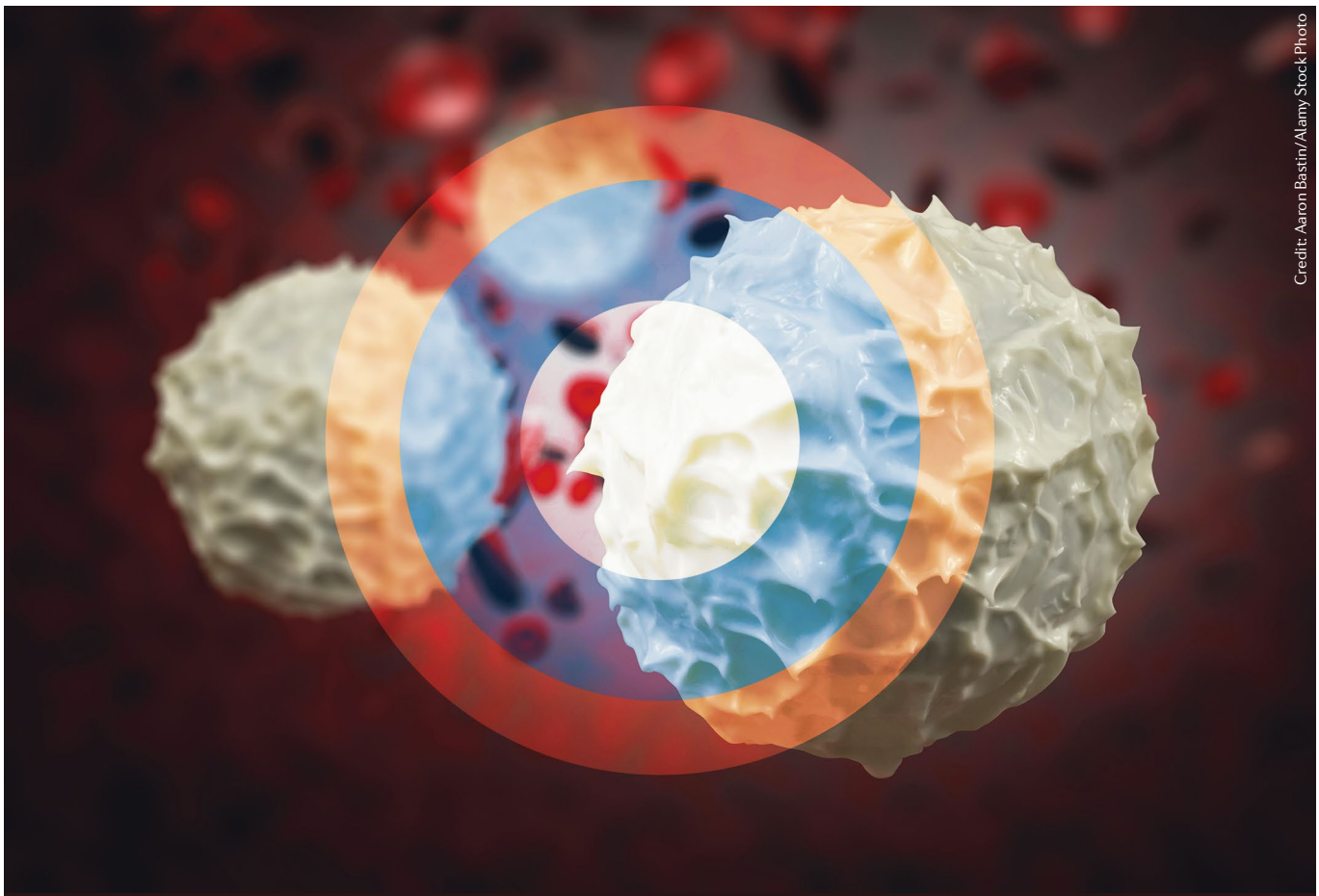

The BCMA bonanza

A long and growing list of anti-BCMA candidates — including chimeric antigen receptor-T cell therapies, antibody–drug conjugates and bispecific antibodies — are contending to transform multiple myeloma treatment.

Asher Mullard

Great targets are scarce, and so researchers across the biopharmaceutical industry tend to pile in when they come along. And when the biology is just right, such targets promise not just new therapeutic options and commercial opportunities, but also rare chances to explore emerging drug modalities. BCMA, for the treatment of multiple myeloma, is the latest case in point.

Leaders in this space are set to submit first-in-class candidates for regulatory approval shortly. GlaxoSmithKline (GSK) is working to finalize the dossier for its antibody–drug conjugate (ADC) belantamab mafodotin, previously known as GSK2857916, by the end of the year. Also out in front, Celgene and Bluebird Bio are anticipating regulatory approval in 2020 for their chimeric antigen receptor (CAR)-T cell therapy idecabtagene vicleucel, previously known as bb2121. But a long list of other ADCs, bispecifics, CAR-Ts and naked monoclonal antibodies are marching to and through the clinic (TABLE 1). Indeed, BCMA is the second most popular defined target in the global cell therapy pipeline, surpassed only by CD19.

"If you think about all the [CAR-Ts], ADCs and bispecifics that are going after this one target, it's pretty remarkable," says Alfred Garfall, a haematologist at the hospital of the University of Pennsylvania. Other historically hot targets like PCSK9 for cardiovascular disease and immune checkpoint PD1/PDL1 blockers for oncology hold promise for large populations, but the BCMA activity is all the more impressive for its focus only on multiple myeloma.

Interest here is driven in part by the clinical challenges of multiple myeloma, the second most common haematological malignancy after non-Hodgkin lymphoma. Despite big advances in recent years with chemotherapy, proteasome inhibitors, immunomodulating thalidomide derivatives and CD38-targeted antibodies, nearly all patients still eventually relapse. A dire need for new drugs remains, and a market exists

Table 1 | **Select list of anti-BCMA candidates**

Drug name	Sponsor	Properties	Status
CAR-T			
Idecabtagene vicleucel (bb2121)	Celgene/Bluebird Bio	CAR-T	Phase III, approval anticipated in 2020
JNJ-4528/LCAR-B38M	Johnson & Johnson/Nanjing Legend Biotech	CAR-T	Phase II
P-BCMA-101	Poseida Therapeutics	CAR-T, with safety switch	Phase II, filing anticipated in 2020
bb21217	Celgene/Bluebird Bio	CAR-T, enriched for memory T cells	Phase I
JCARH125	Celgene/Juno Therapeutics	CAR-T	Phase I/II
ALLO-715	Allogene	Allogeneic CAR-T, with an off switch	IND approved
Antibody–drug conjugate			
Belantamab mafodotin (GSK2857916)	GlaxoSmithKline	Afucosylated antibody conjugated to monomethyl auristatin F	Phase II, filing anticipated in 2019
MEDI2228	AstraZeneca	Antibody conjugated to pyrrolobenzodiazepine	Phase I
CC-99712	Celgene/Sutro Biopharma	Undisclosed	IND approved
Bispecific format			
AMG 420	Amgen	BiTE	Phase I/II
AMG 701	Amgen	Half-life extended BiTE	Phase I
CC-93269	Celgene	Bispecific antibody	Phase I
REGN5458	Regeneron	Bispecific antibody	Phase I/II
JNJ-64007957	Johnson & Johnson	Bispecific antibody	Phase I
PF-06863135	Pfizer	Bispecific antibody	Phase I
Monoclonal antibody			
SEA-BCMA	Seattle Genetics	Afucosylated monoclonal antibody	Phase I

BiTE, bispecific T cell engager; CAR-T, chimeric antigen receptor-T cell; IND, investigational new drug.

to support this. Multiple myeloma drugs achieved sales of nearly US$14 billion in 2017, and are forecast to reach nearly $29 billion in sales by 2027.

The BCMA target is also so clean in its expression profile that it provides an irresistible testing ground for novel modalities. "This is a good opportunity to really explore different platforms, without worrying about the target itself. And hopefully, this will help us to better examine different targets in the future," says Yusri Elsayed, vice president of haematological malignancies at Janssen, a company that is exploring multiple BCMA-targeting modalities.

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"When one looks at antibody–drug conjugates, bispecifics and CAR-Ts, we do envision a world where all these therapies are going to coexist, and that they will have different profiles that will be dependent on the patient populations and the targets," adds Greg Friberg, head of oncology development at Amgen, a company that works on all three modalities. "The reality is we're going to have to wait and see how that plays out."

BCMA beginnings

The BCMA gene was identified in 1992, and was found shortly after to be associated with B cell maturation and with multiple myeloma. Further work revealed that BCMA is only expressed on plasma cells, that it is over-expressed on multiple myeloma cells and that it is dispensable for overall B cell health and homeostasis. These characteristics make it a compelling target, with a rock solid disease association and limited risk of off-tissue toxicity.

By 2007 researchers across industry had identified monoclonal antibodies and ADCs that bound BCMA and killed cancer cells, but early development work with these stalled. For as yet undetermined reasons, early candidates just didn't drive sufficiently strong efficacy signals to push the field forward. And at the same time, the multiple myeloma community was so focused on the development of proteasome inhibitors, thalidomide derivatives and CD38 blockers that BCMA fell by the wayside, says Yu-Tzu Tai, who studies multiple myeloma at the Dana–Farber Harvard Cancer Center and who has collaborated with GSK, Amgen, AstraZeneca and Johnson & Johnson on the preclinical validation of BCMA-targeted biologics.

"This is unfortunate because it kind of delayed the development of antibody formats for multiple myeloma, but it is also very important because clinicians now know how to use those other drugs," says Tai.

The delay created an opening for CAR-T developers, mainly in academia initially, who were working on a then-emergent and now burgeoning modality in which T cells are extracted from patients and

engineered ex vivo to seek out and destroy cells expressing antigens of interest. By 2014, as GSK was just starting trials of its ADC, researchers at the NIH were enrolling patients into a phase I trial of BCMA-targeted CAR-Ts. CD19-targeted CAR-Ts were inducing long-lasting responses in leukaemias and lymphomas, and haematologists hoped that this strategy would offer durable remissions — if not cures — in multiple myeloma as well.

With initial tweaking of the CAR-T technology, researchers started seeing remarkable responses. In a phase I trial of Celgene and Bluebird's idecabtagene vicleucel in 33 patients with relapsed or refractory multiple myeloma, who had undergone at least 3 prior lines of therapy, 85% of patients had an objective response with treatment and the median time to progression was 11.8 months. Reporting these results in the *New England Journal of Medicine* in May, the study investigators noted that this compared favourably with past trials of several salvage therapies in multiple myeloma, associated with response rates of 30% and medians of 4 months to progression.

Celgene and Bluebird now anticipate an approval for their CAR-T in 2020, and are already working on follow-on CAR-T products that they hope will offer better results yet. "The field of CAR-T cells is still in its early adolescence in terms of what is the optimal way to engineer and manufacture these products. It's important to iterate and to test different concepts," says Kristen Hege, vice president of translational medicine for hematology/oncology at Celgene. With bb21217, for example, Celgene and Bluebird are culturing the CAR-T cells with a PI3K inhibitor to skew them more towards an early memory phenotype.

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Other firms are also enjoying BCMA-targeted CAR-T successes. At the American Society of Hematology (ASH) annual meeting last year Johnson & Johnson and Nanjing Legend Biotech reported an 88% overall response rate and median progression-free survival of 15 months in 57 relapsed or refractory patients who had undergone on average 3 prior therapies, for example.

Given the small sizes of these trials and key differences in their designs — in terms of patient inclusion criteria, average prior lines of therapy, whether lymphodepleting chemotherapy was used and more — the results of the various anti-BCMA trials should not be compared with one another.

"They're all impressive," says Garfall, who was an investigator on a trial of a BCMA CAR-T that was partially funded by Novartis. This marks an often overlooked breakthrough, he adds, because one of the big questions for the CAR-T field was whether it would be possible to make these therapies with any target other than CD19. "The one big take-home lesson from BCMA is that CAR-T cells will work for other targets," he adds.

And yet the durability of the CAR-T responses, even in the patients who respond best to these treatments, has not been as high as initially hoped. Patients are still relapsing at around the 1-year mark. "This is a little disappointing," says Garfall. With Novartis's CD19 CAR-T tisagenlecleucel in relapsed or refractory diffuse large B cell lymphoma, by contrast, median duration of response had not been reached after an average of 19 months of follow-up, the company reported last December.

The biology behind the lack of durability with BCMA CAR-Ts remains to be resolved. Myeloma-intrinsic factors may be to blame, for instance if the nature of the myeloid cells or the microenvironments in which they reside help diseased cells to hide out until after the CAR-Ts pass. Or, it might have to do with patient-specific factors, for instance if prior lines of therapy are compromising T cell health, with downstream consequences for the collection and production of the autologous cell therapies.

"The next big thing for multiple myeloma that we need to crack is what makes a difference in terms of durability and cure-ability," adds Garfall. "I would love to see some focused effort on that, rather than just more of the same or similar BCMA CAR-Ts being churned out."

But at the same time, CAR-T developers see BCMA as an invaluable opportunity to debug the emergent modality. First-hand experience with manufacturing and delivery bottlenecks is key to figuring out how to overcome these burdens, for example. And while the potentially fatal cytokine release syndrome that is associated with this modality is manageable, the BCMA programmes could provide important lessons as to how to further lower the risks of systemic inflammatory responses.

"A core aim of ours is to learn and improve as we go along, so this is definitely a great opportunity for us," says Elsayed. "We will learn from this with regard to the CAR-Ts, how to use them in the clinic, how to combine them with other drugs, and more."

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Antibody advances

Drug developers are also making a move with enhanced antibody formats.

GSK's ADC belantamab mafodotin, the most advanced of these, uses a BCMA-targeted antibody to deliver a chemotherapeutic monomethyl auristatin F warhead directly to cancerous cells. The expression profile of BCMA is so clean — restricted to plasma cells and overexpressed in myeloma — that it is the perfect candidate for an ADC, adds Hal Barron, CSO at GSK. "If you can find an overexpressed antigen that is unique to a disease, it is really an ideal target for an ADC. There may not be as many of these as we had hoped, and ADCs might have been a little overhyped, but I think there are more cancers where these antigens are overexpressed and can be taken advantage of."

The antibody portion of belantamab mafodotin has been afucosylated, he adds, to optimize the ADC's ability to induce antibody-dependent cellular cytotoxicity (ADCC) and cell killing via the recruitment of natural killer cells.

Here too phase I results have been encouraging. In a trial of belantamab mafodotin in 35 relapsed or refractory patients, the majority of whom had received at least 5 lines of prior therapy, 60% of patients achieved an overall response, investigators reported in *Lancet Oncology* last year. The median progression-free survival was 12 months, they added in an update in *Blood Cancer Journal*. The most common side effects include corneal events, thrombocytopenia and anaemia, all linked to the ADC's cytotoxic warhead.

These results have prompted GSK to double down on BCMA, launching a broad

development plan that is already testing the drug in more than 300 patients, with more combination trials to come. An ongoing pivotal trial is underway and anticipated to read out before the end of the year, with a regulatory filing for this first-in-class agent expected shortly after. And Barron is optimistic about this ADC's ability to compete.

If the current data hold out, the ADC offers response rates and durability that are in line with the effects of CAR-Ts, he explains, without the risk of cytokine release syndrome. As an off-the-shelf agent, it is simple to manufacture and get to patients, likely translating into faster access and lower costs. It can be readily tested, combined and sequenced with other agents to improve efficacy further still. And it has the potential to be first to market.

"When I think about all those things in aggregate, that makes me very excited about [belantamab mafodotin] and its ability to help patients," says Barron. "Having an agent that can be used off the shelf offers a big advantage over things that require plasmapheresis and reinfusion, and because of that autologous cell therapies have to have exceptionally better efficacy or safety profiles to warrant the cost and inconvenience," adds Barron, who was on the board of Juno Therapeutics and remains excited about the overall prospects of CAR-Ts.

Off-the-shelf bispecific formats are also in contention. These are designed to bind the BCMA antigen on myeloma cells with one arm, and to bind CD3 on the surface of T cells with the other, resulting in T cell activation, cell killing and cytokine production.

Amgen's AMG 420, the most advanced of these, belongs to a subgroup of bispecifics called bispecific T cell engagers (BiTEs). These are smaller than traditional antibodies, and consist of two antibody domain fragments joined via a linker. They are thought to offer exquisite activity, but with shorter half-lives than full-length antibodies.

In a cohort of ten patients with relapsed or refractory multiple myeloma who had been on at least two lines of prior therapy and who received the recommended dose of AMG 420, 70% achieved an overall response, the company reported at the ASH meeting last year. The median duration of response was 9 months, the company reported at the American Society of Clinical Oncology annual meeting in June.

Adverse events in this trial included infections and cytokine release syndrome, although at a lower rate and lower severity than with CAR-T products.

Amgen has long been working in the BCMA space, says Friberg, and their decision to advance a BiTE is informed by their own false starts. "We've actually brought three different ADCs into the clinic, and in all cases we were able to see responses but we just didn't see the depth and the durability that we wanted. We think BCMA is a perfect target for a BiTE, which we hope can unlock more profound activity."

> We need to do more to under-stand how to best manage the disease using these tools

Other antibody-based agents are in earlier phases of development, including naked antibodies that are still in the running. Seattle Genetics advanced an afucosylated naked antibody into phase I trials late last year, for example.

Spoilt for choice

In many ways, drug developers, oncologists and patients stand to benefit from having so many BCMA-targeted agents to choose from.

"They are all powerful," says Tai, who also emphasizes that results from phase I trials cannot be compared. Given unique sets of advantages and disadvantages, and the near universal relapse rate of multiple myeloma, more is better. "Now we need to do more to understand how to best manage the disease using these tools."

For instance, the therapeutics may have different activity profiles in different patient populations. ADCs that bring chemotherapeutic warheads directly to cells, for instance, can induce cell death even when the immune system is depleted, potentially offering activity even in the most immunocompromised patients. Bispecific formats that rely on the functional T cells to kill cancerous cells, by contrast, may have their place earlier in the disease when the disease bulk is lowest and the immune system is in the best shape.

The field is also going to have to figure out how to combine and sequence the various BCMA-targeted agents with other drugs to achieve the best results. GSK already has trials ongoing to evaluate its belantamab mafodotin in combination with current standard-of-care regimens, as well as with Merck & Co.'s PD1-blocking pembrolizumab. Because the ADC induces cell death not only through its warhead but also via ADCC and immune effector cells, researchers speculate that it might act synergistically with immune-modulating drugs.

Combination and sequencing strategies are in the works for bispecifics and CAR-Ts.

Administration profiles offer another level of differentiation, with implications for patient preferences, optimal combination use and sequencing strategies. CAR-Ts, while onerous to make, are only administered once. GSK doses its ADC via a 1-hour infusion, once every 3 weeks. And Amgen's AMG 420 is delivered by continuous infusion via a pump for 4 weeks at a time. (Amgen's AMG 701 is a half-life-extended BCMA-targeted BiTE that might offer more convenient delivery.)

Given all of the patient-population hypotheses and treatment-combination permutations, the multiple myeloma community has years of BCMA research ahead of it. "It's one of those success problems, and it's a great problem to have," says Celgene's Hege, whose company has five different BCMA candidates, in three modalities, in the clinic.

But there is also a risk that the field is approaching a place of diminishing returns — with a cost for patients that is hard to quantify. At the American Association for Cancer Research meeting in Atlanta earlier this year, the director of the FDA's Oncology Center of Excellence Richard Pazdur called out drug developers for chasing the crowd with PD1/PDL1 blockers, to the detriment of the clinical trial system and the rest of the cancer pipeline. "Do we just have too many of these same drugs here?", he asked in the session 'PD-1 Pandemonium'.

BCMA, once itself passed over in favour of trendier targets, could soon prompt the same questions. With so many agents already in the clinic, are trials that dip into a limited pool of patients asking the most important questions? And, are other targets falling through the cracks as a result?

> When is enough enough? That's a hard question

"When is enough enough? That's a hard question," says Hege. "You want to really prosecute on outstanding targets with as many novel strategies as you can. And at the same time, you can't lose sight of the reality that there is probably another great target out there waiting to be discovered."