Hevylite: New strategies for Diagnosis, Monitoring and Prognosis of monoclonal gammopathies

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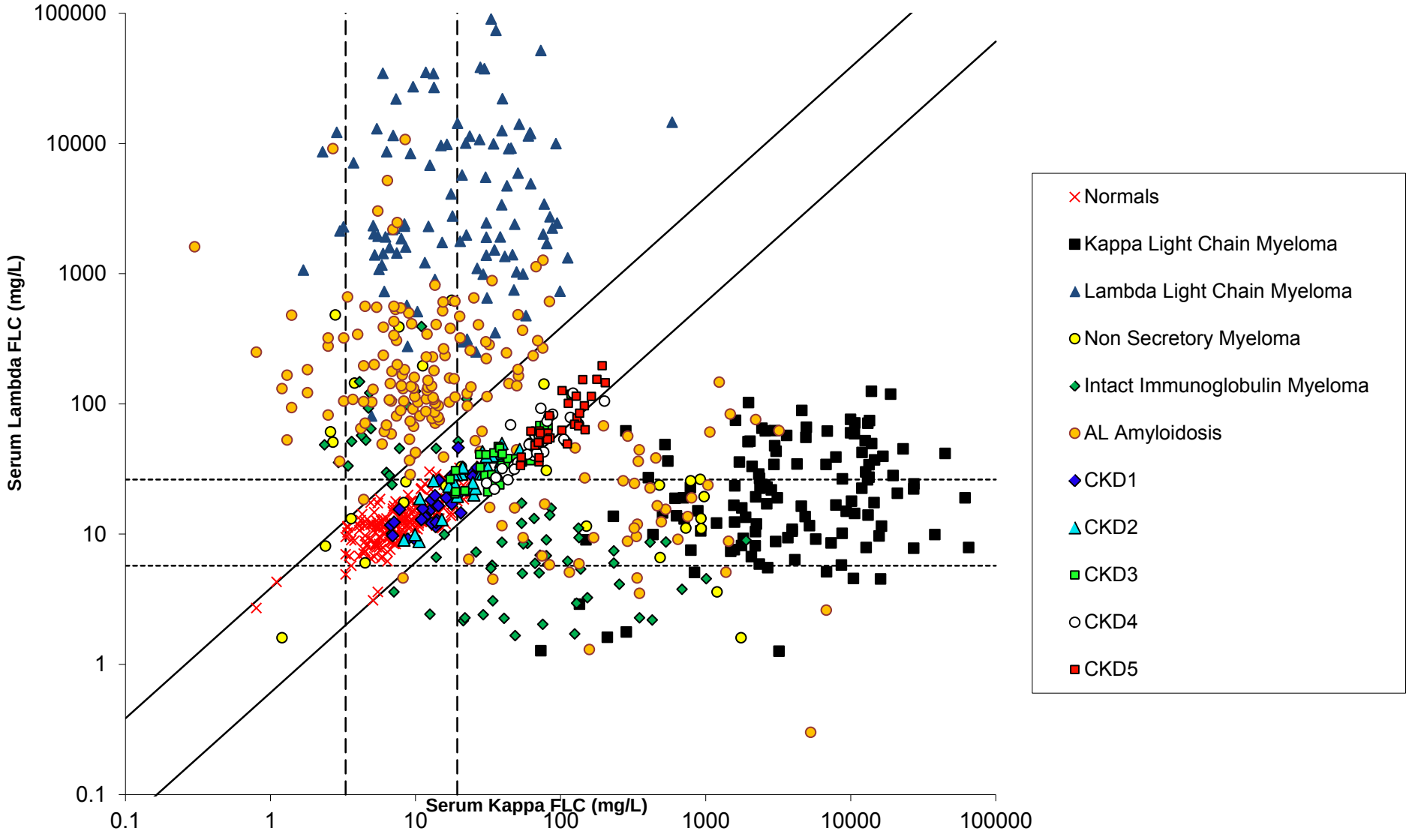
and Binding Site Ltd

How good are tests for monoclonal monoclonal proteins?

	FLC	Igs
1. Diagnosis – sensitive and specific	+	+
2. Monitoring – reproducible	+	+/-
3. Prognostic	+	-

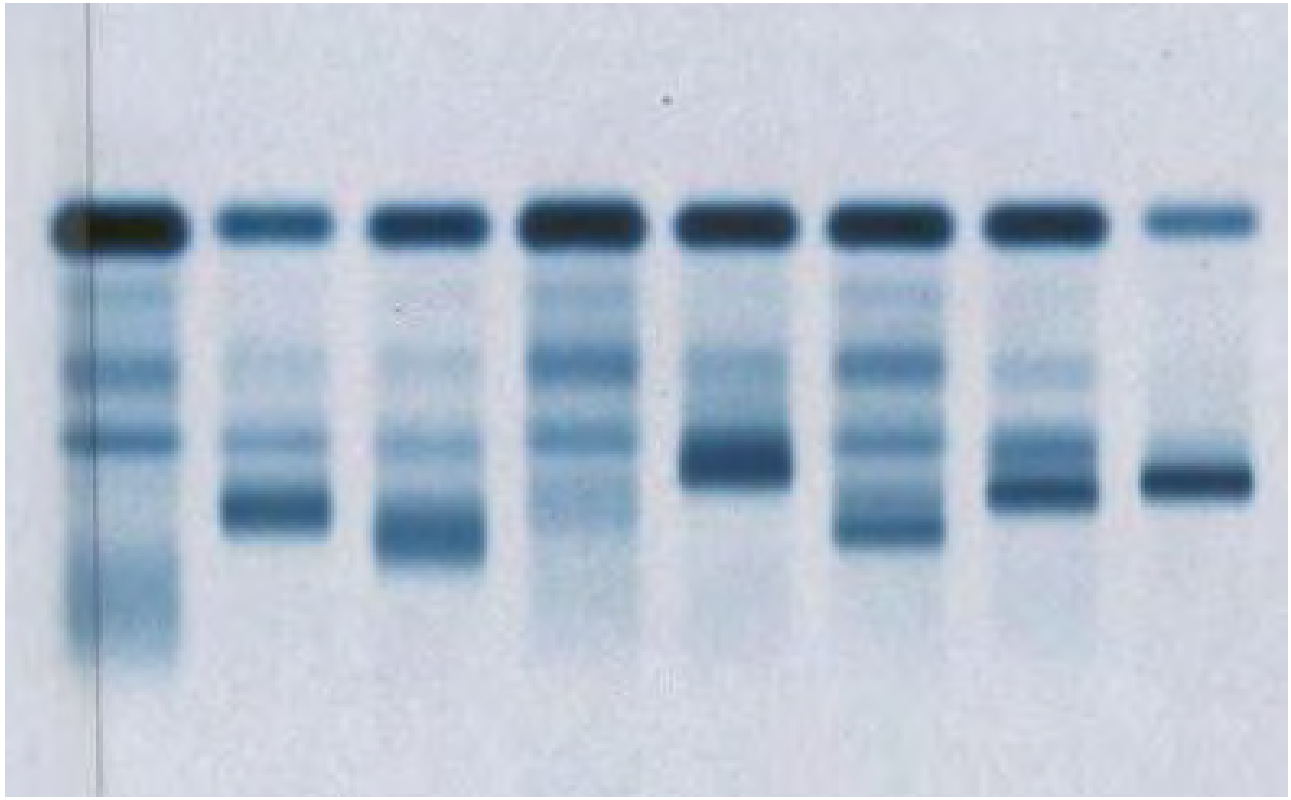
Diagnosis


100000
10000
1000
100
10
1
0.1
Serum Lambda FLC (mg/L)
0.1
1
10
100
1000
10000
100000
Serum Kappa FLC (mg/L)
Normals
Kappa Light Chain Myeloma
Lambda Light Chain Myeloma
Non Secretory Myeloma
Intact Immunoglobulin Myeloma
AL Amyloidosis
CKD1
CKD2
CKD3
CKD4
CKD5

Problems with IgG, IgA and IgM assays

1. There is no Igκ/Igλ ratio
2. Nephelometry measures the total immunoglobulin but the patient is Ig'κ or Ig'λ

SPE Analysis of MRC MM VII Presentation Samples



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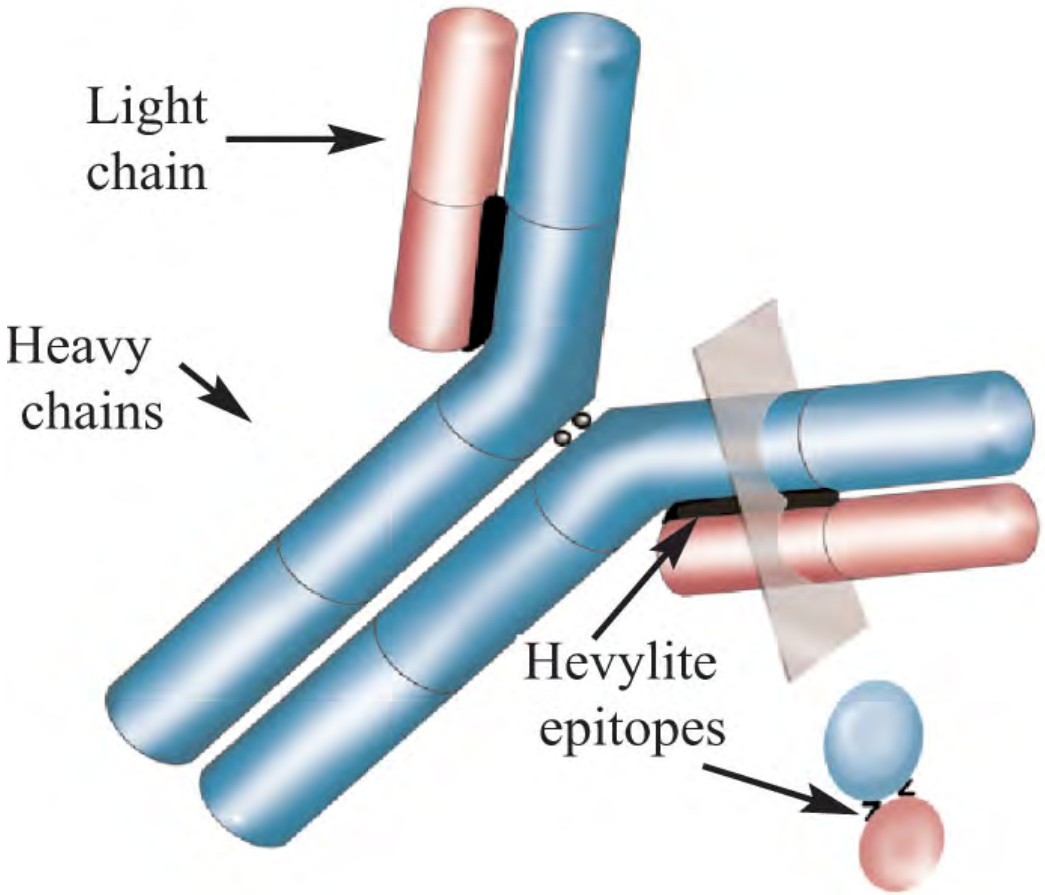
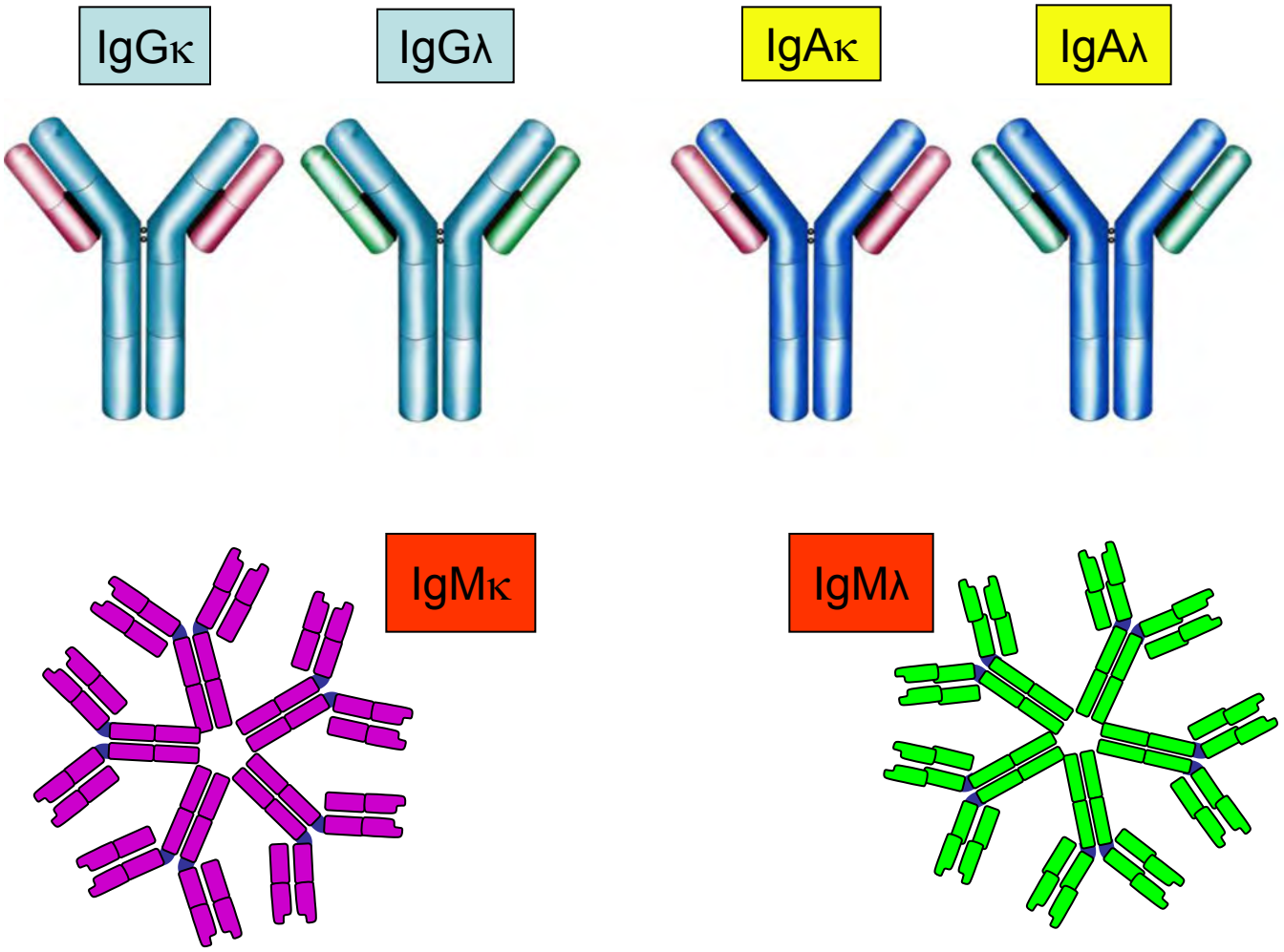
4. IgA bands may be hidden with transferrin

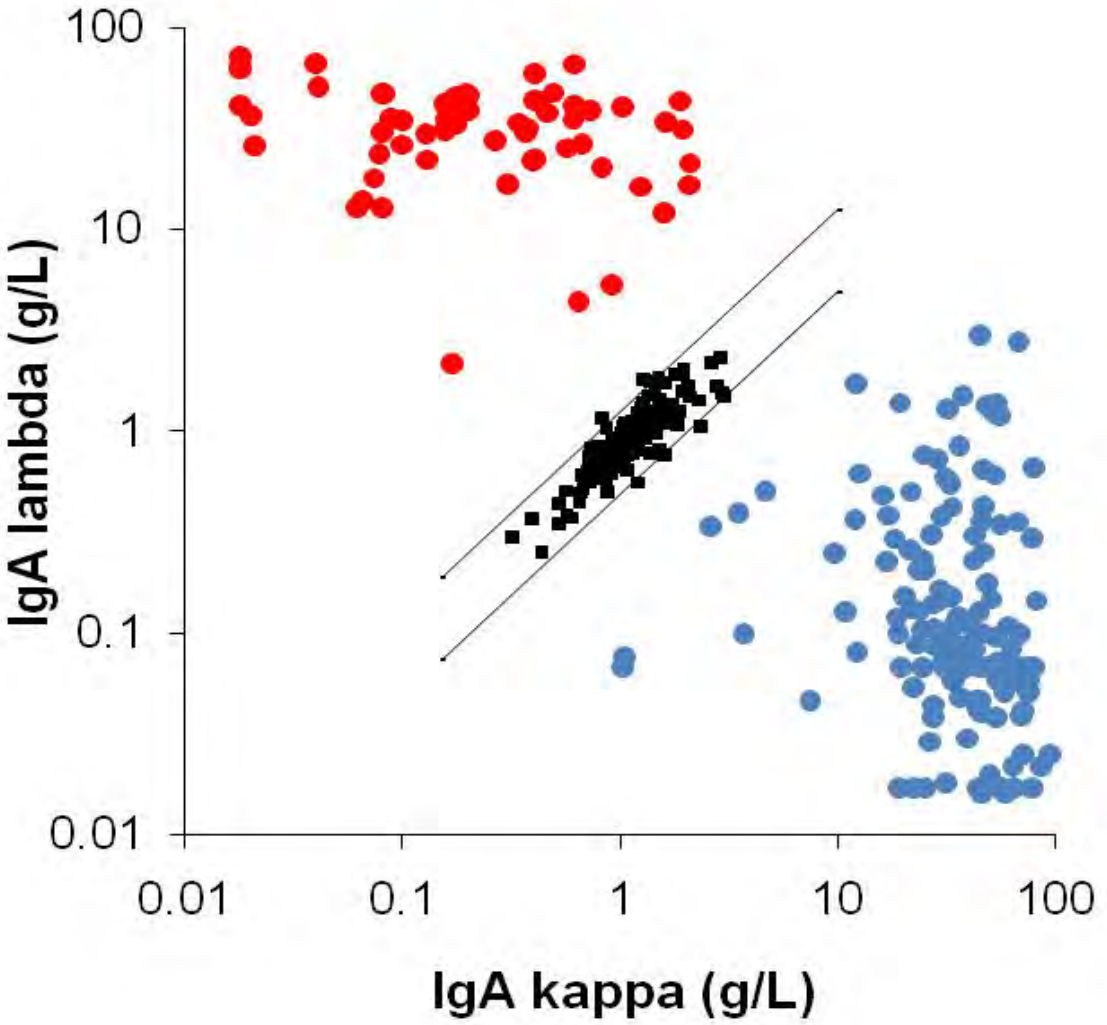
Immunoglobulin molecule and Hevylite (HLC) epitopes



Different heavy chain/light chain immunoglobulins



IgA Multiple Myeloma



Monitoring

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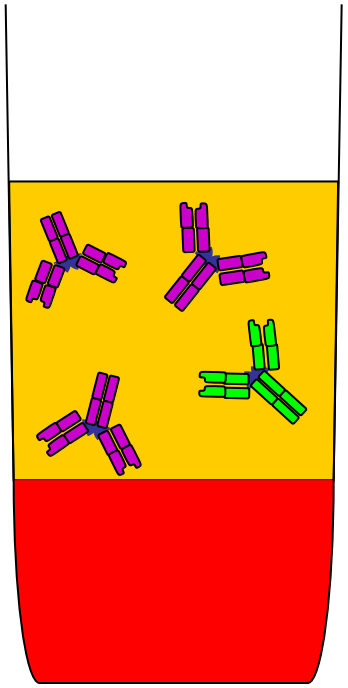
3. Scanning densitometry is not accurate
4. IgA bands may be hidden with transferrin
5. Haematocrit and plasma volume changes affect immunoglobulin measurements

Effect of volume changes on Ig' measurements

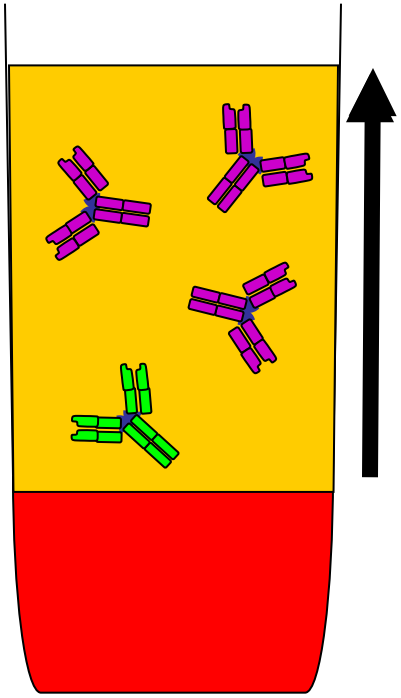
IgGκ- 50g/L

Ig'κ/Ig'λ
= 3/1



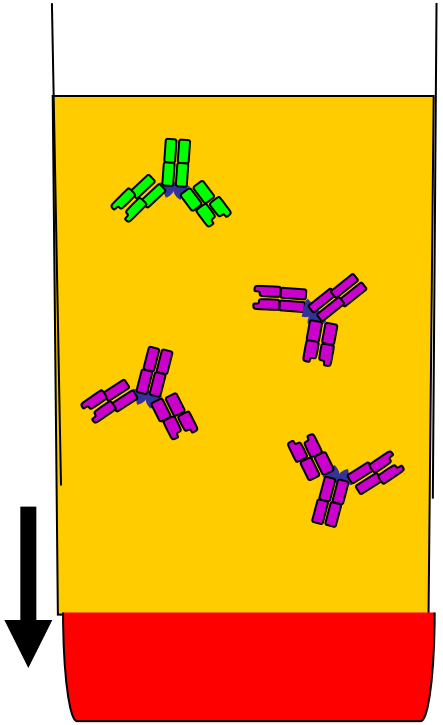
IgGκ- 30g/L

Ig'κ/Ig'λ
= 3/1

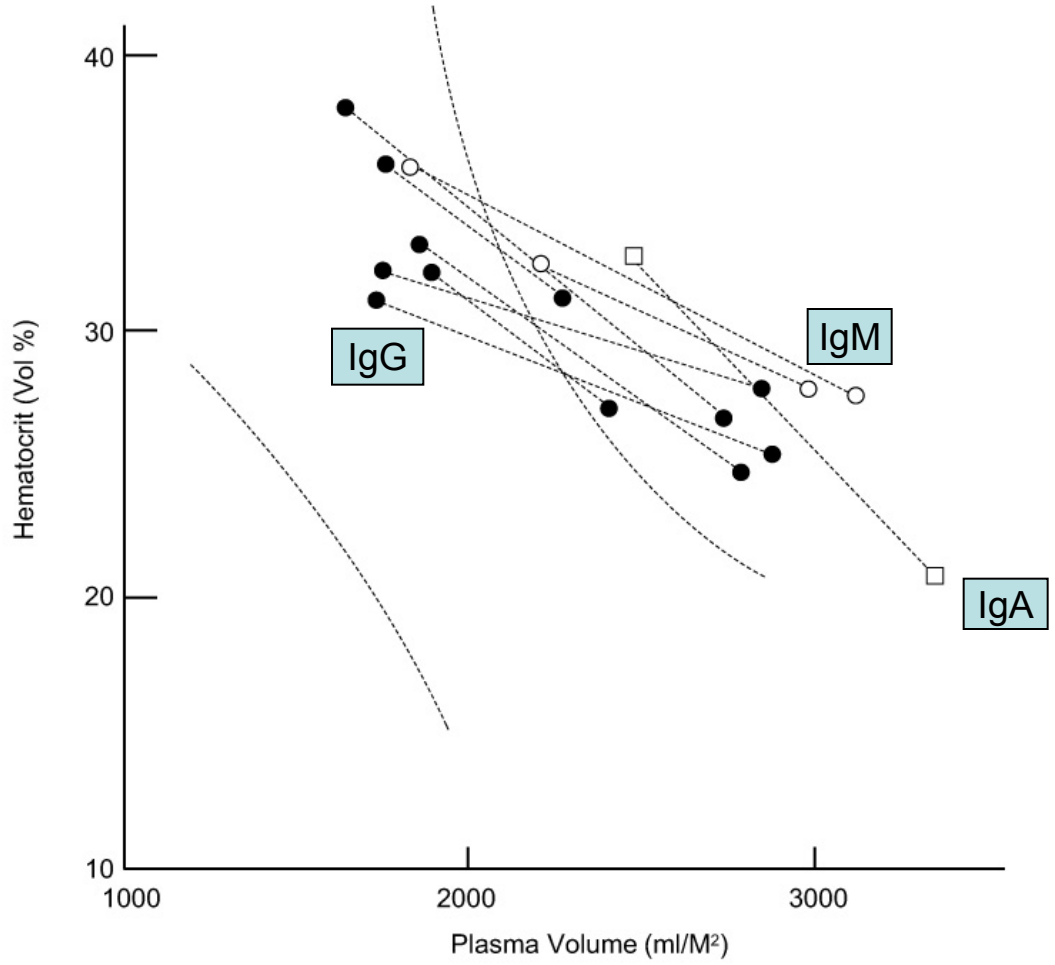


IgGκ- 20g/L

Ig'κ/Ig'λ
= 3/1



Relationship of monoclonal immunoglobulin changes to plasma volume and haematocrit



Alexanian. Blood 1977 **49**: 301-307

Problems with IgG, IgA and IgM assays

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2. Nephelometry measures the total immunoglobulin but the patient is Ig'κ or Ig'λ
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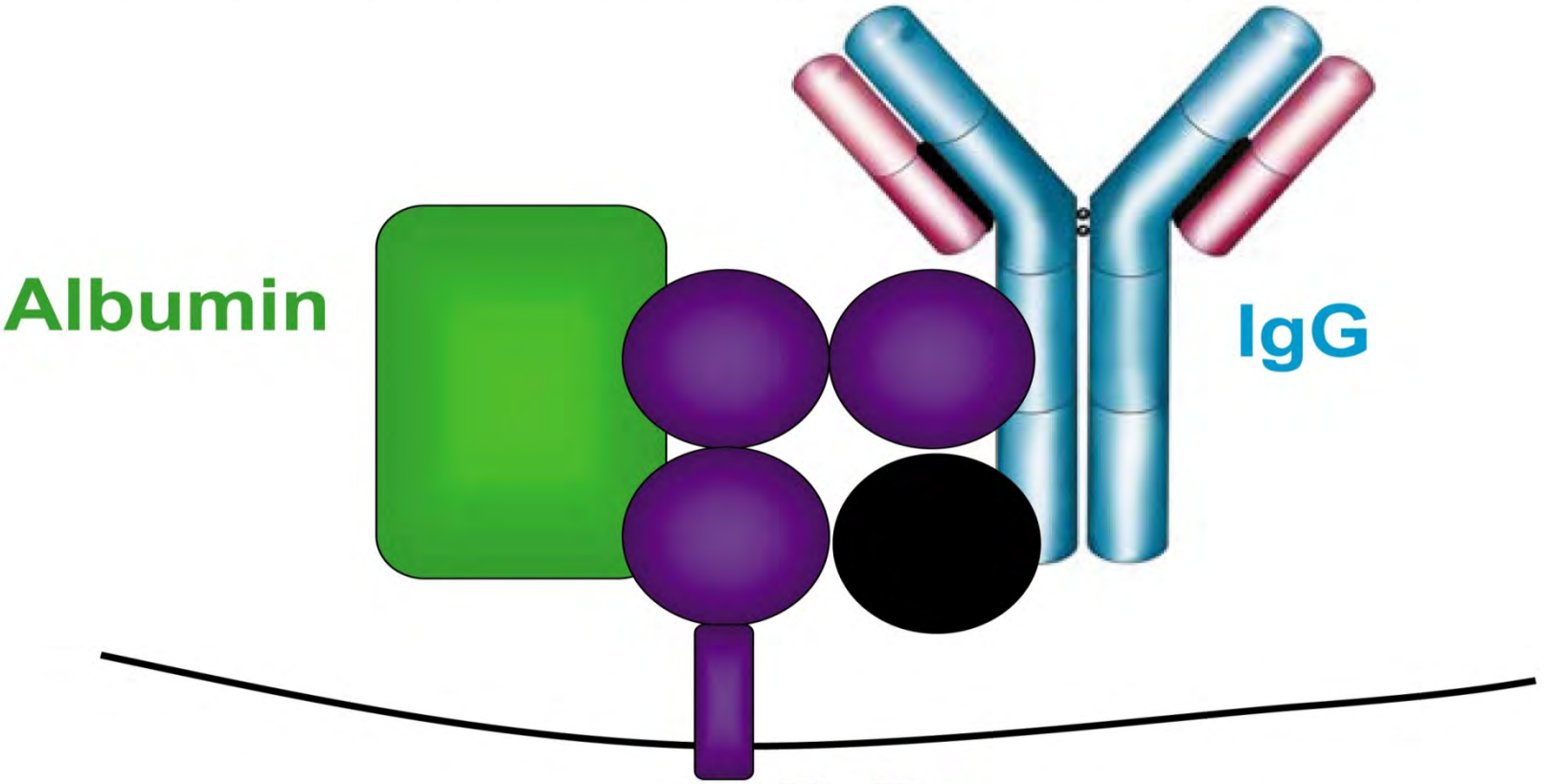
6. IgG metabolism is variable

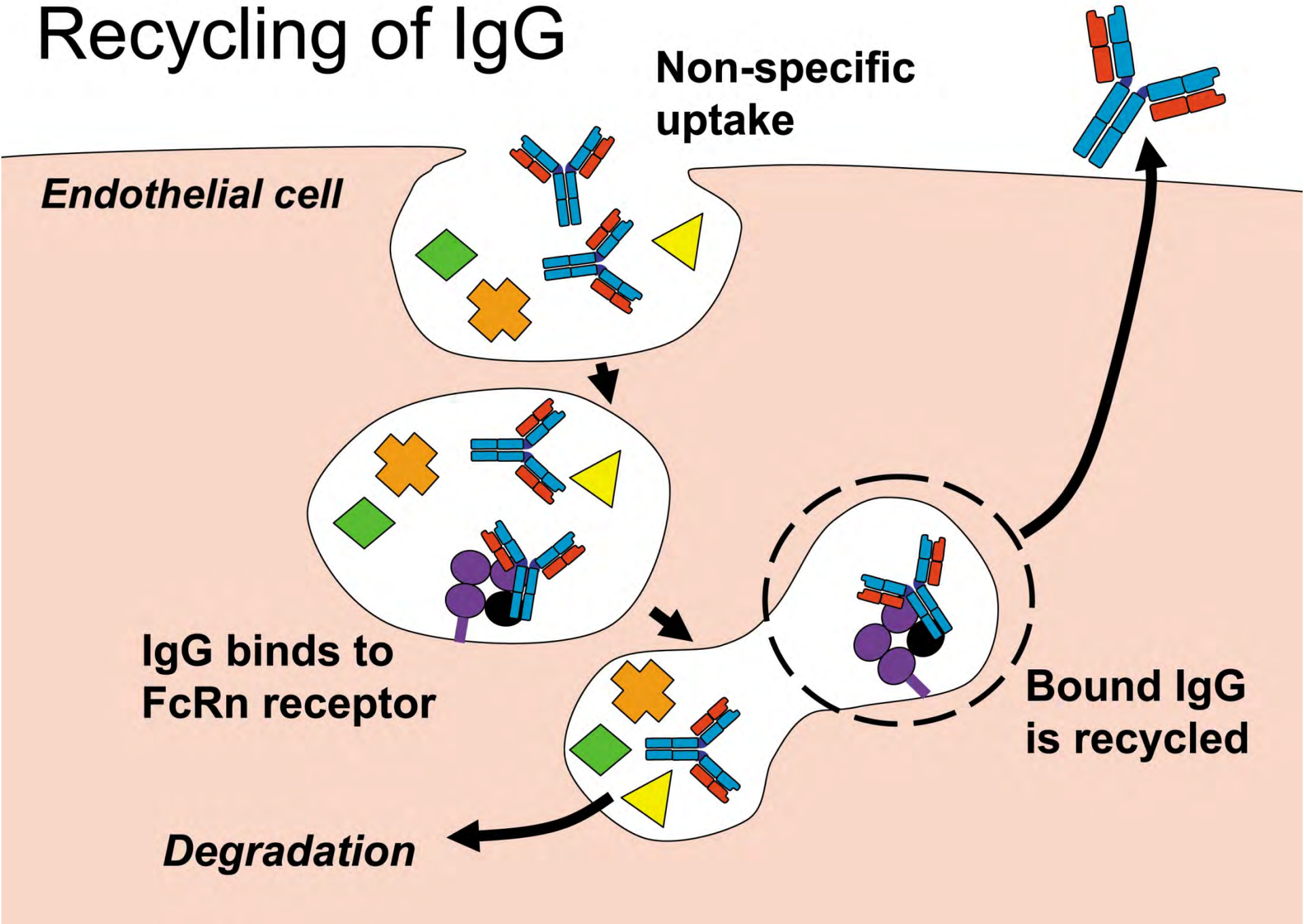
IgG metabolism is controlled by cellular recycling receptors

FcRn binds IgG and albumin



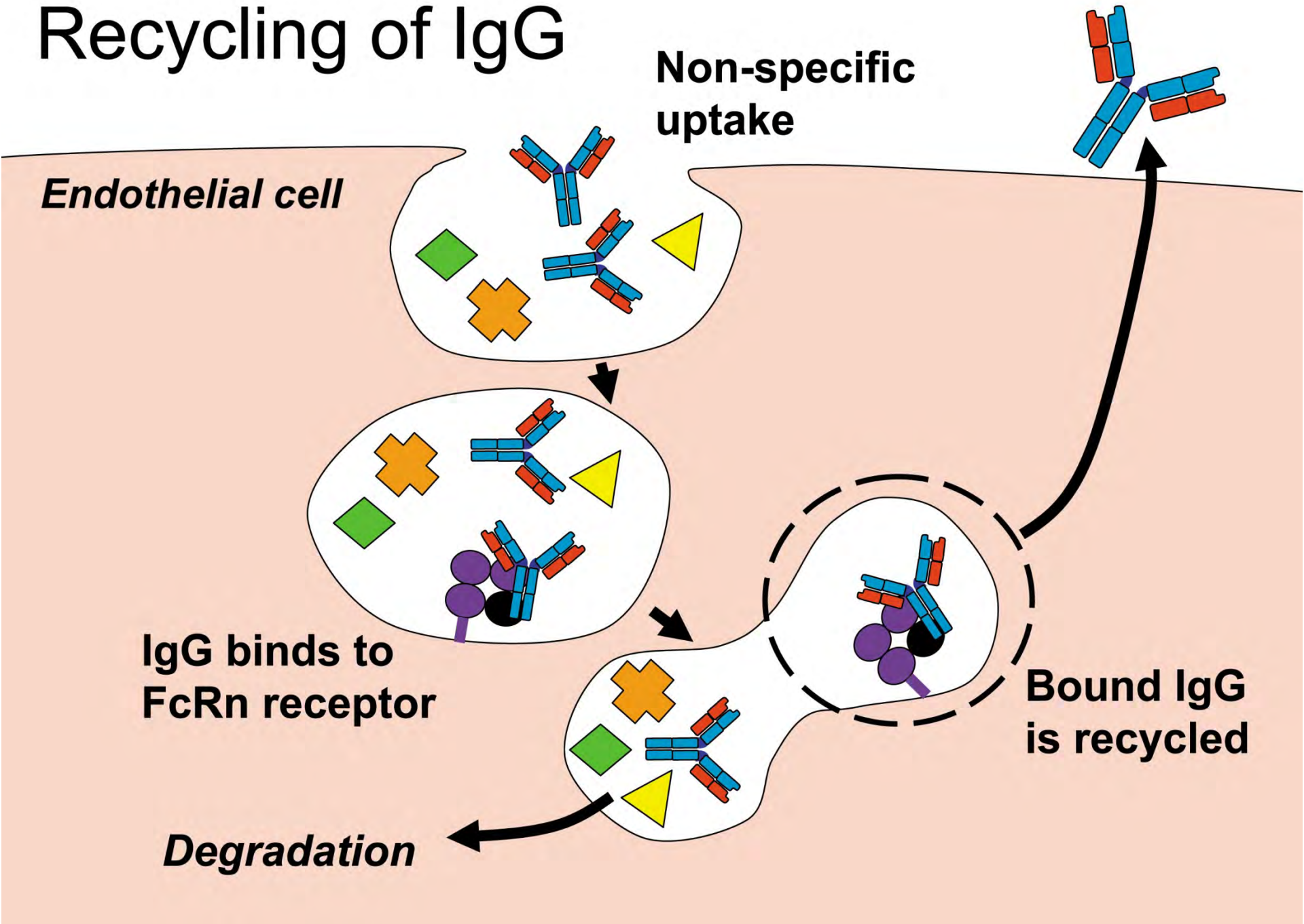
"Neonatal or Brambell receptor"

Recycling of IgG

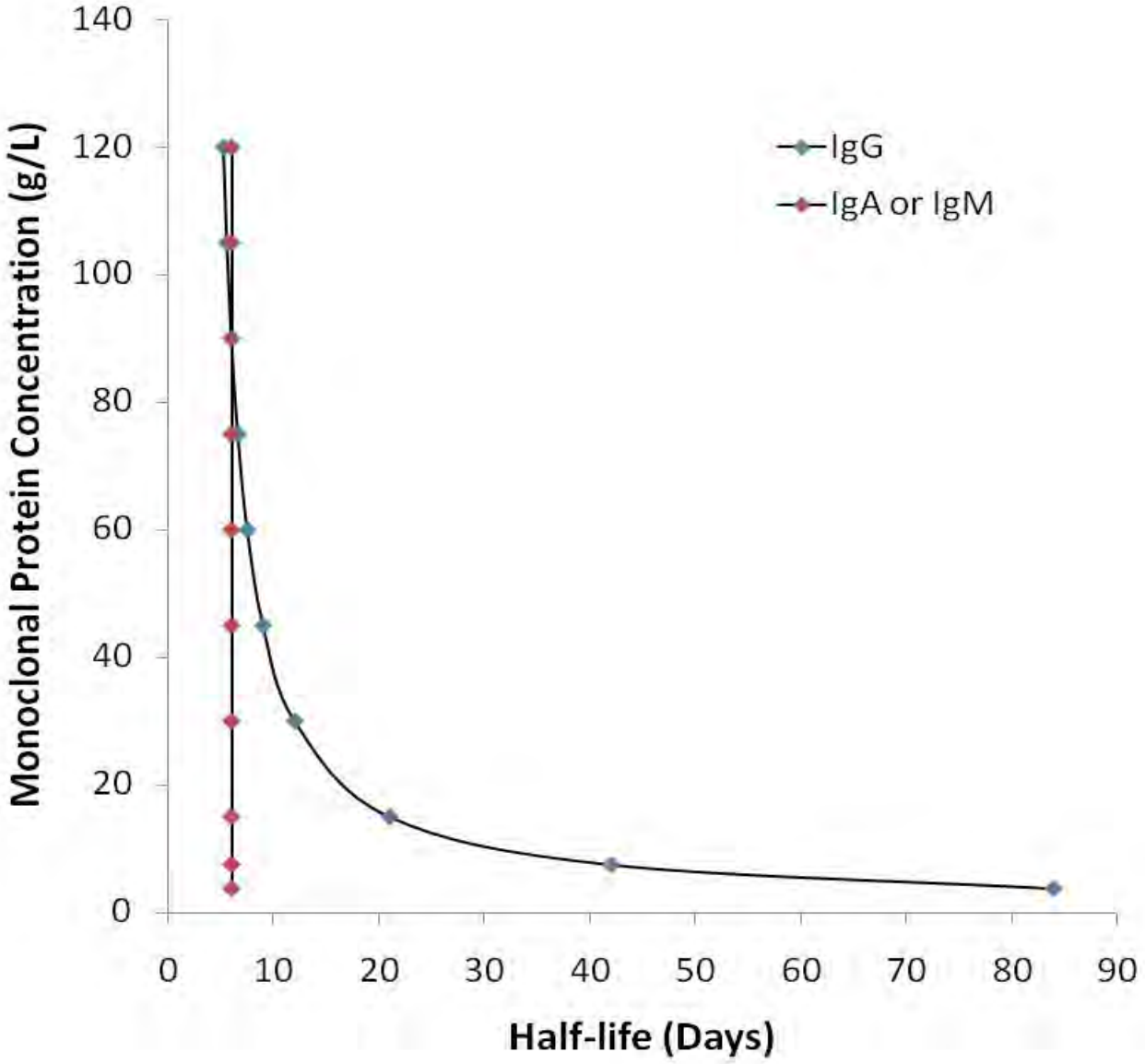


IgG FcRn receptors are saturated at normal IgG concentrations

Recycling of IgG



Relationship between immunoglobulin concentrations and serum half-life



Hence, % changes in IgG measurements depend upon the initial concentrations

For example:-

A patient with 100g/L of IgG and 100% tumour kill by chemo-therapy has an 80% fall of IgG in 15 days (100 to 20g/L)

A patient with 10g/L of IgG and 100% tumour kill by chemo-therapy has only a 20% fall of IgG in 15 days (10 to 8g/L)

Thus, comparison of reductions in IgG concentrations in patients is not reliable

What does a partial response really mean?

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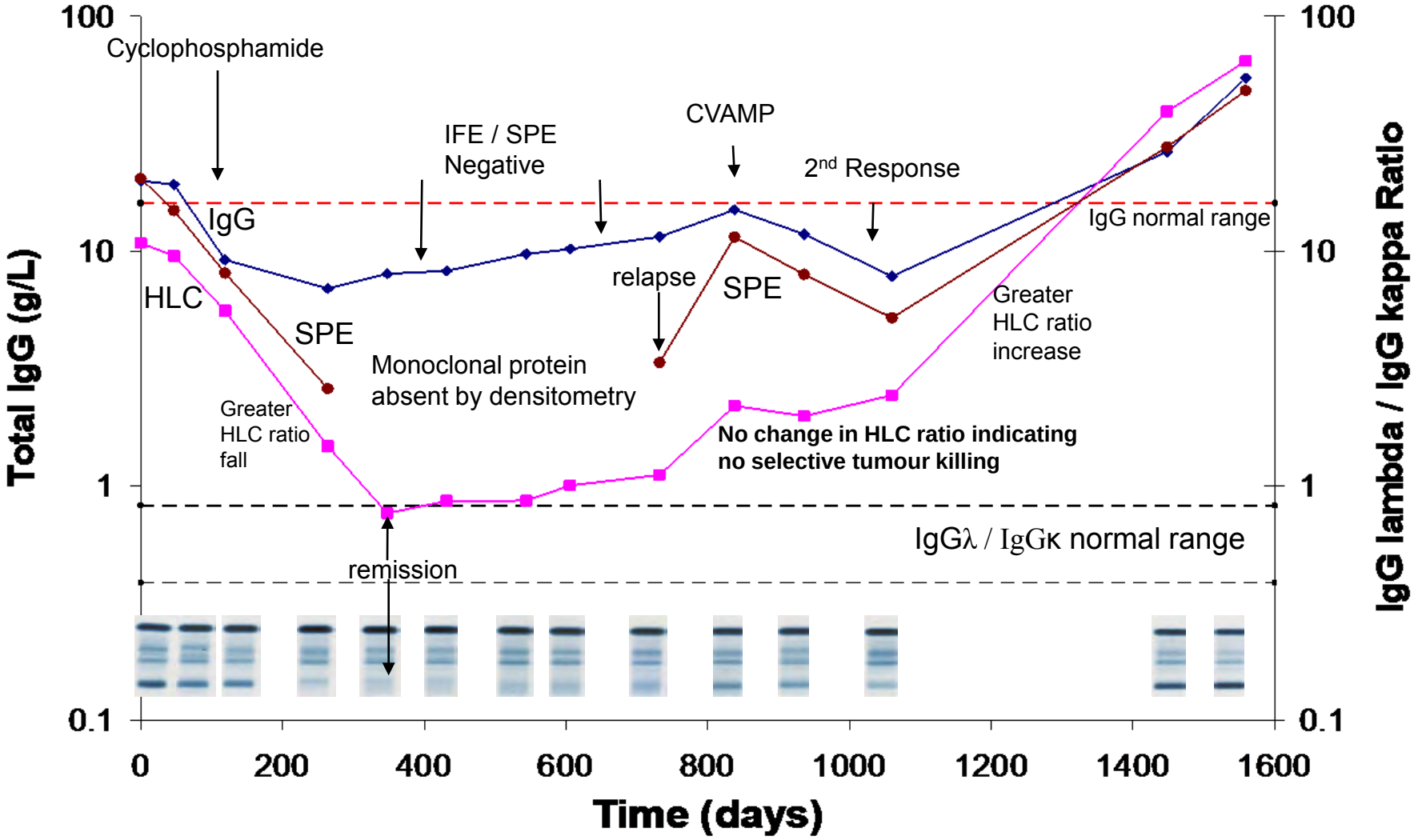

Bradwell et al. Clin Chem 2009

Prognosis

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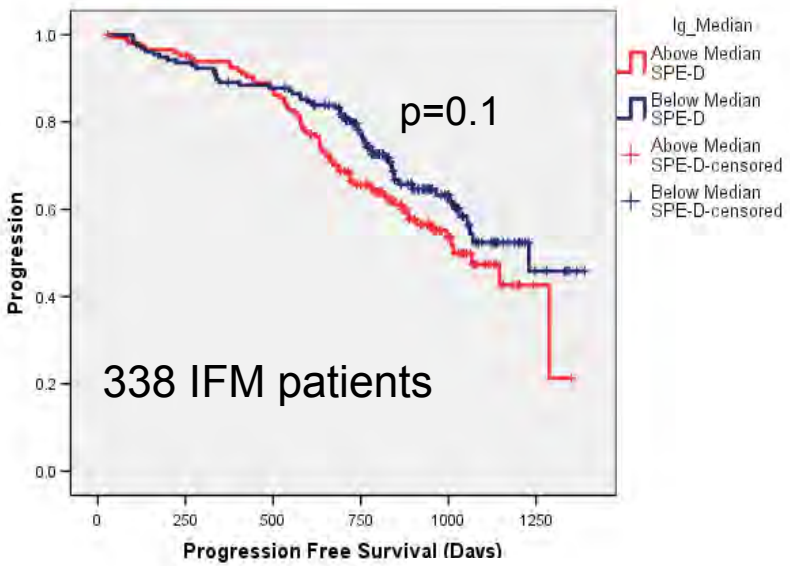
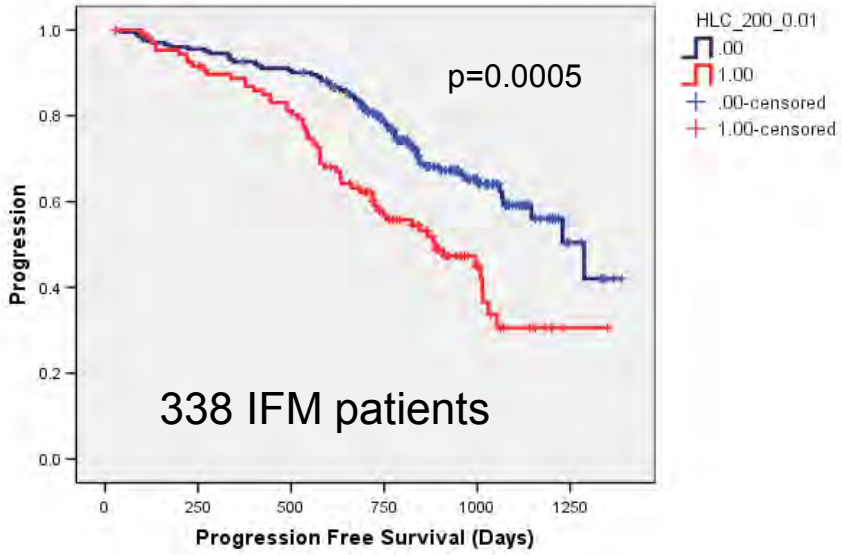
2. Nephelometry measures the total immunoglobulin but the patient is Ig'κ or Ig'λ
3. Scanning densitometry is not accurate
4. IgA bands may be hidden with transferrin
5. Haematocrit and plasma volume changes affect Immunoglobulin measurements
6. IgG metabolism is variable
7. Monoclonal IgG, IgA and IgM measurements have no prognostic value and are not in any guidelines

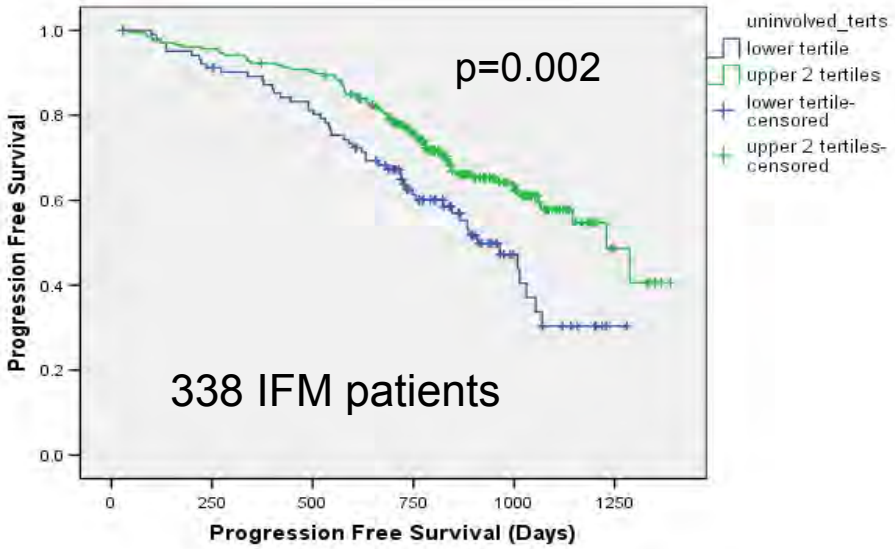
Monoclonal immunoglobulin concentrations



Hevylite ratios - 0.01>HLCr>200



Un-involved immunoglobulins



Comparison of prognostic factors in MM

Covariates	Univariate Analysis	Multivariate Analysis (n=242)
Del_13	0.03* (n=283)	0.546
T4_14	0.05* (n=252)	0.515
Del_17p	0.08 (n=277)	0.457
β_2M>5.5mg/L	0.51 (n=308)	0.407
β_2M>3.5mg/L	0.001* (n=308)	0.045*
Albumin<35g/L	0.153 (n=302)	0.828
FLC Tertiles	0.589 (n=307)	0.689
Monoclonal Tertiles**	0.16 (n=300)	0.748
200<HLC<0.01	0.017* (n=308)	0.001*

* $p<0.05$ is considered significant

**SPE densitometry measurement

Conclusions for Hevylite

1. **Diagnosis**: More sensitive than SPE and IFE in patients at presentation and with residual disease

2. **Monitoring**: Provides more accurate quantitation than SPE and IFE, particularly at low concentrations

3. **Prognosis**: Better than current markers

Acknowledgements

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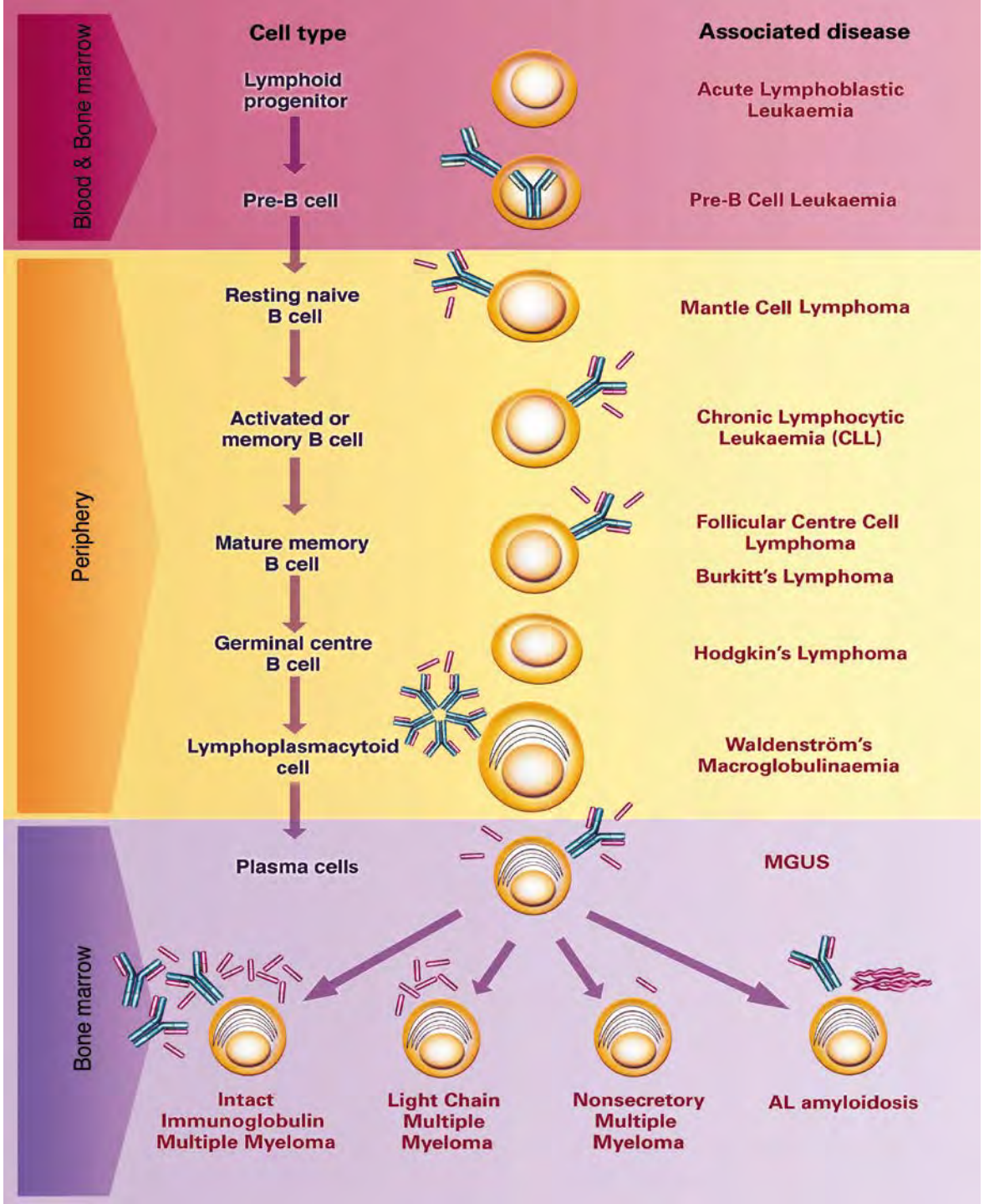
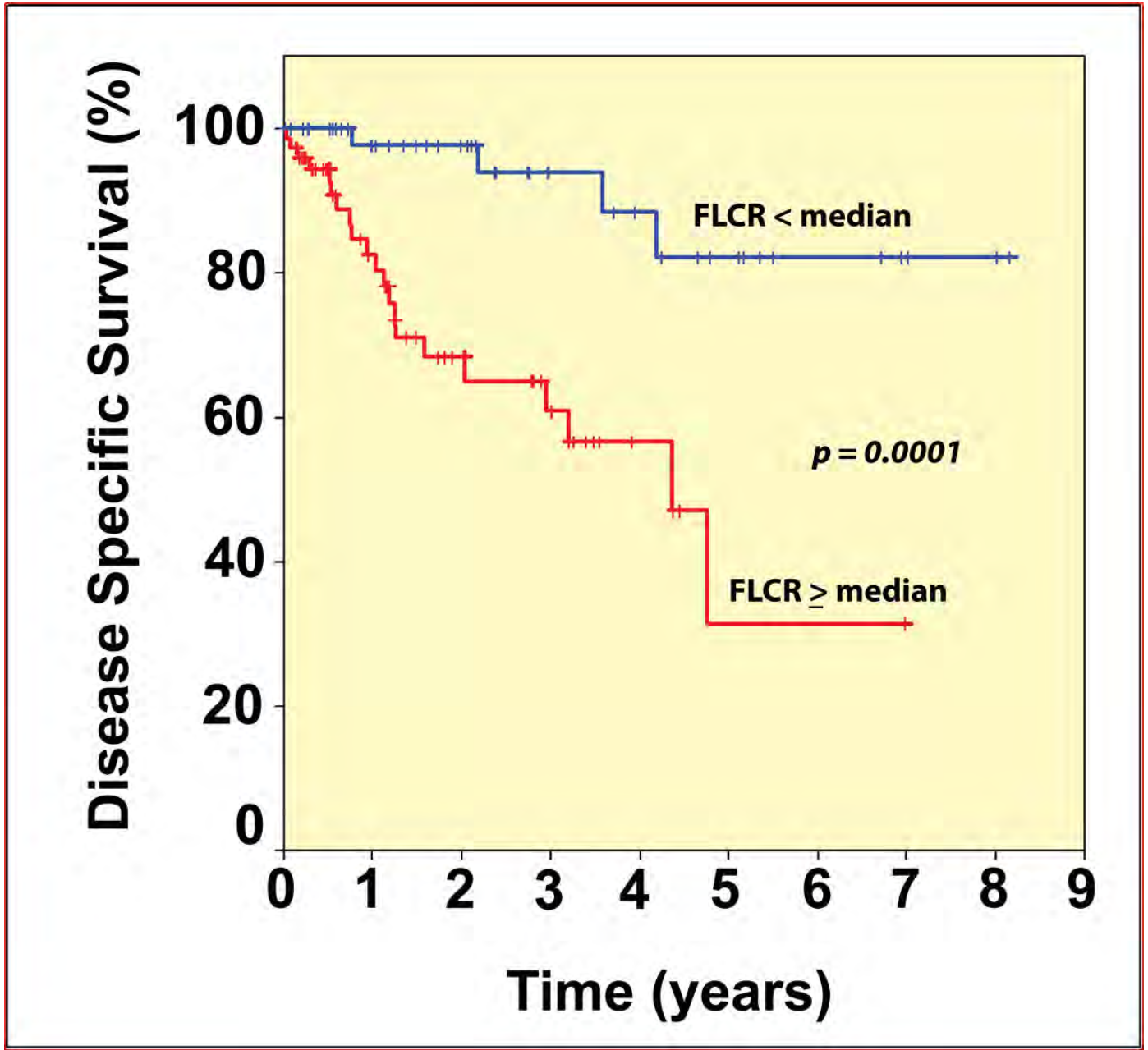
S Harding, H Carr-Smith, G Mead, P Showell,
J Overton and others at The Binding Site


Blood & Bone marrow
Cell type
Associated disease
Lymphoid progenitor
Acute Lymphoblastic Leukaemia
Pre-B cell
Pre-B Cell Leukaemia
Periphery
Resting naive B cell
Mantle Cell Lymphoma
Activated or memory B cell
Chronic Lymphocytic Leukaemia (CLL)
Mature memory B cell
Follicular Centre Cell Lymphoma
Burkitt's Lymphoma
Germinal centre B cell
Hodgkin's Lymphoma
Lymphoplasmacytoid cell
Waldenström's Macroglobulinaemia
Plasma cells
MGUS
Bone marrow
Intact Immunoglobulin Multiple Myeloma
Light Chain Multiple Myeloma
Nonsecretory Multiple Myeloma
AL amyloidosis

What makes a good cancer test?

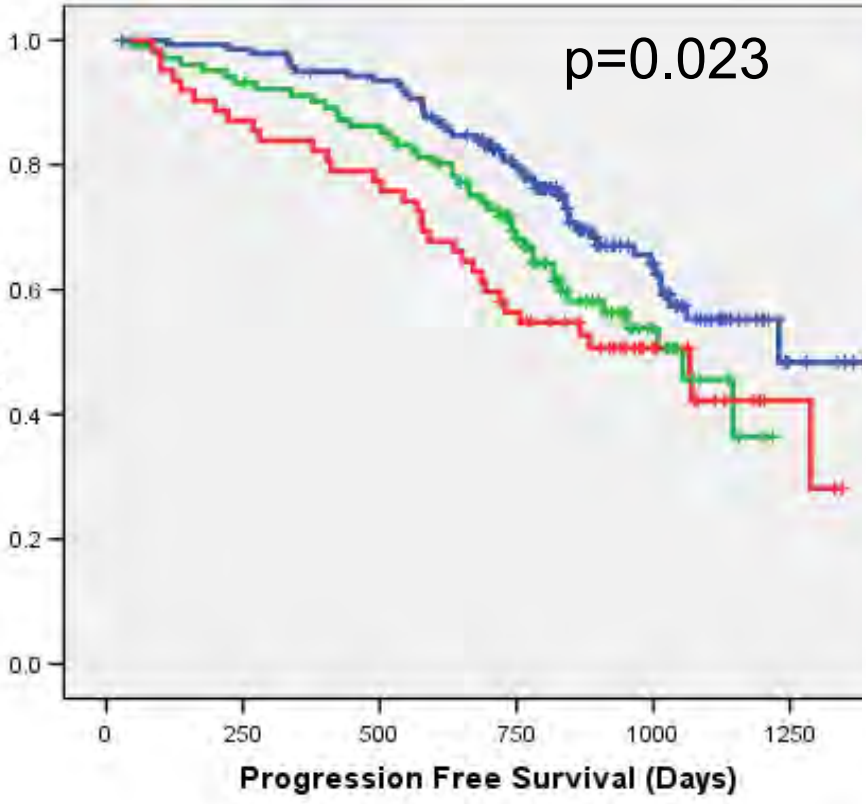
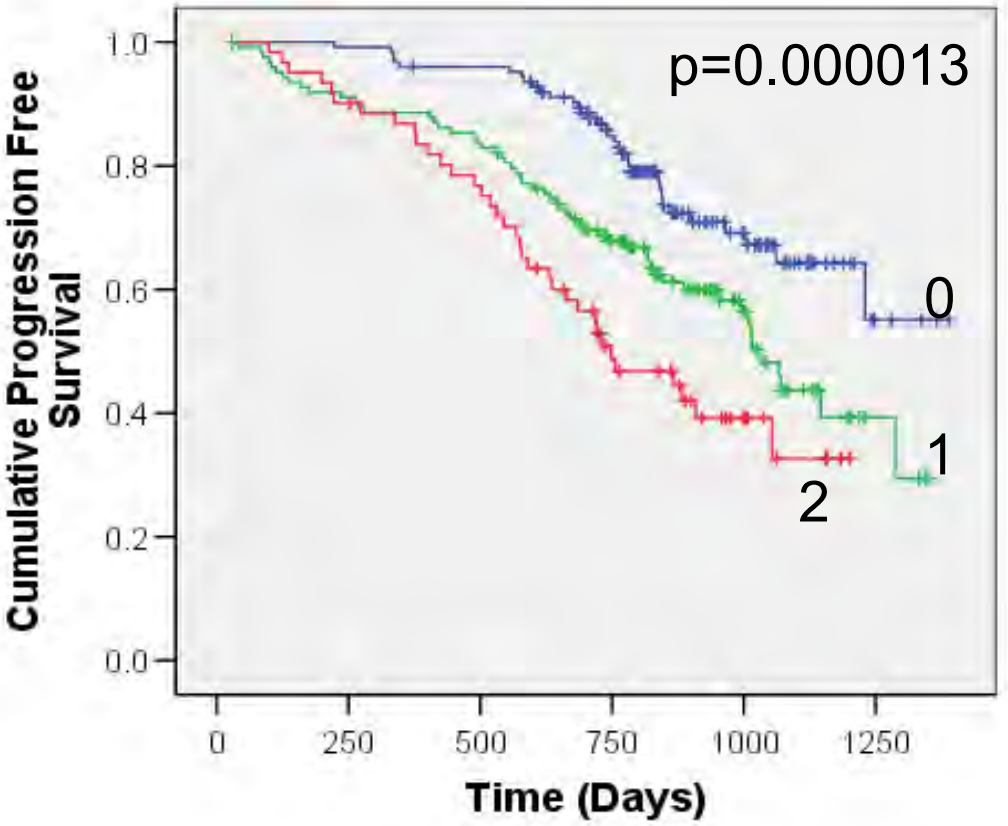
1. Diagnosis – sensitive and specific
2. Monitoring – quantitative and reproducible
3. Prognostic

sFLCs at myeloma presentation are prognostic



ISS for progression in 338 IFM patients

β2m+albumin



β2m+hevylite ratio