Degrader-Antibody Conjugates 2024: A Landscape Analysis of Stakeholders, Technologies, Pipeline and Partnering from an Industry Perspective

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The technologies and constructs differ in the degradation pathway, either the proteasomal or the lysosomal degradation machinery. Both pathways and more can be stimulated by activating a transmembrane E3 ligase, such as ZNFR3.

For the proteasomal degradation pathway, two different, distinct constructs can be used: the monofunctional molecular glue type or the bifunctional PROTAC type, but both constructs act inside the cell. For the lysosomal degradation pathway, the two major receptors addressed for lysosomal shuttling are the mannose-6-phosphate receptor (M6PR) and the asialoglycoprotein receptor (ASGPR), while binding to a transmembrane E3 ligase such as ZNRF3 induces a broad catalytic activity including proteasomal and lysosmal degradation. Preclinical proof-of-concept studies have been published for most of the DAC technologies, while clinical data are not yet available.

4.2 Degrader-Antibody Conjugates with Molecular Glue-type Degraders

Targeted protein degradation by molecular glue type small molecules is a clinically and commercially validated strategy. Therefore, Orum Therapeutics and Bristol Myers Squibb have prioritized to pursue a strategy where molecular glue molecules are used as the degrader in DACs.

CELMoD ADCs pursued by BMS are DACs which combine an antibody against a clinically validated tumor target and a clinically validated tumor cell-biased CELMoD as the protein degrader molecule. **C**ereblon **E**3 Ligase **Mo**dulation **D**rugs (CELMoDs) are molecules that act as molecular glue to alter the protein-binding properties of cereblon (an important component of the protein degradation cellular machinery) to promote interaction with and degradation of disease-causing proteins. Bristol Myers Squibb's CELMoD library identifies novel substrates and novel degrons which lead to 10 CELMoDs for oncology in full discovery & IND enabling studies.

Orum Therapeutics' dual-precision Targeted Protein Degradation (**TPD^2**) approach covalently attaches protein degraders to antibodies to drive localization to specific cells. The TPD2 technology generates viable drug candidates through an ADC-friendly traceless linker platform which enables the stable conjugation to the glutarimide ring of the cereblon-based degraders (glue or heterobifunctional) to an antibody, without necessitating any modification to the degrader's chemical structure. Upon targeted delivery and intracellular triggering, the linker undergoes rapid hydrolysis, thereby unleashing the active degrader, achieving a seamless and

(IND) application by the end of the year, but did not disclose which modality of EpiTACs have been chosen for the lead program.

5.1.1 ORM-6151

Orum Therapeutics discovered and initially developed ORM-6151, an anti-CD33 antibody-enabled GSPT1 degrader for acute myeloid leukemia (AML). ORM-6151 is the second drug candidate from Orum's Dual-Precision Targeted Protein Degradation (TPD2 TM) approach, which combines the catalytic mechanism of TPDs with the precision of tumor-targeting therapeutic antibodies. Palacino et al. (2022b) generated conjugates using a CD33-targeting antibody (OR000283) produced by engineering the FAb (H&L) sequences from gemtuzumab onto an IgG1 Fc with N297A variant to inhibit Fc-γR binding. Medicinal chemistry optimization of linker-payloads led to the identification of ORM-6151, which is composed of SMol006, a highly potent GSPT1 degrader conjugated to OR000283 via a novel β-glucoronide releasable linker. G1 to S phase transition 1 protein (GSPT1) is a translation termination factor that plays a central role in messenger RNA (mRNA) translation and regulation of the G1/S checkpoint of the cell cycle. GSPT1 may also contribute to tumor cell survival. The degradation and loss of GSPT1 results in the activation of an integrated stress response (ISR), which is hypothesized to lead to cell death in cancer cells, including acute myeloid leukemia (AML) cells.

In November 2023, Orum Therapeutics entered into a definitive agreement under which Bristol Myers Squibb (BMS) has acquired Orum's ORM-6151 program, the anti-CD33 antibody-enabled GSPT1 degrader that has received the FDA's clearance for Phase 1 for the treatment of patients with acute myeloid leukemia or high-risk myelodysplastic syndromes (Press Release Nov 06, 2023). BMS continues the development of ORM-615 under the drug code BMS-986497.

ORM-6151 treatment in CD33-expressing cell lines showed picomolar activity with 10-1000-fold greater potency compared to several GSPT1 degrader molecules including CC-90009 or Mylotarg, and had robust activity in Mylotarg-resistant lines (AML193 and Kasumi6). ORM-6151 also exhibited picomolar potency in in vitro cytotoxicity to primary relapsed/refractory AML patient blasts, with better potency than CC-90009 and Mylotarg. Moreover, ORM-6151 showed minimal cytotoxic activity to healthy hematopoietic progenitor cells, with 10-10,000 fold less toxicity than CC-90009 or Mylotarg.

- Novel EpiTACs were rapidly selected and tested using the EpiAtlas of 270+ tumor- and tissue-specific degraders, including transmembrane E3 ubiquitin ligases, chemokine/cytokine receptors and tissue-enriched internalizing receptors
- EpiTACs drove robust *in vitro* tumoricidal activity in colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) models, independent of KRAS or EGFR mutational status
- *In vivo* tumor models demonstrated EpiTACs degraded mutant EGFR and disrupts downstream signaling, suppressing tumor growth and increasing survival beyond osimertinib standard of care

Cotton et al (2021) published proof-of-concept data from a preclinical study for AbTacs. They developed antibody-based PROTACs (AbTACs), fully recombinant bispecific antibodies that recruit membrane-bound E3 ligases for the degradation of cell-surface proteins. They showed that an AbTAC can induce the lysosomal degradation of programmed death-ligand 1 by recruitment of the membrane-bound E3 ligase RNF43.

R&D Pipeline

According to the company's CEO, EGFR is a good proof-of-concept, but the company is also looking at ion channels or G-protein-coupled receptors (GPCRs) that are hard to target with small molecules. The company's goal is to nominate a candidate to file an investigational new drug (IND) application by the end of the year (GEN Apr 08, 2024).

7.2.5 Firefly Bio

Based in South San Francisco, CA, USA, Firefly Bio emerged February of 2024 from stealth mode with a $94 million Series A financing (Press Release Feb 15, 2024). The financing was co-led by founding investor Versant Ventures and by MPM BioImpact alongside Decheng Capital and with participation from Eli Lilly & Company. Firefly employed 22 people as of June 28, 2024 and plans to expand to as many as 40 by end of the year.

CSO John Flygare, previously at Genentech and Merck, and CTO Bernhard Geierstanger, previously at Novartis and Merck founded Firefly Bio together with 2022 Nobel Prize winner Carolyn Bertozzi. Firefly has developed a novel platform to treat cancer using degrader antibody

the new construct provides a plug-and-play platform with lower complexity compared to other antibody-PROTAC conjugates.

Lehmann et al. (2024) reported the development of a modular approach to quickly generate PROxAb Shuttles by **enzymatically coupling** PROTAC-binding VHHs to off-the-shelf antibodies. The resulting conjugates retained their target binding and internalization properties, and incubation with BRD4-targeting PROTACs resulted in formation of defined PROxAb-PROTAC complexes. These complexes selectively induced degradation of the BRD4 protein, resulting in cytotoxicity specifically to cells expressing the antibody's target. This chemoenzymatic approach provides a versatile and efficient solution for generating antibody-VHH conjugates for targeted protein degradation applications, but it could also be used to combine antibodies and VHH binders to generate bispecific antibodies for further applications.

8.10 REULR Technology

Conventional therapeutics seek to modify natural ligand/receptor signaling biology. InduPro differentiates through its ‘proximity by design’ approach that utilizes induced proximity via bispecific antibodies to create targeted pairings. These designed cis-interactions of cell-surface proteins provide a new paradigm for affecting therapeutic pathways. Proximity by design defines the epitopes driving pairing geometry, the spacing between pairs via the bispecific format, and the relative affinities of the binding pairs. This design effort is key to discovering and refining productive induced-proximity pairs.

At the heart of InduPro’s proximity by design approach is its industry-leading proximity-discovery toolbox. InduPro has created a proprietary Membrane Interactomics (MInt) database that captures information about naturally, or inherently, proximal surface proteins in disease-relevant systems. An essential component of understanding inherent proximity is InduPro’s microenvironment mapping technology that profiles native protein environments in high resolution with exquisite spatio-temporal control. The insights provided by MInt include identifying the most compelling applications of induced proximity, enabling selective dual targeting within tissue environments and cellular subtypes, as well as revealing new biology and therapeutic opportunities. The MInt platform is combined with the ability to broadly create and screen bispecific pairings of antibodies with diverse epitope, affinity and spacing to create optimal molecules.