Welcome to the M Lab™ Collaboration Centers

Step into a global network of collaboration spaces for exploring cutting edge ideas and solving the toughest problems in life science.

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Creating the Future of Biologics…Together

It seems not that long ago that monoclonal antibodies were considered "novel" and using gene therapies to cure rare diseases was just a dream. The mAb process is now about 30 years old. In that time, the industry has become smarter, more agile, and is keener than ever to make the dreams of the 1990s a reality.

With this enthusiasm and drive comes process challenges. Manufacturers are looking to suppliers for integrated solutions as they think holistically about their process and visualize future scale up. The industry is buzzing about continuous processing because it will have a significant impact on how our customers bring therapies to market, delivering them to patients faster and more cost-effectively than ever before. The industry is moving towards intensified, connected, and continuous bioprocessing. Merck's vision goes beyond continuous manufacturing and will deliver contiGuous bioprocessing — a seamless confluence of digital and intensified bioprocessing building blocks. ContiGuous manufacturing goes beyond just connecting the individual unit operations — it will include the digital orchestration and data management of all the processing steps (materials, production, testing and analytics) with an industry-leading streamlined and optimized approach.

This industry paradigm shift, fueled by novel modalities and forward-looking bioprocessing applications, has reinforced the need for better integration, collaboration and education. High-growth regions like China are moving at the speed of light, and the entire APAC region is thirsty to train its workforce in biologics GMP best practices to meet the demand for skilled labor. Emerging regions like Africa, the Middle East, Eastern Europe and LATAM are all in the race to get affordable medication to local patients.

This is our chance to come together as an industry and solve problems together. Welcome to our global network of M Lab™ Collaboration Centers. Whether you are a small biotech on the East Coast of the United States, a large player in APAC seeking to train your expanding workforce, or a mid-sized biosimilars company in Brazil looking to bring therapies to market faster, our 200+ technical experts around the globe want to walk with you on your journey and see you cross the finish line. Let's collaborate.

Dr. Andrew Bulpin
Executive Vice President,
Head of Process Solutions, Merck

A Vibrant Collaboration

The future of medicine and drug development has never been more exciting. Biopharmaceutical processing was once considered a highly specialized process – even the idea of copycat biosimilars once seemed dubious because of processing complexities. To an extent, biopharma processing, particularly scale up, is still full of challenges, but overall the industry understands the art of biopharma manufacturing well enough now to begin to dramatically improve facilities and procedures using "next generation" approaches that promise to reduce manufacturing costs and get new medicines to patients faster. And new therapies are emerging too – cell and gene therapies are being widely discussed across the industry because they can potentially cure devastating diseases that once had few effective options. Many once believed that manufacturing such therapies on a commercial scale would be impossible, but approved therapies have proven otherwise, although certainly it is still early days for the advanced medicine field. And there is much to do if advanced biomanufacturing for biopharmaceuticals and cell and gene therapies is ever to reach its full potential.

How do we get there? Collaboration and knowledge sharing will be essential. This industry has tremendous skills and experience as a whole. By speaking to one another, companies will be able to overcome the hurdles and I have no doubt that the future will be packed with breakthrough therapies that benefit from advanced science in terms of drug design and drug manufacturing, which help to bring costs down and make drugs more affordable and widely available to patients across the globe.

Partnering with Merck for this series on the M Lab™ Collaboration Centers has been inspiring. Merck describes the M Lab™ Collaboration Centers as a "global network of vibrant collaboration spaces where industry professionals can explore ideas, learn innovative techniques and work side-by-side with technical experts to solve critical process development challenges." Collaboration is the key word – the centers are all about connecting customers with experts to share best practices and knowledge on a range of different areas, from troubleshooting to training and more. In this article series, find out more about the M Lab™ Collaboration Centers from those who work in them, as well as those who have used them.

Stephanie Sutton
Editor of The Medicine Maker

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Welcome to the M Lab™ Collaboration Centers!

Enter a space where you can explore new ideas, learn innovative techniques, and work side by side with technical experts to solve your toughest problems in life science.

By Chin Bin Tan

The M Lab™ Collaboration Centers were set up as non-GMP spaces that pharmaceutical manufacturers could visit to explore both novel and proven processes and technologies, such as renowned core technologies, but also applications offered as part of our BioContinuum™ Platform for intensified, connected or continuous bioprocessing, without interrupting operations at their own plant. Engineers and scientists from both sides – the customer's scientists and engineers and the experts at the M Lab™ Collaboration Center – can come together to test, optimize, intensify and troubleshoot processes. In addition, customers can visit the M Lab™ Collaboration Centers to learn best practices and techniques through our training programs.

The first M Lab™ Collaboration Center was set up in Asia because this is a rapidly growing market where there is a need for access to expert biomanufacturing knowledge and training. The population as a whole is demanding improved medicines and can afford new medicines, which has led to a boom in the biopharma market. There is a real need for new biologics and new technologies (intensified processes and single-use systems hold particular interest in Asia, as well as cell and gene therapies). Asian biopharma companies are rapidly trying to catch up with their western counterparts, but there is a shortage of experienced biopharma workers in the region. As a result, we are seeing a desire to train large numbers of people in a short space of time to get new facilities up and running.

Host countries have welcomed the M Lab™ Collaboration Centers. The centers aren't just used by private companies; we also partner with governments. In Singapore, we signed an agreement with the government training agency to be one of their key training centres for the biologics industry. Since then we've done a significant amount of industry training, including training with big pharma companies who have signed up to the government program. To date, we have trained 70 percent of the Singapore pharmaceutical workforce – 80 percent of whom are employed today in manufacturing operations. In China, we have been training NMPA (National Medical Products Administration) inspectors. China has more than 30 provinces, and the technology management team (part of the M Lab™ Collaboration Centers network) partnered with the NMPA to train inspectors at the provincial level. The team in China says our key differentiator in the region is the depth of our expertise.

Training can be customized, depending on the customer's needs, but we also offer our own training programs, which are all tailored to the different countries where they take place due to local regulatory requirements and language. We also have a lot of good interactions with associations like the PDA (Parenteral Drug Association) and ISPE (International Society for Pharmaceutical Engineers) – and sometimes they even arrange for their own meetings or training to take place at our M Lab™ Collaboration Centers.

Today, there are nine M Lab™ Collaboration Centers spread out across North America, South America, Europe and Asia – and we have 200 experts working in the centers. Initiatives like the M Lab™ Collaboration Centers are seen by governments as active investments that will help them to develop their own biopharmaceutical workforces because of the opportunities for training – and I'm really proud that the M Lab™ Collaboration Centers are helping to develop human resource ecosystems.

Chin Bin Tan, Head of Technology Management, APAC at Merck.

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The Customer View

Samsung Biologics give their opinion on working with the M Lab™ Collaboration Centers.

Tell us about Samsung Biologics and how the company is growing...

In 2007, Samsung's Chairman, Lee Kun-hee, organized a special task force team to discover Samsung's next-generation growth engine. Samsung's executive team nominated CEO, Dr. TH Kim, as the one responsible for finding this new growth. Dr. Kim spent 3 years with a team to review dozens of new business candidates, including solar cells, electric cars and so on, but he finally selected biopharmaceuticals to become the new business of Samsung.

Samsung Biologics was established in April 2011. Everything in the biopharma industry is a first experience for Samsung. We decided to build our first plant to a standard size – around 30,000 L capacity. We built this first plant in 13 months and it took 25 months to receive approval from regulatory authorities. Our clients were very satisfied with our services, and since the first plant we have built two more facilities (150,000 L and 180,000 L) over the past 4 years. We have also expanded the scope of services to include development. We can now provide solutions to our clients from cell line development to manufacturing in one site.

But we are not satisfied with where we are now. We will continue to expand our business both for clients and shareholders. We are so excited to be a world class biopharmaceutical company that will cover all value chains in the near future!

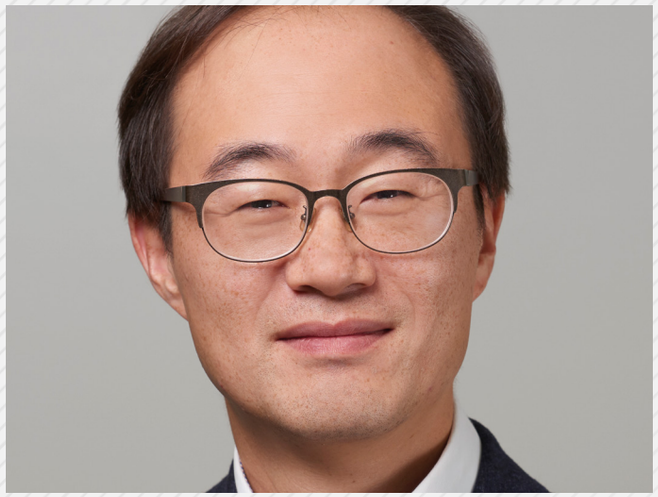
How did you come to collaborate with the M Lab™ Collaboration Centers?

Samsung Biologics initiated its first GMP product manufacturing in Plant 1 in 2014 – just three years after the company's foundation. Although we had experienced experts from around the globe in key areas of manufacturing operations and technical support, the majority of our employees were quite new to this industry. At the same time, Plant 2 was under construction and we anticipated an increased number of batch output and tech transfers in the following years.

As a CMO company, we faced challenges with manufacturing processes that are being transferred from each client, with variations in raw materials, equipment and facility variations. We wanted professional expertise to overcome the challenges, and we also felt that training was required to

The Training Challenge

With Charles Park, Manager, Manufacturing Science and Technology at Merck.



One of the biggest challenges that biopharmaceutical companies have is adequately training new employees. Even though new people may have a bio-related education, they will no doubt have much to learn about applying this in practice and will need training. Some companies try to prepare training with their own internal resources, but this can become a burden. Asia has seen a dynamic increase in the number of projects transitioning to the clinical phase in the last two to three years, which means more skilled labor is required.

Samsung Biologics has been growing fast with a strong focus on the market – and is now considered the world's largest biopharmaceutical CMO company. When Samsung's needs were growing, we opened our M Lab™ Collaboration Center in Songdo. I was involved in the customized training program for Samsung, which is an ongoing partnership today.

Samsung had three main requirements. First, they needed targeted content for the audience, including risk assessment and troubleshooting for the engineers, and optimization and tech transfer for R&D. Second, they requested different course levels based on trainees' experience level – basic and advanced training. Lastly, there was a requirement for hands-on experience for trainees to adapt to the field more quickly. To meet these demands, we customized the training classes. We provided automatic filter integrity testing and normal flow filtration training for engineers, and clarification and tangential flow filtration for process optimization. These trainings combined hands-on experience with the required theory sessions. For all hands-on training courses, we utilized workshop sessions that allowed us to discuss, in depth, test results, troubleshooting and any risks that might happen in the real process.

The feedback from Samsung has been very positive and constructive. After attending sessions in the M Lab™ Collaboration Center, trainees became more confident about their work. I've been very proud of the trainees' proactive attitude; they were active participants and found the training so useful that they recommended it to their colleagues. It's a great motivation for me! And this is just the beginning…

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enable our new employees to develop their capabilities – this was a key element of growth for the Korean biologics industry.

We undertook an initiative with the Korean government to establish a research and training center, similar to Ireland's National Institute for Bioprocessing Research and Training (NIBRT) to develop a qualified industry resource pool in Korea. We worked with several partner companies to establish application development/process development, and training capability in the country to help troubleshoot and provide customized in-depth training around raw materials, equipment and manufacturing processing.

Merck was an early member who recognized the challenges we faced and they knew the industry trends and needs around the globe. Merck finally opened the M Lab™ Collaboration Center in Songdo, Korea, in 2016.

What type of training did Merck develop for Samsung?

Understanding biomanufacturing processes is fundamental for CMOs. Some might think that technical training is not so important for operators that are manufacturing client products, but this is wrong. Training is crucial for everyone who is involved in biomanufacturing, from upstream to downstream and final.

Did You Know?

- There are more than 50 in-house certified trainers in the M Lab™ Collaboration Centers worldwide.
- Customers can take a range of biopharmaceutical and classical pharma courses at the M Lab™ Collaboration Centers, from upstream to downstream and formulation.
- Both hands-on training and classroom-style theory courses are offered in our M Lab™ Collaboration Centers around the world.
- The M Lab™ Collaboration Centers also provide focused training on Merck products to help customers optimally implement them in their production setting and reduce the need for technical support.
- As an extension of our M Lab™ Collaboration Center services, our team of experts also delivers customized training directly at the customer site.

Learn more at merckmillipore.com/training

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Single-Pass Promise!

When the healthcare business of Merck wanted to increase drug production, they found that their manufacturing process did not have the required capacity. The answer? Working with the M Lab™ Collaboration Centers to intensify the upstream process and implement single-pass tangential flow filtration to overcome downstream bottlenecks.

With Matteo Costioli and Torsten Bisschop

How did you become involved with the project?

Matteo Costioli: I've been working with the healthcare business of Merck for over 10 years and I am responsible for all new biological entities (NBE) process development at our site in Switzerland – from bench to GMP manufacturing at 2,000L scale, for Phase I and II. Our company had seen great success with our new immuno-oncology therapy, BAVENCIO® (avelumab), and clinical trial data revealed that we needed to increase production to accommodate a larger patient population. My role at the time was to optimize the process for commercial manufacturing and to validate the process for marketing submission. Our facility and processes, however, did not have the capacity to support this increased production. Even if titers were increased upstream, we didn't have the tank space downstream. The facility was also used for other products so we couldn't make big changes.

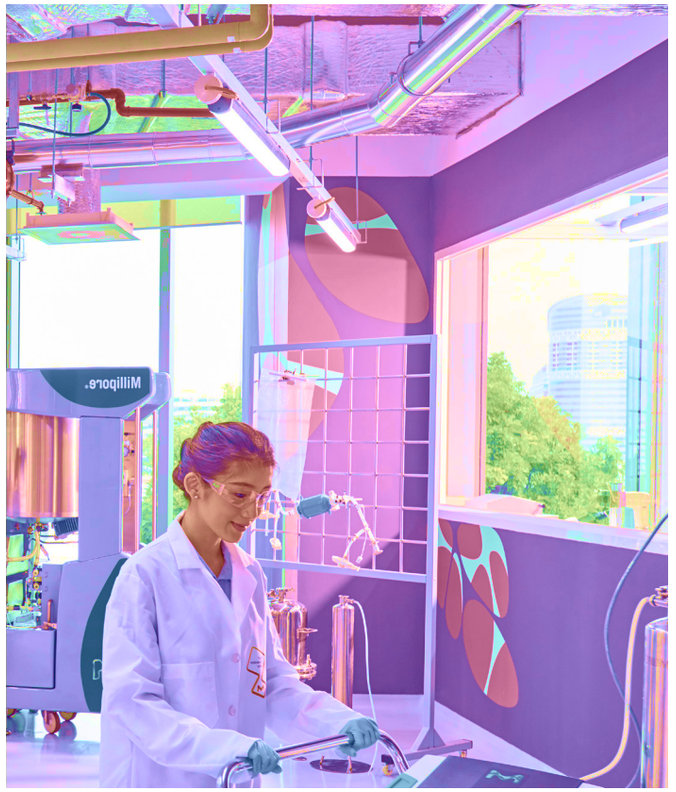
Torsten Bisschop: The team from the healthcare business of Merck came to us because they wanted to enhance their existing tangential flow filtration technology (TFF) by applying single-pass TFF (SPTFF). The team there had already done some experiments with lab-scale SPTFF to reduce volumes after dilution and liked the results, but they wanted additional expertise to scale up the process.

Why SPTFF?

MC: Downstream processes have not evolved to cope with the increasing titers upstream, so bottlenecks are an issue in many biopharma companies. SPTFF has been very helpful because the concentration of the protein solution reduces the volume of liquid, allowing scientists and engineers to work with higher titers, in an environment designed for lower titers, without altering the facility. SPTFF is relatively easy to implement – it can almost be considered plug-and-play – and it is already very well known in the industry.

TB: TFF is present in all biopharma manufacturing processes and SPTFF is a different way of using the existing technology. With SPTFF, the flow over the membrane is serialized to prolong the residence time of the feed under pressure. This allows you to achieve the desired concentration in a single pass, whereas in standard batch TFF you need to recirculate and pass the material over the membrane multiple times. After the single pass, your concentration is ready immediately. It's a much simpler process than traditional TFF.

SPTFF is a next-generation manufacturing project which is part of our new BioContinuum™ Platform for intensified, connected, or



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continuous processing and is seen as an important technology to help improve the productivity of biopharma manufacturing. SPTFF is a versatile application and can be coupled to other process steps for process intensification. After linking different process steps, SPTFF can be used to change the concentration or composition of feed material to enhance the proceeding step. With some steps, efficiency improves at higher concentrations or compositions.

What was the end result?

MC: To ensure that the technology really fits our needs, there was a workshop between the teams at the healthcare business of Merck and the M Lab™ Collaboration Centers. Even when a technology is relatively easy to implement, there will always be many questions about how it fits into the facility and scales up. The team at the M Lab™ Collaboration Centers tried to answer all of these questions in the workshop to help smooth implementation. Ultimately, implementation of SPTFF resulted in a cost of goods reduction, while the plant capacity required for molecule production decreased from 90 percent to 26 percent.

How did you find collaborating with the M Lab™ Collaboration Centers?

MC: Working with the M Lab™ Collaboration Centers really helped reduce the development time. If we'd done this alone, we would still have reached our goal but I think there would have been more failures along the way! It was very valuable to collaborate with experts who were very familiar with the SPTFF application and could explain to our team how it worked, what tests and experiments were necessary to identify the correct process parameters, and what the overall benefits would be.

At the start, new collaborations can be difficult. The healthcare business of Merck is an organization with its own way of doing things and established infrastructure, and we can't always make changes easily. The experts at the M Lab™ Collaboration Centers were very open and understanding about our various constraints and worked within that. They were very flexible and, ultimately, we were able to put in place something together that works really well.

The Next Generation

There is industry-wide consensus that biopharma manufacturing must become more efficient and agile so that it can better react to new market demands and trends; often referred to as next generation bioprocessing. Merck recognizes that there are different paths on how exactly this can be achieved: for some biomanufacturers, next generation bioprocessing is about intensifying processes and reducing manufacturing footprints; for others, it is about connecting processes into continuous manufacturing lines or rolling out single-use facilities – or a combination of all of these approaches. Whether developing an intensified, connected or continuous bioprocess, Merck's BioContinuum™ Platform provides the building blocks to help biomanufacturers achieve their specific goals and to confidently enter the era of next generation processing by delivering increased speed, greater flexibility and enhanced quality while reducing costs and risks.

Herb Lutz, Global Principal Consultant, Manufacturing Sciences & Technology, Merck, believes that next generation bioprocessing is not necessarily about developing new technologies, but adapting the technologies already available, such as TFF. SPTFF is already seeing increasing uptake because it can help streamline efficiencies in stainless steel facilities. Genentech, for example, wanted to introduce a new molecule for manufacture at one of their plants and found that the necessary process would not fit in the tanks they had. "By employing SPTFF, they reduced the volume sufficiently to fit their existing infrastructure," says Lutz. "Inserting a SPTFF step to increase product concentration can also improve a subsequent step. People often get excited about a new resin giving a 15 or 20 percent increase in capacity, but adding a SPTFF step gives a 400 percent improvement! And there's more: given that we reduce the volume of liquid as we concentrate it, we can run the process more quickly."

Merck is combining new advances with TFF for new applications. For example, the company is running its strong anion exchanger in-line with TFF cassettes and has devised procedures for assessing the feasibility of this application with monoclonal antibodies.

Read more about the move to next generation bioprocessing and the role that SPTFF can play at: www.merckmillipore.com/SPTFF.

At the M Lab™ Collaboration Centers, we are always interested in welcoming scientists and engineers for exploring the different technologies and solutions for next generation processing. Feel free to join and collaborate!

How are the M Lab™ Collaboration Centers positioned to help biomanufacturers?

TB: We often talk about the M Lab™ Collaboration Centers as a physical space, but it is more than that – it is also all the people with their experience and passion to solve problems. The global network also allows us to support biomolecules when they move around the globe. Our projects often pull in the expertise of our network, with many different people contributing to solving the bioprocessing challenge. For example, this project was very "global" in nature: the feasibility and scale up experiments were done in the US and Europe at M Lab™ Collaboration Centers and at the Merck healthcare site; supporting static cleaning studies were performed in the M Lab™ Collaboration Center in Singapore; and the system design, build and qualification were done in close collaboration with Matteo's team, the MSAT and application engineering teams, and the hardware group in the US and Europe.

The team at the healthcare business of Merck knew their processes, their molecule, their own limitations, and had a good idea of what they wanted to achieve. We contributed our knowledge of SPTFF and how it could be integrated into the existing environment. It is very rewarding to work collaboratively with customers and to come up with solutions that make a big difference.

Matteo Costioli is Director BPS, Early Process Development at the healthcare business of Merck, and Torsten Bisschop is Biomanufacturing Engineer Consultant at Merck.

Safety in Numbers

Viral contamination can shut down a plant for months – affecting manufacturing, causing business disruption and ultimately threatening drug supply and patient safety. Comprehensive viral safety means taking the right steps to prevent viral contamination upstream and using the right technologies to remove viral contaminants downstream.

With Sladjana Tomic-Skrbic and Gregory Voyta

How did you find yourself at the M Lab™ Collaboration Centers?

Gregory Voyta: Before joining Merck, I worked for a consultancy firm on biotech processes. I was involved in a variety of activities, including membrane testing, working with bioreactors, and engineering downstream filtration processes. I presented a tangential flow filtration project when being interviewed for Merck, and today I am a biomanufacturing engineer with the company. I work with customers in the M Lab™ Collaboration Centers.

Sladjana Tomic-Skrbic: I studied biotechnology and completed a doctoral degree in biology and biochemistry. Then, I spent three and half years in academia working on designing and purifying artificial binding proteins, alternatives to monoclonal antibodies, before joining Merck's process development scientist team in Europe. Now, I lead a field-based team of process development scientists that provide high-quality scientific and technical support, as well and collaborate with customers developing or manufacturing biopharmaceuticals. Our support is mainly at the customer sites, but occasionally we also have joint activities in the well-equipped M Lab™ Collaboration Centers. I am also the focal point of a dedicated worldwide team within technology management and the Manufacturing Sciences and Technology (MSAT) team with expertise in process development and viral clearance for virus filtration studies.

Why is viral safety such a crucial topic?

STS: There's always a risk of microbial contamination when you're making biopharmaceuticals. The aim of biosafety is to minimize the risk of contamination and protect patients from the impact of viruses and bacterial contaminants of the drug production process.

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"The aim of biosafety is to minimize the risk of contamination and protect patients from the impact of viruses and bacterial contaminants of the drug production process."

A Continuous Trend

By Gregory Voyta

Currently, there is a lot of interest in the biopharma industry in intensified manufacturing and continuous processing. For that reason, we've set up a new initiative called the BioContinuum™ Platform, which is designed to help intensify and evolve manufacturing processes while still maintaining purity and viral safety. Many of the technologies within the BioContinuum™ Platform are not new technologies, but new approaches using established technologies. Many customers have shown interest in coming to the M Lab™ Collaboration Centers to look at new ways to run their existing systems more efficiently.

At the M Lab™ Collaboration Centers, we often work with traditional batch style mAb processing. However, we have been receiving a growing request for demonstrations covering intensified processing technologies and applications, where customers can see how this might operate in practice and ask questions. With more traditional batch processes, companies typically ask questions about implementation, but with intensified processes, the questions are a little more diverse – for example, customers may be looking at small scale or pilot-scale systems only and are wanting to know how the technologies work. Many customers are interested in our BioContinuum™ Platform offering for intensified, connected or continuous processing and how the technologies and systems will integrate with their current manufacturing processes. As intensified processing and increased process efficiency is a focus for the industry, and we have a legacy of experience in filtration and purification, many customers come to us looking for answers on how to implement it in their processes.

More information about viral safety and virus filtration is available at:
www.MerckMillipore.com/virus-prevent-detect-remove

You can also visit our M Lab™ Collaboration Centers:
www.MerckMillipore.com/MLabs

It's critically important in both upstream and downstream processes, and manufacturers must demonstrate sufficient level of biosafety to regulatory agencies before their products can reach the market. My team works with customers on various pain points in viral filtration, which is a critical step in downstream biosafety. Projects may include to gain and/or broaden knowledge in virus filtration, expand capacity limits, explore prefiltration options, sizing, spiking options and validations.

GV: A multitiered approach is needed to ensure viral safety, and includes methods to prevent adventitious viruses entering production processes, detect contamination in raw materials and process intermediates, and remove viruses in downstream purification. Virus filtration is a key focus of any viral safety strategy, as it is implemented across all downstream purification processes. Virus filtration is a key focus for us – largely because its mode of virus removal and size exclusion can provide effective viral clearance. This is a critical step implemented in most downstream purification processes. Many customers have questions about how to maximize the performance of parvo- or retro-virus filters in their processes, and we have technical experts that can support customers at every stage. A customer can have one of our process development scientists on site to do the initial sizing before moving to MSAT, who will focus on implementation and scale up. These discussions could cover everything from customer training, to troubleshooting a problem, to helping with a virus spiking trial, depending on the customer needs. As one example of a recent project, a customer came to us because the volume they could process through a filter was too low to be economically viable and they needed help optimizing their filtration process. We did a lot of troubleshooting looking at different filters, adjusting pH and looking at processing efficiency of different concentrations of protein solution. We ultimately optimized their process and wrote a publication describing the different steps we took and why the process added value to the customer, to share the benefits of filtration optimization with other customers (1).

On what other viral safety topics do customers seek additional advice and expertise?

GV: One company came to us because they didn't have any experience with virus filtration. We brought them into the M Lab™ Collaboration Center and replicated their existing system. This gave the customer the opportunity to bring in their engineers, operators, and staff who write the batch records, to learn more about the process, how it works, and what to look out for to anticipate potential issues.

STS: In addition to customer visits, implementation work and hands-on training, our colleagues focusing on the BioReliance® biosafety portfolio conduct viral clearance studies at testing laboratories, which customers find very helpful. During spiking studies, some customers sometimes experience lower volumetric throughput than they typically observed in process development studies. This can be caused by a number of different issues, and the engineers of the M Lab™ Collaboration Centers have a lot of technical expertise in troubleshooting such issues. They have also published in this area, providing a good technical explanation of the sources of some of these problems, including the impact of the virus spike quality (2, 3).

What feedback have you received from customers?

GV: Customers are generally delighted with the hands-on support they receive; and if they have any concerns or questions – now or in future – they understand that they can reach out and speak with us. When it comes to virus filtration studies, we help our customers feel confident that there is plenty of technical support to ensure that implementation, prospective virus spiking studies and process development can be done efficiently and easily. Whenever we support a customer, we also provide them with reports for their specific process to help them understand the variables and critical steps in the process.

STS: Customers like to proceed as fast as possible because "time is money" and they often have set deadlines to solve problems. We have more than 20 years of experience in virus filtration and can solve most customer problems. Recently, I worked with a customer on virus filtration and their feedback was that we are professional, quick to react, highly knowledgeable, and have state-of-the-art equipment. I think all of these factors are crucial for success.

The projects involve meetings at the M Lab™ Collaboration Center, as well as the customer site. Why is it important to have both?

STS: Having access to the expertise at the M Lab™ Collaboration Centers can be invaluable. There is a huge benefit to customers coming to the M Lab™ Collaboration Center to use the equipment without disrupting their own production lines to perform testing or process troubleshooting. But on the other hand, it can be useful for some customers to use their own equipment and fresh feed.

GV: It is personal preference and the decision comes down to how closely the customer wants to mimic their processes and how easy it is for them to have everything they need at the M Lab™ Collaboration Centers versus their own labs. We think it is important to offer both options.

Do you work internationally?

STS: Absolutely! As a global organization, we have facilities and resources worldwide. A recent client required a viral clearance study and spent time in our viral clearance BioReliance® facility in the UK. It's so important to have in-person discussions with scientists to troubleshoot any issues. Besides the individual support teams in each region, we also have a dedicated global team (more than 200 experts) supporting the M Lab™ Collaboration Centers network, with a lot of experience in different aspects of viral safety. The team exchanges ideas, troubleshoots problems, presents at conferences, and shares the knowledge with customers to help prevent issues with newer customers or processes. The European team recently performed a viral clearance study for an Asian customer who traveled to Europe for the studies so that they could observe and discuss the results in person. The project overview given by the Asian colleague and working face to face with the customer like this is very handy if issues crop up, which they invariably do – and these studies are not cheap to repeat!

GV: There can be differences in how tech transfer works in other regions so ongoing dialog is important to keep everyone on the same page. We have viral safety experts in all fields, including regulatory experts, process development expertise from pre-clinical to manufacturing scale, not only in virus filtration but also in raw materials and in process testing, material treatment such as HTST, chemical inactivation, and other removal technologies such as chromatography. We do a lot of tech transfer between groups in the different regions, and we can provide customers around the world with the same levels of support – regardless of location.

Sladjana Tomic-Skrbic is Manager, Process Development Scientist-EMEA and Gregory Voyta is Biomanufacturing Engineer, MSAT – Downstream Americas, both at Merck.

www.merckmillipore.com/virus-prevent-detect-remove

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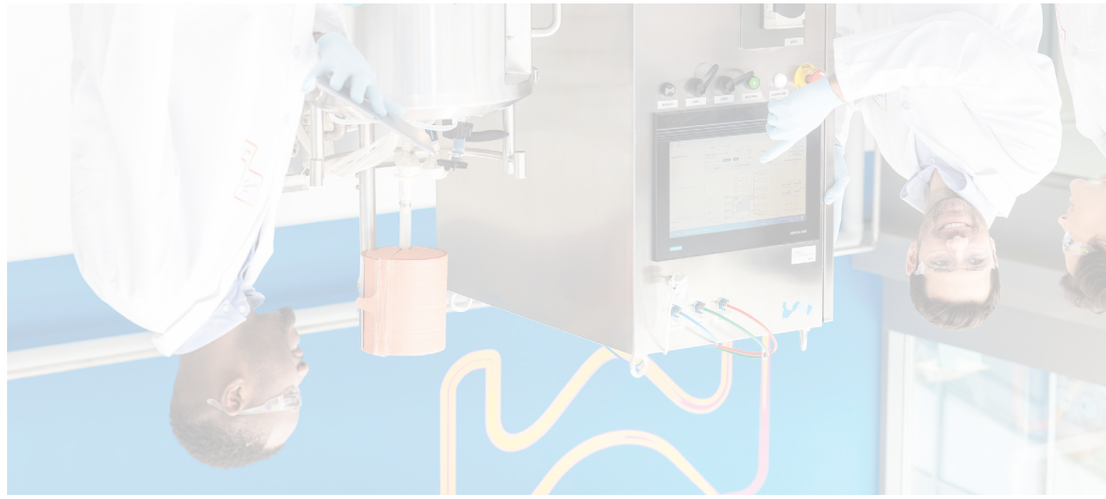

On the Cusp of Curing Disease

Welcome to the M Lab™ Collaboration Centers – where customers can use non-GMP lab spaces to operate equipment, evaluate processes and receive real-time technical support without disrupting production.

With Elizabeth Goodrich and Ranjeet Patil

What is your role at the M Lab™ Collaboration Centers?

Elizabeth Goodrich: I lead the Application Engineering team worldwide, and most of our projects are run in the M Lab™ Collaboration Centers. We don't work in product development, but we do work with products that are already launched to develop best practices and other useful information that we can deliver to customers to help them streamline their own process development efforts. Often, customers come into the M Lab™ Collaboration Centers so that we can address their specific concerns – they can also learn more about our products and test out different processing strategies. These labs are situated in nine different locations worldwide, so we can reach customers wherever they are.

Ranjeet Patil: I lead the vaccine and viral therapies group, which works with customers in a consulting capacity. Many customers come to the M Lab™ Collaboration Centers to look at our systems and hardware to get a feel for what would be a good fit for them. Gene therapy products are attracting a great deal of attention so my group talks to customers in this area.

What are the biggest needs of gene therapy manufacturers?

RP: There is now rapid growth in the pipeline and this translates to a need for speed. Speed to market is nothing new, but it resonates with gene therapy customers for a few different reasons. Firstly, many companies are targeting rare diseases – and, in many cases, patients won't have long to live without treatment. Secondly, many of these drug programs qualify for expedited approvals and other companies may be chasing the same targets. You may not have a viable business because there isn't a large population to go after if your competitor is first to market.

Given that companies want to get to market fast, many decide not to invest in a physical footprint and instead look for a CMO, but capacity at such companies is extremely limited given how many people are developing gene therapies. On the other hand, even if a company wanted to expand and have their own manufacturing capacity, it is extremely challenging to build and effectively operate spaces suitable for gene therapy manufacturing. Infrastructure for any kind of viral

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process is significantly more expensive than for other classes of biopharmaceuticals. Although there is clarity on the clinical aspects of the process, the manufacturing aspects are challenging because there is no template approach – every process is different and regulatory guidance isn't straight forward.

What do the M Lab™ Collaboration Centers offer to customers?

EG: Many of the companies working on gene therapies are small – perhaps even virtual – so they have limited human and laboratory resources at their disposal. The M Lab™ Collaboration Centers can be an extension of their resources, giving them relevant tools to work with and a place where they can test new processing options.

We also have a full suite of single-use products available in the centers for customers to evaluate. Single use is a great option for gene therapy manufacturers because there is a huge need for sterility and eliminating the potential for cross contamination. Again, the M Lab™ Collaboration Centers are spaces where customers can visit to see what technology is available, receive hands-on experience, and test to see what will work for their process.

Finally, we offer a wide range of training for equipment, process strategies and manufacturing strategies, under different types of operating conditions. The M Lab™ Collaboration Centers can be used by the process development team to train new hires, and we also see training being delivered to manufacturing operators. If speed to market is critical, you don't want to have a product approved and then have a delay in getting the product manufactured. There have also been instances where customers come to us and we work side by side with them to create and test their process.

And how have customers responded to the M Lab™ Collaboration Centers?

RP: Feedback from customers has been excellent. Many developers of gene therapies are still in small research labs (many have been spun out of academia) – and the teams will often under-estimate the real difficulties of manufacturing a therapy at scale. At the M Lab™ Collaboration Centers, the customer brings their understanding of their product and expectations for scale, and we contribute our expertise in each unit operation and our holistic understanding of the implications of certain processes for commercial scale manufacturing.

How is Merck preparing for the future?

EG: Gene therapies could dramatically change world health, and will also cause a shift for companies like ourselves. We need to contribute product and application expertise to ensure that these therapies are manufacturable to high safety and quality standards. This also needs to be done in a cost-efficient manner so that patients can access these important treatments.

RP: Product and technology innovation is very important to Merck. We are looking at purpose-built tools for gene therapy manufacturers, such as more productive cell lines, more efficient downstream tools, and the biosafety testing services to consistently satisfy regulatory expectations. We are also working to understand how we can become a better business partner for gene therapy developers, as well as other players in the ecosystem, such as other CMOs.

Elizabeth Goodrich is Director of Global Applications Engineering within Manufacturing Sciences and Technology, and Ranjeet Patil is Segment Head, Vaccines and Viral Therapies, both at Merck.

Heading to the Clinic

With Michael Mercaldi, Ph.D, Director Purification Process Development at Homology Medicines.

Homology Medicines is a gene therapy and gene editing company that was started based on the discovery of 15 novel adeno-associated viruses (AAV) naturally found in human hemopoietic stem cells (AAVHSCs). This set of novel serotypes enables the selection of optimal AAVHSC capsids for genetic medicines that exhibit differentiated biodistribution, lower immunogenicity and enhanced potency compared to other AAV serotypes. We have discovered that AAVHSCs can perform nuclease-free gene editing in addition to gene transfer. The gene editing capability of these AAVs was shown to harness the mechanism of homologous recombination, the body's natural DNA repair process. This is different than other gene editing technologies (i.e., CRISPR, ZFNs, etc.), which require a nuclease to cut the DNA and, in doing so, promote another DNA repair pathway called non-homologous end joining, or NEHJ, a more common yet error prone process. Homologous recombination-based gene editing has shown to be highly efficient and precise, and utilizes a single component system (i.e., one vector, one construct), making it a more straightforward method.

Currently, we are moving toward the clinic with our lead gene therapy construct, HMI-102. HMI-102 is designed to treat and potentially cure phenylketonuria (PKU) in adult patients.

There are many challenges in the gene therapy space. Leveraging the industry's experience with proteins (mAbs) is a great start to manufacturing gene therapies, but it's insufficient, and in some cases provides counter-productive directions. Unlike mAbs and recombinant proteins, where there is a 30 to 40-year bedrock of understanding on how to efficiently and effectively design and produce these therapies, the industry is only just beginning to learn how to do this with AAVs. To this, we feel that the big drivers to advance the field are to increase upstream and downstream productivity, develop more in-depth analytical methods, and to drive development of more specific AAV raw materials and equipment.

At Homology, we are building our own internal process development and GMP manufacturing capabilities and to this point we understand that it requires collaboration among Homology and key partners to solve the challenges in this field. We decided to visit the M Lab™ Collaboration Center this year to work with Merck on developing some of our platform manufacturing processes for our AAV therapies. We found Merck to be extremely helpful with identifying equipment and consumables that we are testing and may want to implement in our new facility. Their expertise and openness toward collaboration has been very valuable for us as we build out our pipeline and capabilities.

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