



How the Next Generation Antibody Drug Conjugates Expands Beyond Cytotoxic Payloads for Cancer Therapy

By **Jon Gingrich, Ph.D.** - April 7, 2020



[Antibody-drug Conjugates](#) or ADCs combine the selectivity of antibodies with the efficacy of small molecule drugs, allowing for more precise, targeted, therapeutic applications.

Combining the advantages of antibodies in binding a specific target with the capabilities of a therapeutic payload, [the majority of ADCs in preclinical and clinical development are for indications in oncology and hematology](#), where the cytotoxic payloads linked to antibodies are targeting antigen-expressing cancer cells.[1]

Over the last two decades, researchers have also explored opportunities to develop ADCs *beyond cancer*, into other disease indications including autoimmune disease, difficult-to-treat bacterial infections, and atherosclerosis.

However, to succeed in the development of these non-oncologic ADCs, a number of challenges need to be resolved in order to fulfill the larger promise of ADC technology.

In an article published in *Methods in Molecular Biology*, Michael J. McPherson and Adrian D Hobson at Abbvie Global Biologics, AbbVie Bioresearch Center, Worcester, MA, USA, demonstrate that the modulation of pathogenic cellular activity via ADC-mediated delivery of bioactive small molecules is indeed an attractive concept for non-oncology indications. And in the article, McPherson and Hobson explore a variety of payload mechanisms beyond cell killing, from early *in vitro* proof-of-concept experiments to clinical trials. [2]

With a growing understanding of ADC-technology, it's only predictable that the development of these compounds in therapeutics areas for diseases outside the realm of oncology and hematology will rapidly increase. Some of these novel ADCs will be developed with curative intent, some as a precursor or conditioning to further therapies.

Current status

But let's go back to the current 'status quo.' To date, seven ADCs have received approval from the *U.S. Food and Drug Administration (FDA)* and *European Medicines Agency (EMA)* and are commercially available to meet the needs of patients; all carrying a cytotoxic payload for various liquid and solid tumors.



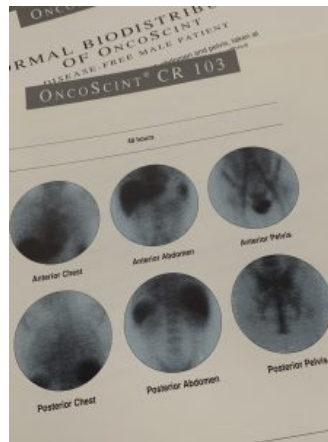


Photo 1.0: "Scan Atlas – OncoScint® CR 103 (Indium¹¹¹ satumomab pentetide)" (1994) was developed by The Royal Free Hospital and School of Medicine, London, UK in collaboration with EuroCetus/Chron. Indium¹¹¹ satumomab pentetide was originally developed by the National Cancer Institute's (NCI) principal researcher [Jeffrey Schlom, Ph.D.](#)

From failure to success

A major advancement in the understanding of the concept of ADCs followed research studies arming antibodies with toxic molecules, such as *diphtheria toxin* (first proposed in 1970 by Frederick L. Moolten and Sidney R. Cooperband) and *radioisotopes*. These studies, in which antibodies were conjugated to *radioisotopes*, initially failed in early clinical development due to an inadequate radiation dose delivered to the tumor site to obtain adequate tumor imaging and clinically meaningful responses. [3]

However, the concept of antibody-mediated delivery of radionuclides to the tumor sites ultimately resulted in the development of a number FDA-approved agents, including Indium¹¹¹ satumomab pentetide (OncoScint® CR/OV^[a]; Cytogen^[b] and EuroCetus/Chiron^[c]; manufactured by Lonza Biologics) the first labeled monoclonal antibody to be approved by the FDA for *tumor imaging*, ibritumomab tiuxetan (Zevalin®; Biogen Idec/Spectrum Pharmaceuticals/Acrotech Biopharma), a CD20-directed murine-derived antibody conjugated to ⁹⁰Y, β-emitting radionuclide for the *treatment* for relapsed or refractory, low grade or transformed B cell non-Hodgkin's lymphoma, and ¹³¹I-tositumomab (Bexxar®, GlaxoSmithKline/GSK)^[d], indicated for the treatment of certain types of non-Hodgkin's lymphomas that have recurred after, or have not responded to prior treatment.

Early investigational ADCs such as the *antibody-vinca alkaloid conjugate*, KS1/4-DAVLB (LY256787), being developed by [Eli Lilly and Company](#), included murine-derived antibodies and were evaluated in clinical trials. But the development of 'human anti-murine antibodies' (HAMA), which resulted as a response to the antibody rather than the payload, compromised the efficacy of these investigational drugs and increased the possible risk of adverse reactions. This resulted in a discontinuing of these agents.

Ongoing research and advances in the understanding of ADC-technology resulted in the development of humanized and fully human antibodies.[4]

The complexity of the development of ADCs was adequately illustrated with the failure of *BR96-Dox* (also known as SGN-15)^[e], an anti-Lewis^y mAb conjugated to *doxorubicin* via a *hydrazone* linker. In phase II trials designed to study the drug for the treatment of patients with metastatic breast cancer, the investigational agent failed and development was discontinued due to low potency of the doxorubicin as the payload and to the instability of the linker.



Researchers soon realized that one of the major limitations of ADCs was their inability to penetrate (solid) tumors. Along with limited target molecules on the cell surface ($<10^5$ copy numbers per cell), they considered that more potent payloads were required.^[f] This resulted in the development of cytotoxic agents to target tubulin (e.g., auristatin and maytansinoids), DNA (e.g., [calicheamicin](#)), or RNA (e.g., [amanitin](#)) with in vitro IC₅₀ values in the subnanomolar range.



Packaging of Gemtuzumab Ozogamicin (GO, Mylotarg®; Pfizer/Wyeth Laboratories).

Second generation

The realization that more potent payloads could change the future potential of ADCs as a class of therapeutic agents resulted in the development and approval, in early 2000, of [gemtuzumab ozogamicin](#) (Mylotarg®; Pfizer). With this approval, the antibody-drug conjugate (ADC) 'industry' really started in force.^[g]

It would, however, take more than a decade later before the next ADCs, [brentuximab vedotin](#) (Adcetris®; Seattle Genetics), and [ado-trastuzumab emtansine](#) (Kadcyla®; Genentech/Roche), were approved.

Following the approval of these ADCs, development slowed, and some experts believed that with a growing number of discontinuations of clinical trial programs and setbacks, there was no real future for this class of targeted agents.

And while these failures and setbacks temporarily limited investment and slowed the development of antibody-drug conjugates from reaching their true potential, many in the industry remained confident that ADCs would have a future. With the approval of inotuzumab ozogamicin (Besponsa®; Pfizer), their confidence proved to be warranted.

A growing number of approvals

With the approval of [polatuzumab vedotin](#) (Polivy®; Genentech/Roche), [enfortumab vedotin-efjv](#) (Padcev™; Astellas/Seattle Genetics) and [fam-trastuzumab deruxtecan-nxki](#) (Enhertu®; Daiichi Sankyo/AstraZeneca), there were more ADCs carrying cytotoxic payloads approved by the FDA in 2019 than *any other year* thus far. And 2020 is also shaping up for additional approvals.

The concept of adding a cytotoxic agent with the targeting ability of a monoclonal antibody has been widely embraced by the scientific community over the last 20 years.

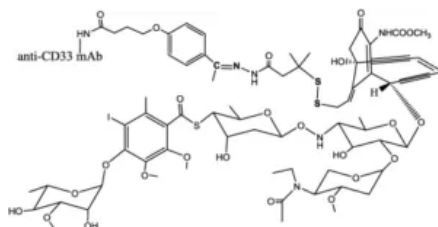


Image description: Structure of Gemtuzumab Ozogamicin (GO, Mylotarg). Gemtuzumab ozogamicin consists of a semisynthetic derivative of calicheamicin (N-acetyl-γ calicheamicin 1,2-dimethylhydrazine dichloride), a potent enediyne DNA-binding cytotoxic antibiotic, linked to hP67.6, an engineered humanized monoclonal IgG4 antibody, directed against the CD33 antigen present on leukemic myeloblasts in most patients with AML (~80%).

And while conventional cancer treatments, including chemotherapy, have changed the outlook for patients with cancer and hematological diseases, they may not always be as efficacious as hoped, creating an urgent medical need. For example, scientists have been looking for methods in which the off-target side effects of chemotherapy could be limited or ideally eliminated. Such an approach would vastly improve the patients’ health-related quality of life (hrQoL).

ADCs have indeed, been part of this approach, allowing the delivery of super-cytotoxic agents into tumor cells.

It has taken over two decades since the first cytotoxic antibody-drug conjugate was approved by the FDA, gemtuzumab ozogamicin and the commercial onco-therapeutic ADC market was established.

After more than 20 years of ADC development employing mostly cytotoxins conjugated to monoclonal antibodies or radio-isotopes being chelated to monoclonal antibodies, there are now multiple new approaches and mechanisms of action using antibodies to target diseased cells and tissues to achieve a therapeutic effect.

A new dawn – and more setbacks

Today, a new chapter is being written in the long story of antibody-drug conjugates. While this chapter does relate, as mentioned earlier, stories of an industry troubled by higher than average discontinuation rates of novel investigational agents, as evidenced by some high-profile setbacks, including, for example, AbbVie’s disappointing results of *rovalpituzumab tesirine* (Rova-T)^[h], this chapter is primarily about a growing optimism of ADC as a novel class of agents expanding *within* and *beyond* the realm of oncology and hematology. This new chapter also shows how ADCs have become a highly investible target for development and commercialization.

For example, a global development agreement signed in March 2019 between Daichi-Sankyo and AstraZeneca, worth up to U.S. \$ 6.9 billion confirms that ADCs have attracted the biopharmaceutical industry’s interest as a class of drugs, while the growing number of preclinical development programs and novel molecular entities entering clinic and approvals of ADCs, demonstrated the industry’s desire for research and development in this field.

A non-traditional approach

There are several new start-ups as well as established biopharmaceutical companies that are taking advantage of the targeting and internalization abilities of monoclonal antibodies. Many of these approaches are using non-traditional payloads to effect disease tissues. The range of the various compounds being developed is quite broad.

For example, these new strategies include:

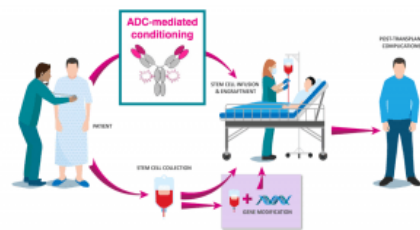


- [Abbvie's ABBV-3373](#), an anti-TNF Glucocorticoid Receptor Modulator (GRM) steroid ADC being investigated to treat rheumatoid arthritis;
- [Bolt Biotherapeutics'](#) Immune Stimulating Antibody Conjugate (ISAC), *BDC-1001* combining Toll-Like Receptors (TLR)^[1] with tumor-targeting antibodies for localized immune-stimulation at the tumor site;
- [Silverback Therapeutics'](#) *ImmunoTAC™ SBT6050*, an anti-HER2 antibody-drug conjugated to a potent TLR8 agonist for the treatment of moderate and high HER2 expressing tumors;
- [Rakuten Medical's](#) ASP-1929, combining an EGFR targeting antibody, cetuximab, and a dye called *IRDye 700DX* that is activated with a low-intensity laser for localized tumor destruction;
- [Avidity Biosciences'](#) antibody oligonucleotide conjugates (AOC™) used to modulate RNAs in disease tissues.

Patient Conditioning

More recently, a new approach – without curative intent – employs cytotoxin carrying antibodies to eliminate disease-causing cells prior to replacing them with healthy cells to rebuild the immune system. Being developed by [Magenta Therapeutics](#), this approach eliminates the need for non-specific, myeloablative (high-dose) or non-myeloablative (low-dose) chemotherapy alone or in combination with total body irradiation (TBI) to destroy T-cells prior to *hematopoietic stem cell transplantation* (HSCT; bone marrow transplantation), stem cell transplants or gene therapy.

The overall goal of such a conditioning regimen is to suppress the immune system (In essence, making “space” in host bone marrow (BM) for donor HSC engraftment) so that the patient will not reject the donor HSC engraftment, without causing significant collateral damage.



The engineered CD117-ADC shows potent activity on human and NHP CD34+ cells ex vivo. The ADC robustly depletes rhesus HSCs in vivo, has a favorable safety profile, spares the immune system and is cleared rapidly to allow for optimal timing of graft infusion. Preclinical data demonstrate that a single dose of the CD117-ADC enables the engraftment of β -globin gene-modified HSCs in a primate model without chemotherapy. These results validate the use of CD117-ADC for targeted stem cell depletion prior to transplant and support development as a new conditioning agent for autologous HSC-based gene therapy approaches. This targeted approach for safer conditioning could improve the risk-benefit profile for patients undergoing transplants and enable more patients to benefit from these potentially curative therapies including gene therapy for sickle cell disease and severe combined immunodeficiency. Image courtesy: © 2020 Magenta Therapeutics.

Magenta Therapeutics' approach – still in *preclinical development* – aims to condition patients by selectively removing the specific cells to enable a successful transplant or gene therapy procedure. The company's methodology involved a CD117-Amanitin antibody-drug conjugate (CD117-ADC; MGTA-117) which may, in the near future, 'replace' current, the standard of care treatment options that are associated with significant toxicity, including the development of cancers, infertility, organ toxicities, or even death.

In preclinical studies, researchers at Magenta demonstrated that a single dose of their disease-modifying antibody-drug conjugate CD117-ADC to saporin resulted in > 99% depletion of host hematopoietic stem cells (HSCs), enabling rapid and efficient donor hematopoietic cell engraftment. Furthermore, preclinical data, presented during the 2019 annual meeting of the [America Society of Hematology](#) (ASH), confirmed that CD117-ADC selectively targets HSCs without causing clinically significant side-effects. Blood counts and immune cell functions are preserved following CD117-ADC treatment, with effective responses by recipients to both viral and fungal challenges. [6]

"We've generated landmark data from our ADC-based targeted patient preparation platform, which is delivering a new class of antibody-drug conjugates (ADCs) that have the power to bring one-time treatment to more patients with autoimmune diseases, blood cancers, and genetic diseases," noted Jason Gardner, D. Phil., President, and Chief Executive Officer, Magenta.

"[These] results highlight the potency, safety [and broad therapeutic index of the novel ADCs, going well above that of currently approved ADCs," Gardner added.

"There is a significant opportunity to allow more patients to benefit from immune reset through stem cell transplant with a novel, targeted medicines for conditioning. We believe that our CD117 antibody-drug conjugate (MGTA-117) is the optimal agent for depleting stem cells to enable safe immune reset, and we look forward to moving this product candidate into the clinic, with initial clinical data expected in 2021," added John Davis, M.D., M.P.H., Chief Medical Officer, Magenta.

"The additional impressive results with CD117-ADC in the NIH gene therapy study provide further validation of the safety and potency of the antibody-drug conjugates approach in the field of conditioning," Davis concluded.

Autoimmune diseases

In November 2019, during the annual meeting of the *American College of Rheumatology* (ACR) in Atlanta, Ga, Magenta's researchers reported new preclinical data showing successful immune resets with a single dose of the company's investigational CD45-ADC, a CD45 targeting antibody linked to Heidelberg Pharma-amanitin payload, in models of three autoimmune diseases, including multiple sclerosis, systemic sclerosis, and inflammatory arthritis.

While the current standard of care for patients with multiple sclerosis involves years of chronic dosing of medications that do not halt the progression of the disease, for patients with systemic sclerosis, a potentially fatal disease, there are no approved therapies.

Immune reset through *autologous hematopoietic stem cell transplant* (autoHSCT) has demonstrated durable remissions in autoimmune diseases, and it is recommended by the *European League Against Rheumatism* (EULAR) in treatment guidelines for systemic sclerosis.

This reset process involves two main steps: removing the disease-causing cells and replacing them with healthy cells to rebuild the immune system to a healthy state.

Magenta CD45-ADC has shown to precisely remove the disease-causing cells without the need for chemotherapy or radiation.

Multiple Sclerosis

Data from a single dose of CD45-ADC removed disease-causing reactive T-cells, enabled successful immune reset and rebuild the immune system and was well tolerated in a reliable murine model of autoimmune disease, the *experimental autoimmune encephalitis (EAE) model*. The single dose of CD45-ADC significantly reduced disease incidence and delayed disease onset in this model that has successfully provided preclinical proof of concept for many clinically validated standard-of-care therapies.

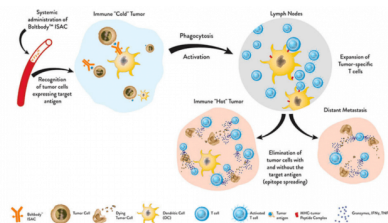


Systemic Sclerosis

Preclinical data also demonstrated that a single dose of CD45-ADC eliminated disease-causing effector cells and ameliorated disease in a humanized murine model of systemic sclerosis with skin involvement. Mice treated with CD45-ADC showed clear resolution of skin lesions and regrowth of hair, while animals treated with an isotype ADC showed no improvement. CD45-ADC was well tolerated.

Inflammatory Arthritis

Finally, preclinical data confirmed that a single dose of CD45-ADC enabled immune reset and rebuild and halted disease progression in a murine model of inflammatory arthritis. The disease-modifying effects of this well-tolerated one-time approach were equivalent to multiple doses of a neutralizing anti-TNF α antibody, which replicates a clinically validated approach to the treatment of rheumatoid arthritis.



The promise of Immunological memory. Bolt Biotherapeutics' Immune-Stimulating Antibody Conjugate (ISAC) selectively target tumors for destruction by the immune system. Tumor-associated myeloid cells engulf ISAC-bound tumors, become armed with tumor neoantigens, and migrate to the lymph nodes where they mediate the activation and expansion of tumor-reactive T-cells. In preclinical tumor models, ISAC therapy leads to the regression of established tumors and generation of immunological memory, which guards against the recurrence of tumors that express tumor neoantigens even if they no longer express the ISAC target antigen. Image courtesy: © 2020 Bolt Biotherapeutics.

Bolt Biotherapeutics

Therapies targeting *Toll-Like Receptors* (TLRs) in tumors are designed to re-activate the immune system, enabling tumor shrinkage alone or in combination with checkpoint therapies. However, systemic delivery of traditional TLR agonists can promote non-specific immune activation, leading to safety or tolerability issues. An intratumoral injection is one option to avoid this side effect.

A different approach involves Bolt Biotherapeutics' Boltbody™ Immune Stimulating Antibody Conjugate (ISAC) platform technology which is designed to unleash the power of the immune system to treat cancer. Boltbody technology links powerful immune-stimulating payloads, such as TLR agonists, to tumor-targeting antibodies.

In preclinical studies, researchers at Bolt have demonstrated profound antitumor efficacy for BDC-1001, the company's lead HER2-targeted ISAC therapeutic program when administered as a monotherapy. Treatment results in activation of the innate immune system that subsequently generates an adaptive immune response leading to complete and durable T-cell mediated clearance of large tumors. These studies also showed that BDC-1001 produces an immunologic memory – the immune system retained the ability to attack tumors even after the Boltbody was no longer present in the body, even protecting against tumors that had lost HER2 expression. BDC-1001 is now in Phase 1 clinical trials.

“Immune Stimulating Antibody Conjugates (ISACs) bring a new dimension to the field of antibody-drug conjugates – the payload stimulates the innate immune system to locally turn on an anti-tumor

immune response rather than through direct cytotoxic killing of tumor cells,” noted Nathan Ihle, Ph.D., Vice President, CMC & Quality at Bolt Biotherapeutics.

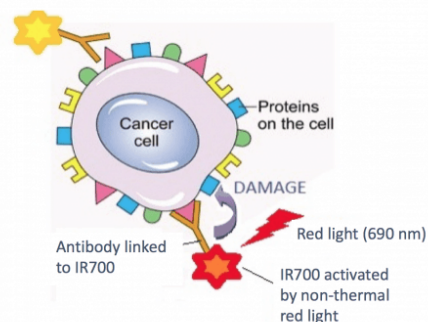
“We use payloads that are non-cytotoxic and act on *toll-like receptors* (TLRs). Agonists that bind to TLR7 and TLR8 actually train immune cells to attack tumors. As a result, we’ve shown in GLP toxicology studies that these Boltbody ISACs avoid the toxicities of current ADCs,” Ihle added.

“The mechanism of action for Boltbodies can be tuned to take advantage of specific subsets of the patient’s immune cells. As such, these agents hold the promise of training the patient’s immune system to attack tumors without the complexity and cost of personalized cellular therapy,” Ihle concluded.

Silverback Therapeutics

Based on Silverback Therapeutics’ ImmunoTAC™ platform, researchers developed *SBT6050*, a novel, potent TLR8 agonist conjugated to a HER2-directed monoclonal antibody, allowing for systemic delivery of an immune modulator with activity localized to tumor sites and secondary lymphoid structures. The investigational agent potently activates conventional dendritic cells that, in turn, drive a Th1/CTL program in T-cells. [7]

“Our preclinical studies demonstrate that systemic delivery of our TLR8 agonist targeted to HER2-expressing tumors potently activates myeloid cells to kill cancer and reprograms the tumor microenvironment, resulting in durable, curative single-agent activity,” noted Peter Thompson, M.D., co-founder, Chairman, and Chief Executive Officer of Silverback Therapeutics.



Cancer Killing is mediated by the activation of the antibody conjugate bound to cancer cells with laser illumination of the tumor. ASP-1929 PIT induces cancer cell killing following a two-step process: (I) systemic administration of the antibody conjugate with IR700 that targets antigens at the surface of the cancer cells leading to tumor binding and selective accumulation of the drug in the tumor; (II) following binding of the antibody conjugate to the cancer cells, laser-mediated illumination with non-thermal red light (690 nm) leads to activation of the drug conjugate and rapid selective destruction of the cancer cells that are bound to the antibody. The unbound drug is inert, even upon light illumination, and consequently, the treatment is highly cancer-specific sparing damage to healthy tissue around the tumor. Image Courtesy/Source: © 2020 Rakuten Medical.)

Rakuten Medical

Another approach involves ASP-1929 photoimmunotherapy being developed by Rakuten Medical. ASP-1929 photoimmunotherapy utilizes a light activatable payload (IRDye® 700DX, IR700) conjugated to a monoclonal antibody (cetuximab). (Table 2.0)

Targeted binding of this *antibody-dye conjugate* to a specific antigen, the *epidermal growth factor receptor* (EGFR) followed by activation of the dye with non-thermal red light (690 nm) results in rapid and selective tumor cell killing.[8]



Light activation of the non-toxic payload results in the generation of singlet oxygen species that damage the cell membrane integrity, [9] resulting in necrotic and immunogenic cell death of tumor cells, resulting in minimal damage to surrounding normal tissue.[10]

Photoimmunotherapy can also lead to local and systemic anti-cancer immune responses.[11][12]

“Photoimmunotherapy is a new antibody-based cancer treatment which employs a light activatable payload that enables rapid destruction of tumor cells, thereby inducing tumor necrosis and activation of anti-cancer immunity.”

“Using the Photoimmunotherapy platform technology, a Phase I/IIa clinical study using *cetuximab-IR700 conjugate* has shown promise in treating recurrent locoregional head and neck cancer and is currently being evaluated in a global phase III clinical trial,” explained Miguel Garcia-Guzman, Ph.D., Chief Scientific Officer, Rakuten Medical.

Rakuten Medical is developing antibody conjugates based on the photoimmunotherapy platform as a new precision tumor-targeting anticancer approach that is being investigated for use as a single agent or in combination with Immuno-oncology modulators to treat locoregional and disseminated cancers from a broad range of solid tumor types.

Avidity Biosciences

Avidity Biosciences’ AOC™ approach includes specific antibodies designed to target cells and tissues and facilitate the uptake and internalization of oligonucleotide payloads.

Oligonucleotide-based therapeutics, considered to be a third major drug development platform, specifically focuses on modulating gene expression by targeting specific *single-stranded deoxyribonucleic acid* (DNA) or *ribonucleic acid* (RNA).

One of the unique distinguishing features of this therapeutic approach is the ability to access the “undruggable” space left by small molecules and biologics, allowing drug developers to address a wider range of diseases, and particularly those with limited or no therapeutic options.



Antibody oligonucleotide conjugate (AOC™) technology being developed by Avidity Biosciences uses antibodies to target cells and tissues of interest and facilitate the uptake and internalization of oligonucleotide payloads. By combining the cellular and tissue selectivity of antibodies with the selectivity and efficiency of oligo-based approaches, researchers at Avidity Biosciences have demonstrated modulation of disease-related RNAs in diverse cell types and tissues including muscle, heart, liver, tumors and immune cells.

In addition, Avidity’s AOCs avoid the typical lipid-based toxicities that have been observed in the context of therapeutic candidates utilizing liposomes or other lipid-based delivery technologies.



By combining the cellular and tissue selectivity of antibodies with the sequence of a rationally-designed oligonucleotide payload, researchers at Avidity have confirmed the potential of modulation of disease-related RNAs in diverse cell types and tissues, including muscle, heart, liver, tumors and immune cells. And their approach has attracted investments from 'Big Pharma' leading to a strategic partnership with Eli Lilly in April 2019, to pursue therapeutic targets initially focused on immunology but also on other indications.

"We're pioneering a new class of targeted RNA medicines, that if successful, can deliver oligonucleotides to a broad range of cell types. This opportunity is extremely compelling," said Joseph Baroldi Avidity Chief Operating Officer.

In addition to companies like Avidity, other companies are also eager to design RNA-based therapies that target specific cells. Taking an idea directly from ADC playbook, in early 2019, Dyne Therapeutics raised \$50 million in series A financing to develop antibody-oligo conjugates designed to "shuttle" oligo therapies to treat genetic muscle disease.

"It is very difficult to deliver a naked oligo to muscle cells," said Romesh Subramanian, Chief Executive Officer of Dyne.

"However, by attaching oligos to antibodies specifically designed to bind receptors on the surface of muscle cells, we are able to boost the number of oligos that get into muscle cells and are able to engulf the antibody-oligo complexes whole. In turn, this approach may lead to more effective, and safer, therapies for genetic muscle diseases," Subramanian explained.

The development of targeted oligo therapies isn't completely new. A number of companies have, unsuccessfully, tried to develop antibody-oligo conjugates. But, just like the development of antibody-drug conjugates, using the right linker chemistry to conjugate the oligo to the antibody and finding the right place on the antibody to attach the linker, has shown to be crucial.

Outsourcing standard

"The arduous history of the development of ADCs over the last decades has shown that the development of these targeted agents will always be far more complex than that of a small-molecule *new chemical entity* (NCE)," noted Yongjian Wu, Ph.D. Chief Operating Officer of [MabPlex USA](#).

And the development will also be less predictable.

"You'll need to get all three parts, the antibody, linker, and payload to work together in order to be successful. Issues with any one of the three components could result in clinical failure," Wu added.

So, how to select an experienced partner?

"The CDMO you contract with should have the experience in antibody manufacturing as well as in the linker-payload synthesis and conjugation. They should appreciate the complexities involved with the manufacturing processes. New non-toxic ADCs are no different from this perspective than the traditional ADCs. The same kind of attention is needed for constructing a successful non-toxic ADC," Wu noted.

Embracing this understanding, companies outsource nearly 70% of the manufacturing steps to specialized *Contract Development and Manufacturing Organizations* (CDMO). [15]

And while there are several CDMOs that specialize in manufacturing the various components of an ADC, not all master the full manufacturing process. Some CDMOs focus on the bioproduction of the intermediate antibody while others specialize in the synthesis of the linker and payload. There are



only a handful of CDMOs that can provide an “End to End” service offering to manufacture cytotoxic and non-cytotoxic ADCs world-wide.

“With our experience, we can help our clients in several ways. First, we can leverage our experience for the developability assessment to help select the best candidate molecule to develop. Slight differences in the linker-payload, conjugation site, and conjugation chemistry can make a significant difference clinically,” Wu explained.

“Throughout the development, we design the process to be simple (i.e. *manufacturing friendly*), efficient (i.e. *cost-effective*) and robust (i.e. *scalable, simple tech transfer*) and results in a product that is as homogeneous and consistent as possible. The analytical characterization skills accumulated over the years from making the traditional ADCs is highly relevant for the design of a better product and process and ensure the consistent quality all the way from IND to the commercial scale,” Wu concluded.

With the expansion of ADCs into areas that do not require the same level of containment that a traditional cytotoxic ADC manufacturing facility requires, CDMOs offering conjugation services to the ADC field will need to expand their capabilities to offer conjugation of less hazardous payloads in many cases.

The high cost of high containment isolators and disposal of unconjugated cytotoxic linker-payloads will be reduced in many cases. In the end, patients with a variety of illnesses may benefit from these new and creative applications of combining a targeting antibody with a compound that can provide a beneficial effect specifically to the cells or diseased tissue of interest.

After more than 120 years, Paul Ehrlich’s concept of a “Magic Bullet” is much closer to a reality for many more patients than just those suffering from cancer or hematological malignancies. [16]

Clinical Trials

A Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Participants With Extensive Stage Small Cell Lung Cancer (MERU) – [NCT03033511](#)

A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Participants With Moderate to Severe Rheumatoid Arthritis – [NCT03823391](#)

A First-in-human Study Using BDC-1001 in Advanced and HER2-Expressing Solid Tumors – [NCT04278144](#)

Study of RM-1929 and Photoimmunotherapy in Patients With Recurrent Head and Neck Cancer – [NCT02422979](#)

Photoimmunotherapy (PIT) Study in Recurrent Head/Neck Cancer for Patients Who Have Failed at Least Two Lines of Therapy – [NCT03769506](#)

About MabPlex International

MabPlex International, Ltd., (MabPlex), a leading and fully integrated, global Contract Development and Manufacturing Organization (CDMO), offers an advanced biologics platform and comprehensive and integrated solutions to global (bio-) pharmaceutical developers. Founded in 2013, MabPlex currently has two sites in China (Yantai and Shanghai) and one site in the United States (San Diego, CA) offering high-quality services from biologics drug development to commercial manufacturing. MabPlex currently has over 60,000 square meters of R&D and production facilities, a total of 9 monoclonal antibodies (mAb) Drug Substance (DS) production lines, 2 Antibody-drug Conjugate (ADC) DS production lines, as well as mAb formulation and ADC formulation lines. The commercial production service designed to help customers accelerate the progress of clinical trials and support market launch.



MabPlex has established a talented team of more than 400 employees providing Contract Development and Manufacturing Organization (CDMO) services to more than 40 pharmaceutical companies around the world resulting in more than 12 Investigational New Drug application (IND) approvals with the United States Food and Drug Administration (FDA), the Australian Therapeutic Goods Administration (TGA) and China's National Medical Products Administration (NMPA). For more information, [please visit our website](#).

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Notes

[a] While Indium¹¹¹ satumomab pendetide (*Oncoscint*® CR/OV), which included a murine monoclonal antibody specific for tumor-associated glycoprotein (TAG-72), a cell surface antigen associated with almost all colorectal and ovarian adenocarcinomas, conjugated to with DTPA as a linker for the added Indium¹¹¹, was found to be safe and effective in detecting tumors, this product was eventually *discontinued* in December 2002 with further development ceasing in 2006, due to fact that researchers demonstrated that positron emission tomography (PET), had been shown to have similar or higher sensitivity.

[b] Now part of Jazz Pharmaceuticals.

[c] Now part of Novartis.

[d] *Bexxar* was discontinued and marketing approval was withdrawn in February 2014 due to the decline in usage.

[e] BR96-Dox (SGN-15) being developed by *Seattle Genetics* was licensed from *Bristol-Myers Squibb (BMS)* and included technology licensed from *Enzon Pharmaceuticals*.

[f] In contrast, Immunomedics approach in the development of *sacituzumab govitecan* (IMMU-132) utilizes SN-38, an active metabolite of Irinotecan, delivered in high concentrations because the payload, in contrast to the majority of payloads used in the development of ADCs, is not super toxic, permitting higher doses, in repeated therapy cycles, that are believed to provide a better therapeutic index.

[g] Gemtuzumab ozogamicin was initially approved in May 2000 under the FDA's accelerated approval program, however, when a *post-marketing clinical trial* was discontinued early because researchers did not observe an improvement in clinical benefit in the randomized *SWOG 106 study* while, at the same time, noticing a greater number of deaths in the group of patients who received *gemtuzumab ozogamicin* compared with those receiving chemotherapy alone, Pfizer voluntarily withdrew *gemtuzumab ozogamicin* from the market in mid-2010. On September 1, 2017, the FDA (re)approved gemtuzumab ozogamicin with a lower recommended dose, a different schedule in combination with chemotherapy or on its own, and with a new patient population. The FDA reapproved the drug-based, in part, on the results of the ALFA-0701 (NCT00927498), randomized, open-label, multicenter phase III trial including 271 patients with newly-diagnosed *de novo* AML, using a new, lower fractionated dose of *gemtuzumab ozogamicin*.

[h] Due to lack of survival benefit for patients receiving *rovalpituzumab tesirine* (Rova-T) compared with the results from the placebo control arm, an Independent Data Monitoring Committee (IDMC) recommended terminating the MERU trial (NCT03033511), a randomized, double-blind, placebo-controlled Phase III study evaluating Rova-T as first-line maintenance therapy, following first-line, platinum-based, chemotherapy for advanced small-cell lung cancer (SCLC).

[i] A study of ISAC, consisting of an anti-HER2 monoclonal antibody conjugated to a TLR 7/8 dual agonist.

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