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Expression of kappa myeloma antigen (KMA) and lambda myeloma antigen (LMA) on bone marrow plasma cells in patients with multiple myeloma; implications for antibody and cellular therapy

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The logo for HaemaLogiX, featuring the company name in white text on a dark red rectangular background.

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Introduction

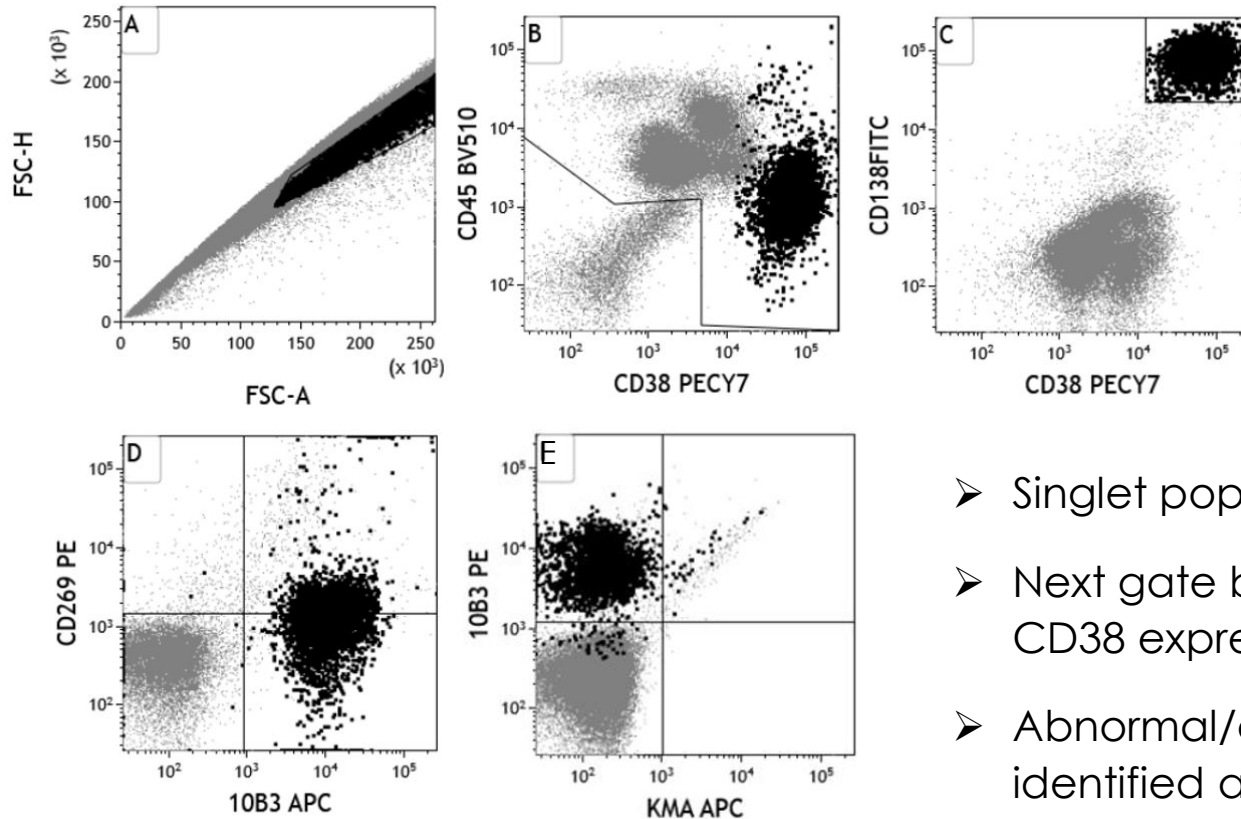
- Kappa Myeloma Antigen (KMA) and Lambda Myeloma Antigen (LMA) are cell-surface antigens found on:
 - ✓ Malignant plasma cells
 - ✓ MM cell lines
 - ✓ Occasional mononuclear cells in tonsils and secondary mucosal lymphoid tissues
- KMA and LMA are NOT found on:
 - × Normal bone marrow
 - × Normal immune cells
- The mAb KappaMab targets KMA, while the mAb 10B3 targets LMA
- KMA and LMA are conformational epitopes within the free light chain. KappaMab and the LambdaMabs do NOT bind intact immunoglobulin

1. Asvadi P et al. *Br J Haematol*. 2015 May;169(3):333-43.
2. Asvadi P et al. *Haematologica*, 2013; 98(s1):316. Abstract no. P756.
3. Hutchinson AT et al. *Biochem J*. 2013 Sep 15;454(3):479-89.

Methodology

- Antibody panel
 - CD269 (BCMA) PE
 - CD38 PE-Cy7
 - CD138 FITC
 - KMA / LMA APC
 - CD56 BV 410
 - CD45 KO
 - SLAMF7 PE-Cy5.5
- Antigen density was calculated using QuantiBrite beads in PE

Flow Cytometry Gating Strategy



This bone marrow sample was from a λ -type NDMM patient.

- Singlet population gated (A)
- Next gate based on lack of CD45 and CD38 expression (B)
- Abnormal/clonal PC population identified as CD38⁺⁺/CD138⁺⁺ (C)
- The expression of LMA and BCMA was assessed in each sample (D)
- LMA vs KMA showed no KMA binding in this sample (E)

10B3 = LMA, CD269 = BCMA

KMA in Newly Diagnosed (NDMM) and Relapsed, Refractory (RRMM) Multiple Myeloma

Number and % of Positive Cases						
Diagnosis	KMA n(%)	CD269 (BCMA) n(%)	CD319 (SLAMF7) n(%)	CD56 n(%)	Co-exp of KMA & BCMA n(%)	Co-exp of KMA & CD56 n(%)
NDMM n=23*	15 ^{***} (65)	21(91)	23(100)	17(74)	15(65)	11(48)
RRMM n=15**	12(80)	11(73)	15(100)	10 ^{***} (67)	10(67)	9(60)

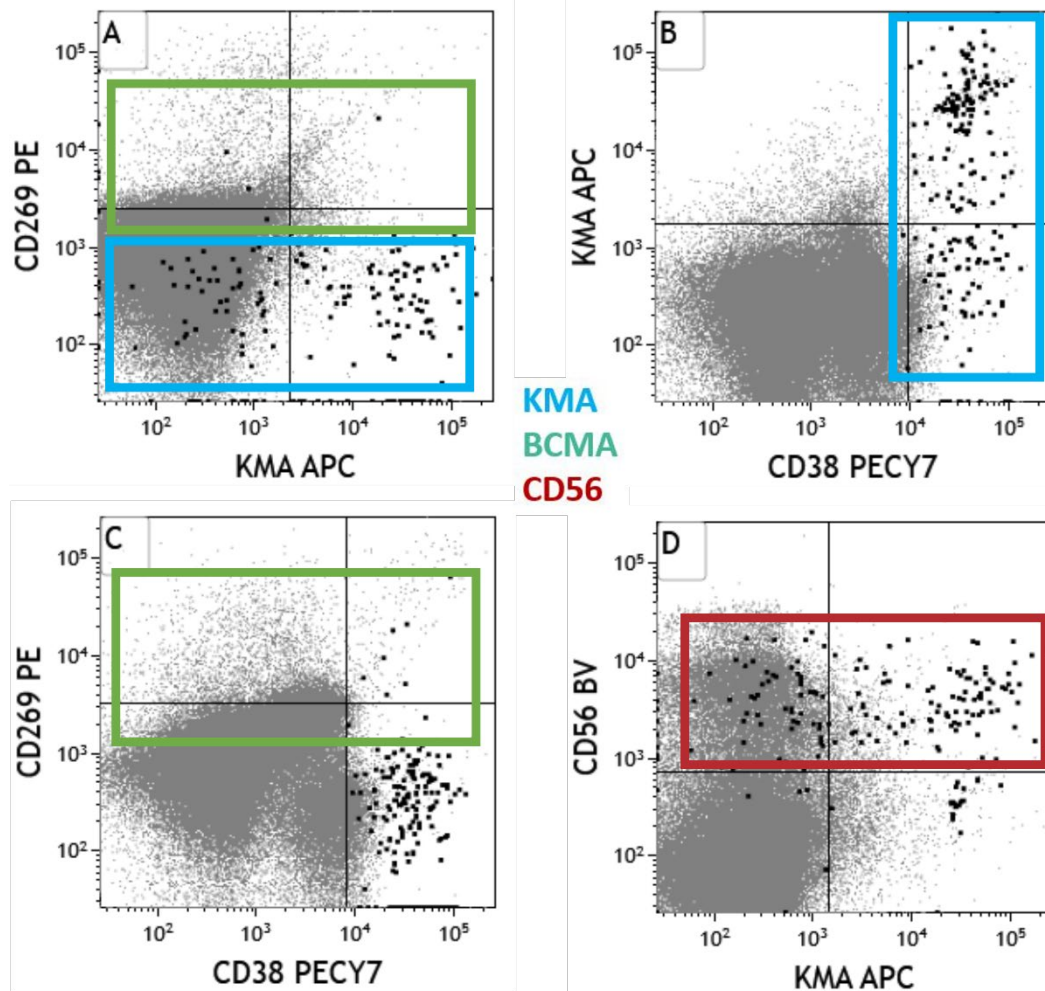
*Sample numbers increased after publication of the abstract from 21 to 23. **Two patients each have 2 timepoints, thus n=15 samples from 13 patients. ***Includes one patient with both positive and negative PC populations. NDMM=newly diagnosed MM, RRMM=relapsed, refractory MM, Co-exp=Co-expression

Antigen Density (molecules of PE/cell)		
Diagnosis (BM samples)	KMA mean (range)	BCMA mean (range)
NDMM n=23	1447 (204-12022)	1439 (364-5370)
RRMM n=15	1899 (468-7943)	1426 (350-2630)

BM=bone marrow

- KMA expression increased in RRMM cases relative to NDMM cases, while BCMA expression decreased (top table).
- Mean KMA antigen density increased in RRMM relative to NDMM, while BCMA remained the same (bottom table).

Persistence of KMA+ Plasma Cells in a Patient on Lenalidomide After ASCT



- There were very few plasma cells in this BM sample (<0.1%).
- This case showed two populations of plasma cells.
- 60% of the plasma cells expressed bright KMA (A and B) but lacked expression of CD269 (BCMA) (C) though they were positive for CD56 (D).

LMA in Newly Diagnosed (NDMM) and Relapsed, Refractory (RRMM) Multiple Myeloma

Number and % of Positive Cases						
Diagnosis	LMA n(%)	CD269 (BCMA) n(%)	CD319 (SLAMF7) n(%)	CD56 n(%)	Co-exp of LMA & BCMA n(%)	Co-exp of LMA & CD56 n(%)
NDMM n=12*	6(50)	11(92)	12(100)	5**(42)	15(65)	1(8)
RRMM n=4	2**(50)	4(100)	4(100)	2**(50)	2(50)	0(0)

*Sample numbers increased since publication of the abstract from 11 to 12

**Includes one patient with both positive and negative PC populations

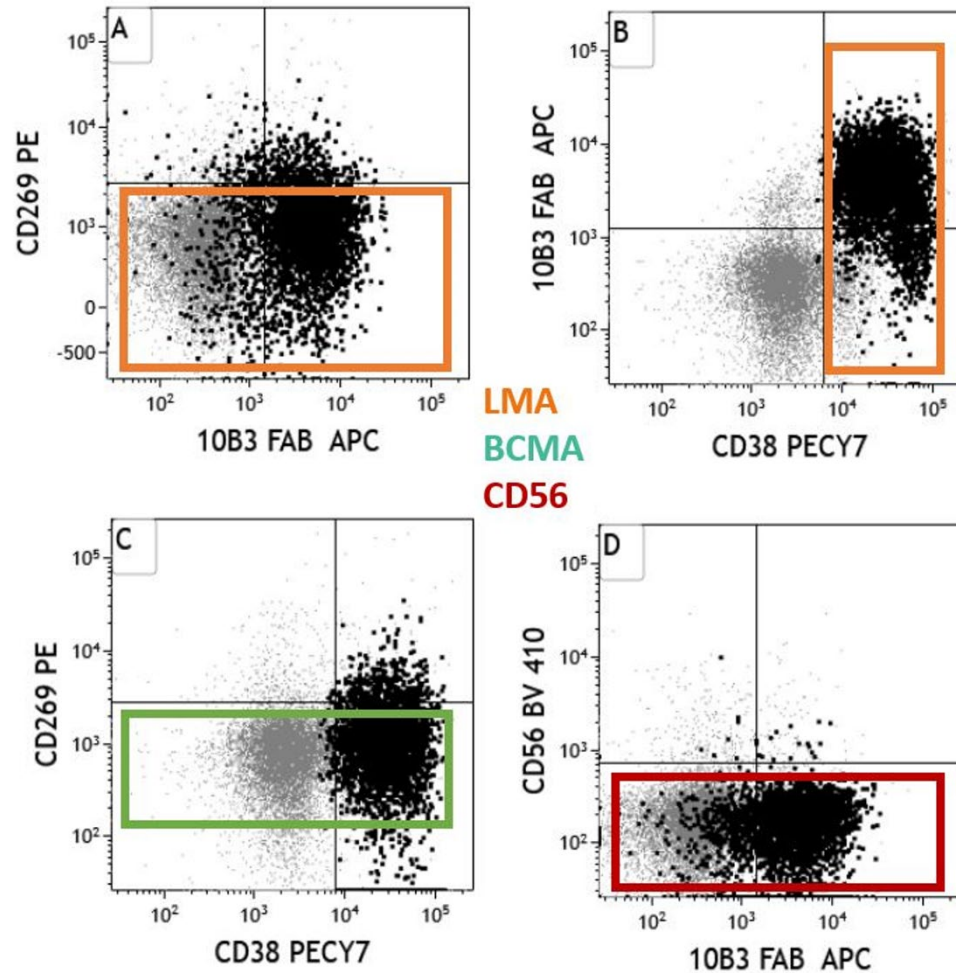
NDMM=newly diagnosed MM, RRMM=relapsed, refractory MM, Co-exp=Co-expression

Antigen Density (molecules of PE/cell)		
Diagnosis (BM samples)	LMA mean (range)	BCMA mean (range)
NDMM n=12	1652 (130-8949)	1897 (395-6990)
RRMM n=4	2439 (263-6664)	817 (537-1065)

BM=bone marrow

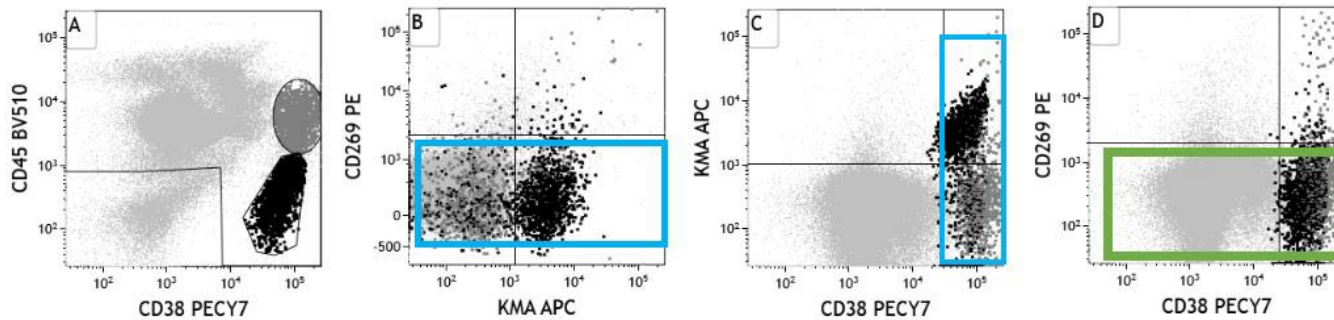
- Although the RRMM sample number is low, there is a trend of increased mean LMA and decreased BCMA densities in RRMM relative to NDMM.

Antigen density of LMA vs BCMA in Relapsed, Refractory Multiple Myeloma



LMA (10B3) expression on malignant PCs was positive (A, B) compared to negative expression for both CD269 (BCMA) (A and C) and CD56 (D).

KMA is Expressed Only on Malignant Plasma Cells in MGUS



- Plot A shows 2 populations of PCs: normal PCs expressing CD45 and bright CD38 (grey dots) and abnormal PCs showing no CD45 expression and slightly weaker CD38 expression (black dots)
- Plots B and C show abnormal PCs expressing KMA
- Plot D shows dim expression of CD269 (BCMA) in abnormal PCs
- Normal PCs are negative for KMA (C) but have dim expression for CD269 (BCMA) (B and D)

Conclusions

- KappaMab and LambdaMab are specific antibodies that target KMA and LMA found on malignant plasma cells, MM cell lines and occasional secondary lymphoid tissue, but not on normal plasma cells or other normal immune cells.
- The antigen density of KMA and LMA is enriched in RRMM samples relative to NDMM samples, while BCMA density is decreased or unchanged, indicating a treatment-resistant clone.
- KMA and LMA represent valuable therapeutic targets in RRMM with the combination of high antigen density and target restriction to the malignant PCs.