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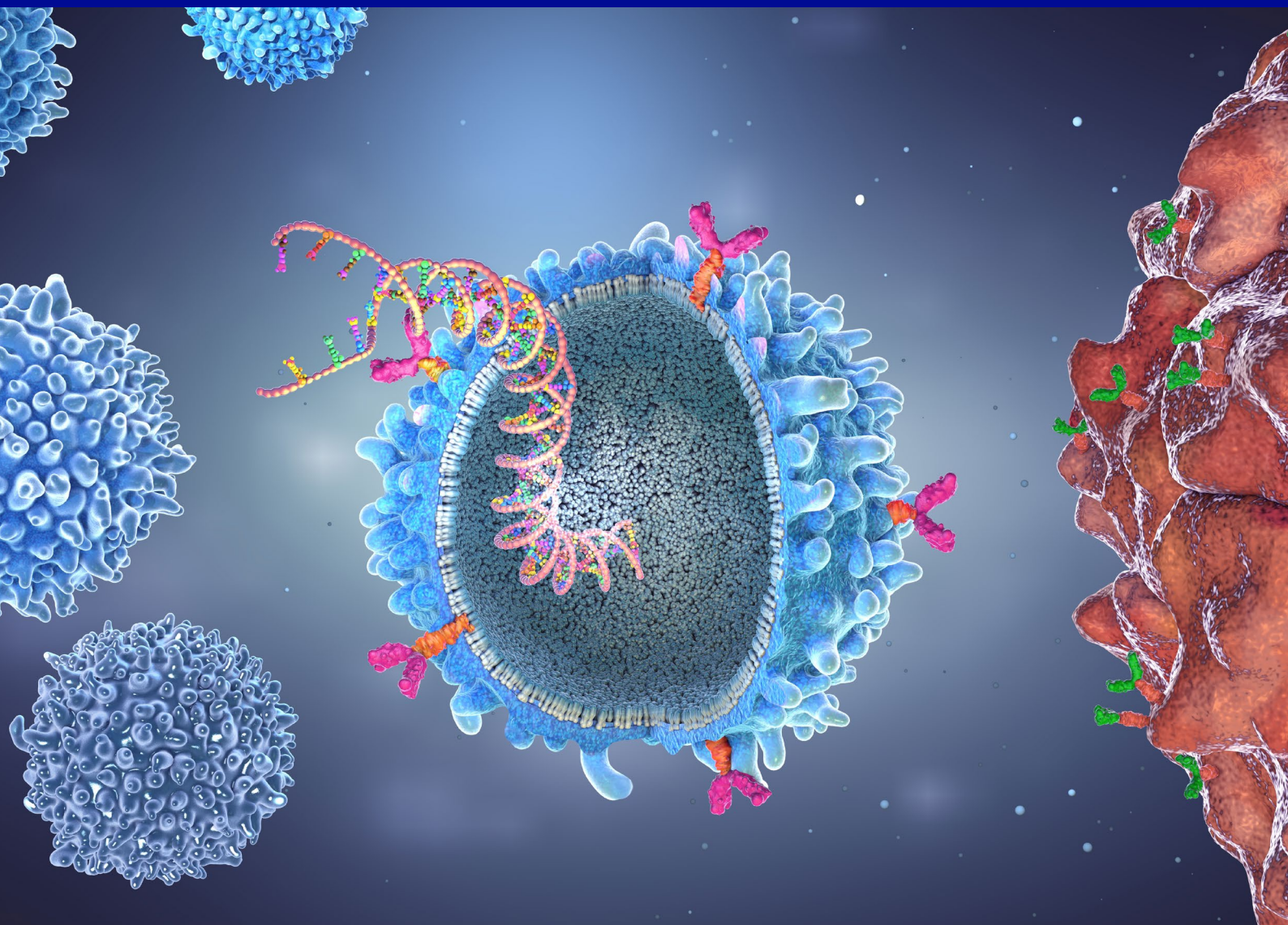

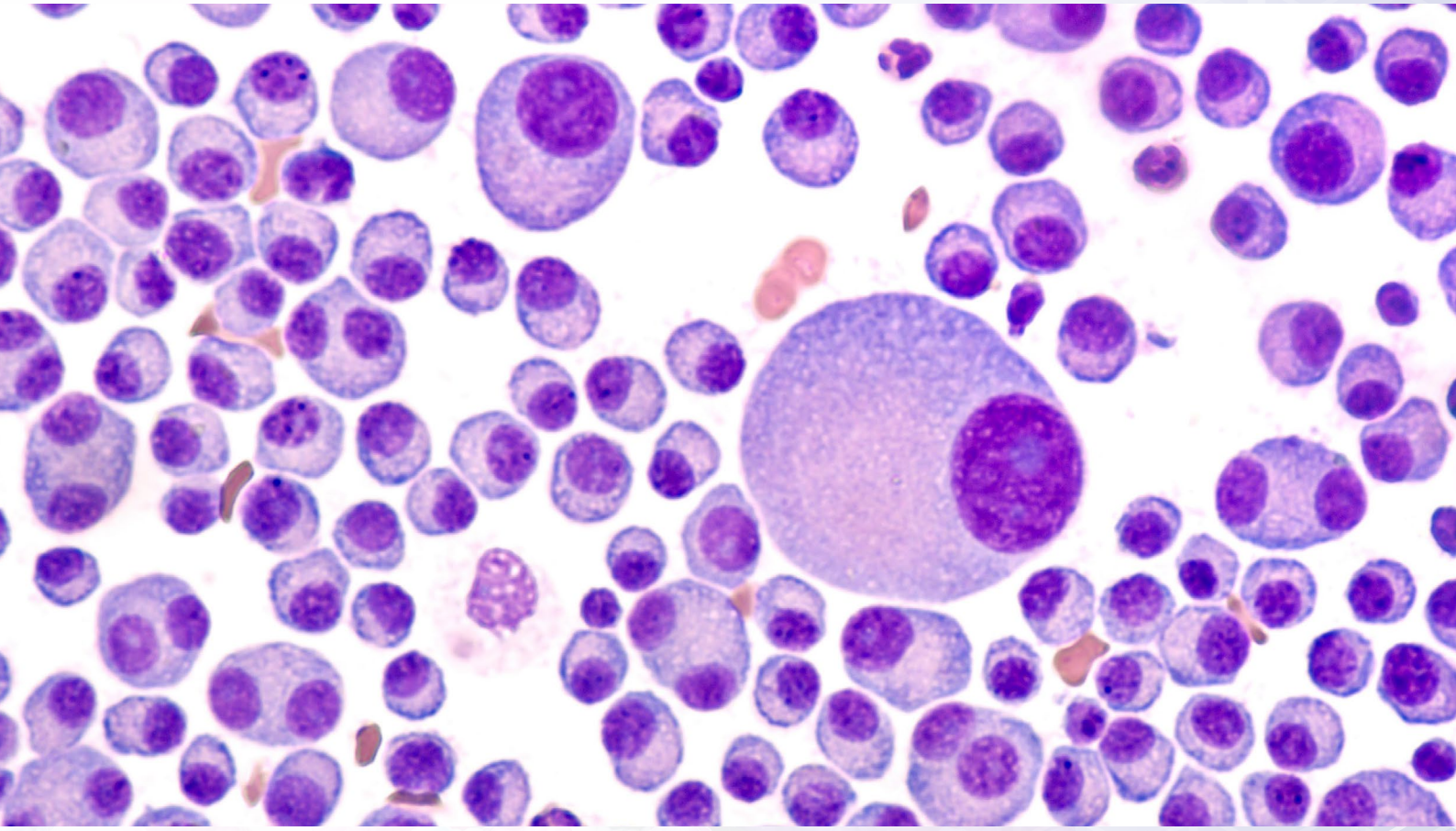

Redefining targeted immunotherapy in multiple myeloma through antigen innovation

For more than two decades, progress in multiple myeloma has been marked by sustained advances in drug development that have not translated into true curability.

Proteasome inhibitors, immunomodulatory drugs, anti CD38 antibodies, and, more recently BCMA directed CAR-T cells and bispecifics, have each extended survival and transformed expectations. But the malignant plasma cell clone adapts, escapes, and ultimately progresses through every line of therapy. The central limitation is not the ingenuity of modalities but the biology of the targets themselves.

The antigens exploited by current immunotherapies are shared between malignant and normal plasma cells. Eliminating the tumour inevitably means ablating the patient's healthy antibody producing compartment, precipitating profound hypogammaglobulinaemia and long term immunodeficiency. This trade off has been accepted as unavoidable, and the Australian biotech HaemaLogiX has spent the past decade challenging that assumption.

Its founders, Rosanne Dunn and Alan Liddle, work began with a simple question: What if the malignant plasma cell expresses a target that its healthy counterpart does not? The answer, now validated across hundreds of patient samples and multiple clinical studies, has the potential to reshape how we treat plasma cell dyscrasias.

A new class of myeloma targets: KMA and LMA

Kappa myeloma antigen (KMA) and lambda myeloma antigen (LMA) are conformational, lipid associated epitopes that arise when free light chains bind sphingomyelin within the malignant plasma cell membrane. This presentation is unique to short lived plasmablasts and transformed plasma cells. HaemaLogiX's immunotherapies bind specifically to these conformational epitopes presented on the free light chain constant regions and do not bind immunoglobulin. KMA and LMA are not expressed on normal bone marrow plasma cells, however, they are present on a tiny population of cells found in normal tonsillar and other normal mucosa associated lymphoid tissue.

In every dataset HaemaLogiX has generated or analysed, normal bone marrow plasma cells are spared.

In collaboration with clinical researchers at the University of Sydney and University of Melbourne, it characterised KMA and LMA expression across 195 bone marrow aspirates spanning MGUS, smouldering myeloma, newly diagnosed and relapsed multiple myeloma, AL amyloidosis, and plasmacytoma. The findings were striking:

- KMA was expressed in 72% of kappa restricted samples
- LMA in 76% of lambda restricted samples
- Antigen density exceeded BCMA in relapsed/refractory disease, where target loss is most problematic
- Expression was independent of paraprotein levels, serum free light chains, or bone marrow plasma cell percentage, ensuring consistent accessibility
- In AL amyloidosis, 18 of 20 samples expressed KMA or LMA, including cases where BCMA was absent

These data, now published in *Clinical Lymphoma, Myeloma and Leukemia*, establish KMA and LMA as high value, lineage restricted targets with broad applicability across plasma cell dyscrasias. They also highlight a critical biological insight: as myeloma evolves under therapeutic pressure, KMA and LMA expression appears to increase rather than diminish.

In a field where antigen escape is a defining challenge, this is a rare and important advantage.

Building a first in class pipeline

Translating these targets into therapeutics required a modality capable of exploiting their tumour specificity while preserving normal immune function. Lead programme KappaMab, is a humanised monoclonal antibody that binds the KMA conformational epitope with a fivefold preference for membrane bound KMA over soluble free light chain.

This selectivity is essential. It ensures that KappaMab engages malignant cells without being sequestered by circulating light chains, a common obstacle in myeloma biology.

Mechanistically, KappaMab induces tumour cell death through antibody dependent cellular cytotoxicity (ADCC) and phagocytosis, recruiting NK cells and macrophages to eliminate KMA expressing cells. Importantly, because normal plasma cells do not express KMA, KappaMab avoids the on target, off tumour toxicity that constrains CD38 and BCMA directed therapies.

Preclinical work also revealed a synergistic interaction with immunomodulatory drugs Revlimid (lenalidomide) and Pomalyst (pomalidomide). These drugs upregulate KMA surface expression and enhance NK cell activity, providing a strong rationale for combination development.

Clinical progress

HaemaLogiX's clinical programme has progressed through Phase I, IIa, and IIb studies without encountering dose limiting toxicities or the haematological suppression typical of current immunotherapies.

In a Phase IIb sequential cohort study led by Professor Andrew Spencer in Melbourne, KappaMab combined with lenalidomide and low dose dexamethasone achieved:

- 83% overall response rate (ORR)
- 93% clinical benefit rate
- 46% reduction in risk of death compared with a matched case control cohort receiving lenalidomide/dexamethasone alone
- Two patients remaining on therapy for more than four years
- No KappaMab related lymphopenias or cytopenias

These outcomes are notable not only for their magnitude but for their tolerability. Patients maintained normal immunoglobulin production, and HaemaLogiX observed no evidence of the immune suppression that has become an accepted consequence of myeloma therapy.

For a disease defined by cumulative toxicity and diminishing therapeutic windows, preserving immune competence is a clinical imperative.

Expanding the pipeline beyond KappaMab

While KappaMab is the most advanced programme, it represents only the first application of the antigen platform. The firm is also advancing a KMCAR T-cell first in human Phase I clinical trial that received clinical trial authorisation by the Therapeutics Goods Administration in Australia. It's anticipated that this

study will be initiated in May 2026.

The preclinical stage pipeline includes:
- LMA directed monoclonal antibodies
- The LMCAR T-cell format
- Potential bispecific constructs leveraging KMA/LMA biology
- Therapeutic candidates for AL amyloidosis, where unmet need remains profound

Because KMA and LMA are mutually exclusive based on light chain restriction, they offer a natural path to personalised immunotherapy. Every patient with a plasma cell dyscrasia expresses either kappa or lambda light chains and the therapeutic is matched to the correct therapeutic target.

This is precision medicine in its most literal form.

Pivotal development and regulatory strategy

The next major milestone for the Sydney-based biotech is the initiation of a Phase IIb programme evaluating KappaMab at a higher dose in combination with pomalidomide in multiple myeloma patients who have failed three classes of drug, including Darzalex and Revlimid. The company is designing this study:
- At a higher KappaMab dose because previous studies showed an excellent safety profile
- In combination with pomalidomide which is more effective at increasing cell surface KMA
- To improve clinical benefit in patients with a clear unmet medical need and support regulatory submissions in major markets
- To establish KappaMab as a backbone therapy for kappa restricted disease.

HaemaLogiX is also expanding its translational research partnerships to deepen understanding of KMA/LMA expression dynamics, particularly in post BCMA relapse, a rapidly growing patient population with limited options.

Funding strategy and IPO trajectory

As it advances toward pivotal trials and broadens its pipeline, it is entering a new phase of corporate growth. HaemaLogiX has historically been supported by a combination of private investment, non dilutive funding, and strategic partnerships. This approach has allowed science to progress with discipline and independence.

Looking ahead, it is preparing for a significant expansion in financing strategy, including:

- Strategic collaborations with global oncology partners
- Positioning the company for a potential IPO within the next three to six months, aligned with key clinical inflection points.

HaemaLogiX intends to use this capital to deliver on the full potential of KMA and LMA biology across myeloma, AL amyloidosis, and other plasma cell disorders, while maintaining control of scientific direction.

Why this matters

"The prevailing view in myeloma treatment is that targeting established B-cell markers on both normal and malignant plasma cells means that destroying normal plasma cells is collateral damage. This assumption has shaped every therapeutic strategy," says Rosanne Dunn, Co-Founder and CSO of HaemaLogiX.

"In contrast we have identified targets that are specific to the malignant plasma cell across all stages of myeloma disease, as well as other plasma cell dyscrasias. Biology often reveals more nuance than we expect.

"The discovery of KMA and LMA demonstrated that malignant plasma cells do, in fact, possess unique vulnerabilities, if we look closely enough. Developing therapeutics around these targets has required persistence, collaboration, and a willingness to challenge entrenched paradigms. It has also required a belief that patients deserve therapies that eliminate their cancer without damaging their immune system," she explains.

Conclusion

Multiple myeloma remains a formidable disease, but its biology is not static. As the therapeutic landscape evolves, so too must understanding of what is possible. KMA and LMA represent a new class of tumour specific antigens with the potential to transform how we treat plasma cell dyscrasias. The clinical data generated to date provide a compelling foundation, and the path ahead, through pivotal trials, pipeline expansion, and strategic growth, offers an opportunity to redefine the standard of care.

About the author
Dr Rosanne Dunn is Co-Founder and Chief Scientific Officer at HaemaLogiX. Dr Dunn has more than 20 years of experience in the fields of immunology, haematology, translational medicine and drug development. She was involved in the discovery of the company's lead therapeutic antibody KappaMab and in taking the antibody from the laboratory through to pre-clinical and clinical development.