JEFFREY BUGULISKIS: Welcome to GENCast, a sponsored podcast series brought to you by *Genetic Engineering and Biotechnology News*. I am your host, Jeff Buguliskis.

"Float like a butterfly, sting like a bee" is one of Muhammad Ali's most famous quotes, which is saying a lot for the loquacious former heavyweight champion. Ali is considered by most to be one of the greatest pugilists of all time. As his skill in the ring was unmatched, his one-two combination punch put many a challenger down for the count and solidified his legend in the ring.

Researchers have learned a lot from boxers like Ali, as they are always looking for the one-two punch therapeutic that will cause a disease like cancer to throw in the towel. The current iteration of these one-two punch therapies, called ADCs, or antibody-drug conjugates, combine the unique targeting capabilities of monoclonal antibodies with the cancer-killing ability of cytotoxic drugs. In contrast to traditional chemotherapeutic agents, ADCs target and attack the cancer cell so that healthy cells are less severely affected.

The demand for these novel therapies continues to grow as the global ADC market is expected to reach almost $10

billion by 2025, yet the development of these molecules presents a unique set of challenges, as they are notoriously complex structures that require an exceptional amount of expertise to produce successfully, a scenario that professionals within the M Lab Collaboration Centers at Merck feel right at home tackling head on.

With over 70% of ADC projects being outsourced to contract development and manufacturing organizations, the M Lab Collaboration Centers have gone 15 rounds over some of the toughest ADC production issues and come out victorious. Let us speak with our panelists for this episode of GENCast and find out why you want them working your corner for all your biomanufacturing bouts.

LISA McDERMOTT: My name is Lisa McDermott, and I am the Director of the Process and Analytical Development Department at St. Louis, Missouri. Our major role in this organization is to take and develop processes for bioconjugation and transfer them into our GMP development shops.

BETH GOODRICH: My name is Beth Goodrich, and I am Director of the Manufacturing Science and Technology Application Engineering Team. I am based in Burlington, Massachusetts. My team is responsible for developing

application proof statements and best practices for all the products in our portfolio.

WILL SANDERS: My name is Will Sanders. I am the Director of Process Development in Madison, Wisconsin. Our organization is a contract manufacturing organization. We specialize in the production of active pharmaceutical ingredients under GMP, typically small molecules.

JEFFREY BUGULISKIS: Thanks, even, for joining us today on this GENCast. Let us start to dive into the first question. Analysts, what would you say is the biggest challenge that antibody-drug conjugate manufacturers face in bringing their therapies to market?

LISA McDERMOTT: So ADCs and bioconjugations in general present a unique set of challenges for drug companies. The development is very complex, and their structural exceptionality requires a lot of expertise in a variety of different technologies for both small and large molecules for production, as well as for the analytical methods, to understand them.

In addition, a manufacturer has to have expertise in handling of high-potent compounds at large scale, which is not something that everyone has expertise in. These complexities have led to over 70% of the ADC projects being

outsourced to contract manufacturers for both development as well as manufacturing.

WILL SANDERS: So Lisa mentioned the highly potent nature of these compounds. That is really an important consideration. Payloads for ADCs are very complex molecules, and they present very significant chemistry challenges. But in addition to the normal challenges of chemistry, you have to pay a lot of attention to safe handling with the linker payloads.

So, many of these compounds are extremely toxic and have to be handled in full containment in specially designed isolators to ensure the safety of our employees.

JEFFREY BUGULISKIS: So why do customers working with ADCs visit the M Lab Collaboration Centers?

BETH GOODRICH: Well, I think it is beneficial to bring customers in to the M Lab Collaboration Centers for a few different reasons. You know, the first would be if they are not really sure about their long-term strategy. You know, are they thinking about building their own facility over time?

We can bring them in, and it is great for them to be able to see the capacity and the equipment that we have available for their process while also giving them access

to the technical expertise of the MSAT team, the Manufacturing Science and Technology team.

The M Lab is a great environment to discuss downstream processing, and we do have a full single-use template for ADC manufacturing and bioconjugation. And that single use really increases flexibility and speed while reducing the operator and the environmental risk versus conventional manufacturing. So by having them come in, they really can visualize this process firsthand in a non-GMP lab setting.

In addition, if they are already in the middle of kind of developing that process, we have those technical experts that can help optimize the process parameters, design specific assemblies if that is what is needed for them, develop automated recipes and help with training on the systems. So, really kind of a wide variety of reasons why it can be beneficial for them to come in for a visit in the M Lab Collaboration Center.

In addition, you know, I wanted to point out that for this full single-use template, we do have an on-demand webinar that is available on our website that really kind of goes into what different pieces and parts are included there and what data we have to support them.

LISA McDERMOTT: As Beth describes, we are totally invested in the single-use platform that has been

developed. This has been a cornerstone to our implementation of the single-use GMP process train in our manufacturing facility, and in fact, as part of that webinar, we talk about our ability to be able to work together to implement single use in the GMP environment.

And having the ability of the M Lab and all of the development work they have done within their product profile really helps us understand the scalability of processes from one size to the next. Having them as a resource is also something that is incredibly valuable to us.

So having that resource to be able to lean on as well as take all of our processes to large-scale single-use manufacturing has been a very exciting area for us in the last few years.

JEFFREY BUGULISKIS: Great. Thanks, guys. With an increasing amount of ADCs' manufacturing work being outsourced to CDMOs, how is Merck staying ahead of this trend?

LISA McDERMOTT: In St. Louis, we have a very long history of investing in ADC manufacturing to meet our customers' needs. Back in 2008, we commissioned our clinical ADC facility. This facility really targets early-phase projects, phase 1, potentially even phase 2, really

focusing on having a facility that we can get programs to the clinic very quickly with a robust process and efficient pace.

We followed in 2015 with the implementation of our commercial facility to produce late-stage and commercial products. To date, we have supported more than 25 new INDs coming out of those facilities and have produced more than 125 batches in the GMP space.

In addition to that increase in our manufacturing capabilities, of particular interest to me, we have continued to invest in the process and analytical development infrastructure here in St. Louis. In 2018, we expanded our process and analytical development laboratories with a 6,000-square-foot addition, and this has enabled us to really expand the footprint both in capacity as well as just in size of batches that we have been able to do.

In the development space now, we have the ability to not only do large-scale chromatography, we can produce batches up to 50 l, still within the development space, before we actually do our tech transfer into GMP.

In that space, we have supplied over 600 batches of different ADC constructs to our customers at varying scales, all the way down from milligram scales, all the way

up to about 150 g. This really enables them to be able to make their choices and be able to move forward with their programs very efficiently.

Of particular interest in this podcast that we are doing, talking about the single-use technology in the ADC space, we have worked with Beth's organization very closely to develop and implement single-use reactors not only in our GMP space, but also in our PAD space.

This allows us to be able to scale directly from glass into single-use reactor and PAD, and then into single-use reactors in the manufacturing space. Knowing all of the turndown rates, all of the scalability between all of those different units. This collaboration has really ensured that we are compatible and scalable with our single-use technology.

In addition, we continued to expand our PAD capabilities in automation. These tools not only allow us to gather more information, as much data as possible, it is very valuable for understanding our process and characterization, allows us to gather ranges for our processes, so the way -- transfer into manufacturing, we have more flexibility.

So the addition of not only physical space in the lab, but also all the tools we need to take us to the next level are the investments that we are doing here.

WILL SANDERS: In Madison, we have over 25 years' experience working with highly potent compounds, and we have purpose-built facilities in which to manufacture them. We also have a very experienced process chemistry team and manufacturing group capable of managing the most demanding challenges.

But I think the number-one way that we as a company are staying ahead of the trend is through our network of global facilities. We have a global contract manufacturing organization that includes our facilities in Schaffhausen, Switzerland, in Madison, Wisconsin, and in St. Louis. We also have partner facilities in Buchs, Switzerland, Milwaukee, Wisconsin, and Sheboygan, Wisconsin.

So the existence of this larger organization provides both logistical and technical benefits to clients. For example, we have a number of examples where our facility in Sheboygan produces custom complex starting materials and ships them to Madison. Madison takes these and performs a GMP synthesis of a linker payload construct that we subsequently ship to St. Louis for conjugation to an

antibody. So in this way, we can offer our customers and end-to-end solution for production of both drug, substance.

LISA McDERMOTT: And I would highlight our interaction with Will's group, also, just getting early lots of raw materials and being able to evaluate those in the conjugation process is very valuable to us to be successful. We collaborate quite often to make sure that the drug linkers have the correct specifications and to ensure success in the conjugation campaign.

BETH GOODRICH: And I think, as Lisa mentioned, you know, our teams were able to work together, and this was a great example of combining the expertise of single-use systems development with the expertise of the ADC, you know, manufacturing needs to really come up with built-for-purpose single-use systems.

And here it was not just designing and building those systems, but also a lot of the application testing that went into it to ensure that once they were implemented into the production facility and the development facility that they were going to be successful, meet all the process objectives.

So we were able to utilize the space that we have available in the M Labs to do application testing and to do a lot of solvent compatibility testing, as well. That is

one of the big concerns with the post-conjunction purification, is, you know, is it going to be safe to have solvent exposure on the single-use plastic components?

So we were able to simulate the worst-case conditions that would be expected and show that the systems could operate successfully, and also that the extractable, reachable profile was going to be acceptable. So I think that we are -- having all the capabilities able to work together is really kind of keeping us ahead in this field.

I would also like to headline that we do, with these M Lab Collaboration Centers, have a global network of technical experts. We have centers in eight places around the world, and that is really key to successfully supporting ADC manufacturers.

In today's world, you may have a process that is developed in one location and then transferred to other geographies around the world, so being able to interact with the end users in their local geography, bringing them into the M Lab if they needed to test equipment not in their site and then interact with our experts that can help them optimize their operations, train them on recipes, train them on equipment is really valuable.

JEFFREY BUGULISKIS: Great. Thanks, guys. If you had a crystal ball, how would you predict the future of the ADC market in the next five to ten years?

LISA McDERMOTT: You know, it is a very exciting time for ADCs. With the recent approvals that we have seen and the knowledge that there are another six to ten late-stage projects that we expect to be filed over the next year or so, ADCs have moved into being a viable therapeutic treatment, especially in the field of oncology. It is also exciting that we start to see other bioconjugates for different indications being pushed forward into the marketplace.

WILL SANDERS: I think, as Lisa mentioned, we are going to see that ADC market expand significantly in the coming years. I think it is also going to expand outside the area of oncology. But what I think is going to change the most is a shift to less toxic and less potent payloads.

To date, marketed ADCs contain payloads of extremely toxic molecules that, even when conjugated to an antibody for targeted delivery, have serious toxicity in vivo.

So I think the idea of the targeted delivery of an ADC is to take your therapeutic agent to the cell that you want to kill. And to kill a cell, I do not know that you need to have such a toxic compound. And I think a lot of the

failures in the clinic that have been due to toxicity may very well be mitigated by the use of less toxic payloads.

BETH GOODRICH: And I guess really to just kind of build from what both Lisa and Will mentioned, I think as these therapies continue to be approved, and there is demand for more on the market, the technology used to manufacture is likely to start to head towards standardization and templatization.

Similar to the way MAB manufacturing was templated, I think that the post-conjunction purification will head that way just because it is more efficient and we will need to lower cost of goods.

And so, you know, that has been an impact on the equipment that needs to be used. As things are standardized, it makes it easier for vendors to really come up with solutions that are going to provide the best fit for the process.

LISA McDERMOTT: So I think, in summary, whether we are talking about ADCs as cures or just simply as treatments, they have been validated now as a valuable part of the toolbox for patients. We continue to see expansion into combination treatments, and that, with the ability to increase the therapeutic index with specific targeting

mechanisms, I think means ADCs are going to be around for quite some time.

JEFFREY BUGULISKIS: Thanks very much, guys, for joining me today on this GENCast. Hopefully we will see you all again soon.

Thanks for listening to GENCast. For *Genetic Engineering and Biotechnology News*, I am Jeff Buguliskis.

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