NOVEL THERAPEUTIC TARGETS KAPPA MYELOMA ANTIGEN (KMA) AND LAMBDA MYELOMA ANTIGEN (LMA) ARE EXPRESSED ON MALIGNANT PLASMA CELLS FROM PATIENTS WITH PLASMA CELL DYSCRASIAS BUT NOT ON NORMAL PLASMA CELLS

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INTRODUCTION

Multiple myeloma (MM) and its associated disorders monoclonal gammopathy of unknown significance (MGUS), smouldering myeloma (SMM), extramedullary plasmacytoma and light chain amyloidosis (AL) comprise a spectrum of diseases that fall under the term plasma cell dyscrasias (PCDs). In PCDs, M proteins, including whole immunoglobulin (Ig) and/or free light chains (FLCs), are produced by an abnormal plasma cell (PC) clone that normally resides in the bone marrow (BM)[1]. Treatment of MM typically involves an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) in combination with an anti-CD38 monoclonal antibody (daratumumab or isatuximab) or an antibody targeting SLAMF7 (elotuzumab)[2-6].

More recently, MM therapies harnessing the power of T lymphocytes have been used to target myeloma antigens. The most common target for chimeric antigen receptor-bearing T cells or bispecific antibodies has been the B cell maturation antigen (BCMA, CD269), which is broadly expressed on both normal and malignant B cells as they differentiate[7-8].

We have developed novel monoclonal antibodies called KappaMab, that specifically binds to kappa myeloma antigen (KMA), and LambdaMabs (10B3 and 7F12) that specifically bind to lambda myeloma antigen (LMA). KMA and LMA are antigens expressed on the surface of malignant plasma cells (PCs) and arise from conformational epitopes in the constant regions of lipid-associated kappa (κ) or lambda (λ) FLCs and are not found on PCs in normal bone marrow (BM) or on light chains associated with heavy chains[9,10]. Early clinical studies using naked KMA antibody have shown promising efficacy with little toxicity[11-13]. In this work we determined the expression of KMA and LMA across a broad range of PCDs to ascertain the potential of immunotherapies targeting these antigens for therapeutic purposes.

METHODS

Bone marrow samples were acquired from two major Australian hospitals. Diagnosis was confirmed by reviewing clinical, laboratory and radiological investigations. Patient bone marrow samples (κ=121 and λ=74) were analysed using multiparametric flow cytometric immunophenotyping with APC labelled LambdaMab (10B3) and KappaMab Fab'2 fragments, CD38, CD138, CD269 (BCMA), CD56, CD319 (SLAMF7) and CD45 monoclonal antibodies. Acquisition was performed using a FACSCanto II flow cytometer (BD Biosciences, Australia) and analyses were performed using Kaluza 2.1 software (Beckman Coulter, Miami, FL, USA). The flow cytometry cell gating strategy is shown (**Figure 1**). The gated PC populations were then analyzed for expression of KMA and LMA, CD269 (BCMA), CD319 (SLAMF7) and CD56. KappaMab and 10B3 $F(ab')_2$ fragments were used as negative controls for each other.

Immunohistochemistry (IHC) was performed on snap frozen, unfixed human tissue samples to support sensitive detection of non-target tissue binding (cross-reactivity) by the antibody, as the targets are conformational epitopes prone to denaturation by cross-linking reagents. LMA staining was performed on Ventana Discovery Ultra platform (Roche) using DISCOVERY Purple kit (10B3), with light Meyer's hematoxylin staining with bluing reagent. Images were cropped with the Greenshot™ software from digital whole section images acquired with an Axioscan Z1 HF (4631000285) slide scanner, using the 20x objective EC Plan Neofluar M27 (numerical aperture: 0.5) and visualized using the ZEN2 software (blue-edition), Zeiss Microscopy, Jena, Germany.

RESULTS

A total of 195 samples from 178 patients were included in the analysis (**Table 1**). 121 samples were from 111 patients with kappa PCDs, 74 samples from 67 patients with lambda PCDs. The PC infiltration in BM aspirates ranged from <1% to >90% There was a median of 14% PCs in kappa PCDs and 21% in lambda PCDs. Details of serum paraprotein and free light chain concentrations were available for 99 samples with kappa PCDs and 65 samples with lambda PCDs (**Table 2**).
For all BM samples tested by flow cytometry, KMA and LMA were expressed only on clonal PCs and not on other cell types. KMA and LMA were not co-expressed.

The expression of KMA and LMA was independent of PC numbers within the BM and did not correlate with immunoglobulin subtype, paraprotein concentration or serum free light chain concentration. CD319 (SLAMF7) was ubiquitously expressed on all BM samples tested (data not shown).

KMA, BCMA and CD56 expression is shown in **Table 3.** KMA was expressed in the majority of cases of PCDs of all types. Co-expression of KMA with BCMA was more common than with CD56. KMA and BCMA antigen densities were similar in untreated myeloma cases but KMA antigen density increased in treated cases and appeared higher than BCMA antigen density **(Figure 2).** Three of 121 kappa samples were KMA positive but BCMA negative (3 MM).

LMA, BCMA and CD56 expression is shown in **Table 4.** LMA was expressed in the majority of cases of PCDs of all types. Co-expression of LMA and BCMA was higher than LMA and CD56. As for KMA, LMA and BCMA antigen densities were similar in untreated myeloma cases but LMA antigen density increased in treated cases and appeared higher than BCMA antigen density (**Figure 3**). In two longitudinal cases, the percentage of LMA expression and the LMA density increased during progression from MGUS to SMM (**Figure 4; Panel A**) and from SMM to MM (**Figure 4; Panel B**). Seven of 74 lambda samples were LMA positive but BCMA negative (3 amyloidosis, 3 MM and 1 MGUS).

In AL amyloidosis KMA and LMA were expressed on 83% and 93% of cases respectively (**Table 5**). KMA and LMA antigen density appeared greater than BCMA (**Figure 5** and **Figure 6 respectively**).

We previously conducted studies of staining in normal human tissue and found that KMA was expressed in a tiny population of normal tonsillar and salivary B cells but not in normal bone marrow or blood including normal plasma cells (**Figure 7**). To confirm that the expression of LMA would be similarly restricted, we performed IHC studies on human myeloma cell lines, lambda type lung plasmacytoma and normal human tissue samples using 10B3-FITC or 7F12-biotin conjugated antibodies. The 10B3-FITC and 7F12-biotin staining patterns were similar, so only 10B3 is presented in detail here (**Figure 8**).

The analysis of 38 snap-frozen normal human tissues collected from 3 independent healthy human donors showed positive LMA staining of occasional mononuclear cells in gut and secondary lymphoid tissues. Membranous/cytoplasmic staining was observed in the lamina propria of the mucosa of the gastro-intestinal tract (stomach, duodenum, jejunum, ileum and colon), as well as in lymph nodes, spleen, tonsils and other bronchus-, gut- and mucosa associated lymphoid tissues (BALT, GALT and MALT). In addition, there was positive staining in very rare cells in Peyer's patches in one duodenum tissue sample (not shown). Staining of a lung plasmacytoma showed not only LMA positivity in the malignant cells, but also occasional specific binding in normal bronchus-associated lymphoid tissue (BALT) around bronchi and other airways. The remainder of the tissues tested, including normal bone marrow and blood smears, showed no 10B3- and 7F12-related staining.

DATA

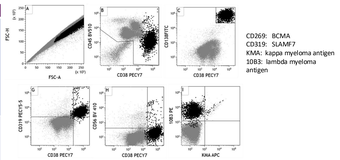
Table 1. Patient Cohort

Samples (n=195)	Kappa positive (n=121)	Lambda positive (n=74)
Patients (n=178) male/female	111 72/39	67 48/19
disease state n (%)		
MGUS	25 (20)	14 (19)
smouldering MM	6 (5)	3 (4)
untreated MM	46 (38)	29 (39)
treated MM	28 (23)	10 (14)
plasmacytoma	10 (8)	3 (4)
AL-amyloidosis	6 (5)	15 (20)
% BM PCs median(range)	14 (<1 to 90)	21 (<1 to >90)

Table 2. Details of paraprotein and free light chain measurements

Samples	Kappa positive	Lambda positive
M protein (g/L); median (range), n	18 (<1-140), 54	13.1 (<1-69), 34
IgG	10.8 (<1-53), 17	18.2 (2-49), 16
IgA	6	7
Not quantifiable (n)	12	4
No M protein (n)	21	12
Result not available (n)		
sFLC (mg/L)		
Kappa FLC; median (range), n	95.8 (6-12500), 86	16 (1-174), 55
Lambda FLC; median (range), n	11.7 (0.2-119), 86	253 (6.9-4130), 55
sFLC ratios		
κ:λ; median (range):	5.9 (1.2-12464)	0.2 (<0.01-0.87)

Figure 1. Gating Strategy for identification of plasma cells



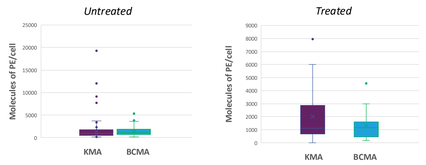
Conclusion: Lambda multiple myeloma with plasma cells CD38⁺ CD138⁺ CD45^{lo} LMA⁺ CD269^{lo} CD319⁺ CD56⁻

KAPPA LIGHT CHAIN POSITIVE CASES

Table 3. Antigen Expression

	KMA	CD269 (BCMA)	Co-expression of KMA & BCMA	CD56	Co-expression of KMA & CD56
MGUS n=25	15 (60)	22 (88)	15 (60)	10 (40)	6 (25)
SMM n=6	5 (83)	6 (100)	5 (83)	5 (83)	4 (68)
MM n=74:	54 (73)	63 (85)	51 (69)	50 (68)	41 (55)
untreated MM n=46	32 (70)	41 (89)	31 (67)	34 (74)	26 (57)
treated MM n=28	22 (79)	22 (79)	20 (71)	16 (57)	15 (54)

Figure 2. Antigen densities Kappa MM



LAMBDA LIGHT CHAIN POSITIVE CASES

Table 4. Antigen Expression

	LMA	CD269 (BCMA)	Co-expression of LMA & BCMA	CD56	Co-expression of LMA & CD56
MGUS n=14	11 (78)	12 (86)	10 (71)	7 (50)	5 (36)
SMM n=3	3 (100)	3 (100)	3 (100)	1 (33)	1 (33)
MM n=39:	26 (66)	33 (86)	23 (59)	26 (66)	15 (38)
untreated MM n=29	20 (69)	26 (90)	19 (66)	21 (72)	13 (45)
treated MM n=10	6 (60)	7 (70)	4 (40)	5 (50)	2 (20)

Figure 3. Antigen densities Lambda MM

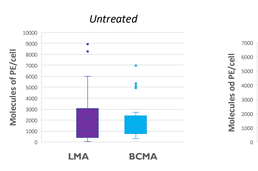
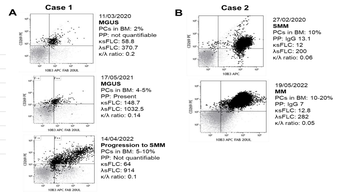


Figure 4. Serial Analysis



AL-AMYLOIDOSIS CASES

Table 5. Antigen Expression

	KMA or LMA	CD269 (BCMA)	Co-expression of KMA/LMA & BCMA	CD56	Co-expression of KMA/LMA & CD56
Kappa (n=6)	5 (83)	6 (100)	5 (83)	5 (83)	5 (83)
Lambda (n=15)	14 (93)	11 (73)	10 (66)	9 (60)	8 (53)

Figure 5. Antigen Densities Kappa Amyloidosis

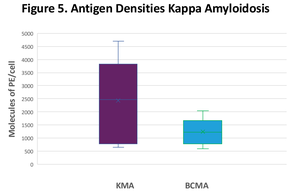
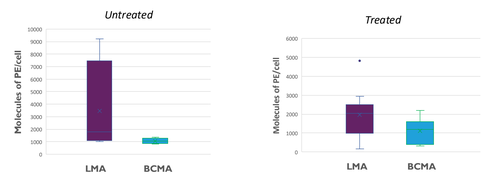


Figure 6. Antigen Densities Lambda Amyloidosis



Immunohistochemistry Examples

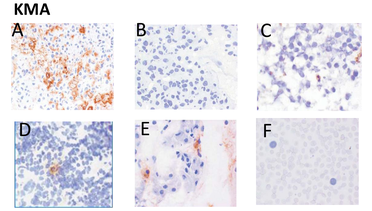


Figure 7. Immunohistochemistry staining for KMA using KappaMab. Panel A shows extensive KMA staining in kappa myeloma BM PCs. Panel B shows KappaMab does not stain lambda positive bone marrow samples. Panel C shows that KMA is not present in normal bone marrow samples. Occasional mononuclear staining occurred in normal tonsil (panel D) and normal salivary gland (panel E) and was negative on normal blood cells (panel F). (Charles River Laboratories, Pathology Associates (PAI), Maryland, USA).

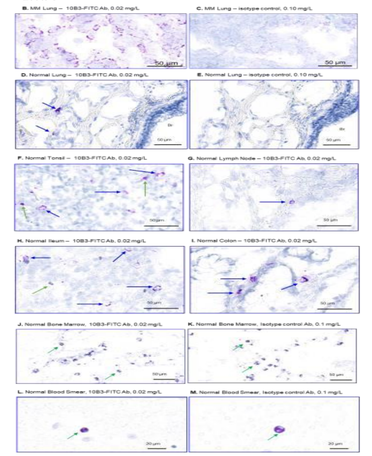


Figure 8. Immunohistochemistry staining for LMA using 10B3. Panel B shows extensive staining in a lung plasmacytoma (MM). As shown in panels C and E the isotype control did not stain LMA. The blue arrows indicate specific membranous/cytoplasmic LMA staining of occasional mononuclear cells present in normal lung (panel D), normal tonsil (panel F), normal lymph node (panel G), normal ileum (panel H) and normal colon (panel I). In normal bone marrow (panels J-K) and normal blood smear there was no evidence of LMA staining. The green arrows show non-specific granular cytoplasmic staining.
(TPL Path Labs GmbH Sasbacher Str. 10 D-79111, Freiburg, Germany).

CONCLUSIONS & DISCUSSION

- Our data demonstrate that KMA and LMA are present on bone marrow PCs in the majority of cases of PCDs of all types and represent a potentially valuable target for immunotherapy
- In a minority of cases, KMA and LMA expression occurs in the absence of BCMA expression
- In AL amyloidosis, KMA and LMA expression is almost universal
- KMA and LMA expression on normal tissue is restricted to occasional mucosal associated lymphoid cells
- Targeting KMA or LMA may leave alternative isotype plasma cells intact and reduce infectious complications and retain vaccine responsiveness after immunotherapy

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