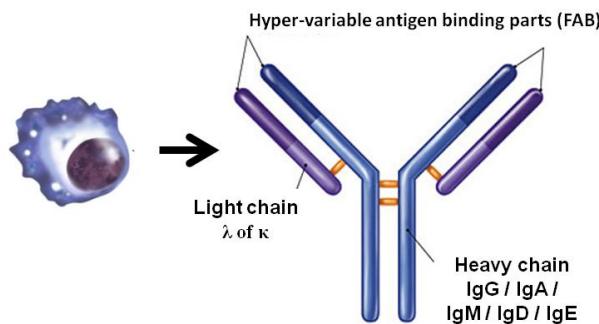
Serum protein electrophoresis (SPE)

the separation of charged proteins in an electrical field



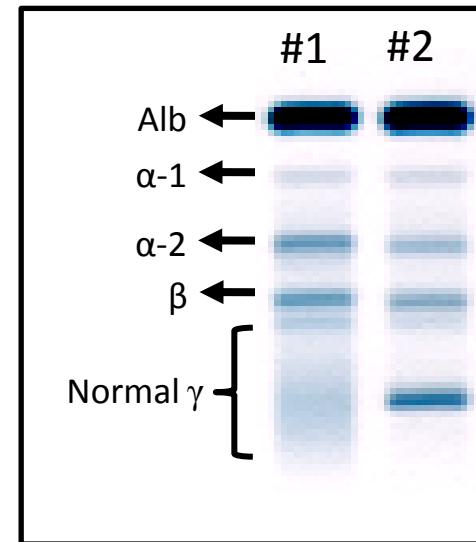
- SPE characterized by albumin, α_1 -, α_2 -, β - and γ -fraction
- Band-intensity corresponds to its concentration

M-protein diagnostics, gel electrophoresis



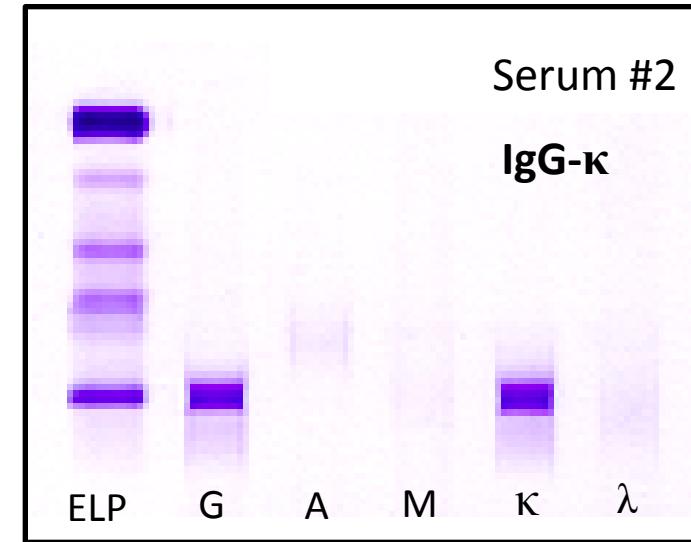
Densitometry

Quantification



Serum protein electrophoresis (SPE)

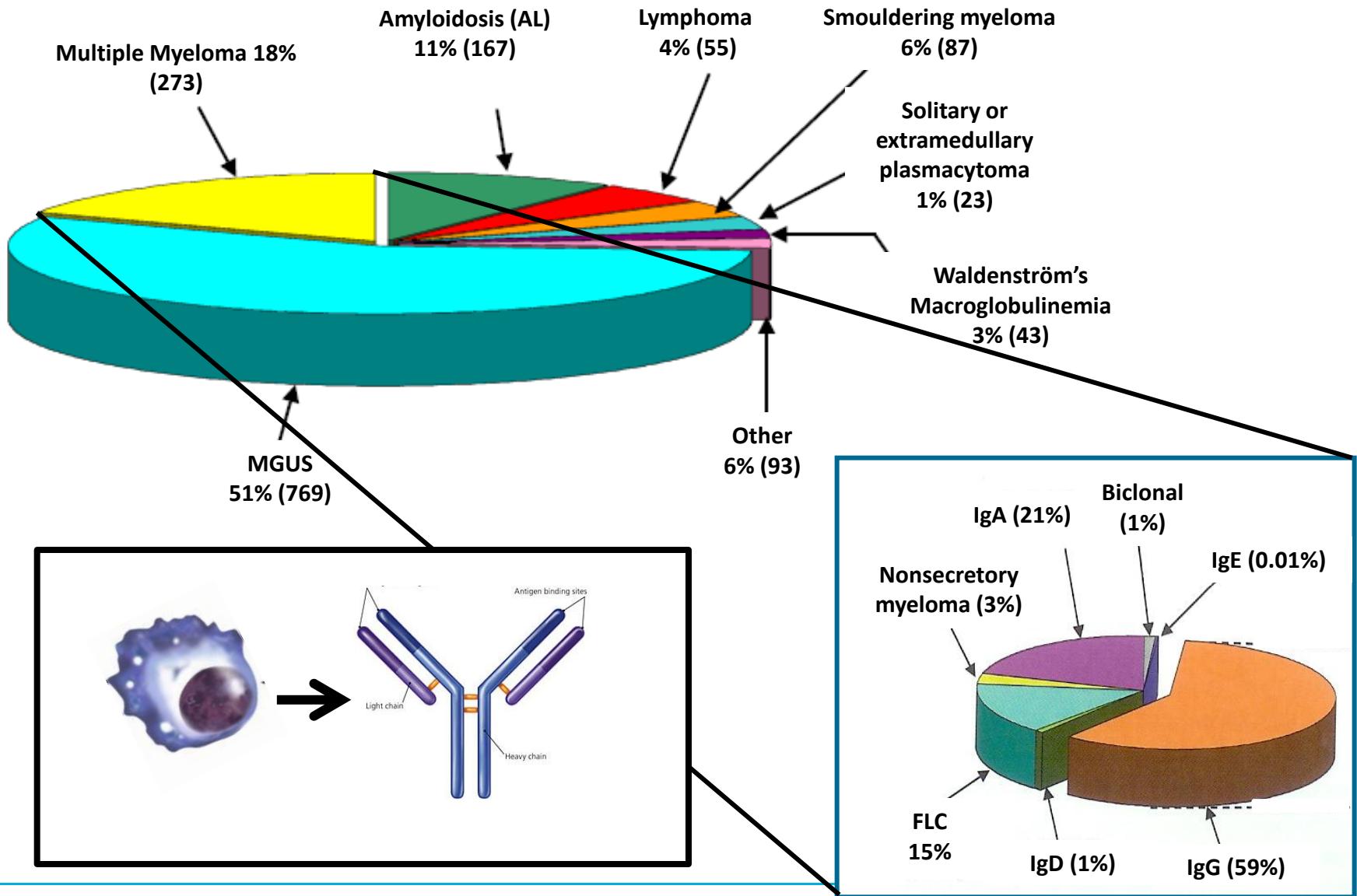
Detection



Immunofixation electrophoresis (IFE)

Typing/Characterisation

Monoclonal gammopathy / Plasma cell dyscrasias



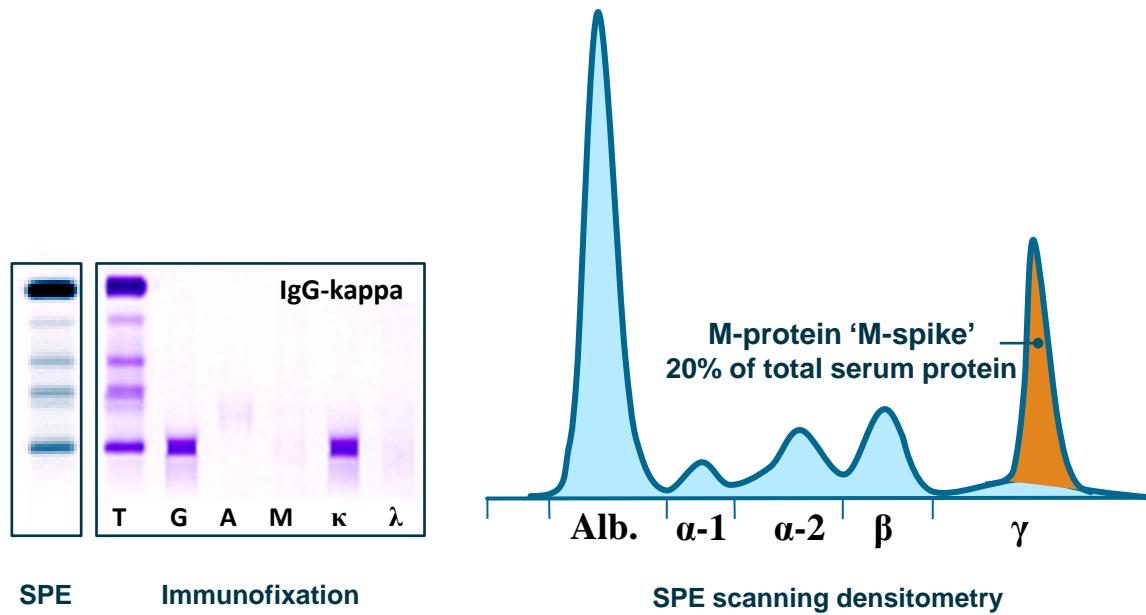
M-protein quantification: Why?

M-protein quantification is required for

- Classification: f.e. MGUS, smouldering myeloma (sMM) or multiple myeloma (MM)
- Staging of symptomatic myeloma (stage I, II and III)
- To monitor disease / therapy-response / or disease evolution (f.e. from MGUS > sMM > MM)

International Myeloma Working Group Response Criteria ^a	
sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine plus disappearance of any soft-tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M protein detectable by immunofixation but not by electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level < 100 mg/24 hr
PR	≥ 50% reduction of serum M protein and reduction in 24-hr urinary M protein by > 90% or to ≤ 200 mg/24 hr If serum and urine M protein are not measurable: ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required AND if serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft-tissue plasmacytomas is also required
MR ^b	All of the following: 25%-49% reduction in serum M protein; 50%-89% reduction in urinary light chain excretion; 25%-49% reduction in the size of soft tissue plasmacytomas; no increase in the size or number of lytic bone lesions; and 25%-49% reduction in plasma cells (for patients with nonsecretory myeloma only)
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	> 25% increase from lowest response value in any 1 or more of M component (serum or urine), difference between involved and uninvolved FLC, bone marrow plasma cell percentage, new bone lesions/plasmacytomas or increase in size of existing lesions/plasmacytomas, hypercalcemia that can be attributed solely to myeloma

M-protein quantification: How?

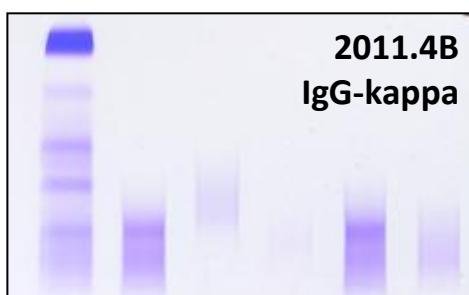
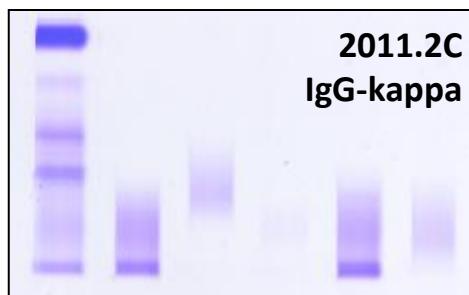
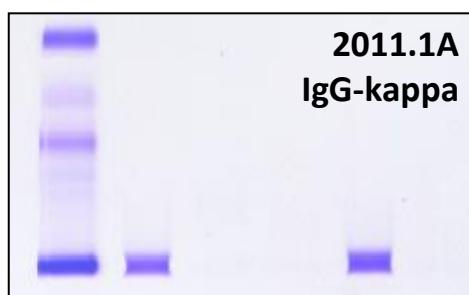
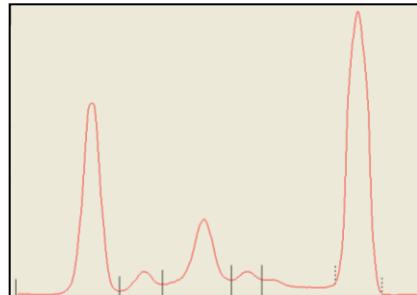


For example:

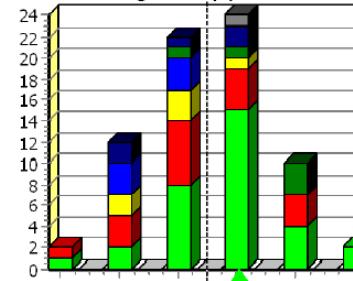
- Total serum protein = 80 g/L
- M-spike = 20% of total serum protein
- IgG-kappa M-protein = 16 g/L

Dutch External Quality Assessment (EQA) M-protein diagnostics

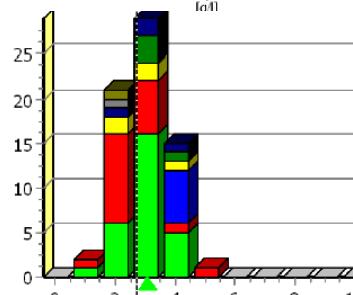
National program organized by Radboudumc (75 participating labs)



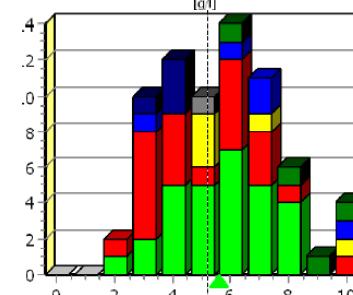
ELP G A M κ λ



100% IgG-kappa
Mean: 42.4 g/L
VC: 13 %



>95% IgG-kappa
Mean: 2.7 g/L
VC: 29 %

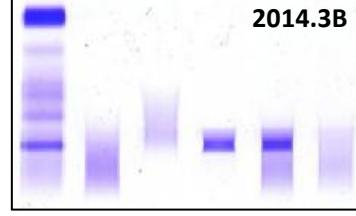
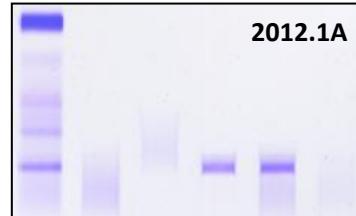
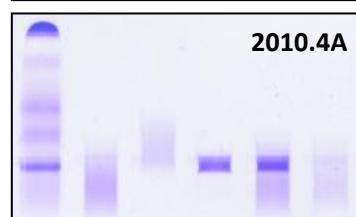
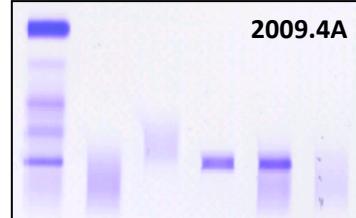
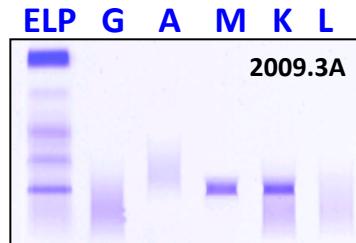
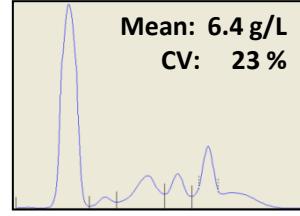
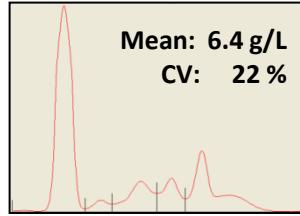
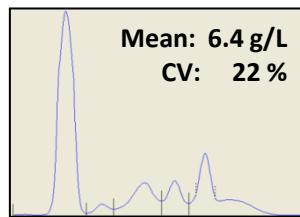
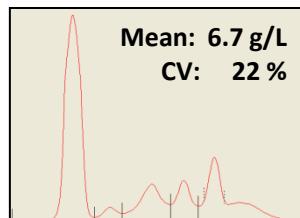
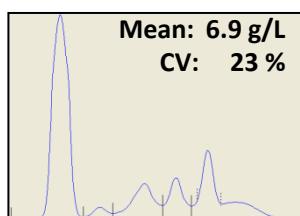


92% IgG-kappa
Mean: 5.5 g/L
VC: 40 %

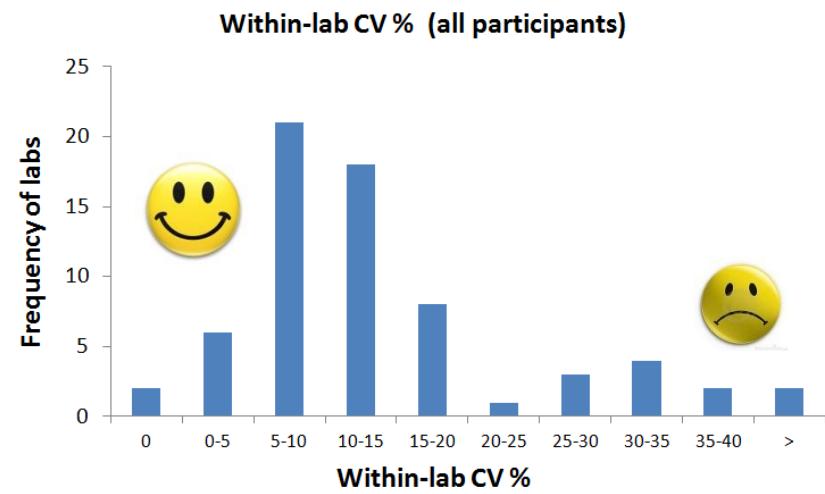


Radboudumc

Monitoring patients, requires good test reproducibility...



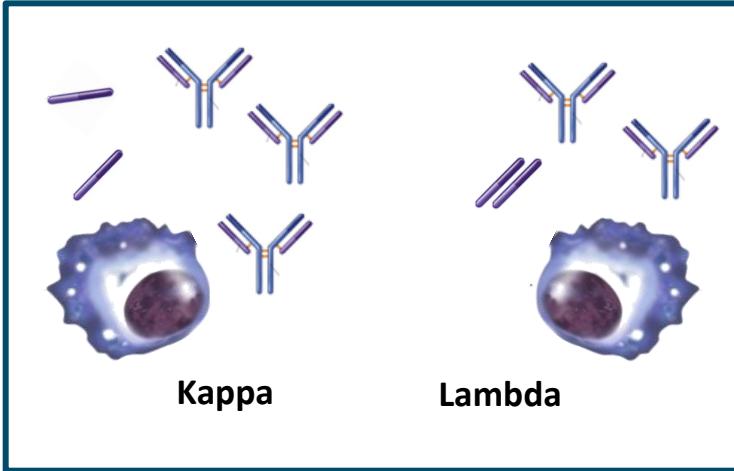
(n=75 labs)



Over 5 measurements
average within-lab VC : 14 %

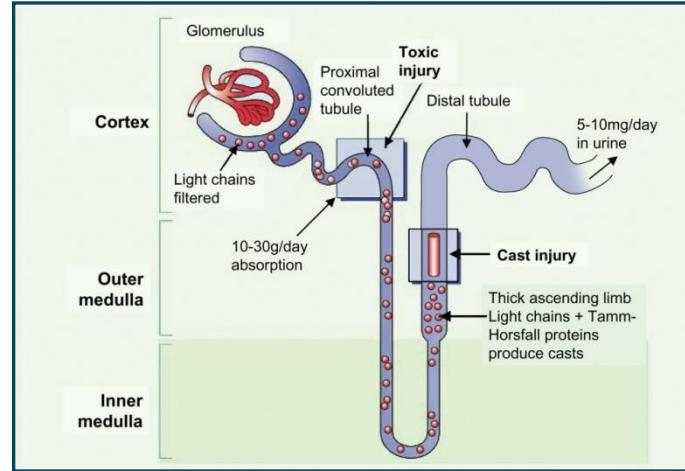


Free Light Chain biology



Bone marrow and lymphoid organs

Polyclonal FLCs produced approx. 500 mg/day



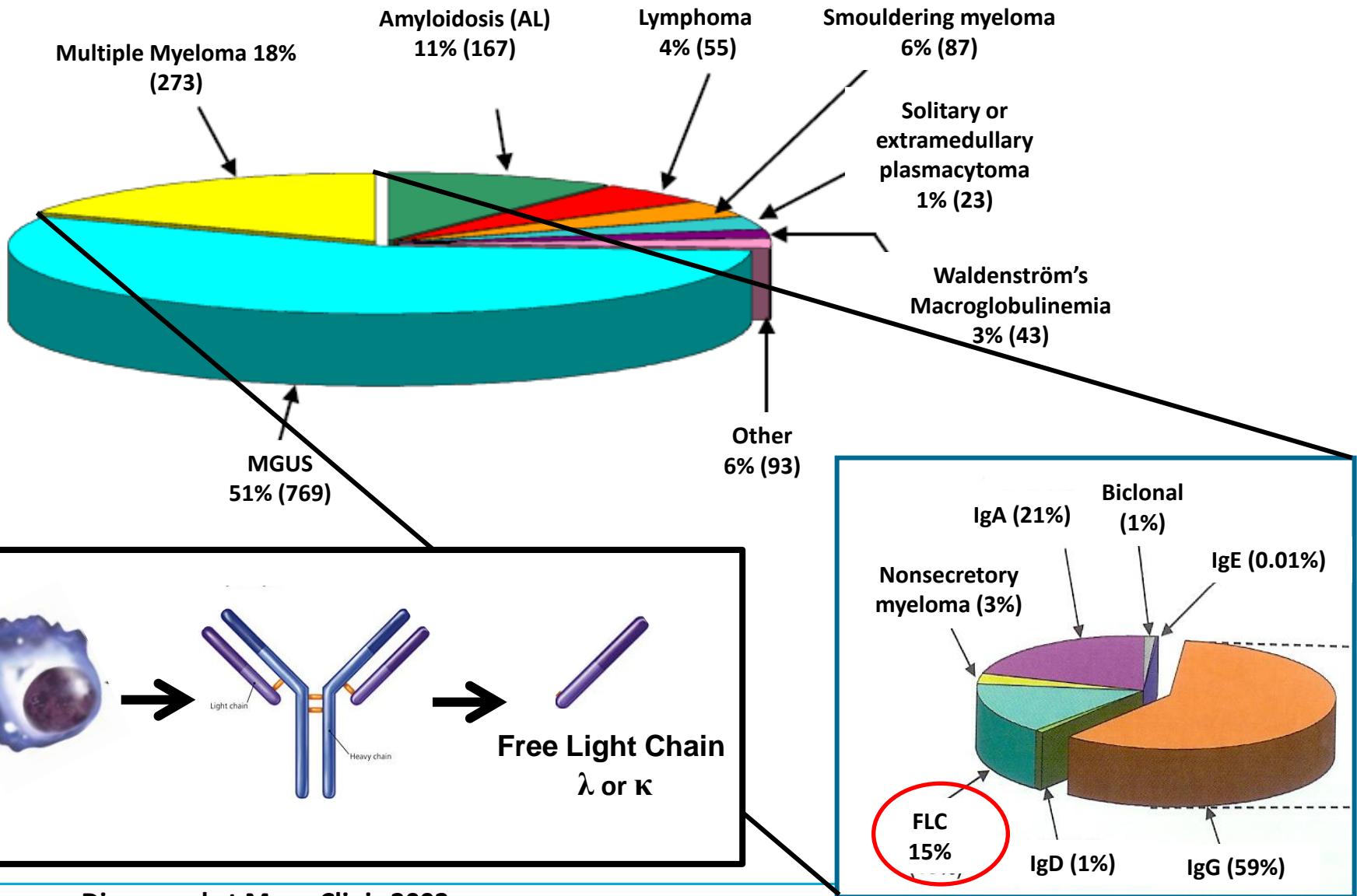
Kidney

Capacity to absorb and metabolize 10-30 gram/day
 $T^{1/2}$ varies from 2-6 hrs to (2-3 days with renal failure)

FLC normal ranges (Freelite, TBS)

Kappa:	3.3 – 19.4 mg/L
Lambda:	5.7 – 26.3 mg/L
Ratio:	0.26 – 1.65

Monoclonal gammopathy



Diagnosed at Mayo Clinic 2002

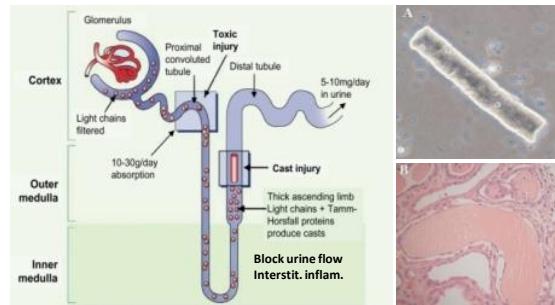
Radboudumc

Multiple myeloma and renal impairment

hyperCalcemia, Renal impairment, Anemia, Bone disease
(CRAB diagnostic criteria MM)

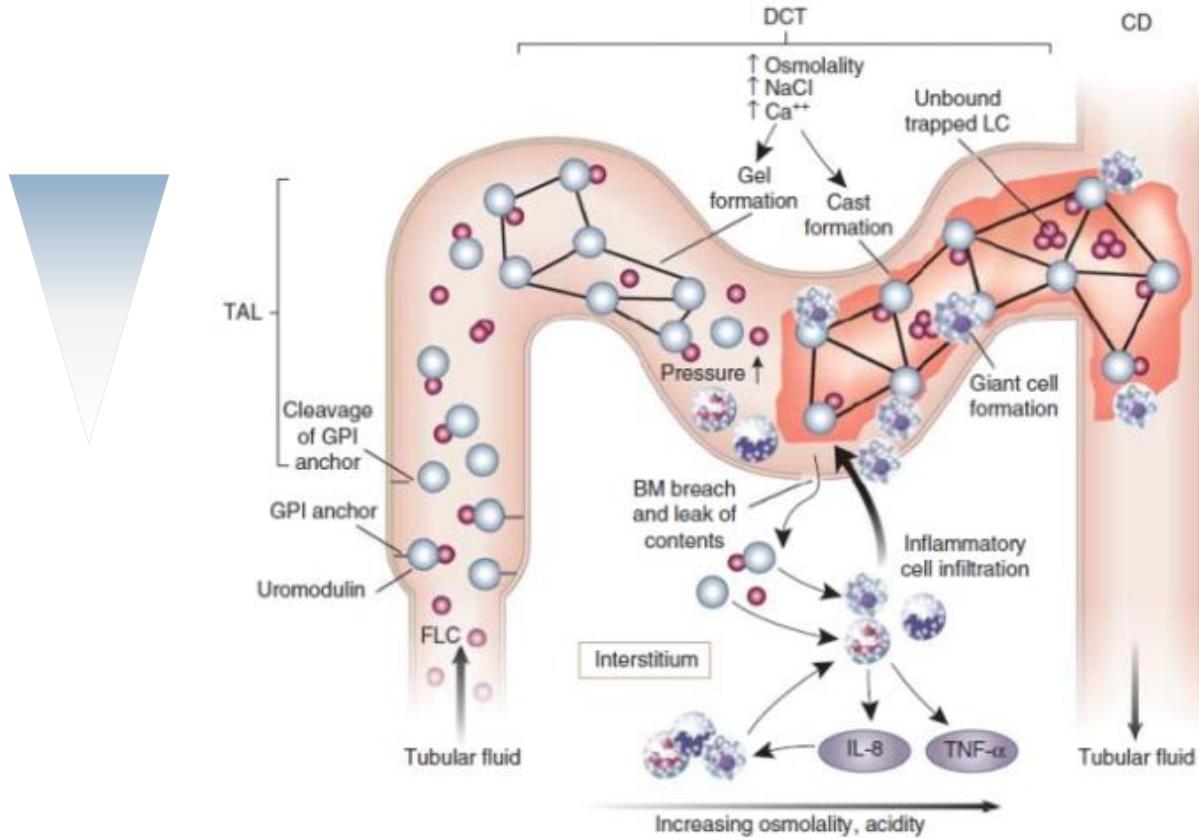
Multiple myeloma at initial presentation

- 18-50% renal impairment (serum creat ↑)
- 12-15% acute renal failure
- 8% become dialysis dependent



Pathology

- Cast nephropathy (myeloma kidney)
- Light chain (AL) amyloidosis
- Light chain deposition disease
- Hypercalcemia
- Nephrotoxic drugs
- Hyperviscosity syndrome



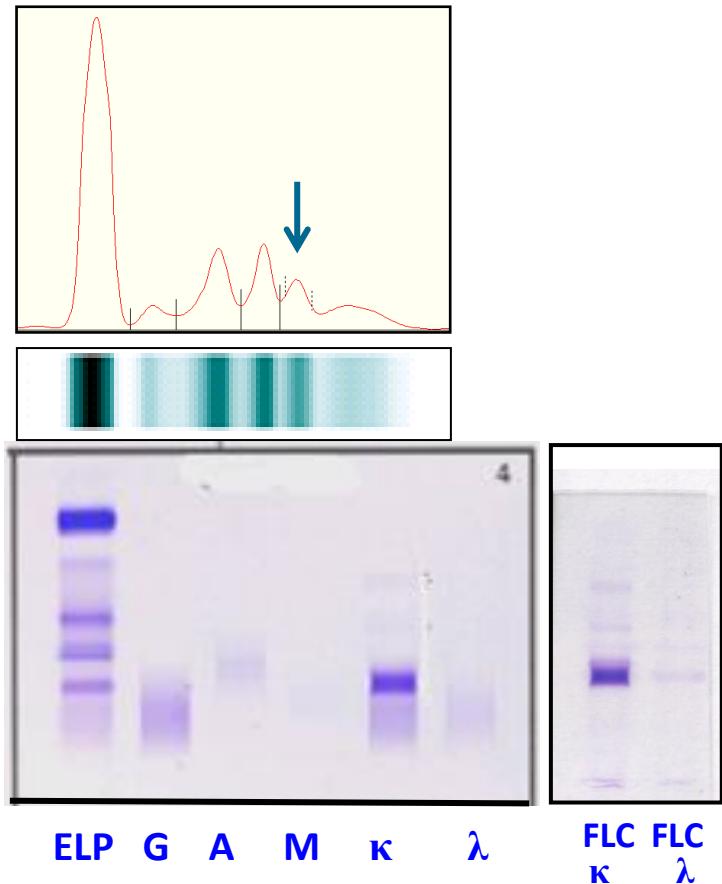
Monoclonal Free Light Chains: not always a monoclonal band



Bence Jones proteins
The very first cancer biomarker:
➤ **The Lancet; 1847**

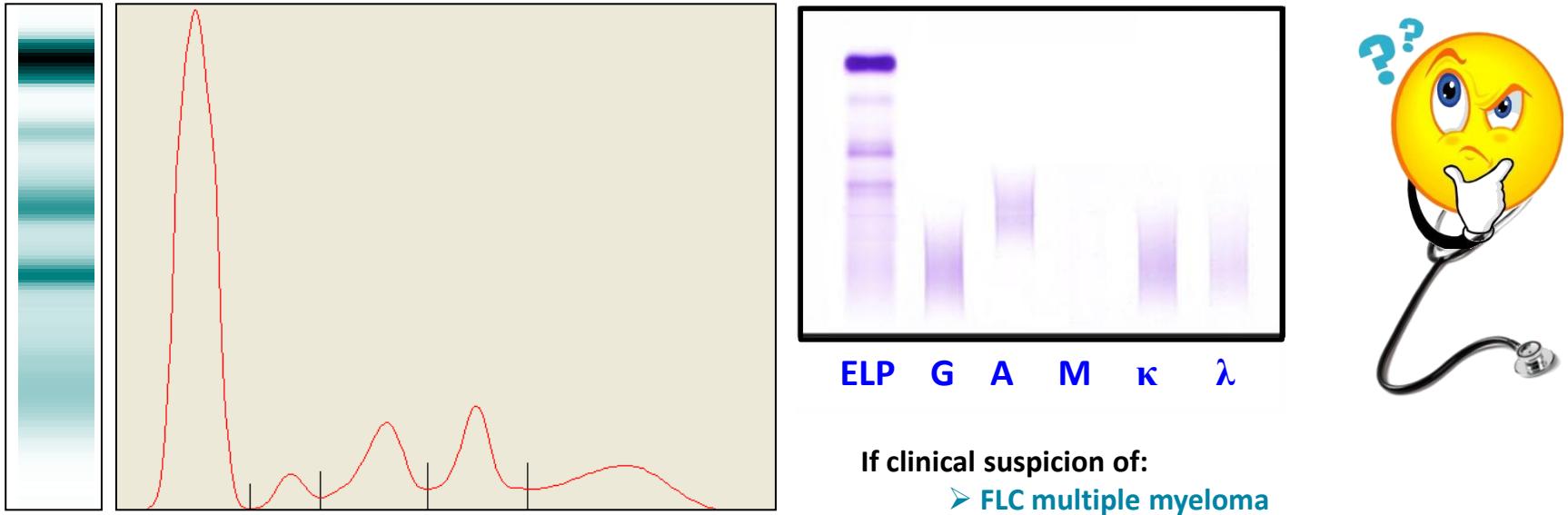
'When urine is heated, a white cloud appears and a precipitate forms. The precipitate disappears on boiling and reappears on cooling...'

Henry Bence Jones



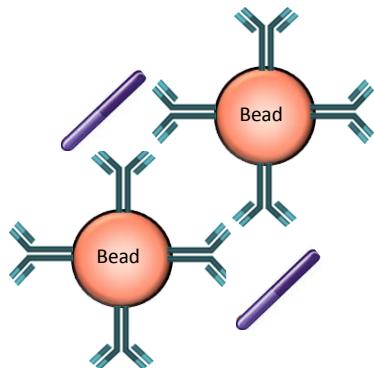
FLC's = short T^{1/2} = low serum concentration = often no 'M-spike'...

No M-protein... no monoclonal gammopathy?



If clinical suspicion of:
➤ FLC multiple myeloma
➤ AL amyloidosis

sFLC nephelometry



REF values (freelite)

Free kappa: 3,3 – 19,4 mg/l
Free lambda: 5,7 – 26,3 mg/l

Ratio: 0,26 – 1,65

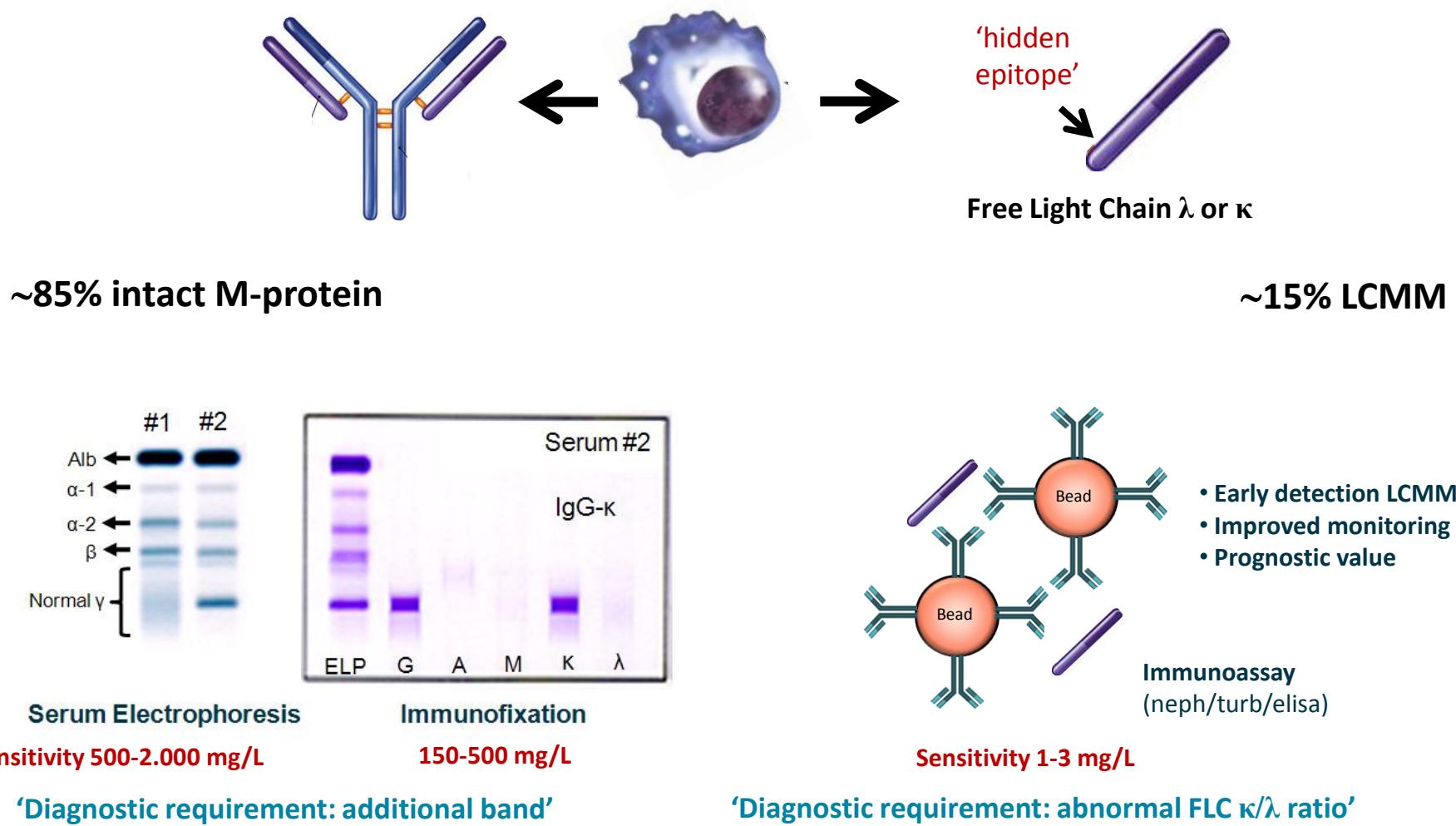
Patient

192 mg/l
6,6 mg/l

29

Diagnosis: FLC kappa plasmacytoma-Th12

M-protein diagnostics: summary

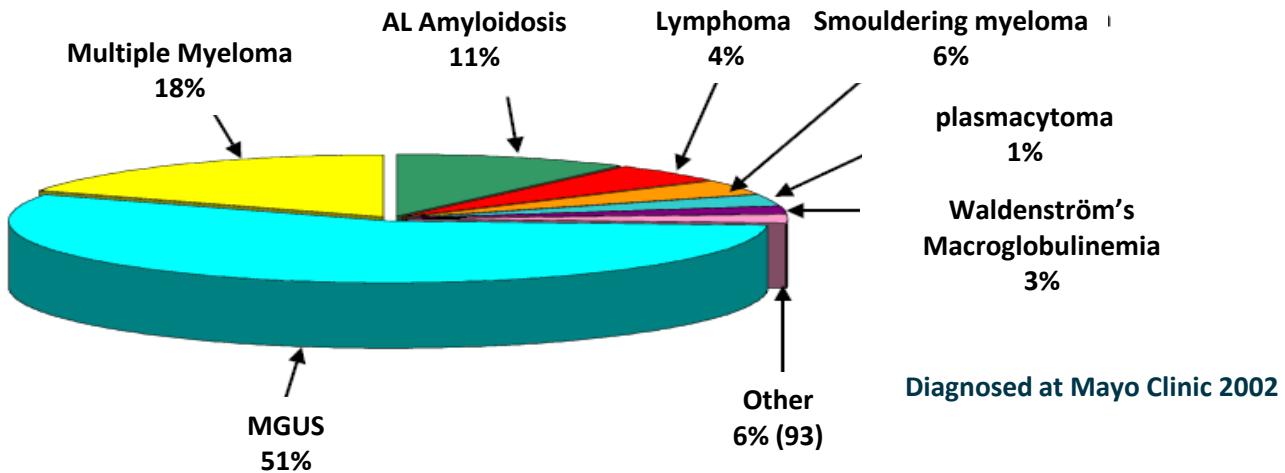


Bradwell et al. 2001 Clin Chem 'immunoassay for quantification of FLC'

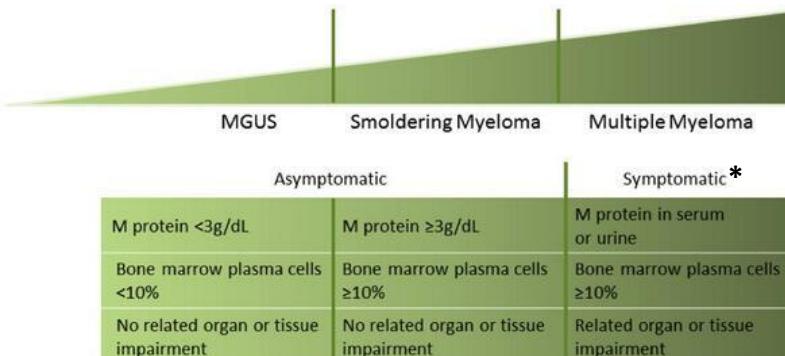
Drayson et al. 2001 Blood 'identifying and monitoring non-secretory MM'

Dispenzieri et al. 2009 Leukemia 'FLC in international guidelines'

M-protein diagnostics: screening, diagnosis and staging



Diagnostic criteria

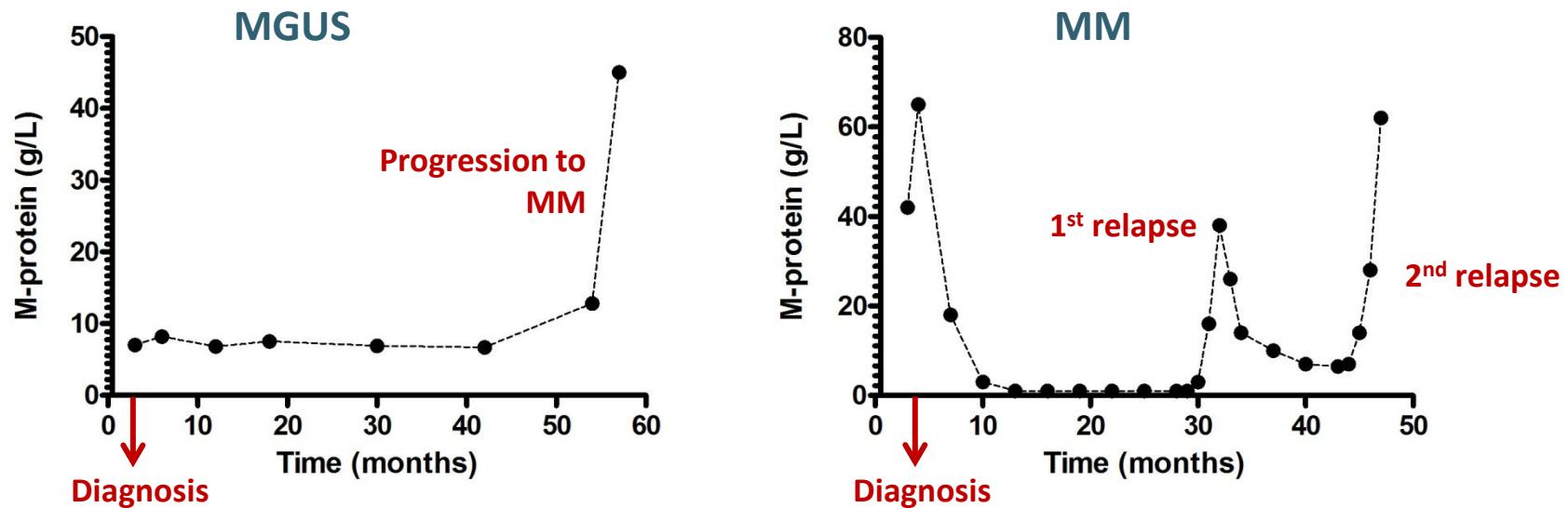


* Or myeloma defining event.

Disease staging

Durie-Salmon Classification			
A serum creatinine < 2 mg/dL	Stage I • Hb > 10 g/dL • normal calcium • normal or single plasmacytoma or osteoporosis • SPEP & UPEP (peak quantitation): - IgG < 5 g/dL - IgA < 3 g/dL - BJP < 4 g/24h*	Stage II • neither I nor III	Stage III • Hb < 8.5 g/dL • high calcium >12 mg/dL • 3 or more lytic bone lesions • SPEP & UPEP (peak quantitation): - IgG > 7 g/dL - IgA > 5 g/dL - BJP > 12 g/24h*
B serum creatinine > 2 mg/dL			

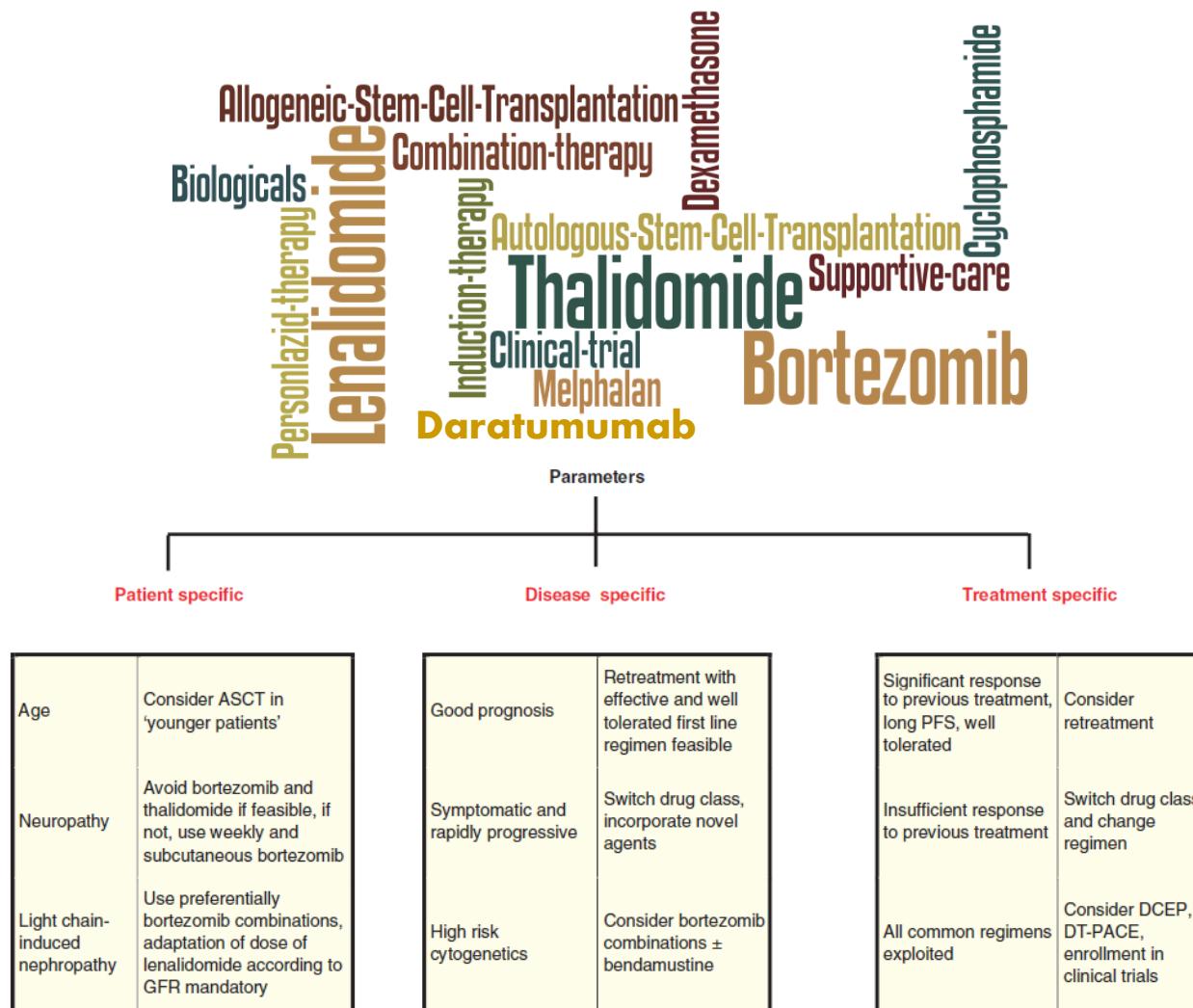
M-protein diagnostics: follow-up and response evaluation



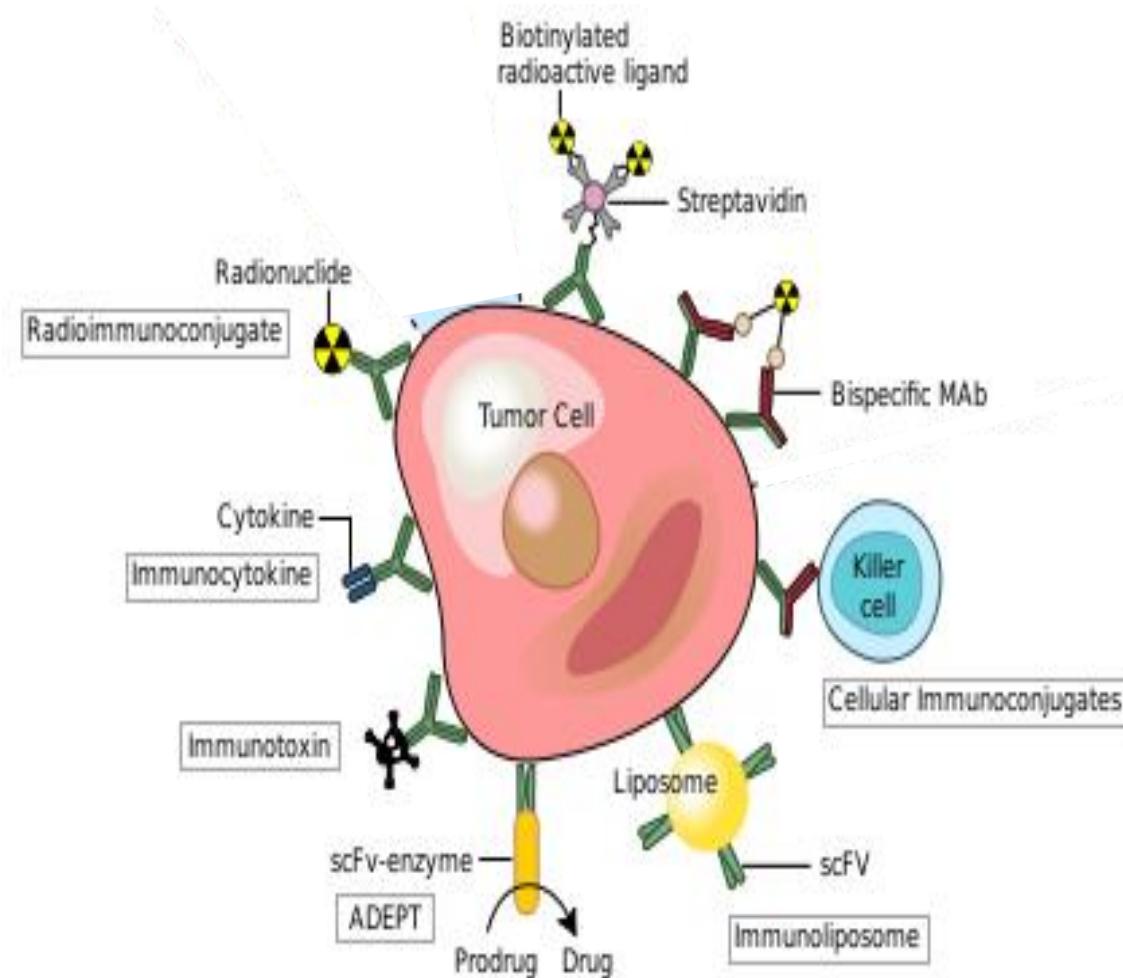
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Improved treatment regimes for MM patients



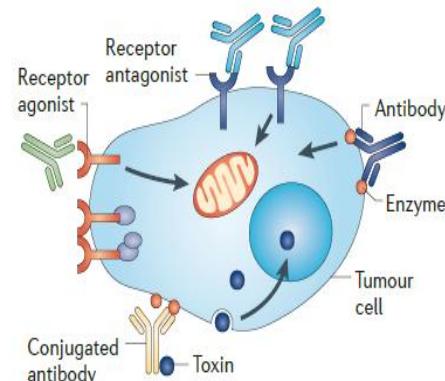
Tumor specific antibodies



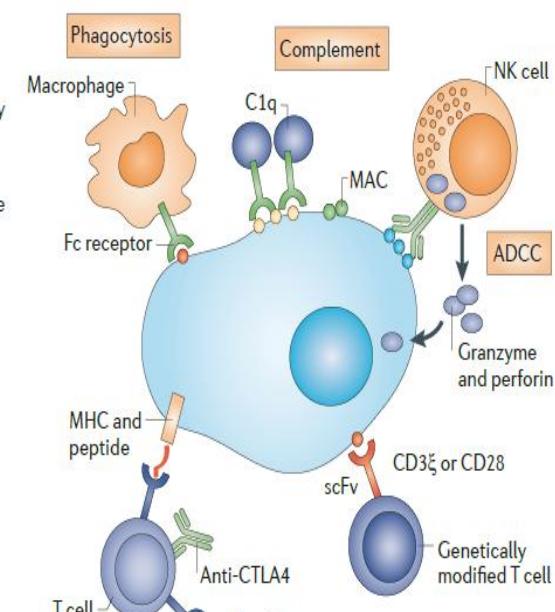
Anti-cancer antibodies used in the clinic*

ANTIBODY	APPROVAL	TARGET	CLINICAL INDICATION
Rituximab	1997	CD20	Non-Hodgkin lymphoma
Trastuzumab	1998	HER2	Breast and gastric cancer
Cetuximab	2004	EGFR	Colorectal and head & neck cancer
Bevacizumab	2004	VEGF	Colorectal cancer, renal cell carcinoma, glioblastoma, lung cancer
Panitumumab	2006	EGFR	Colorectal carcinoma
Ipilimumab	2011	CTLA-4	Melanoma
Nivolumab	2014	PD-1	Melanoma, Lung cancer, RCC
Daratumumab	2015	CD38	Multiple myeloma
Elotuzumab	2015	SLAMF7	Multiple myeloma

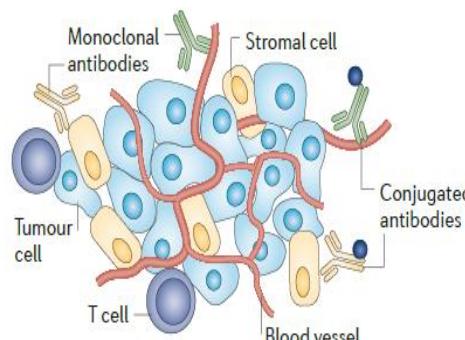
1. Direct tumor cell killing



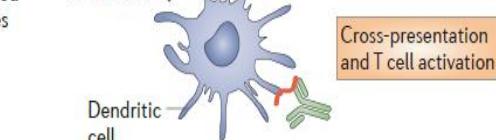
2. Immune-mediated tumor cell killing



3. Vascular and stromal cell ablation

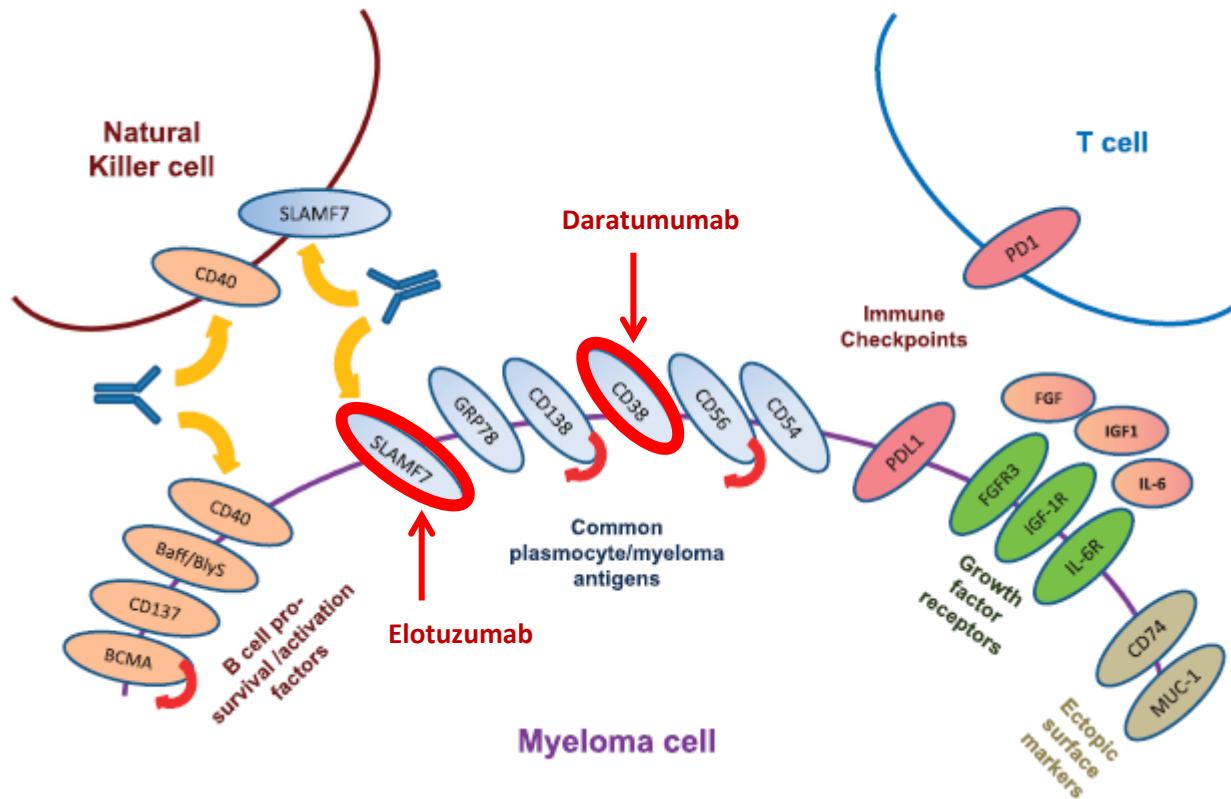


4. Immune modulation tumor micro-environm.

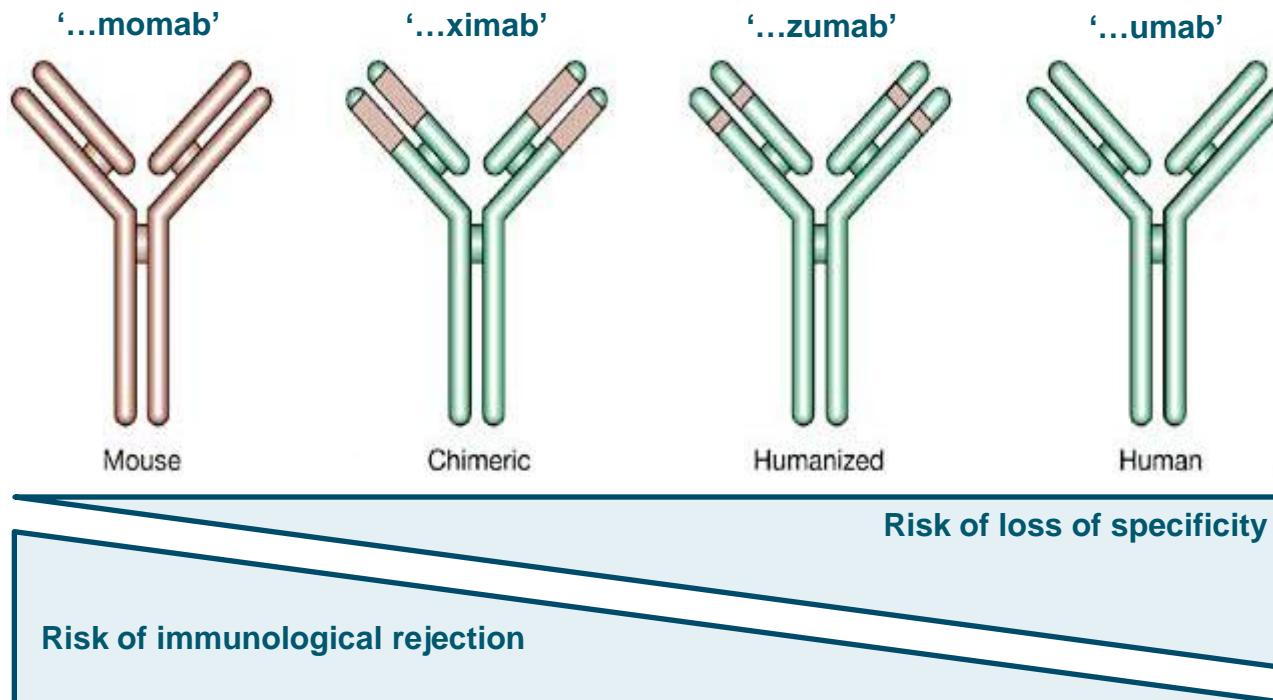


*List is not extensive...

Monoclonal antibody therapy in multiple myeloma



Production and humanization of monoclonal antibodies



Techniques:

- 1) Merge binding portion of monoclonal mouse antibody with human antibody producing DNA.
Use cell cultures to express this DNA product
- 2) Genetically engineered mice that produce 'human' antibodies / Human hybridomas

Biologics for MM patients in clinical practice

The NEW ENGLAND JOURNAL of MEDICINE

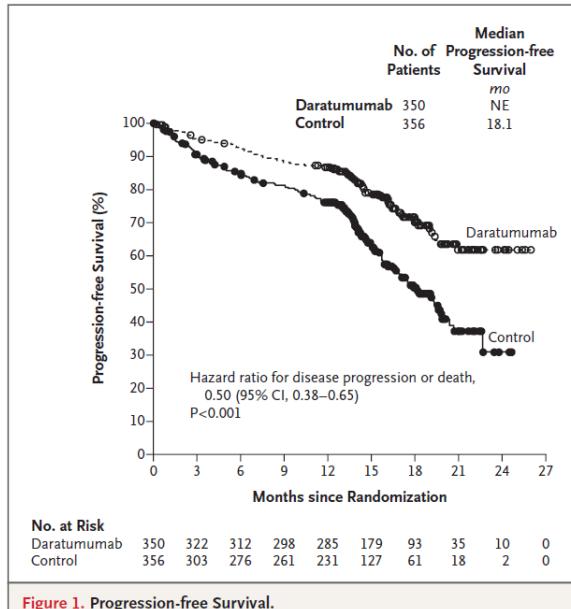
Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M.C. Minnema, U. Lassen, J. Krejciak, A. Palumbo, N.W.C.J. van de Donk, T. Ahmadi, I. Khan, C.M. Uhlar, J. Wang, A.K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun, and P.G. Richardson

The NEW ENGLAND JOURNAL of MEDICINE

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

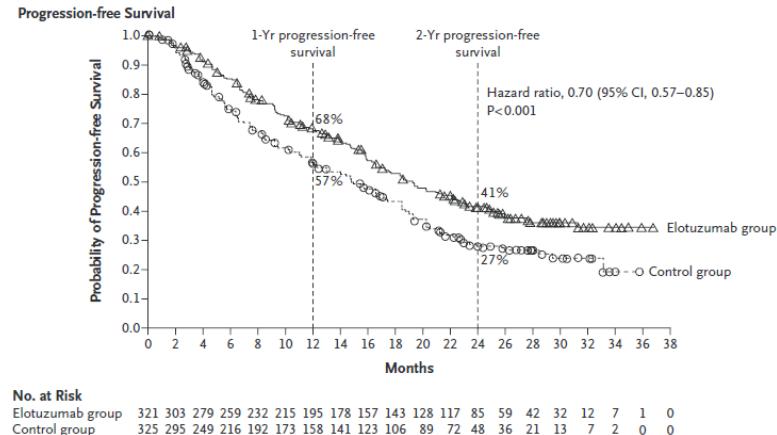
M.-V. Mateos, M.A. Dimopoulos, M. Cavo, K. Suzuki, A. Jakubowiak, S. Knop, C. Doyen, P. Lucio, Z. Nagy, P. Kaplan, L. Pour, M. Cook, S. Grosicki, A. Crepaldi, A.M. Liberati, P. Campbell, T. Shelekhova, S.-S. Yoon, G. Iosava, T. Fujisaki, M. Garg, C. Chiu, J. Wang, R. Carson, W. Crist, W. Deraedt, H. Nguyen, M. Qi, and J. San-Miguel, for the ALCYONE Trial Investigators*



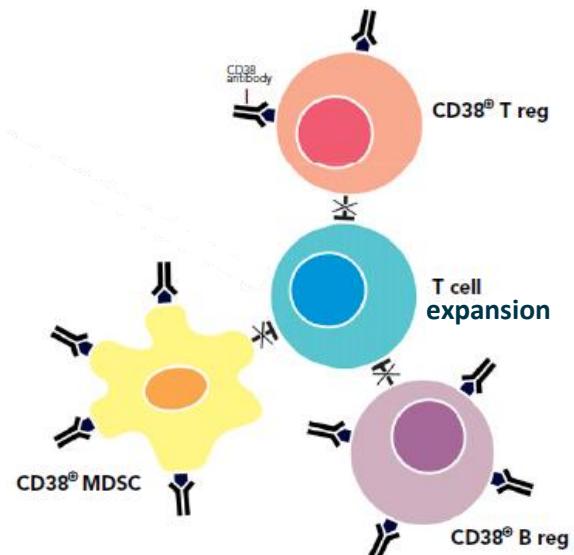
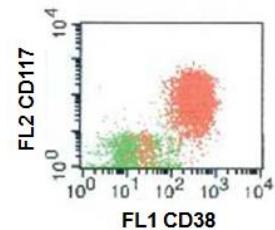
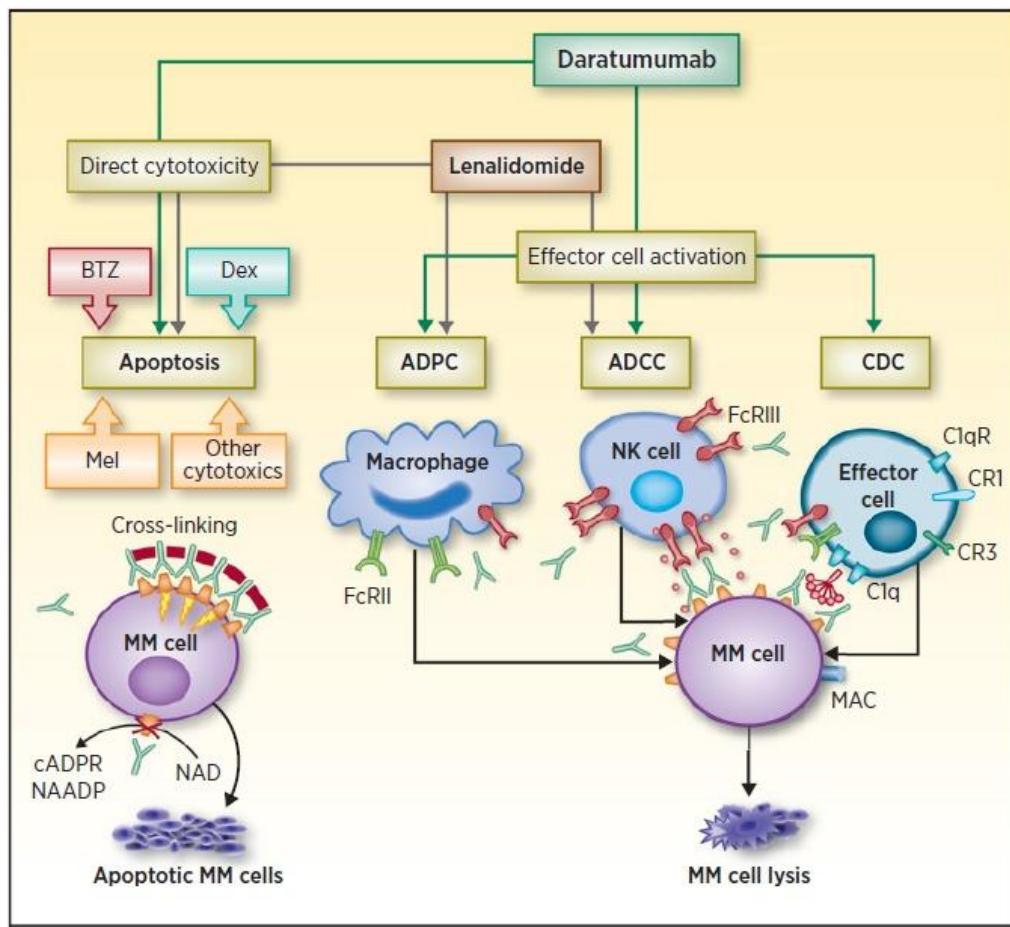
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Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksaç, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickhardt, M.D., Valerie Poulat, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

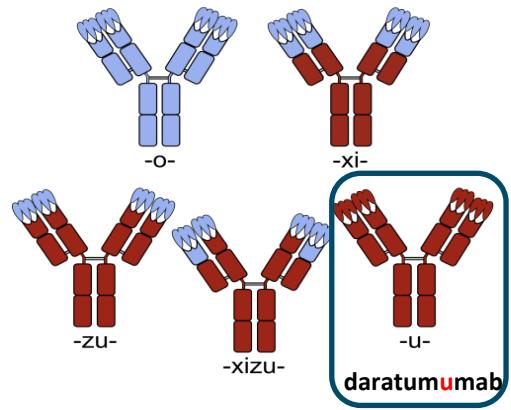


Daratumumab Mechanisms of effect

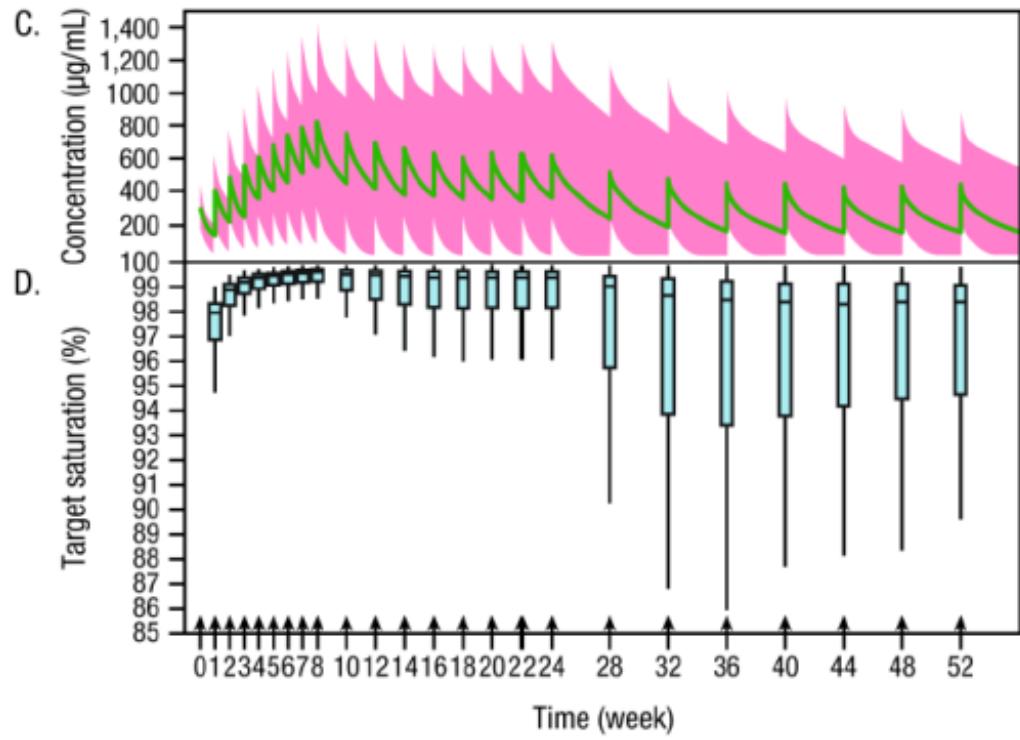


Immunomodulatory effects

Daratumumab pharmacokinetics

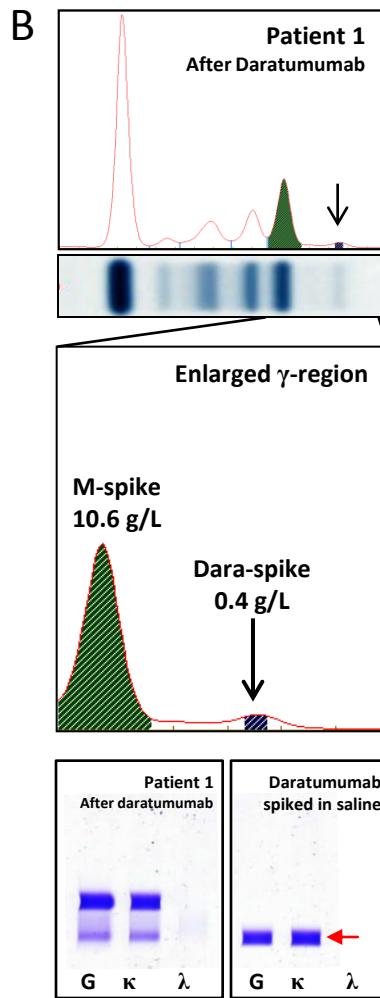
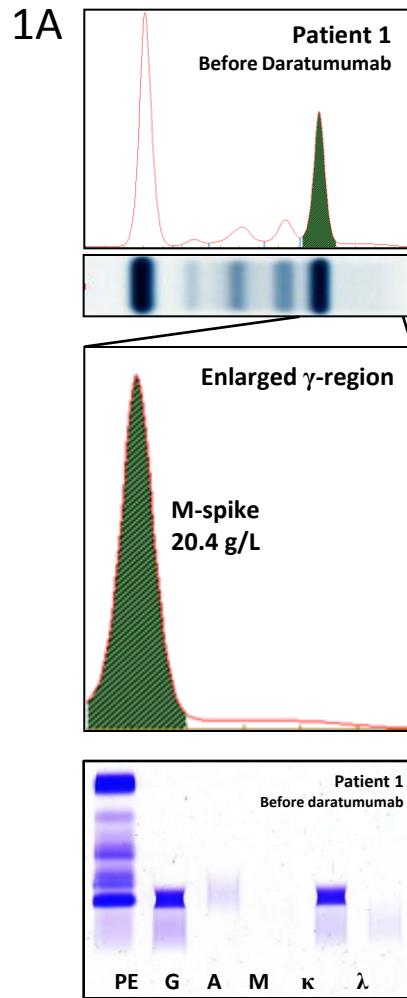


Human IgG1-kappa mAb biologic

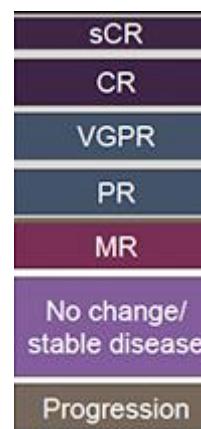


Reaching serum [dara] up to 1 g/L

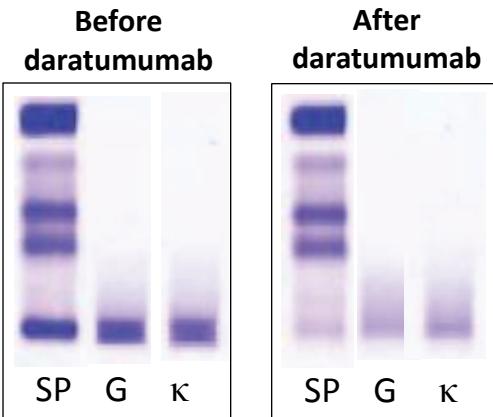
Daratumumab and M-protein interference



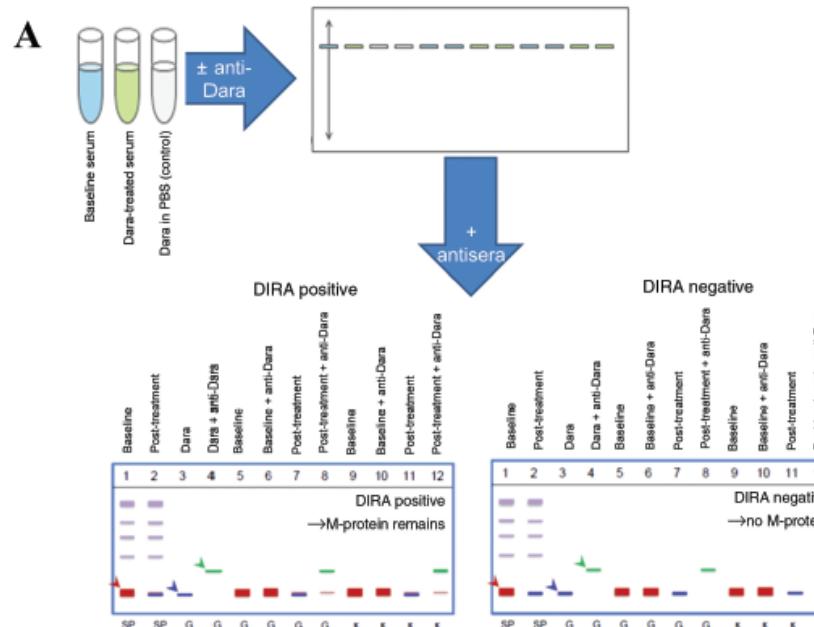
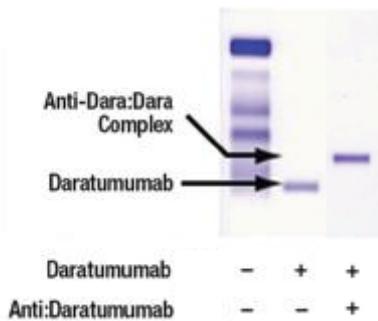
IMWG response criteria (Durie et al. 2006)



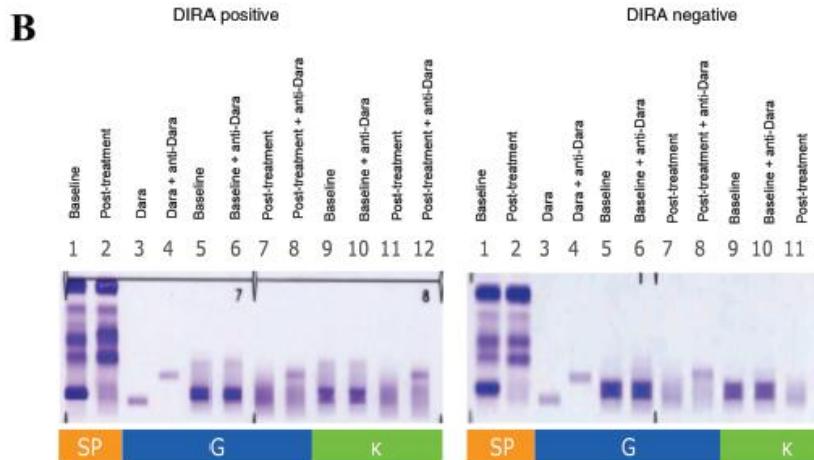
} a.o. IFE negative...



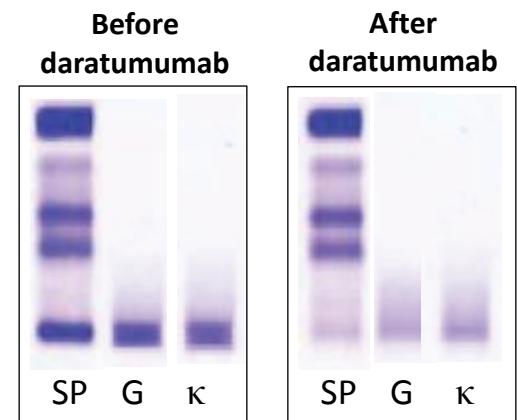
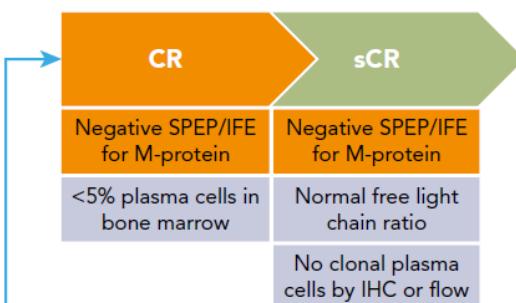
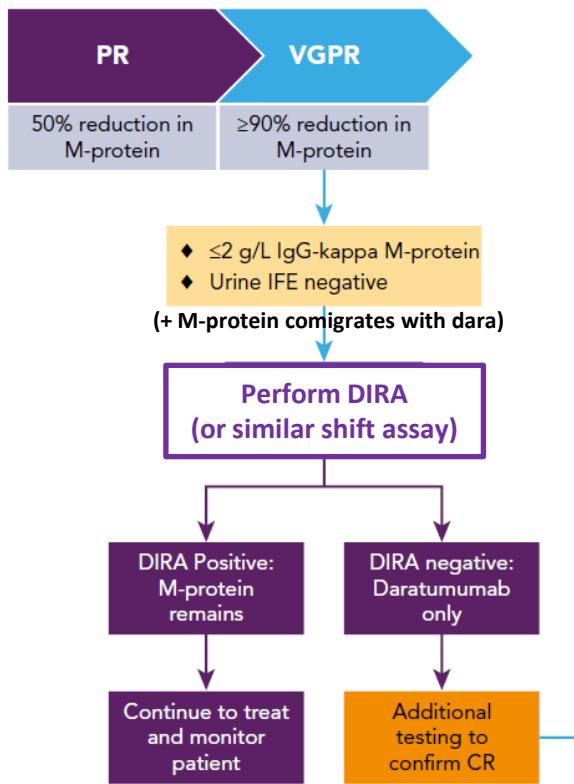
Abrogate interference using mAb against biological



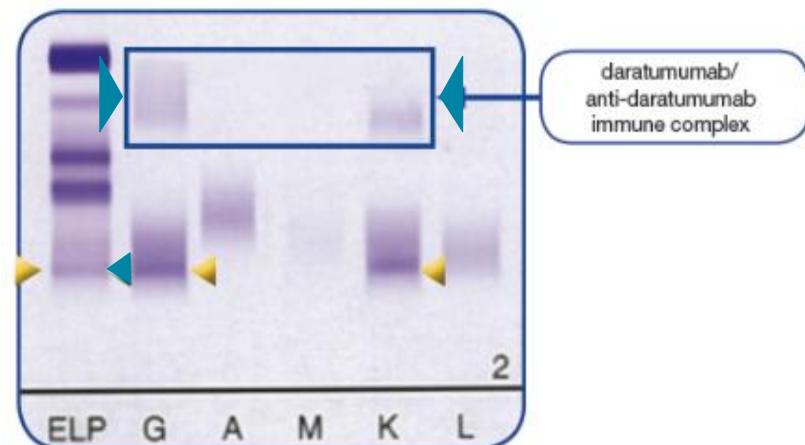
DIRA 'DARA shift-assay' Daratumumab-specific Immunofixation Reflex Assay



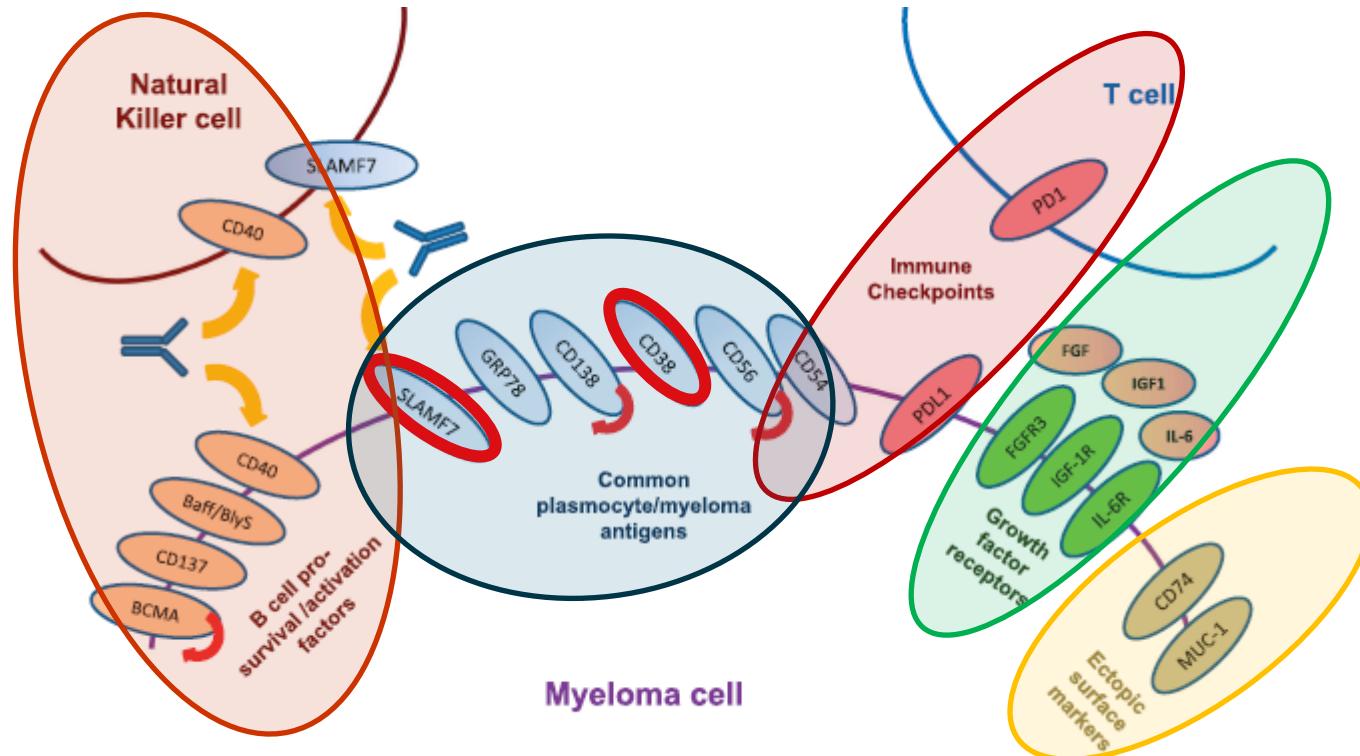
Indication to use DIRA or similar shift-assay



Daratumumab Hydrashift assay (=pos example)



Outlook: synergistic effect of combined mAb in MM patients ??



Alternative techniques to multiplex M-protein / mAb monitoring

DE GRUYTER

Clin Chem Lab Med 2016; 54(6): 1085–1093

Maria Alice V. Wilrich*, Paula M. Ladwig, Bruna D. Andreguetto, David R. Barnidge,
David L. Murray, Jerry A. Katzmann and Melissa R. Snyder

**Monoclonal antibody therapeutics as potential
interferences on protein electrophoresis and
immunofixation**

Journal of
proteome
research

Technical Note

pubs.acs.org/jpr

**Development of a Targeted Mass-Spectrometry Serum Assay To
Quantify M-Protein in the Presence of Therapeutic Monoclonal
Antibodies**

Marina Zajec,^{†,‡} Joannes F. M. Jacobs,[§] Patricia J. T. A. Groenen,^{||} Corrie M. de Kat Angelino,[§]
Christoph Stingl,[†] Theo M. Luider,^{§,†,‡} Yolanda B. De Rijke,[‡] and Martijn M. VanDuijn[§]

Daratumumab does not interfere with serum FLC testing



Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem



Short Communication

Investigation into the interference of the monoclonal antibody daratumumab on the free light chain assay

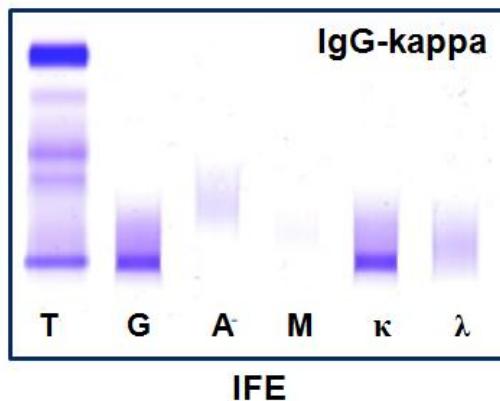
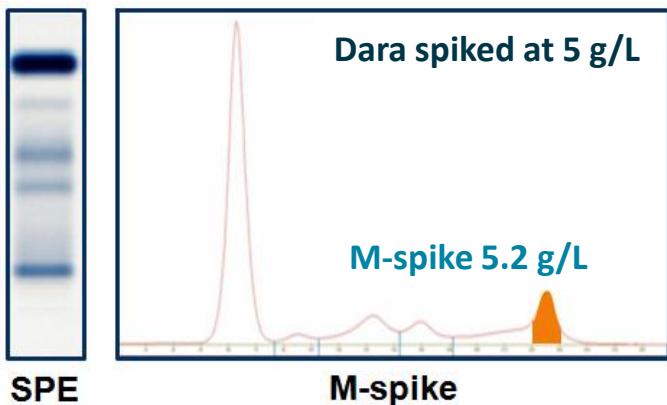


Aaron Seth Rosenberg MD^a, Scott Bainbridge BS^b, Roma Pahwa Ph.D^b, Ishwarlal Jialal MD, Ph.D^{b,*}

Table 1
Levels of free kappa, lambda light chains and FLC ratio in presence and absence of daratumumab.

	Neat sample (N = 20)	Daratumumab-spiked sample (n = 20)	P
<i>IgG-kappa samples</i>			
Kappa, (mg/L)	67.9 (43.6–169.2)	78.1 (46.7–173.7)	0.25
Lambda, (mg/L)	10.3 (5.9–15.1)	11.23 (3.47–16.57)	0.15
FLC ratio	8.9 (2.1–35.2)	11.6 (2.3–30.5)	0.75
<i>Non-IgG-kappa samples (n = 10)</i>			
Kappa, (mg/L)	31.75 (13–50)	33.78 (15.8–51.9)	0.28
Lambda, (mg/L)	35.4 (13.3–48.8)	37.5 (15.4–48.4)	0.57
FLC ratio	0.97 (0.37–1.30)	1.01 (0.41–1.25)	0.92

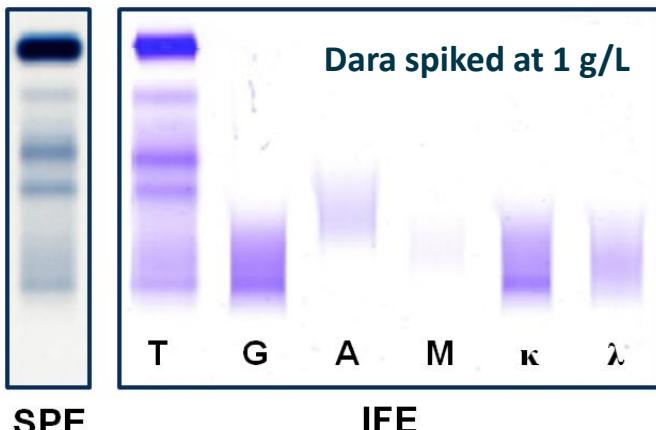
Dira spiked sample in Dutch EQA



100% IgG-kappa M-protein
Mean M-spike (n=66): 4.9 g/L
Inter-lab CV: 22 %

All participants report a normal [FLC-kappa]:

which is in line with observation of Rosenberg et al.: no monoclonal FLC kappa in Daratumumab



98% IgG-kappa M-protein
Mean M-spike (n=44): 1.7 g/L
Inter-lab CV: 46%

Many labs don't spike such small M-proteins and reported <2 g/L

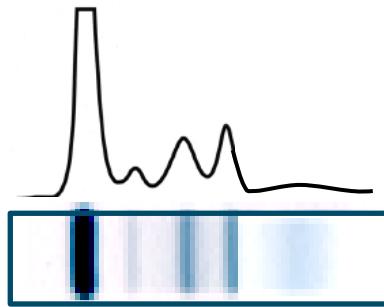


Can mAb's used for other indications also interfere with serum protein electrophoresis?

Theoretically yes, but they often go unnoticed....

Daratumumab in MM patients

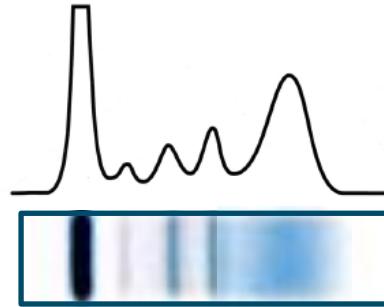
- SPE performed to monitor disease
- Dara dosed at high concentrations (16 mg/kg i.v. weekly in first 8 weeks)
- Hypogamma globulinemia (caused by disease process and therapy)



Low background:
easy to detect small bands

Adalimumab (α -TNF) in Rheumatoid Arthritis

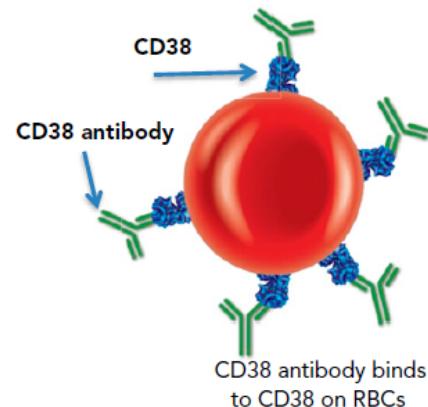
- SPE not commonly performed in RA
- Adalimumab dosed at lower concentrations (40 mg s.c. weekly or every 2 weeks)
- Hypergamma globulinemia (caused by disease process)



High background:
difficult to detect small bands

Daratumumab interferes with blood group compatibility testing

A



**Positive indirect
antiglobulin test**

Antigen Screen

Patient sera is tested for antibodies against a panel of RBCs of known phenotype

Indirect Coombs Test

Patient sera is tested for antibodies against commercially available RBCs

Crossmatch

Patient sera is tested for antibodies against the prospective donor RBCs

B

Before start CD38
antibody therapy

From beginning of CD38 antibody treatment
until pan-reactivity is not observed



Phenotyping, or



Genotyping

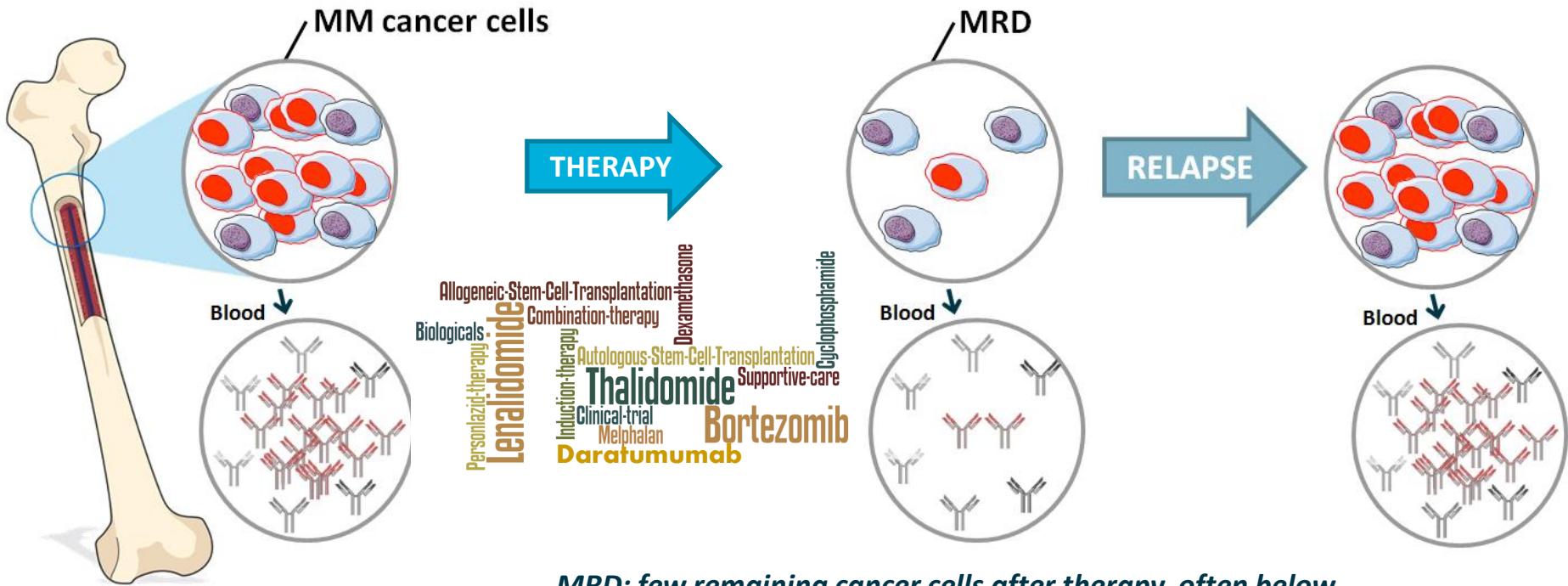


Treat reagent RBCs with DTT or neutralize CD38 antibody with recombinant soluble CD38 or anti-idiotype antibody



Genotyping

Minimal Residual Disease in multiple myeloma



International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Lancet Oncol 2016; 17: e328–46

“...>50% of patients achieve sCR...”

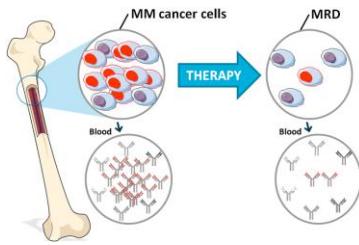
Towards curative therapy for MM...

Perspectives

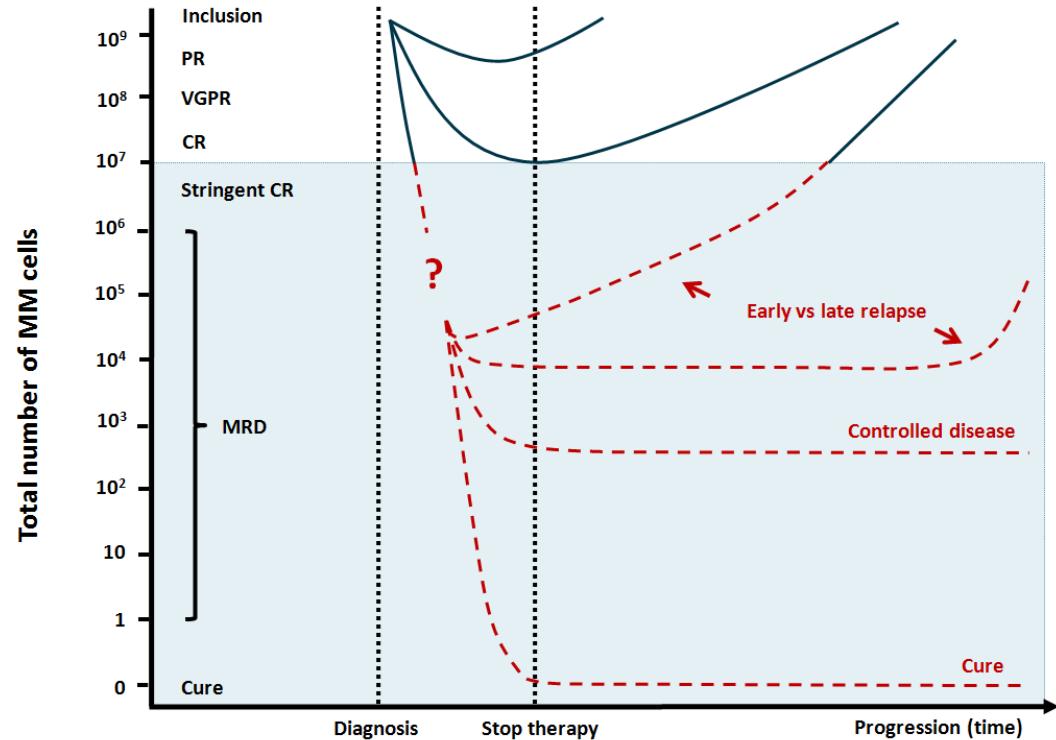
Curing myeloma at last: defining criteria and providing the evidence

Bart Barlogie,¹ Alan Mitchell,² Frits van Rhee,¹ Joshua Epstein,¹ Gareth J. Morgan,¹ and John Crowley²

¹Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and ²Cancer Research And Biostatistics, Seattle, WA



...increases the need for detecting MRD



MRD R&D focus on molecular assays on bone marrow

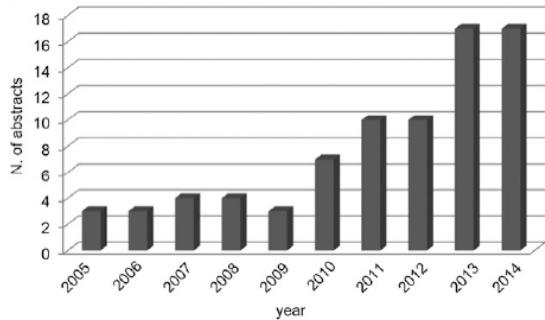
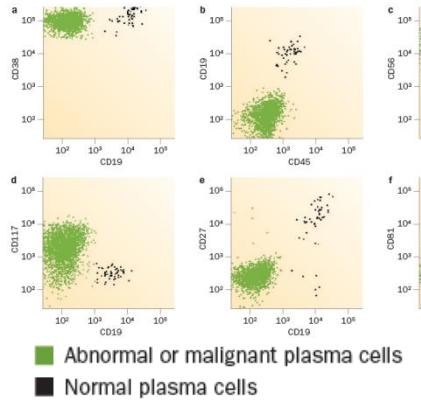


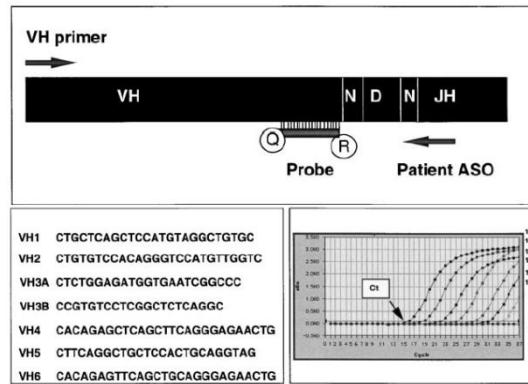
Figure 1. Graphical representation of the increasing number of publications in PUBMED and abstracts reported in the Annual Congress of the American Society of Hematology (ASH) on MM MRD during the past decades. (A)

Focus:
Rearranged B-cell receptor
on MM cells

Paiva et al. Blood 2015



Multicolor flow cytometry



ASO qPCR



Next Generation Sequencing

Landren et al. Am J Hematol 2014; Paiva et al. Blood 2016 (flow cytometry)

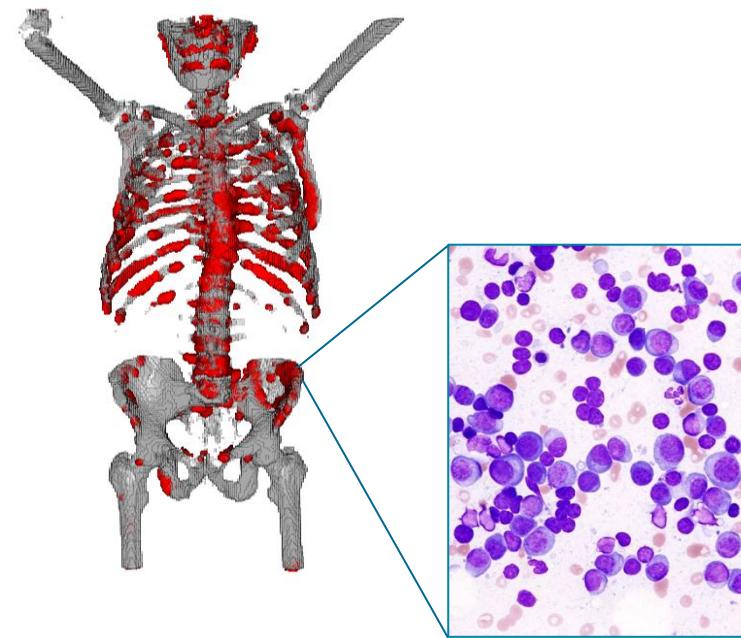
Puig et al. Leukemia 2014 (ASO q-PCR)

Martinez-Lopez et al. Blood 2014 (next generation sequencing)

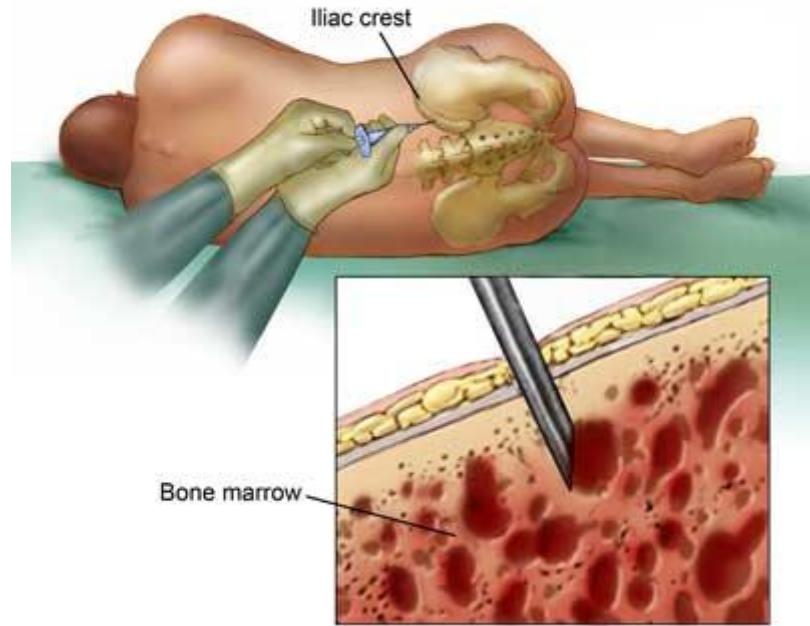
Mailankody et al. Nat Reviews 2015

Radboudumc

Bone marrow not preferred for monitoring MM



Sampling error caused by
tumor heterogeneity



Cumbersome and time-
consuming procedure for
repetitive monitoring

Mass spectrometry as alternative sensitive assay to detect M-proteins in serum*

Based on unique M-protein mass

Journal of proteome research
Article
pubs.acs.org/jpr

Using Mass Spectrometry to Monitor Monoclonal Immunoglobulins in Patients with a Monoclonal Gammopathy

David R. Barnidge,[†] Surendra Dasari,[‡] Chad M. Botz,[†] Danelle H. Murray,[†] Melissa R. Snyder,[†] Jerry A. Katzmann,[†] Angela Dispenzieri,[†] and David L. Murray^{*‡}

RESEARCH ARTICLE WILEY AJH

The utility of MASS-FIX to detect and monitor monoclonal proteins in the clinic

Paolo Milani^{1,2,3} | David L. Murray⁴ | David R. Barnidge⁴ |
Mindy C. Kohlhagen⁴ | John R. Mills⁴ | Giampaolo Merlini² |
Surendra Dasari⁵ | Angela Dispenzieri¹

Citation: Blood Cancer Journal (2017) 7, e590; doi:10.1038/bcj.2017.75
www.nature.com/bcj

ORIGINAL ARTICLE
High sensitivity blood-based M-protein detection in sCR patients with multiple myeloma

JR Mills¹, DR Barnidge¹, A Dispenzieri^{1,2} and DL Murray¹

Clinical Chemistry 62:10
1345-1352 (2016)

Clinical Immunology

Screening Method for M-Proteins in Serum Using Nanobody Enrichment Coupled to MALDI-TOF Mass Spectrometry

Mindy C. Kohlhagen,¹ David R. Barnidge,¹ John R. Mills,¹ Joshua Stoner,¹ Kari M. Gurtner,¹ Andrea M. Liptac,¹ Denise I. Lofgren,¹ Patrick M. Vanderboom,³ Angela Dispenzieri,² Jerry A. Katzmann,¹ Maria A.V. Willrich,¹ Melissa R. Snyder,¹ and David L. Murray^{1*}

Based on unique M-protein peptides

Journal of proteome research
Article
pubs.acs.org/jpr

Monitoring M-Proteins in Patients with Multiple Myeloma Using Heavy-Chain Variable Region Clonotypic Peptides and LC-MS/MS

David R. Barnidge,[†] Renee C. Tschumper,[‡] Jason D. Theis,[†] Melissa R. Snyder,[†] Diane F. Jelinek,[‡] Jerry A. Katzmann,[†] Angela Dispenzieri,^{†,§} and David L. Murray^{*‡}

Clinical Chemistry 62:1
243-251 (2016)

Cancer Diagnostics

Clonotypic Light Chain Peptides Identified for Monitoring Minimal Residual Disease in Multiple Myeloma without Bone Marrow Aspiration

H. Robert Bergen, III,^{**} Surendra Dasari,² Angela Dispenzieri,^{2,4} John R. Mills,⁴ Marina Ramirez-Alvarado,^{1,5} Renee C. Tschumper,⁵ Diane F. Jelinek,⁵ David R. Barnidge,⁴ and David L. Murray⁴

Proteomics Clin. Appl. 2014, 8, 783–795
DOI 10.1002/pcra.201300077

RESEARCH ARTICLE

Quantification of peptides from immunoglobulin constant and variable regions by LC-MRM MS for assessment of multiple myeloma patients

Elizabeth R. Remily-Wood¹, Kaaron Benson², Rachid C. Baz³, Y. Ann Chen⁴, Mohamad Hussein^{3*}, Monique A. Hartley-Brown^{3**}, Robert W. Sprung¹, Brianna Perez³, Richard Z. Liu⁵, Sean J. Yoder⁶, Jamie K. Teer⁵, Steven A. Eschrich⁶ and John M. Koomen¹

Journal of proteome research
Technical Note
pubs.acs.org/jpr

Cite This: *J. Proteome Res.* 2018, 17, 1326–1333

Development of a Targeted Mass-Spectrometry Serum Assay To Quantify M-Protein in the Presence of Therapeutic Monoclonal Antibodies

Marina Zajec,^{†,‡} Joannes F. M. Jacobs,[§] Patricia J. T. A. Groenen,^{||} Corrie M. de Kat Angelino,[§] Christoph Stigl,[†] Theo M. Luijder,^{*,†,‡} Yolanda B. De Rijke,[‡] and Martijn M. VanDuijn[†]

*List of publications is not extensive...

Radboudumc

Questions?



M-protein diagnostics = Personalized diagnostics