Will blood cancer medical advances begin with BCMA?

A surge of efforts focused on the drug target B cell maturation antigen could transform the treatment of multiple myeloma and help to establish the relative merits and optimization strategies for emerging treatment modalities with wider applications.

John Hodgson

Sometimes a drug target is just a drug target. But B cell maturation antigen (BCMA) is not just one of the hottest targets for multiple myeloma; it is also a testing ground for therapeutic platforms that are increasingly becoming established in oncology, such as antibody–drug conjugates (ADCs), bispecific antibodies and cell-based therapies. As such, the clinical advances and dealmaking around the target could help bring substantial changes to the treatment of cancer and potentially also shift the balance of power between major industry players in the oncology area.

Discovered in 1992 at the laboratories of Andrea Tsapis at the Institut de Génétique Moléculaire in Paris, BCMA marks out mature B lymphocytes and contributes functionally to the longevity of these cellular sentinels, the front-line troops of the immune system. But it also aids the survival of the mutated B cell clones that characterize multiple myeloma, a relatively common and still incurable cancer of bone marrow cells.

For drug developers, BCMA is an obvious first port of call in designing a medicine to tackle the disease. "It's a scientifically validated target in multiple myeloma," said Mark Gergen, president and chief business officer at Poseida Therapeutics, a company that is developing cell and gene therapies, including allogeneic chimeric antigen receptor (CAR) T cell products, "and that makes it a 'derisked' target, in a business sense." "You could go for several different targets in multiple myeloma," said Bob Valamehr, chief development officer at Fate Therapeutics, a developer of CAR natural killer (NK) cells, "but BCMA is the most comprehensive. It's the foundation you start off with if you want to capture most of the multiple myeloma population."

At the virtual American Society of Hematology (ASH) conference in December 2020, many of the leading companies developing BCMA-targeted drugs for multiple myeloma presented data. Predominantly, the mood was upbeat: all three classes of BCMA-targeted immunotherapeutics in the clinic—ADCs, T cell-engaging bispecific antibodies and CAR T cell therapies—demonstrated remarkable antitumor activity. "There are some pretty impressive response rates for BCMA therapies," said Gergen, although he warns that some of the leading agents come with serious toxicity.

Antibody opportunities

The most clinically advanced agent targeting BCMA is an ADC: GlaxoSmithKline's (GSK) Blenrep (belantamab mafodotin) was approved by the US Food and Drug Administration (FDA) in August 2020 and established a performance standard for BCMA-targeted agents, but that standard is already being overtaken.

Clinicians and stock analysts often reduce data from cancer trials to a handy single number—the overall response rate (ORR), which is the proportion of treated patients in which there is some sign of tumor shrinkage. In the DREAMM-2 clinical trial on which Blenrep's approval was based, the ORR was 31%, an impressive result in patients who have already failed on many other treatments. To be prescribed Blenrep at all, a patient must have failed to respond to least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent.

At least two other BCMA-based ADCs are in development. Phase 1 data for AstraZeneca's MEDI2228 was shown at ASH last year and indicated an ORR of 61% for its best-performing dose. Heidelberg Pharma's HDP-101 is at the preclinical stage.

The ADCs are effective, but with harsh side effects. Blenrep's approval came with a black box warning of ocular toxicity, including severe vision loss, while in the phase 1 trial of MEDI2228, adverse events stopped most patients taking the drug even at a scaled-down maximum dose.

Meanwhile, other BCMA-directed platforms—such as T cell-engaging bispecific antibodies and CAR T cell therapies—seem to be performing better, although drawing direct comparisons is hampered by important differences in the patient populations studied.

Data on at least seven BCMA-directed T cell engagers in multiple myeloma were unveiled at ASH, with ORRs ranging from 63–83%, albeit with substantial toxicities.

One of the most important and difficult-to-manage side effects is cytokine release syndrome, an incompletely understood phenomenon often seen as a cascade resulting from general activation of bystander immune cells. Part of the solution to cytokine release syndrome may lie in honing the component parts of what are complex therapeutic entities.

T cell engagers (or bispecific antibodies) combine two antibody-like portions: one to attach to a tumor-specific antigen (for instance, BCMA) and one (anti-CD3) to bind the CD3 antigen on the patient's endogenous tumor cell-killing T cells. At this point, it is unclear which of the BCMA/CD3 bispecifics will work best, but their clinical properties are likely to depend on the properties and origins of the components.

For instance, the ASH data presented by Regeneron showed its REGN5458 to be one of the safest of the current crop of BCMA/CD3 bispecific antibodies. But cytokine release syndrome still occurred in 39% of the patients. Regeneron has another BCMA/CD3 bispecific antibody following behind REGN5458, REGN5459. This is not just another "shot on goal" according to Regeneron's senior vice president of translational and clinical sciences, hematology, Andres Sirulnik. "The two assets differ principally in the affinity of the anti-CD3 arm for CD3," he said,

Table 1 | Recent deals involving BCMA-targeted therapies (2017–2020)

Date	Partner 1	Partner 2	Summary
May 2017	TeneoBio	Poseida Therapeutics	Poseida Therapeutics signs deal with TeneoBio to use their UniDabs technology to develop its CAR T programs including P-BCMA-ALLO1 against cancer. Poseida will pay TeneoBio an upfront payment and potential milestone and royalty payments.
August 2017	Sutro Biopharma	Celgene	Sutro Biopharma and Celgene refocus their 2014 immuno-oncology partnership involving four preclinical development programs including their ADC program targeting BCMA. Celgene now has rights to acquire a second program to reach IND status, and will make undisclosed payments to Sutro.
December 2017	ONCOtracker	Juno Therapeutics	Juno Therapeutics enters into an agreement with ONCOtracker and the Fred Hutchinson Cancer Research Center for intellectual property within the field of combinations of GSIs and BCMA-directed engineered T cells.
December 2017	Legend Biotech (a subsidiary of GenScript Biotech Corporation)	Janssen Biotech	Janssen Biotech signs global partnership with Legend Biotech to develop, manufacture and commercialize LCAR-B38M, a CAR T cell drug candidate targeting BCMA for multiple myeloma. The deal includes $350 million upfront in cash to Legend Biotech and potential milestone payments.
April 2018	Pfizer	Allogene Therapeutics	Allogene Therapeutics signs an asset contribution partnership with Pfizer to gain rights to 16 pre-clinical CAR T cell assets (previously licensed from cell therapy specialist Cellectis SA and Servier) to develop into allogeneic CAR T cell therapies.
December 2018	Guizhou Bailing Group Pharmaceutical	Chengdu Kaiyin Pharmaceutical	Guizhou Bailing Group Pharmaceutical and Chengdu Kaiyin Pharmaceutical enter into a cooperation contract to co-develop CAR T cell therapeutics targeting CD24, CD20 and human BCMA for the treatment of cancer.
March 2019	ProMab Biotechnologies	NantKwest	NantKwest and ProMab Biotechnologies sign licensing deal to develop a BCMA-targeted antibody sequence for multiple myeloma in the development of CAR receptor-based natural killer cell therapies. The deal includes an option for up to five undisclosed targeting sequences for exclusive use.
November 2019	MD Anderson Cancer Center	Takeda Pharmaceutical Company	Takeda Pharmaceutical enters into a partnership to develop and commercialize up to four CAR-directed natural killer (CAR NK)-cell therapy programs from the University of Texas MD Anderson Cancer Center's NK platform, including a CD19-targeted CAR NK cell therapy and a BCMA-targeted CAR NK cell therapy for the treatment of B cell malignancies and other cancers.
December 2019	Tongji Medical	Shenyang Pharmaceutical Technology	Tongji Medical College partners with Shenyang Pharmaceutical Technology for the development of a dual anti-BCMA/anti-CD38 CAR T cell therapy against multiple myeloma.
January 2020	Allogene Therapeutics	SpringWorks Therapeutics	Allogene Therapeutics enters into a clinical trial partnership to evaluate ALLO-715 AlloCAR T therapy in combination with SpringWorks Therapeutics's nirogacestat in multiple myeloma.
February 2020	ProMab Biotechnologies	Caribou Biosciences	Caribou Biosciences enters into an agreement to develop its CB-011 program targeting the BCMA$^+$ tumors including multiple myeloma, using ProMab Biotechnologies' humanized single-chain variable fragment (scFv).
April 2020	TeneoBio	Kite Pharma (a subsidiary of Gilead)	Kite Pharma enters into a license and collaboration deal with TeneoBio to develop CAR T cell therapies, that will see Kite acquire exclusive rights to specific antibodies targeted to BCMA, including one antibody in a CAR format.

ADC, antibody–drug conjugate; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; GSI, γ-secretase inhibitor; IND, investigational new drug.

"and we believe this may provide a differentiated pharmacokinetic profile and therapeutic window by modulating the strength of CD3 engagement and, therefore, optimizing T cell activation."

A wider therapeutic window implies that a compound does not have to be administered at concentrations close to the maximum tolerated dose: there is more wiggle room for developers. For immunotherapies, the precise way in which an antibody binds its target will affect the therapeutic window. For engagers, the nature of T cell binding (through CD3, for instance) is also likely to alter clinical performance.

TeneoBio, a small developer of domain antibodies, is not only working with many of the companies in the antibody-targeted cancer therapy space, but is also developing its own BCMA/CD3 bispecific engager, TNB-383B. TNB-383B serves as a showcase of TeneoBio's immunotherapy tool box: it is composed of two separate BCMA-binding antibody domains and a CD3$^+$ T cell engager from TeneoBio's 'plug-and-play' CD3 antibody library.

"We combine a diverse set of CD3 binders with different options for binding tumor antigens," said Omid Vafa, chief business officer at TeneoBio. "Those targets could be biparatopic epitopes on the same antigen or two separate tumor antigens." That kind of flexibility of construction has enabled TeneoBio to sign deals with Gilead's Kite unit, Poseida Therapeutics and ArsenalBio for developing CAR T products, as well as with GSK-acquired Tesaro and Johnson & Johnson for developing multi-specific antibodies. Significantly, said Vafa, the deal with GSK concerns the treatment of solid cancers, a new frontier for multi-specific targeted antibodies.

TeneoBio's broader plan is to spin its therapeutic assets off into individual stand-alone business units. Logically, the first one is called TeneoOne, a vehicle containing BCMA-targeted TNB-383B. AbbVie, TeneoBio's partner for the BCMA program, provides funding for development and—before or soon after phase 1 is complete—has the option to acquire TeneoOne.

Expanding the cell therapy arsenal

The ORRs reported at ASH for two CAR T cell products targeted at BCMA were impressive—97% remission for Johnson & Johnson's cilta-cel (LCAR-B38M CAR T cells) and 73% for bluebird bio's bb21217—although again limited by widespread, if manageable, toxicities.

Johnson & Johnson jumped into the BCMA field through a 2017 deal with Legend Biotech on LCAR-B38M involving a $350 million upfront payment (Table 1), after the drug impressed researchers at the annual American Society of Clinical Oncology meeting earlier that year. However, while multiple pharmaceutical companies and large international biotech firms are active in the development of T cell engagers, fewer have committed to a future in CAR T cell therapy. So far, the field has been dominated by autologous cell therapies that target CD19, another B cell antigen, to treat lymphomas. Working initially with Carl June's group at the University of Pennsylvania, Novartis pioneered the development of the first CAR T cell product, the CD19-targeted tisagenlecleucel, approved by the FDA in 2017. Also in 2017, Gilead Sciences bought Kite Pharma for $11.9 billion and brought another CD19-targeted CAR T cell therapy, Yescarta (axicabtagene ciloleucel) to the market. But Bristol Myers Squibb, which gained the CAR T pioneer Juno via its 2019 acquisition of Celgene, struggled getting its CD19-targeted liso-cel to FDA approval, eventually receiving it in February 2021. Bristol Myers Squibb is also awaiting the FDA's imminent decision on ide-cel, its BCMA-targeted CAR T cell therapy for multiple myeloma. Meanwhile it has stopped development of a second BCMA-targeted CAR T cell therapy orva-cel, writing off costs of $470 million. When the technology is moving fast a back-up CAR T cell therapy may be surplus to requirements.

The bespoke nature of autologous CAR T cell therapy products may be anathema to big pharma. However, off-the-shelf allogeneic cell therapies look at lot more like the traditional 'pill in a bottle'. If they perform successfully in clinical trials, pharma's enthusiasm for cell therapy might change quickly. "As soon as somebody cracks the code on allogeneic CAR T, you're going to see a feeding frenzy," said Gergen. He points to multiple large companies with substantial sales in oncology but little historical activity in cell therapy. "If allogeneic cell therapy works as promised, they have to buy in, because much of their revenue and pipeline could be at risk," said Gergen.

In some quarters, CAR T cell technology is about modular assembly. Poseida has three BCMA-directed cell products for multiple myeloma in development. P-BCMA-101, which is in phase 2 trials, is an autologous product, recycling a patient's own cells; P-BCMA-ALLO1 is an allogeneic version, in which gene editing has been used to knock out cross-reactive functions; and dual CAR T (BCMA/CD19) is a further adaptation of the allogeneic cell that targets two multiple myeloma antigens. Devon Shedlock, Poseida's head of R&D, says the prototypic autologous product P-BCMA-101 has taught the company a lot about manufacturing, about screening for safety and potency, and, perhaps most significantly, about the importance of stem cell memory T cells (Tscm). "One of the mechanisms of relapse or resistance to treatment is that many CAR T cells don't stick around," he said. "However, if you can manufacture a product with Tscm cells enabling them to engraft (in bone marrow), it reduces the possibility of relapse." Shedlock argues that, for allogeneic treatments, persistence of Tscm cells to create long-term bone chimerism in the patient is another mechanism for improving outcomes. "Allogeneic cells come from a different person, and if they don't persist or engraft, it's not clear that a durable response is possible without Tscm cells," he said.

In designing modular and systematic systems, other companies have turned to NK cells—lymphocytic cells that, unlike T cells, do not have to be primed by antigen-presenting cells. Early clinical use of CAR NK cells has shown considerably reduced cytokine release syndrome and neurotoxicity. Furthermore, as they do not cause graft-versus-host reactions, they may be innately suited to off-the-shelf allogeneic uses.

The major challenge with NK cells has been that they are more difficult than T cells to engineer. "NK cells just don't like to take up DNA, whether through transduction or transfection," said Valamehr. So Fate does its engineering and DNA editing in the progenitor cells that develop into NK cells, the induced pluripotent stem cells (iPSC). Having packed in all the right attributes, the iPSC serves as a master cell line for an off-the-shelf manufacturing process. "Just like monoclonal antibodies," said Valamehr.

Fate's BCMA-directed product is on the verge of entering the clinic, and it illustrates the modular nature of CAR NK cell assembly. It contains the high-affinity CD16 receptor to activate NK cell activity, an IL-15 receptor fusion to enable the NK cells to persist and a BCMA CAR to target multiple myeloma cells. On top of that, CD38 expression has been knocked out in order to prevent the agent self-destructing when used in combination with anti-CD38 antibodies such as Johnson & Johnson's Darzalex (daratumumab).

Where BCMA-directed products lead, other targeted immunotherapies may follow. The clinical development of products such as allogeneic T cell therapies and CAR NK cell products builds not only on experiences with autologous cell technology, but also on knowledge of the clinical performance with bispecific antibodies and other T cell-engaging variants. Consistency in manufacturing and mastering host-versus-graft rejection may yet slow matters down, but BCMA-targeted agents are cutting a pioneering path to the development of cancer therapies with much longer lasting effects.

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