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the business of Bio & Health Sciences
ASIA EDITION

How Degrader-Antibody Conjugates Are Transforming Precision Medicine for Oncology & Beyond

01 March 2025 | Opinion | By Dr Suk Namgoong, Lecturer, Chungbuk National University and Advisor, Orum Therapeutics, Korea and USA

Targeted cancer therapy has advanced significantly with the creation of Degrader-antibody conjugates (DACs). The shortcomings of conventional ADCs are addressed by DACs, which combine the specificity of antibodies with the special capacity of protein degraders to eradicate important oncogenic drivers.

Degrader-antibody conjugates (DACs) represent a natural evolution in targeted precision medicines for oncology and other indications, building on the advances of ADCs while addressing their key shortcomings. DACs use targeted protein degraders (TPDs) as their payload—combining the precision of antibodies with the catalytic potential of protein degraders. Unlike ADCs, which release a one-time burst of cytotoxic activity upon internalisation, DACs deliver TPD molecules that trigger the

sustained elimination of oncogenic proteins. When the antibody binds to its target antigen on a tumor cell, the conjugated protein degrader is internalised and recruits components of the ubiquitin-proteasome system (the cell's protein recycling machinery) to mark specific proteins for destruction. This dual-selectivity mechanism—tumour-specific antibody targeting coupled with cancer-specific protein degradation—offers an unprecedented level of precision, significantly reducing off-target effects and expanding the therapeutic window.

Overcoming the Limitations of Traditional Modalities

While small molecule TPDs have shown promise in both preclinical and clinical studies, they come with challenges. Their systemic distribution can lead to off-target protein degradation in healthy tissues, and their high molecular weights (often exceeding Lipinski's rule of five guidelines) complicate oral bioavailability and pharmacokinetics. DACs overcome these issues by exploiting the targeting power of antibodies, ensuring that the protein degrader is delivered directly to cancer cells. This targeted approach minimises systemic exposure, reduces the necessary dose, and potentially lowers systemic toxicity.

Illustrating DAC Innovation

A pioneering example of DAC development comes from Orum Therapeutics with ORM-6151 from the company's Dual-Precision Targeted Protein Degradation (TPD^2) technology. Designed to target acute myeloid leukemia (AML), ORM-6151 combines an antibody directed against the CD33 antigen with a novel protein degrader that induces the degradation of GSPT1—a protein essential for regulating protein synthesis. In preclinical studies, ORM-6151 demonstrated robust anti-tumor activity while maintaining a favorable safety profile compared to conventional small molecule degraders. This breakthrough attracted significant commercial interest, with Bristol Myers Squibb acquiring rights to the ORM-6151 programme in November 2023. In addition, Vertex Pharmaceuticals and Orum established a collaboration in July 2024 to use Orum's TPD^2 technology for developing novel targeted conditioning agents for use with gene editing. This collaboration underscores the broader therapeutic potential of DAC technology beyond oncology applications.

A Call to Innovation

In summary, the development of DACs marks a significant evolution in targeted cancer therapy. By integrating the specificity of antibodies with the unique capability of protein degraders to eliminate key oncogenic drivers, DACs offer a novel and promising solution to the limitations of traditional ADCs. Early clinical candidates like ORM-6151, coupled with strategic commercial partnerships, provide compelling evidence that DACs could reshape the landscape of precision oncology. As research continues and more clinical data emerge—including efforts to target proteins beyond GSPT1—stakeholders are encouraged to support and explore this innovative modality. DACs have the potential to broaden therapeutic options for patients and set a new standard in the treatment of cancer and other significant diseases.

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