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Special Report on Biotherapeutics: Is antibody listening?

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If there is one technology that is evolving faster than its end-users' needs, it has to be the telephone.

A device that once literally tethered its user to a wall evolved into a portable if bulky electronic shoe-box. And as circuitry evolved, so too did the size of the phone, to the point where it can now be secretly palmed from user to user.

And perhaps more aggressively than its physical form, the applications of telephonic technology have changed rapidly.

What was once simply a device for transmission of verbal communication became a mechanism to maintain a personal calendar, exchange emails and text messages, and eventually, to take unplanned photographs at the ends of retractable sticks.

Today, there are so many apps available to phone users that the handheld device—when not secreted over an ear—has become everything from a gaming console to a digital publishing platform to a living record of mundane daily existence. And every now and again, it is even a telephone.

If there is a biotechnology equivalent to the telephone, it is likely the antibody, which outside of its natural biological functions within each of us, served for many years as a detection platform for proteins on gels and pathogens in environmental and medical samples.

It too evolved, however, in the medical sphere to become a vital component of the therapeutic armamentarium, being injected and infused into patients to modulate the activity of cell surface markers linked to everything from cancer to autoimmune disease.

As the first generation of antibody therapeutics go off patent, new applications arise to expand the repertoire of functions for the basic antigen-binding platform, whether in the form of smart-bomb antibody-drug conjugates (ADCs) or immune-cell-recruiting multispecific complexes or reductionist fragment-based therapies.

Cloak and dagger

"The concept of ADCs has been around since before the advent of monoclonal antibodies," says Peter Senter, vice president of chemistry at Seattle Genetics. "But putting it into practice was very difficult because a lot of the clinical parameters for making things work weren't really well understood."

"Several molecules had gone into clinical testing that looked like they might be interesting based on preclinical studies, but they turned out to be fairly toxic and ineffective," he continues. "So, we picked it apart and looked at the impact that drug potency had, the impact that linker stability had, conjugation chemistry, pharmacokinetics and antibody specificity."

The result for Seattle Genetics was FDA approval of one of the two ADCs currently on the market: CD30-directed Adcetris (brentuximab vedotin) for Hodgkin's lymphoma and systemic anaplastic large cell lymphoma.

As Senter suggests, the original idea of ADCs was to use the antibody to simply deliver a toxic payload to the cells carrying specific targets. Upon entry to the cell, the payload would be released and the cell would be destroyed. In part, this is why ADC research has focused so heavily on cancer where cell surface receptors are often over-expressed relative to nearby healthy cells (see also sidebar "Not just cancer" below after the end of this article).

But while this is one mechanism of activity of ADCs, Senter continues, the story may be much more complicated than originally thought.

“What we’ve discovered using heterogeneous tumor models is that once the drug is released inside the target cell, it can not only stay there, but diffuse out and affect cells in the neighboring vicinity that might be antigen-negative,” he explains. Thus, the drug may not only kill the target cells but also the cells in the surrounding environment that would not otherwise be exposed to treatment.

And, he says, there is evidence that another cell found commonly within the tumor microenvironment may also play a role: macrophages.

“We’re finding that macrophages can take the conjugate up and release the drug as well,” Senter offers. “Once it gets released in a macrophage, it can diffuse outside the cell and get into tumors.”

“A third mechanism that we’ve discovered—and this is one that we think is really interesting—is that treatment of Hodgkin’s lymphoma cells with ADCs can lead to a process called immunogenic cell death,” he adds. In this case, treatment triggers changes in the target cell and the release of soluble signals that attract T cells to the tumor, prompting an immune response.

“In a general sense, the field is looking very promising, because there are more than 50 ADCs in various stages of clinical development,” Senter enthuses. “And many of them are showing very pronounced activities.”

“There’s our drug,” he lists. “There’s Kadcyla from Genentech-Roche, an approved drug. And then there are other agents in Phase 3 clinical testing on a variety of different types of malignancies that look rather encouraging.”

Even with only two products on the market, a report published in July suggested that the ADC market in 2015 was worth about $900 million. Furthermore, by 2025, this value could rise to $10 billion with the expected commercial launch of another 10 ADCs. And the prospect of another 60 or so therapeutic candidates in preclinical and discovery-stage development bodes well for the market.

But, as with any biotechnology effort, there is a great distance between discovery and market, and this may be particularly true for ADCs, which are particularly complex molecules.

Into the weeds

ADCs have a lot of working parts—targeting mechanism, payload, linker—and as Senter suggests, optimizing each of those components is essential to generate a viable biotherapeutic.

The choice of the drug component can be critical to the successful application of an ADC, particularly in cases of multidrug resistance (MDR), explains Gregory Adams, chief development officer at Eleven Biotherapeutics.

“If you have treated a patient who has breast cancer for a long time with a chemotherapeutic regimen, you could have a situation where their MDR is up-regulated in tumor cells,” he says. “Then you come in with ADC and that drug payload, once it gets off the antibody in the lysosome and mixes into the cytosol, is pumped out of the cytosol by the MDR pump.”

With this in mind, Eleven’s lead candidates are fusion proteins that include a targeting portion—a Fab or single-chain antibody—linked to a peptide payload as a single gene product that can be expressed in *E. coli*.

“Our payloads, while they’re not huge, are too large to be pumped out of the cells via these pumps,” Adams explains. “So, once we get into the cytosol, we stay there.”

“It means that we’re not going to detoxify the payload within the tumor cells, but it also means you’re not going to have a bystander effect on nearby cells that you don’t want to hit,” he adds. “For instance, if you’re going after head-and-neck cancer, you worry about the nerves.”

Oncomatryx, meanwhile, has addressed MDR-related issues by focusing on synthetic cytolysins, small tetrapeptide payloads that are highly cytotoxic and anti-angiogenic, while also being flexible for a variety of linker technologies and can be synthesized in sufficient quantities for clinical development. Just as importantly, however, is the fact that these compounds—derivatives of natural cytotoxic tubulysins, which inhibit tubulin polymerization—are not substrates for MDR proteins.

The company has conjugated the payload to anti-MTX5 antibodies, testing the ADCs against xenograft murine models of pancreatic cancer and noted 100-percent tumor growth inhibition when used as a monotherapy and tumor regression when used in combination with gemcitabine and/or abraxane. MTX5 is a membrane glycoprotein found predominantly in cancer-associated fibroblasts.

One of the challenges of tubulin-disrupting compounds, however, is the abundance of tubulin naturally occurring within cells. Thus, disruption requires high concentration of drug to be internalized and released.

To overcome such challenges, many companies are exploring the use of DNA-damaging and intercalating compounds such as pyrrolo-benzodiazepines (PBDs) or, in the case of NBE Therapeutics, an anthracycline-based drug related to doxorubicine, which it labels PNU-159682. Using its conjugation platform SMAC-Technology, the company enzymatically links PNU to the C-termini of the antibody's light and heavy chains via sortase and poly-glycine-modified payload.

The company has a variety of candidates for both solid and soft tissue tumors that are heading into preclinical development, and in October, it announced an agreement with Sotio A.S. that will see the latter company pick up clinical development of any new ADCs arising from the collaboration.

Ironically, in something of a twist on typical pharmaceutical thinking, therapeutic efficacy is often very dependent on payload toxicity.

"When you do systemic delivery with an ADC or antibody, you don't get the majority of the antibody and the payload to the tumor; the majority of it goes elsewhere and is processed by the normal tissues," Adams says. "You get a small fraction into the tumor, so you have to make it as potent as possible and as safe as possible. I think something like 0.1 to 0.01 percent injected dose per gram of tumor, which is really not that much."

"You have to get that window set for that payload to be as toxic as possible because you're going to get a little more focus on delivery to tumors," he presses. "In fact, the more recent payloads are often payloads that failed as single agents without the antibody because they were too toxic."

"Another important factor is how many of the drug molecules will be loaded onto the antibody: the drug-antibody ratio (DAR)," Nikolaos Diamantis and Udai Banerji of London's Institute of Cancer Research suggested in a recent review in the *British Journal of Cancer*.

"Attaching too few of the drug molecules will lead to decreased efficacy. Attach too many and the ADC will become unstable with altered pharmacokinetic properties, increased plasma clearance, reduced half-life and increased systemic toxicity," they said. "The currently licensed ADCs with proven activity are produced by nonspecific conjugation to lysine residues and to some degree consist of an undesirable heterogeneous mixture of ADCs containing drug molecules with high DAR."

Mersana Therapeutics developed its Fleximer platform, at least in part, to address the desire to raise the DAR for increased efficacy while limiting immunogenicity. And the polymer is designed to be biodegradable, helping to improve safety. Using this platform, the company can achieve DAR of 15 to 20, a significant improvement over the three to four DAR of earlier generation ADCs.

In April, at the annual meeting of the American Association for Cancer Research, Mersana announced preclinical results from its XMT-1536 program in patient-derived xenograft models of non-small cell lung cancer (NSCLC) and ovarian cancer. With XMT-1536, 15 auristatin molecules are conjugated to a humanized antibody against sodium-dependent phosphate transport protein 2B (NaPi2b), which is highly expressed in the tumors. Citing durable tumor regression as well as its tolerability and pharmacokinetic profiles, Mersana's chief medical officer, Donald Bergstrom, suggested the company was advancing the program into IND-enabling studies.

More recently, in a collaboration with Takeda, Mersana also announced the FDA had cleared the way for the company to begin Phase 1 studies on its anti-HER2 conjugate XMT-1522, which carries 12 molecules of auristatin. The goal, says the company, is to extend HER2-targeted therapy beyond HER2-positive patient populations into those with lower HER2 expression, in cancers such as advanced breast cancer and NSCLC.

For its part, Sutro Biopharma has taken a cell-free protein synthesis approach to improving ADC homogeneity, incorporating non-natural amino acids at key positions within the targeting antibody to ensure precisely positioned drug linkage and consistent DAR. At the recent American Society of Hematology annual meeting, the company presented two studies of investigational ADCs targeting CD74 for cell-killing efficacy against a variety of B cell malignancies. The compounds also demonstrated tumor growth suppression in mouse models of non-Hodgkin's lymphoma and multiple myeloma.

Synaffix takes a different approach to ensuring consistency in DAR, focusing its attention on the glycoprofile of antibodies rather than their amino acid sequences. Specifically, the company uses its GlycoConnect platform to enzymatically clip the two glycans that occur naturally on all antibodies and then modify the remaining glycostructure with a second enzyme, preparing it for site-specific stable conjugation with the ADC payload using metal-free click chemistry.

In July, the company announced it had generated ADCs with significantly improved therapeutic indices over the FDA-approved ADCs Adcetris and Kadcyla using GlycoConnect and its linker platform HydraSpace.

"What is exciting about our technology is that we can now consistently demonstrate in preclinical models of liquid and solid tumors that if we connect the same antibody and payload from each commercially-available ADC product using our proprietary technology,

we are able to increase the efficacy of the drug as well as its safety and tolerability," said Synaffix's chief scientific officer Floris van Delft in an announcement.

More recently, the company entered into a commercial license agreement with ADC Therapeutics for use of the technologies in one of the latter's preclinical programs, as well as options to do the same with other such programs.

Perhaps the loudest conversations around ADCs, however, involve discussions about the linker that tether targeting agent and therapeutic payload together.

"If you go to conferences and talk to people from the major pharma companies working on ADCs, almost all of the presentations have some component on stability of the payload, trying to define where the payload sits on the antibody to things like unnatural amino acids," says Adams.

"How do you conjugate the payload to an antibody in a way that will be stable in circulation but will still be released when it gets inside the cell?" he continues.

"Noncleavable linkers have the characteristic that following ADC lysosomal degradation, the cytotoxic payload remains active while still being attached to the linker and an amino acid residue," explained Diamantis and Banerji, citing the example of trastuzumab-DM1 (Kadcyla).

"Cleavable linkers use different methods to release cytotoxic drug, increasing the possibility of the bystander effect," they continued.

For this category, they highlighted acid-sensitive linkers that respond to the low pH conditions of lysosomes and endosomes, protease-sensitive linkers such as brentuximab vedotin (Adcetris), and glutathione-sensitive linkers that leverage the higher glutathione concentrations typical of tumors.

A debate continues, however, on whether the large macromolecular complexes that antibodies and ADCs represent really provide the optimal pharmacological profiles to treat a variety of diseases. Interestingly, each side often uses the same characteristics to argue their points (see also the table "One Man's Poison" below after the end of this article).

"In our hands, the big advantage of antibodies for therapy is that they stay in the body for a long time," explains Senter. "As long as the drug remains bound to the antibody while it is in circulation, it's not going to be really toxic."

Senter's last sentiment, however, represents a big "if" to Adams.

"Having an intact antibody that is going to circulate for weeks actually could increase the potential for toxicity," he worries, citing the systemic release of DM1 from its trastuzumab antibody in Kadcyla.

"It is unclear as to whether it is falling off in circulation or whether it is being taken off by processing in normal tissue," he says. But, "about five percent of DM1 falls off of trastuzumab-DM1 per day in a clinical setting. The free drug then leads to neuropathies and neutropenias."

"Another advantage of full antibodies is that they can have effector functions that can participate in the activity of the ADC," Senter continues. "If you step down to fragments of non-antibody-based targeting agents, you move away from that."

Diamantis and Banerji echoed those sentiments.

"The antibodies, once part of the ADC, can retain their original properties and activate immune functions such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity," the authors suggested. "They could still act as receptor inhibitors or signal modulators."

But this autonomous activity of the antibody outside of the drug payload is a double-edged sword, the researchers cautioned.

"The independent function of the antibody is not always beneficial and complementary to ADC efficacy, especially when Ab binding is sufficient to produce a cytotoxic effect. The Ab's independent effector functions could lead to increased toxicity, reduced tumour localization and internalization of the ADC."

For these reasons as well as several others, companies like Eleven Biotherapeutics are looking to antibody fragments and other polypeptides, in some cases, incorporating characteristics of multispecific immunotherapeutics and ADCs.

Going to pieces

Within the sphere of oncology, one of the concerns about using full antibodies as targeting agents revolves around their ability to penetrate tumor masses.

“It is all a matter of trade-offs,” offers Adams. “If you’re going with an intact antibody and you’re going after a diffuse malignancy or liquid tumors, that intact antibody doesn’t have to do much in terms of penetration in that environment. There it makes sense to use something larger.”

“But if you have to get into these solid tumors, you really want to go smaller,” he argues.

Senter, however, points to the currently marketed and near-market products to suggest that this may not be so big a problem.

“Kadcyla demonstrated the feasibility of actually developing a good therapeutic ADC for the treatment of solid tumors,” he begins his list. “The Immunomedics ADC has shown significant activities in breast cancer and other solid tumor indications, as well.”

“AbbVie has a molecule that is against an antigen in gliomas. That’s a very difficult tumor to treat, and they have up to Phase 1 data,” he recounts. “We have enfortumab vedotin, which is from our joint partnership with Astellas, and then we also have another program called ASG-15ME, and both of those are for urothelial cancer.”

Thus, he thinks there is a definite sense of optimism that ADC technology can be used for solid tumor therapy.

From Eleven’s perspective, the decision to go with a single-gene fusion protein was partly due to the relative simplicity and reproducibility of the final product.

“If you want to make an ADC, you have to make GMP drug, GMP antibody and chemically link them, which results in an average of DAR, so there will be some antibodies that have no drug on them, some antibodies have six drugs on them,” Adams explains. “The difference between an antibody with no drugs and an antibody with six drugs can be profound.”

“There are charge differences with a lot of these payloads that are put on,” he continues. “You could also have a naked antibody that is blocking receptors that you need to occupy with an ADC.”

Interestingly, however, this area of development is relatively new for Eleven, which acquired the technology platform and candidates when it purchased Canadian firm Viventia Bio in September. Its lead products are Vicinium, which is in Phase 3 in non-muscle invasive bladder cancer, and Proxinium, which it expects to shortly enter Phase 2 studies in head-and-neck cancer, both of which are administered locally.

It is also pursuing a systemic candidate for solid tumors that utilizes the ribosome-inactivating protein de Bouganin as its therapeutic payload. In its natural environment, the protein helps protect the bougainvillea garden plant from viral infections.

Crescendo Biologics, meanwhile, relies on a fully human V_H domain-based approach to therapeutics that it calls Humabody. Using a modular approach, these small domains—about a quarter the size of more typical Fab domains—can be mixed and matched to provide multiple specificities or linked to drugs or radioisotopes that provide the therapeutic effect. And unlike antibodies, Humabodies do not require hetero-dimerization to be effective.

The company has several candidates in preclinical development, most involved in immuno-oncology modulation. In October, the company announced a collaborative agreement with Takeda Pharmaceutical to leverage the Humabody platform against a variety of Takeda targets. Crescendo CEO Peter Pack describes the deal as a validation of the methodology and an important step in his company’s evolution.

“This first major collaboration enables us to potentially broaden and accelerate innovative Humabody-based product candidates,” Pack said in the announcement.

The move was just the latest by Takeda, which in September also announced it had signed a research collaboration deal with Affilogic to develop central nervous system therapies.

Affilogic has an antibody mimetic platform it dubs Nanofitins—polypeptides that are about one-twentieth the size of antibodies and are easily produced in biofermentors. Like Humabodies, Nanofitins were designed not only to be used alone, but also to be conjugated to other molecules such as drugs or nanoparticles, or to be assembled as multimers, offering the option for multiple specificities and multivalencies.

Among its 42 applications of Nanofitin technology, the company has several partnered and independent candidates in its pipeline, all in preclinical development presently, across therapeutic indications ranging from oncology to autoimmunity to infectious disease. The Takeda agreement will see Affilogic receive upfront payments and research funding with options on downstream development and sales milestone payments in exchange for global commercialization rights.

Avacta Group, meanwhile, has developed a variety of research tools and therapeutics with its Affimer platform. Affimers are small protein scaffolds derived from the cystatin protein fold, and can function both at the surface of and within cells.

Therapeutically, Avacta is focusing on checkpoint inhibition, and in September, the company announced positive results from its first preclinical animal studies of its PD-L1 inhibitor. In a pharmacokinetics study, the anti-PD-L1 Affimer fused to an Fc domain demonstrated good *in-vivo* half-life and was well tolerated at clinically relevant doses. In a second, efficacy study in a syngeneic mouse tumor model, the inhibitor was able to significantly reduce tumor growth with no observed adverse events.

"These results demonstrate that Affimer molecules possess good *in-vivo* drug-like properties in terms of efficacy, serum half-life and tolerability, which is a hugely important milestone in the development and de-risking of the technology as a therapeutic platform," commented Alastair Smith, Avacta Group chief executive, in the announcement. "We are very encouraged by these initial, positive results and will continue to focus on developing both our internal and partnered therapeutic programs towards clinical validation."

Bottom line

Thus, as larger pharmas and biotechs fight in the biosimilar market to simply reproduce the success of first-generation antibody therapies and others continue to ply the full antibody trade with next-generation therapeutics, several other players are applying the lessons of the previous generation to evolve the art form.

The success of products like Adcetris, Kadcyla and Blincyto will undoubtedly impact how much effort people will put into this research in the years to come, and will provide lessons of their own.

Bits and BiTEs; BiKEs and TriKEs

In 2014, the FDA approved Amgen's blinatumomab (Blincyto) for treatment of relapsed/refractory acute lymphoblastic leukemia. Blinatumomab was the first approved compound from a new category of immunotherapy known as a bispecific T cell engager, or BiTE.

Comprised of two single-chain Fv modules, blinatumomab binds to CD19 on the surface of B cells with one arm, and then recruits and activates T cells, which triggers apoptosis via granzymes and perforins.

The BiTE platform also formed the basis of solitomab, which recruits CD3+ T cells to EpCAM+ cancer cells and is currently in preclinical study in uterine and ovarian cancer. As Yale University's Alessandro Santin and colleagues noted last year, exposure to solitomab made EpCAM+ cell lines sensitive to T cell-mediated killing and significantly reduced the number of viable ovarian tumor cells in ascites.

"The widespread expression and membranous localization of EpCAM in ovarian cancer cells, combined with its negative expression in mesothelial type cells in the abdominal cavity, suggests that this protein could represent an accessible tumor target antigen for both intravenous and intraperitoneal antibody/BiTE-based therapies," the authors enthused in *Cancer*. "Consistent with this view, a Phase 1 study of EpCAM/CD3-bispecific antibody (MT110) in patients harboring advanced tumors is currently ongoing."

Others have taken the principal behind BiTEs, but rather than tether cancer cells to cytotoxic T cells, they have instead targeted natural killer (NK) cells with constructs known as bispecific killer cell engagers (BiKEs) and more recently, TriKEs (a trispecific variation on the theme).

Daniel Vallera and colleagues at the University of Minnesota generated a bispecific molecule (1633 BiKE) that targeted CD16 on NK cells and CD33 on myeloid cells for the treatment of acute myeloid leukemia (AML). Not only did 1633 BiKE stimulate NK cells to destroy AML cells, but it also restored NK cell functions that had previously been inhibited in patients with myelodysplastic syndrome, a precursor to AML.

Given these results, the researchers then added a third component—crosslinked human IL-15—to drive NK cell expansion. The resulting molecule (161533 TriKE) was superior to its predecessor BiKE in almost every way, including enhanced cancer cell killing, NK cell proliferation and survival and significantly reduced tumor load in mice engrafted with human CD33+ myeloid cells.

"As TriKEs can be generated with different specificities, they provide the option to re-target NK cells in accordance with the emergence of tumor-associated antigens during tumor escape and immunoediting, which can impede the long-term success of cancer therapies," commented Szun Szun Tay and colleagues at the University of New South Wales and University of Sydney in a recent issue of *Human Vaccines and Immunotherapeutics*.

"The TriKE platform not only provides options to target different receptors, or novel tumor ligands, but also provides a way to explore new targeting strategies based upon newly discovered molecules reasonably rapidly," the authors enthused.

Recently, Christoph Rader and colleagues at The Scripps Research Institute and the U.S. National Institutes of Health looked to make bispecific antibodies more modular in design, commoditizing the actual antibody component and adding variability to the T cell binding arm via an array of small molecules.

As they described recently in the *Journal of Biological Chemistry*, the researchers utilized the DART (dual-affinity re-targeting) format, which involves two peptide chains linked by a disulphide bond (diabody). Each chain contains one of the two variable light and heavy domains that form the antigen and hapten binding site. They then chemically programmed the complexes with folate derivatives that would target the folate receptor (FOLR1) on ovarian cancer cells.

Not only did the diabodies bind both CD3 and FOLR1 individually, but the researchers used flow cytometry to show the diabodies could crosslink CD3+ and FOLR1+ cells. The diabodies also exhibited strong cytotoxic effect on ovarian cancer cells both *in vitro* and *in vivo* in xenotransplanted mice. Treated mice also showed reduced tumor burden without signs of toxicity.

"A key advantage of chemically programmed antibodies and [bispecific antibodies] is their generic design that not only enables [one] to confine lead optimization to the small molecule component but also permits targeting a virtually unlimited number and variety of antigens with a single protein," the authors wrote.

Thus, they concluded, "our chemically programmable DARTs afford a versatile plug-and-play platform with broad utility in cancer immunotherapy."

It seems that as the number of potential targets increases, so too do the methods with which to tether them to the body's immune response and on an as-needed basis.

Not just cancer

Across the spectrum of ADCs, multispecific antibodies and antibody fragment biotherapeutics, the predominant focus has been on developing treatments for cancer.

"In other types of diseases, the most important aspect of drug development that leads to failure is toxicity," suggests Peter Senter, vice president of chemistry at Seattle Genetics, describing the ADC perspective. "So, if you're trying to deal with an autoimmune disease or inflammation and things like that, usually you have to use drugs that don't have significant side effects."

"But in cancer," he continues, "a lot of those side effects are accepted because of the nature of the disease."

The mode of action of the ADC payloads can also influence the disease selection.

"Most ADCs are anti-mitotics," explains Gregory Adams, chief development officer at Eleven Biotherapeutics. "They shut down the ability of the cell to proliferate."

Thus, the focus has been on diseases that involve rapid or uncontrolled cell proliferation, squarely within the oncology wheelhouse.

That said, there is increasing interest in areas outside of oncology, and for its part, Eleven's drug payloads are not anti-mitotics but rather anti-transcription agents or anti-translation agents, including the ribosome-inactivating protein de Bouganin.

"We are in discussions with a number of people about indications outside of oncology," Adams continues. "We think we're uniquely positioned for that, not just because of the ability of our payloads to go after cells that aren't rapidly dividing, but also because of the stability of our molecules."

In the bispecific antibody space, Cidara Therapeutics has focused on immunotherapeutic approaches to infectious disease. In September, the company described its efforts to tackle the growing problem of multidrug resistant bacteria.

Using its Cloudbreak discovery platform, the company designed a bispecific antibody (CD201) that binds a range of gram-negative bacteria, including recently discovered superbug MCR-1, while drawing components of the host immune system to the infection site, promoting infection clearance.

CD201 has demonstrated strong antibacterial activity in vitro across a number of bacterial species, including *Klebsiella*, *Pseudomonas* and *Enterobacter*, and preliminary work with animal models suggests the therapeutic is safe and effective.

"Harnessing the immune system to fight harmful bacteria such as gram-negative and resistant pathogens has the potential to significantly improve outcomes in patients with life-threatening infections," offered University of Pittsburgh's Cornelius Clancy in the announcement. "The approach taken with CD201 could fundamentally change the way we treat serious gram-negative infections across multiple patient populations."

According to Cidara President and CEO Jeffrey Stein, the company expects to file an IND to initiate clinical development in 2017.

Senter is equally optimistic about the application of ADCs in other indications.

"Looking ahead," he says, "we believe that there will be applications for the technology, especially when we can succeed in optimizing all aspects of it so that the side effects are minimized."

One Man's Poison

The biological actions of full-sized antibodies can excite as well as frustrate

Characteristic	Negative	Positive
Long systemic half-life	May increase risk of side effects if drug is released off-target	May allow decreased dosing frequency
ADC bystander effect	May kill nearby healthy cells, triggering side effects (*e.g.*, neuropathy)	Kills tumor cells lacking target antigen
Immunogenicity	Potential side effects	Stimulates immune system to fight tumor

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Some Companies in the Biotherapeutics Space and Where Their Efforts Lie