The Inventive Step: Rosanne Dunn

How antigen discovery could redefine multiple myeloma

For more than two decades, the treatment of multiple myeloma has operated within a framework of managed incurability. Proteasome inhibitors, immunomodulatory drugs, anti-CD38 monoclonal antibodies and more recently BCMA-directed CAR-T cells and bispecific antibodies, have each advanced response rates and survival. Yet the malignant clone persists through every line of therapy by adapting, escaping, and ultimately progressing, and the disease remains treatable but incurable. The central limitation of every approved approach is target biology.

The antigens exploited by current immunotherapies, most prominently BCMA and CD38, are expressed not only on malignant plasma cells but on their normal counterparts at various stages of B cell differentiation. This shared expression profile creates an inescapable trade-off. Effective clonal elimination requires destroying the normal plasma cell compartment, precipitating severe hypogammaglobulinaemia that renders patients profoundly immunocompromised and dependent on immunoglobulin replacement to combat infections. In targeting the tumour, these agents wound the immune architecture they are meant to protect.

A therapy that selects for the malignant cell and spares its benign counterpart has long been the theoretical ideal. For multiple myeloma, that ideal now has a rigorous biological basis.

Kappa myeloma antigen (KMA) and lambda myeloma antigen (LMA) are cell-surface antigens expressed on malignant plasma cells but absent from normal bone marrow plasma cells. Their molecular identity reflects a conformational epitope arising when free kappa or lambda light chains associate with sphingomyelin in the malignant cell membrane, which is a lipid-associated presentation inaccessible on circulating immunoglobulin and entirely absent from normal B cells. Vitally, normal plasma cells are spared.

Recently published study

A recently published study in *Clinical Lymphoma, Myeloma and Leukemia* (Sartor et al., 2025), sponsored by HaemaLogiX Ltd in partnership with clinical experts from Sydney University and the University of Melbourne in Australia characterised KMA and LMA expression across 195 bone marrow aspirates. This spanned the full spectrum of clonal plasma cell dyscrasias, from monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma through to treated multiple myeloma, AL amyloidosis, and plasmacytoma.

KMA was present on 72% of kappa-restricted samples and LMA on 76% of lambda-restricted samples. Critically, in relapsed and refractory disease (where antigen escape poses the greatest clinical challenge) the surface density of both KMA and LMA exceeded that of BCMA. The antigen most exploited by current CAR-T platforms is present at lower surface density in heavily pre-treated patients than are KMA and LMA, which appear enriched as the malignant clone evolves under selection pressure.

KMA and LMA expression was independent of paraprotein concentration, serum free light chain levels, and bone marrow plasma cell percentage, decoupling these targets from conventional disease burden metrics and confirming consistent accessibility across the treatment continuum. In AL amyloidosis, 18 of 20 samples expressed KMA or LMA, including four in which LMA was detected without BCMA, extending this biology beyond myeloma.

HaemaLogiX, which characterised the novel targets and established clinical proof of concept, has built its lead programme around KappaMab, a humanised monoclonal antibody binding the KMA conformational epitope with a fivefold preference for membrane-bound KMA over soluble serum free kappa light chain. Because KappaMab does not engage normal bone marrow B cells, it avoids the on-target, off-tumour toxicity constraining current therapies. Tumour cell elimination proceeds through antibody-dependent cellular cytotoxicity and phagocytosis, engaging natural killer (NK) cells and macrophages against KMA-expressing myeloma cells. Lenalidomide (Revlimid) upregulates KMA surface expression and potentiates NK-mediated cytotoxicity, the pharmacological rationale for combination development.

In a Phase 2b sequential cohort study led by Professor Andrew Spencer at Bayside Health in Melbourne, KappaMab combined with lenalidomide and low-dose dexamethasone was evaluated in relapsed and refractory kappa-type myeloma patients with one to three prior lines. The combination achieved an overall response rate of 83% and clinical benefit rate of 93%, against 45% ORR in a contemporaneous matched case-control cohort receiving lenalidomide and dexamethasone alone, and conferred a 46% reduction in the risk of death without any KappaMab-related haematological toxicities or lymphopenias. Two patients have remained on therapy for more than four years. No dose-limiting toxicities were observed across the Phase 1, 2a and 2b programmes.

What distinguishes HaemaLogiX's approach from every other immunotherapy in clinical use for myeloma is the preservation of normal immunological function. By targeting an antigen expressed exclusively on malignant plasma cells, KappaMab and its emerging pipeline offer the possibility of eradicating the malignant clone while leaving the patient's capacity for protective antibody generation intact.

To our knowledge, there are no competing therapies targeting KMA or LMA in global clinical development.

This article was written by Rosanne Dunn, chief scientific officer of HaemaLogiX Ltd and co-discoverer, with Dr Robert L Raison, of the KMA antigen and antibody therapy.