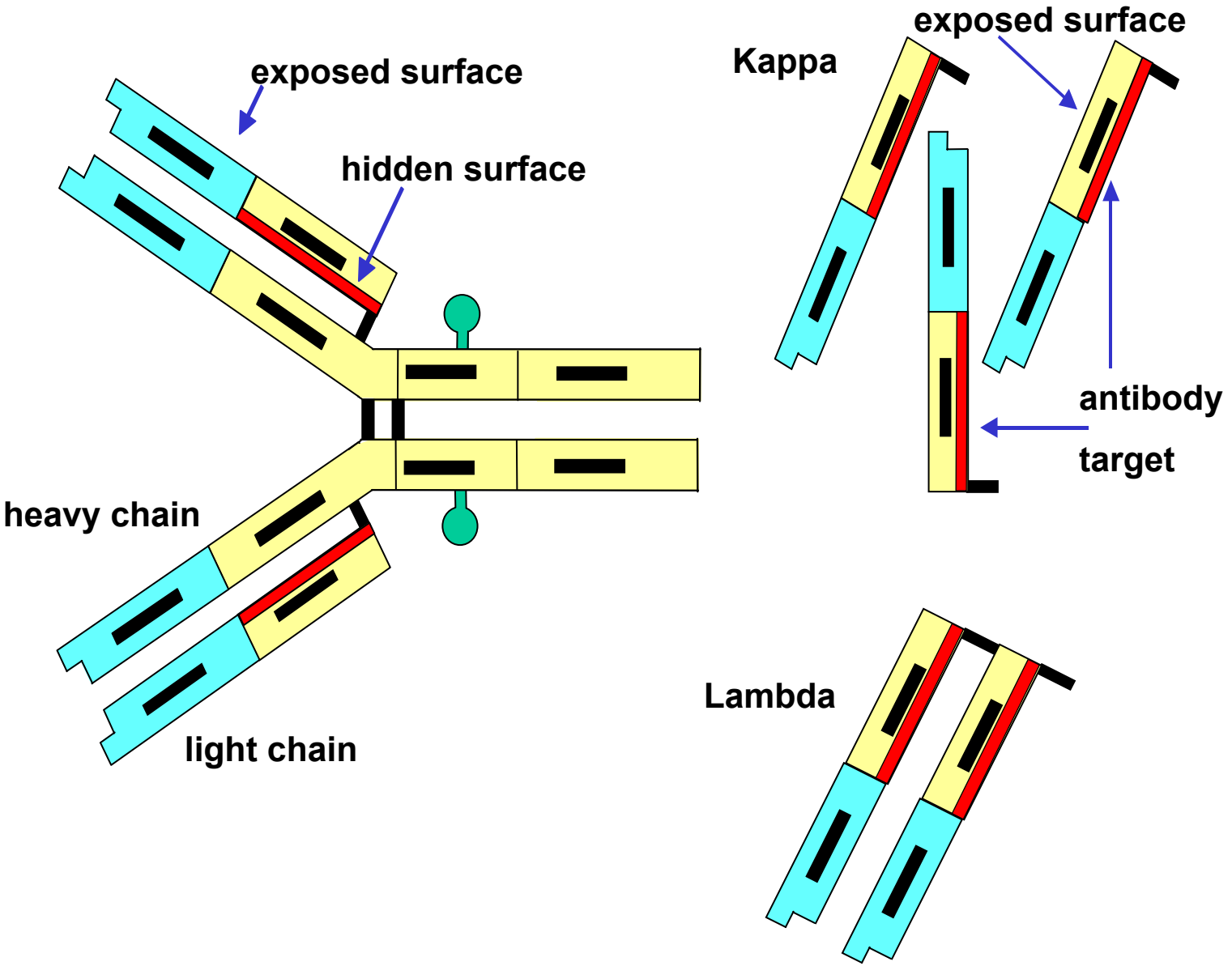
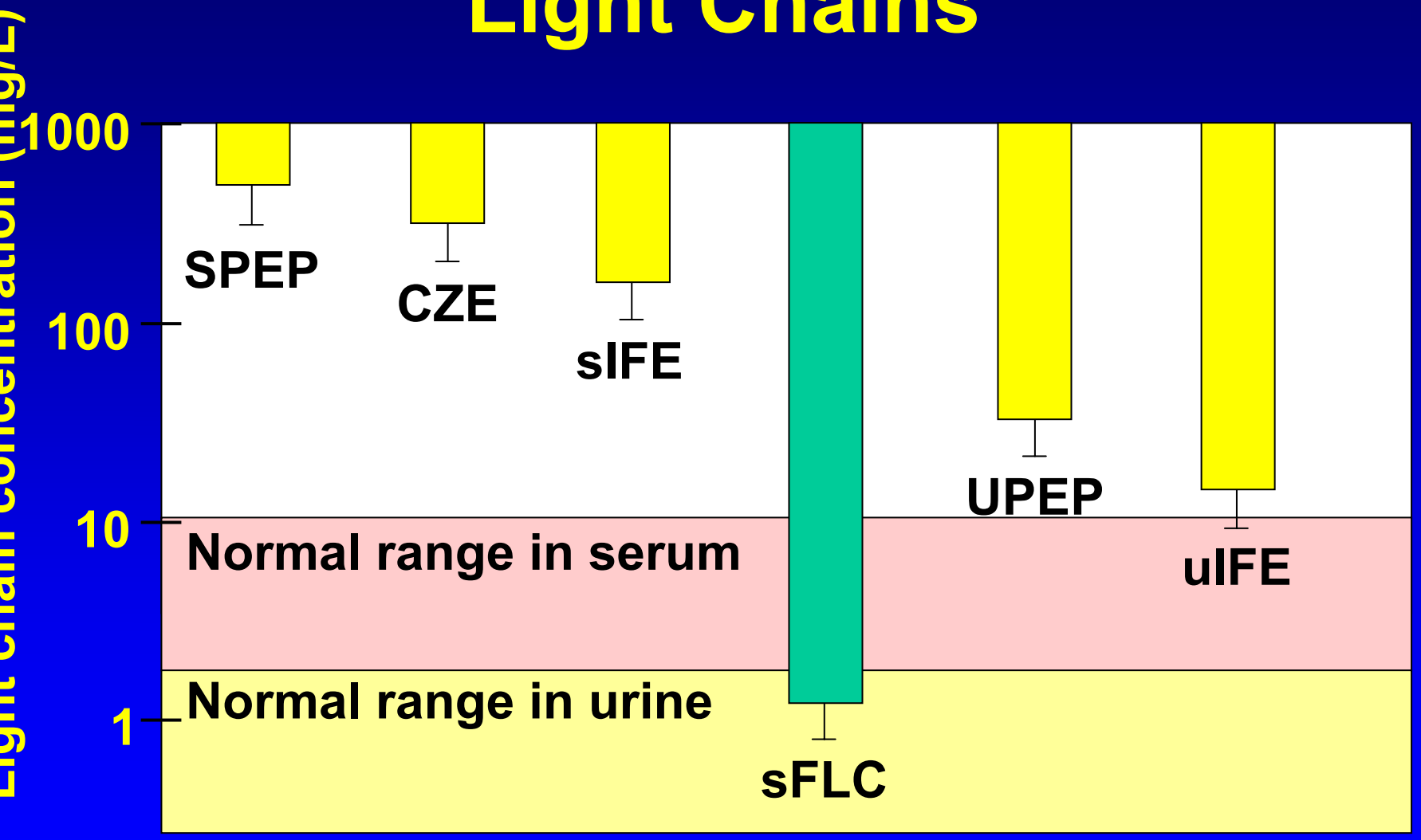
Serum Free Light Chain Measurement: Recent Developments

Graham Mead
(University of Birmingham
and The Binding Site)


exposed surface
hidden surface
heavy chain
light chain
exposed surface
Kappa
antibody
target
Lambda

Sensitivity of Assays for Light Chains

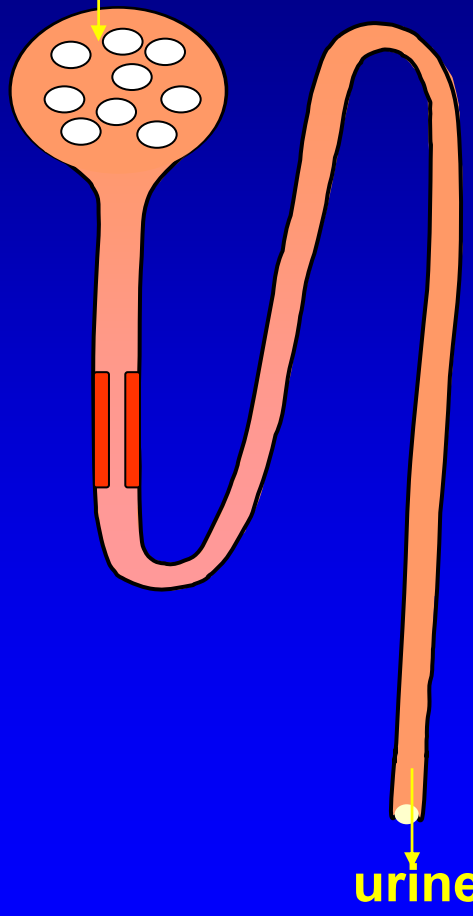


FLC - monomer 25 kDa

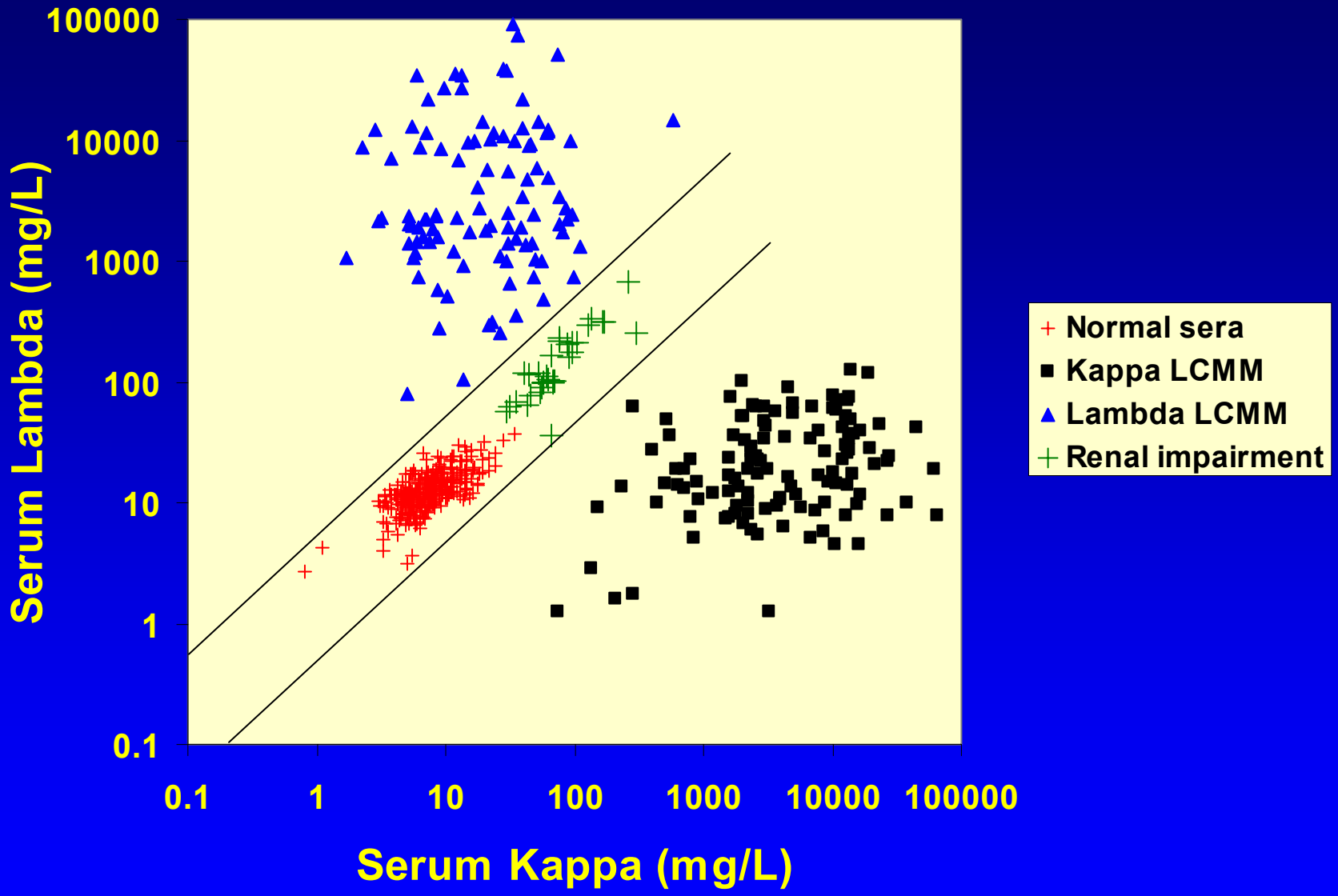
dimer 50 kDa

Glomerulus
40 kDa
pores

10-30g/day
reabsorption



urine



Lancet 2003; **361**: 489-49

AL Amyloidosis

> 25 Articles

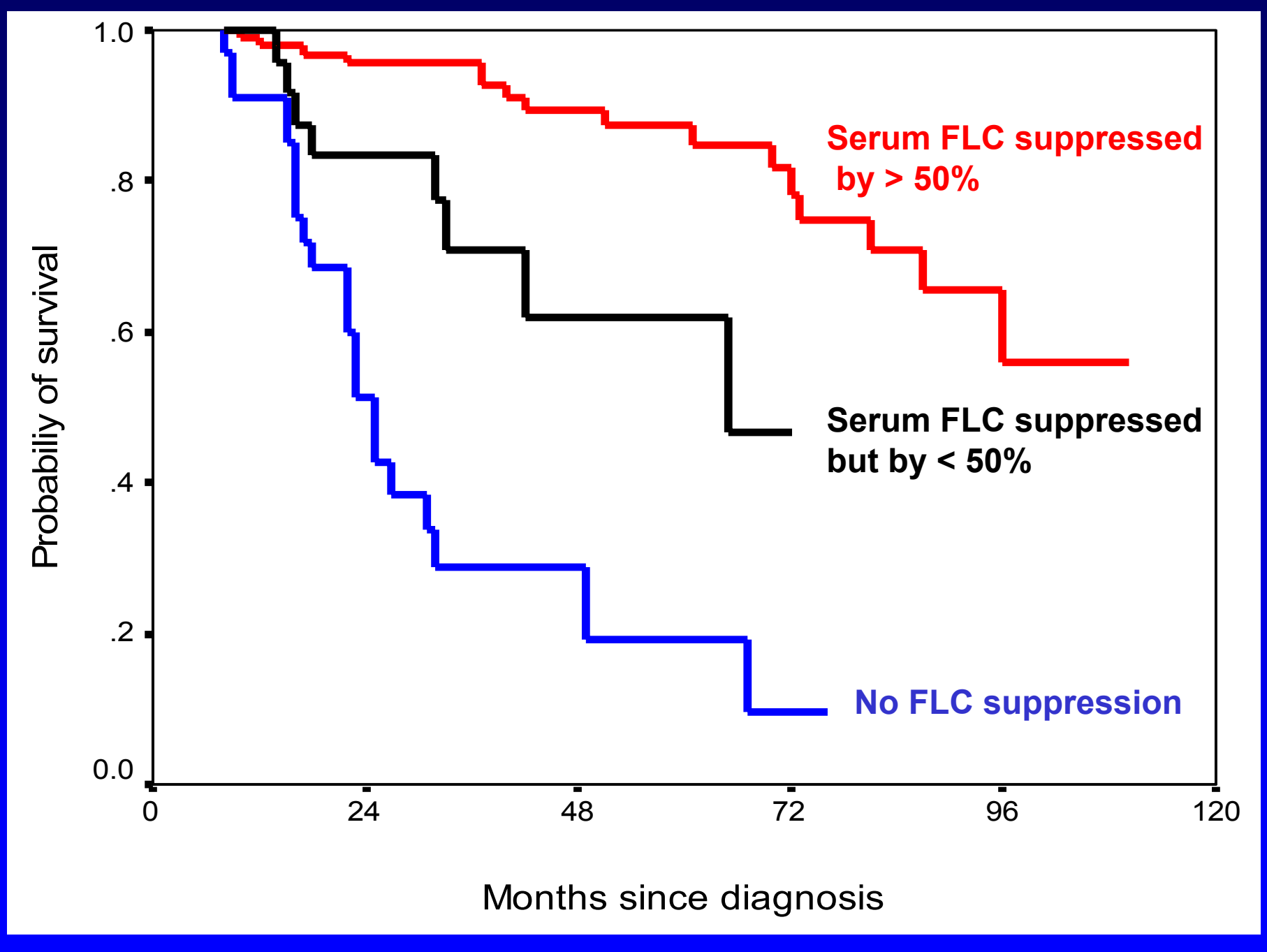
> 60 Abstracts

Guidelines on the diagnosis and management of AL amyloidosis.

British Journal of Haematology
2004; **125** (6), 681-700.

Gertz, M.A. *et al.* (2005). Consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis.

American Journal of Hematology 79, 319-328.


1.0
.8
.6
.4
.2
0.0
Probabiliy of survival
0
24
48
72
96
120
Months since diagnosis
Serum FLC suppressed by > 50%
Serum FLC suppressed but by < 50%
No FLC suppression

Sanchorawala *et al* Bone Marrow Transplantation. 2005; 36: 597-600.

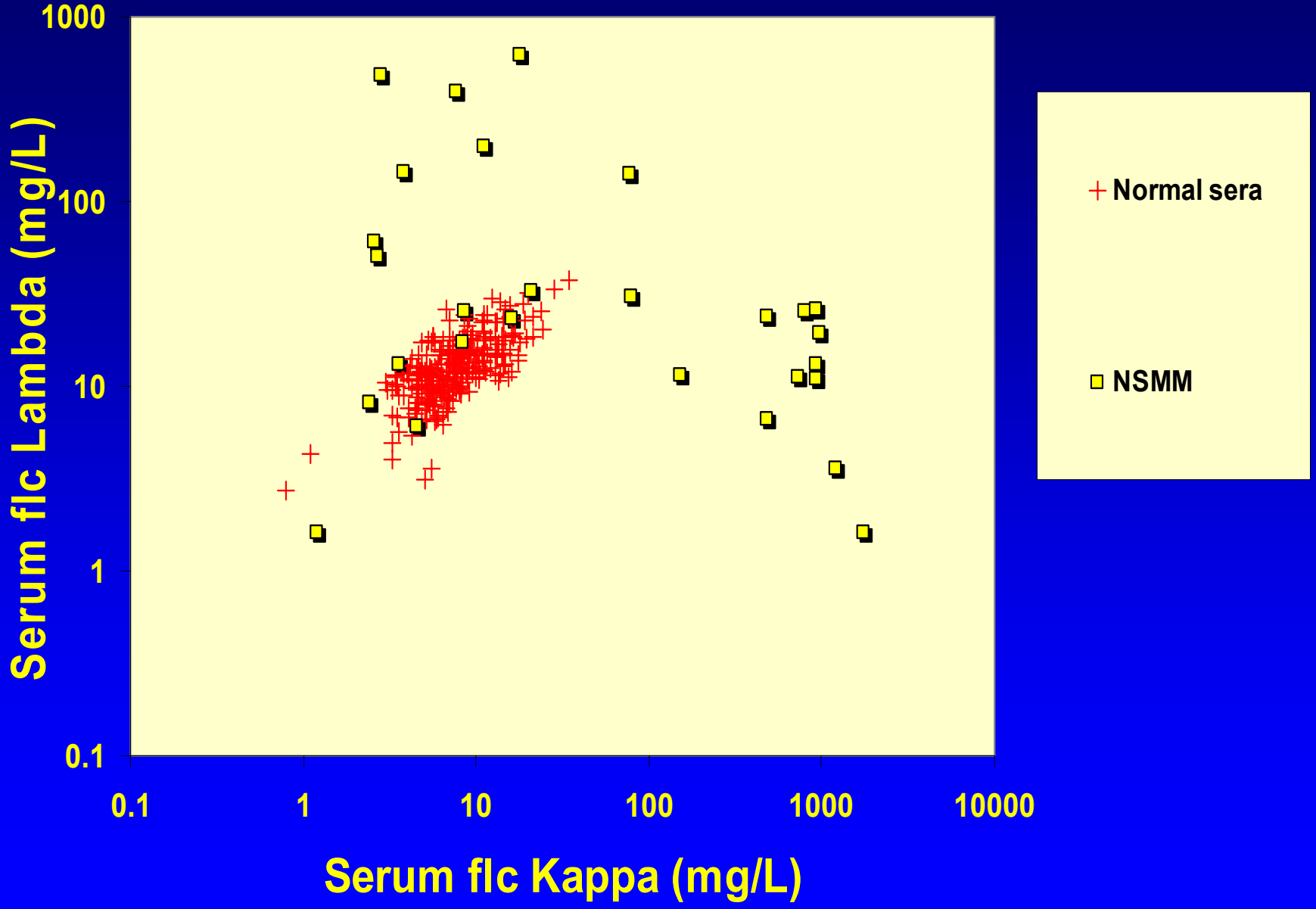
>90% reduction in FLC required for improved prognosis

Dispenzieri *et al* Blood. 2006; 107: 3378-3383.

% reduction did not predict survival, absolute level of FLC did.

Nonsecretory multiple myeloma

*Blood 2001; **97**: 2900-2902*



Blood 2001; 97: 2000-200

Light chain only multiple myeloma (Bence Jones myeloma)

*Lancet 2003; **361**: 489-491*

International uniform response criteria for Multiple Myeloma

Durie, B.G. *et al.* Leukemia (2006):

- "Incorporation of response criteria for the serum FLC assay to enable assessment of response in patients with non- or oligo-secretory disease"

- Stringent CR (sCR) requiring normal FLC (in addition to normal bone marrow and negative immunofixation)

Screening for lymphoproliferative disorders

Bakshi, N.A. *et al* (2005). Am J Clin Pathol *124*, 214-218. *9/1003 extra confirmed disorders*

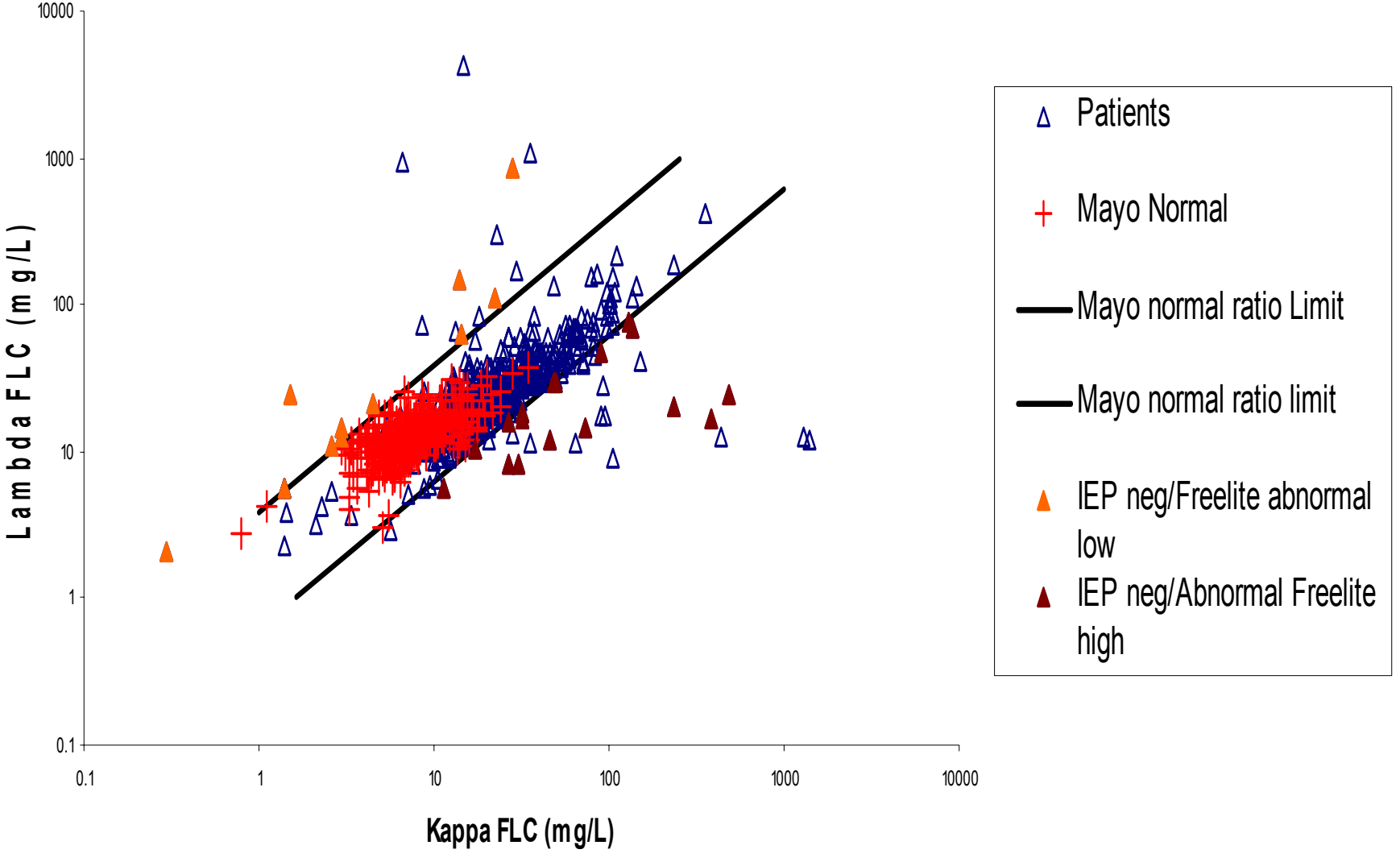
Abadie, J.M., and Bankson, D.D. (2006). Annals of Clinical & Laboratory Science *36*, 157-162. *20/312 extra disorders*

Hill, P.G. *et al* (2006). Clin Chem. *52*, 1-6.
No "significant pathology" missed if urine tests replaced by serum (370/923)

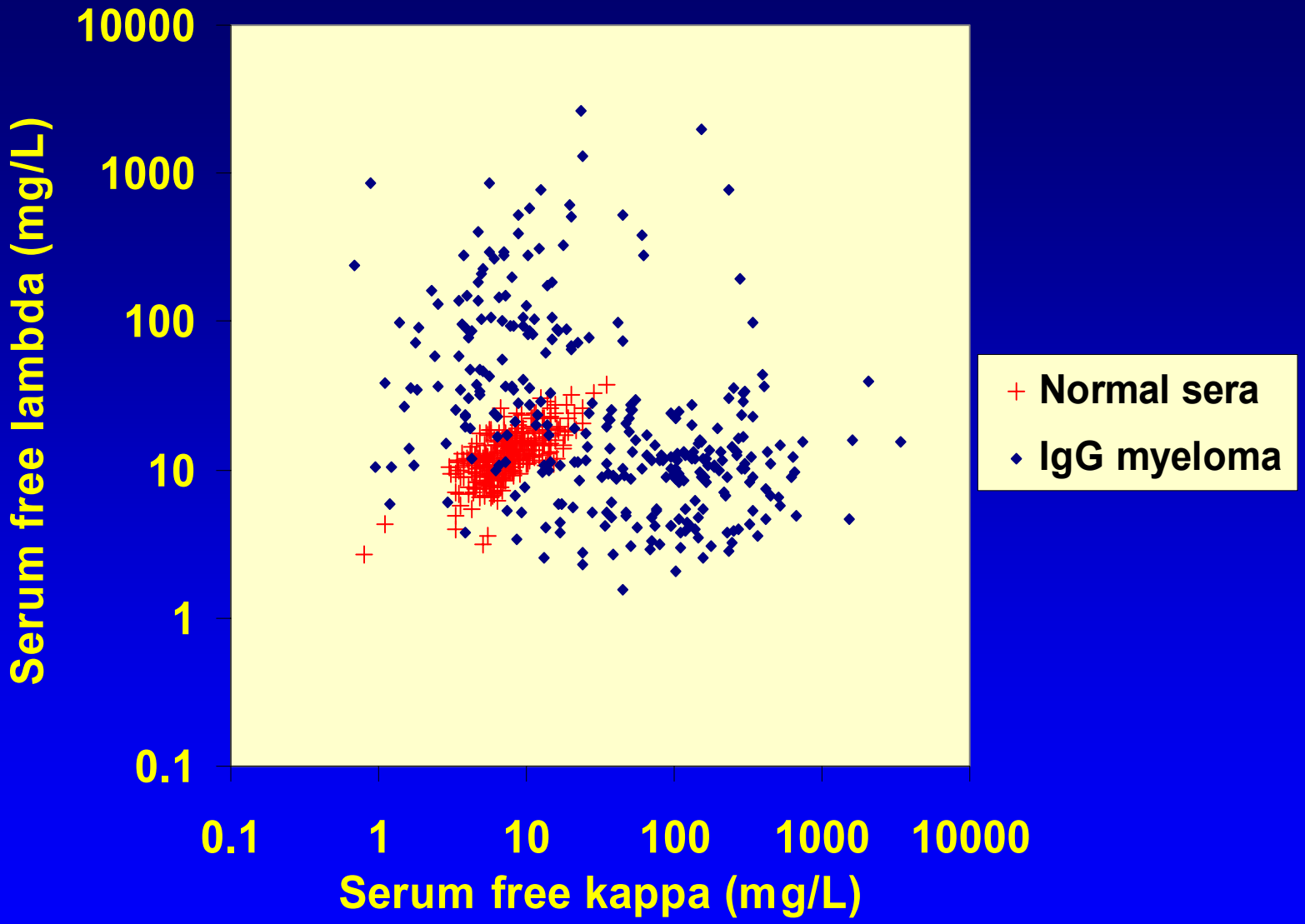
Katzmann J.A. *et al* (2006). Mayo Clin Proc. 81, 1575-8.
Elimination of the need for urine diagnostically

Laboratory test	No. abnormal
Urine IFE	428
Serum IFE	400
Serum PE	346
Serum FLC κ/λ ratio	367
Serum IFE or FLC ratio	426

Katzmann et al; Mayo Clinic Proceedings. 2006; 81 1575-1578

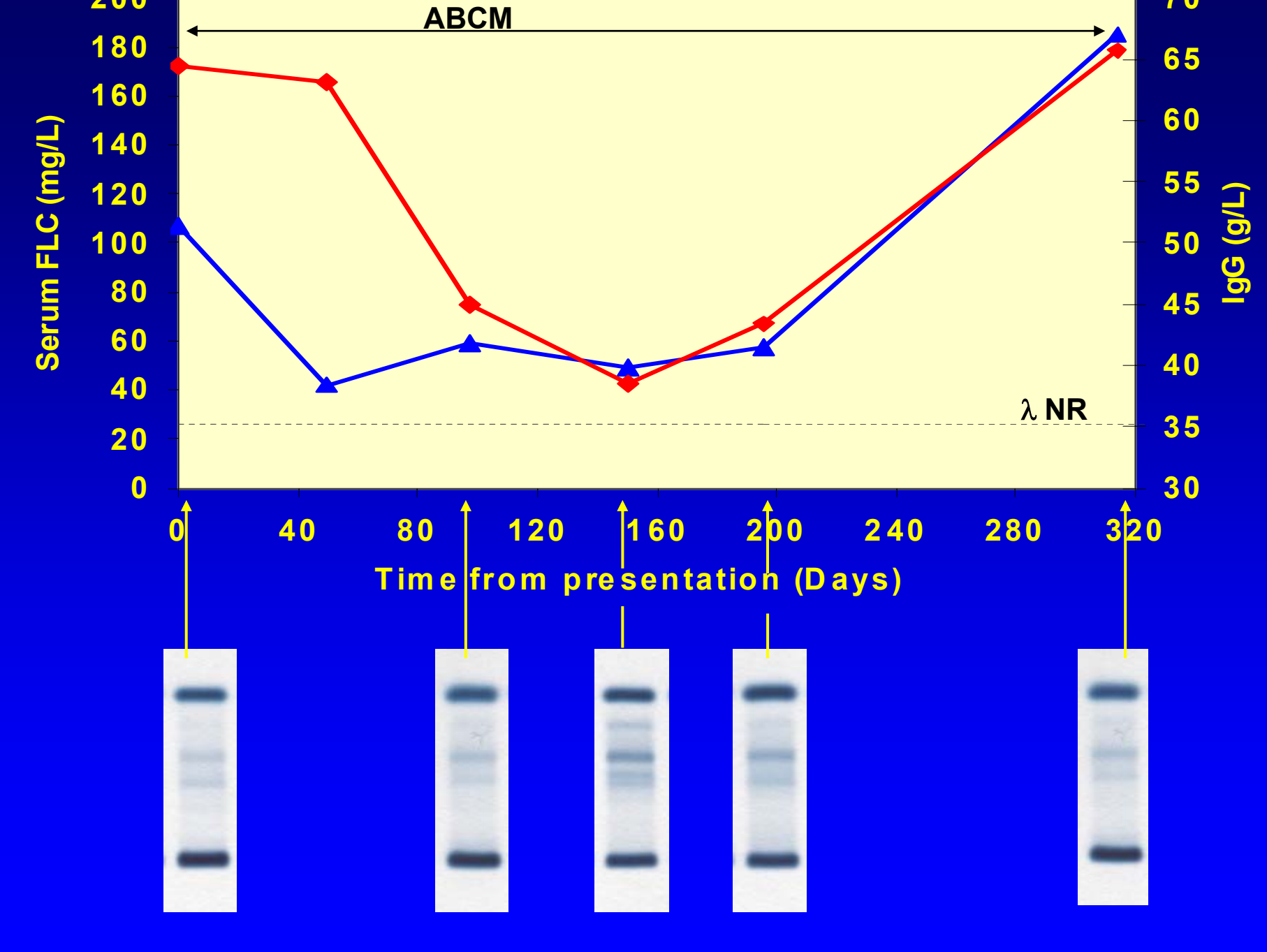

10000
1000
100
10
1
0.1
Lambda FLC (mg/L)
0.1
1
10
100
1000
10000
Kappa FLC (mg/L)
Patients
Mayo Normal
Mayo normal ratio Limit
Mayo normal ratio limit
IEP neg/Freelite abnormal low
IEP neg/Abnormal Freelite high

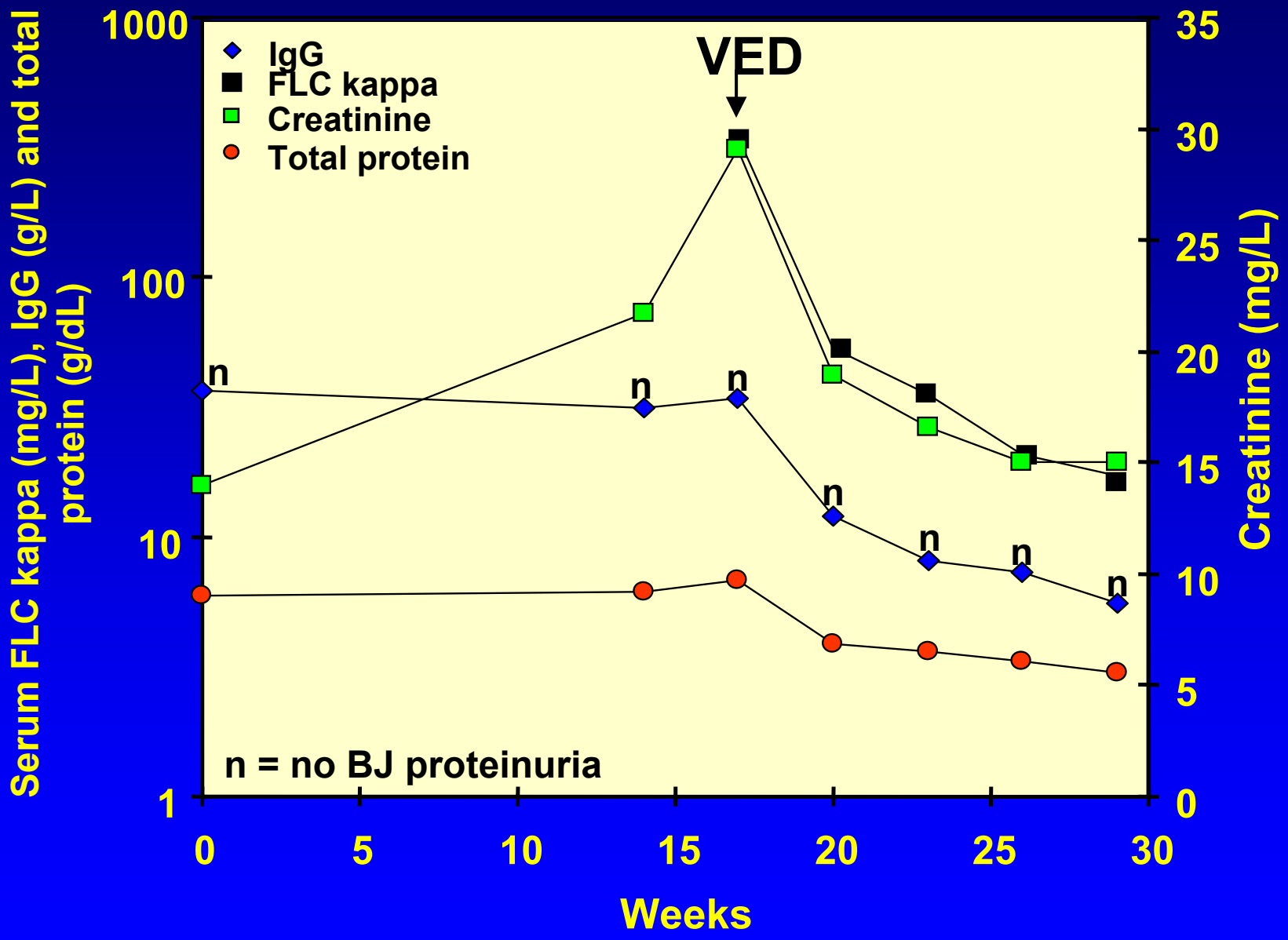
Intact immunoglobulin multiple myeloma

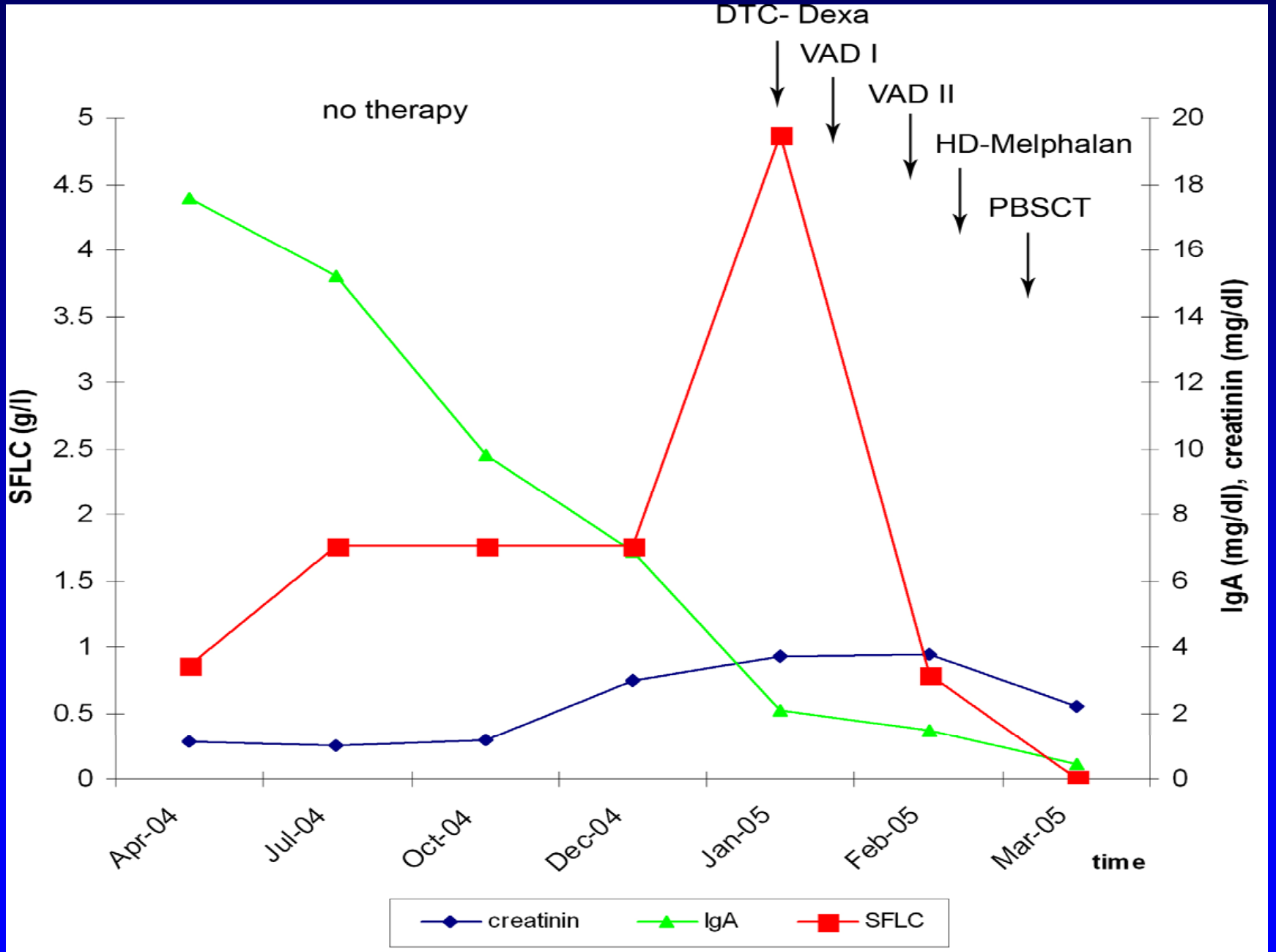

10000
1000
100
10
1
0.1
Serum free lambda (mg/L)
0.1
1
10
100
1000
10000
Serum free kappa (mg/L)
Normal sera
IgG myeloma

Addition of FLC assays for monitoring intact imunoglobulin myeloma

- Fast response markers
- Forewarning of renal impairment
- Detecting light chain “escape”
- Prognostic at presentation?


ABCM
λ NR
Serum FLC (mg/L)
IgG (g/L)
0
20
40
60
80
100
120
140
160
180
30
35
40
45
50
55
60
65
0
40
80
120
160
200
240
280
320
Time from presentation (Days)

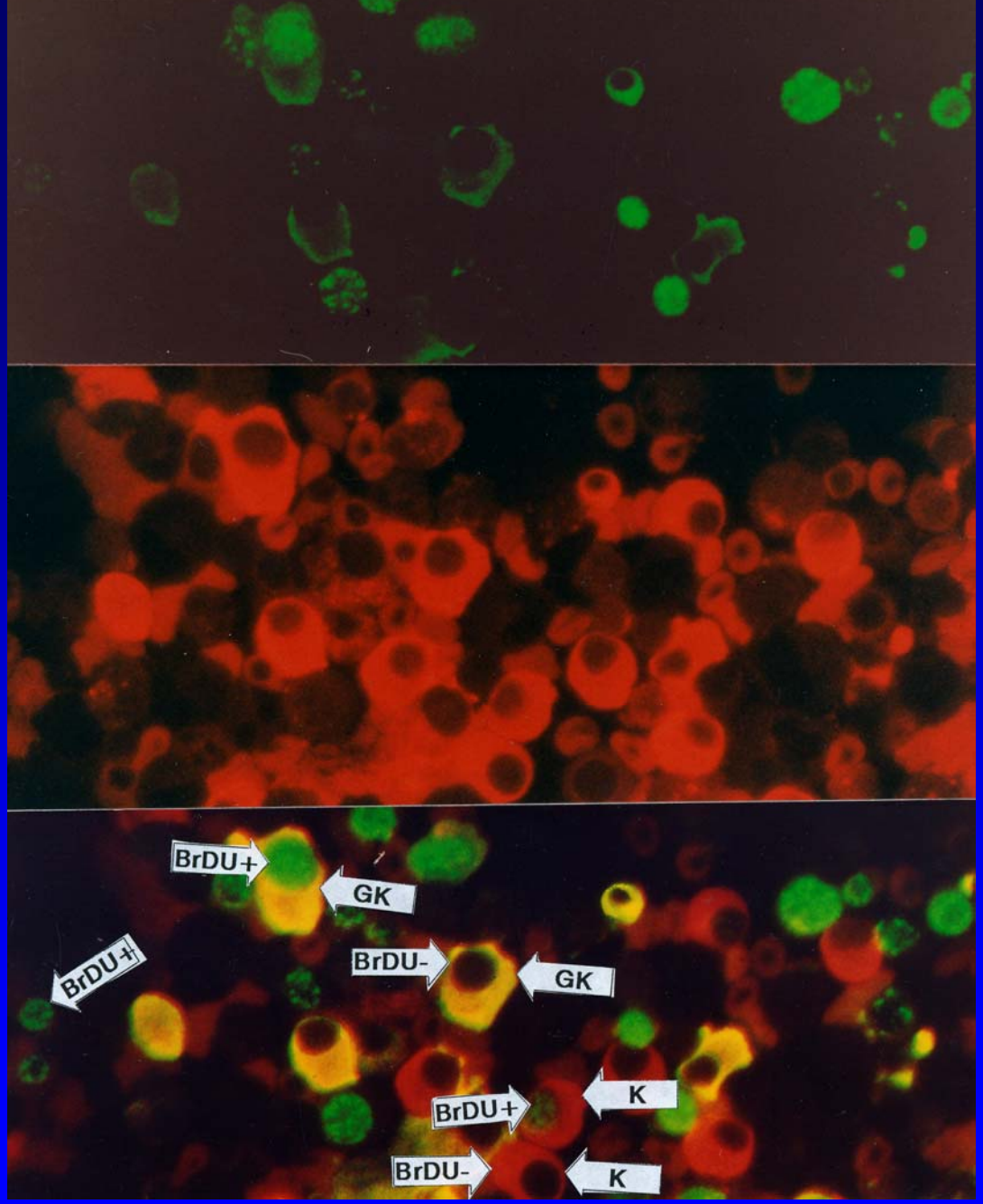

IgG
FLC kappa
Creatinine
Total protein
VED
n = no BJ proteinuria
Serum FLC kappa (mg/L), IgG (g/L) and total protein (g/dL)
Creatinine (mg/L)
Weeks
1000
100
10
1
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
n


DTC- Dexa
VAD I
VAD II
HD-Melphalan
PBSCT
no therapy
SFLC (g/l)
IgA (mg/dl), creatinin (mg/dl)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
20
18
16
14
12
10
8
6
4
2
0
Apr-04
Jul-04
Oct-04
Dec-04
Jan-05
Feb-05
Mar-05
time
creatinin
IgA
SFLC

Cytoplasmic γ FITC
Nuclear BrDU

Cytoplasmic κ TRITC

Double exposure.
cyGK cells yellow.
cyKappa only cells red.
Nuclei of cells in cycle labelled with BrDU are green.



- Kyrtsonis M-C et al BJH 2007; **137**: 240-243. *Lower 5-year survival with abnormal ratio (n=94)*

- van Rhee et al Blood 2007; Prepublished online. *Worse 24 month OS/EFS if FLC >750mg/L (n=301)*

MGUS

(Monoclonal Gammopathy of Undetermined Significance)

Risk stratification model incorporating all 3 predictive factors

Risk Group	No. patients	Relative risk, 95% CI	20 year risk of progression , %	20 year risk accounting for death. %
Low risk (serum M protein < 15g/L, IgG subtype, normal FLC ratio 0.26-1.65)	449	1	5	2
Low-intermediate risk (any 1 factor abnormal)	420	5.4	21	10
High-intermediate risk (any 2 factors abnormal)	226	10.1	37	18
High risk (all 3 factors abnormal)	53	20.8	58	27

Blood, 2005. 106:812-817

Acute renal failure with multiple myeloma

Patient 1. IgGκ and FLC kappa