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NO. 4, 2020

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Rare Genetic Mutations May Hold Promise for Alzheimer's Disease

By Mae Pyer

Alzheimer's disease affects roughly 5.8 million people in the United States. There's no cure or way to slow disease progression. And one of the biggest risk factors, aging, is inevitable. But one Colombian family could be critical to understanding the disease and finding more effective prevention methods and treatment options.

Of the family's 5,000 members, roughly 1,000 have a genetic mutation that often leads to Alzheimer's disease. While those with inherited forms usually present symptoms around age 40, one member of their family managed to avoid symptoms until her 70s.

Navigating the Genetic Roadmap

In 2016, researchers sent the Colombian woman to Boston for a series of brain scans, revealing a significant accumulation of amyloid, a sticky protein often associated with the disease. It was evident the protein had been amassing for decades.

For this woman, whose story was reported in *Nature Medicine*, a mutation in a gene called *presenilin 1* destined her and members of her family for early-onset Alzheimer's disease.

Referred to as the Paisa mutation, it interferes with a process that rids the brain of excessive amyloid.

Even though the protein had been building up for quite some time, which is one of the clearest signs of the disease, another rare genetic mutation protected her from experiencing symptoms. Instead of guaranteeing dementia, a mutation to the gene *APOE* spared her until later in life.

Staying the Course

When *presenilin 1* mutates, it causes amyloid to bind to plaques between brain cells. Those with the mutation begin accumulating amyloid in excess in their 20s.

In the woman's case, a mutation known as Christchurch, named after the city in New Zealand, served as protective armor for her brain and body. A single amino acid in the *APOE* gene was changed from arginine to serine, preventing the protein from binding to heparan sulfate proteoglycans (HSPGs). The interference with this relationship is what ultimately slowed disease progression.

Other factors, including tau tangles and brain shrinkage, contribute to cell death and memory loss, so amyloid isn't solely to blame. For many, it's merely a precursor. A period of 10 or 15 years can go by between the development of amyloid plaques and presentation of symptoms. For the Colombian woman, the time period was twice as long.

While her experience appears to shed light on the inherited form of the disease, it's believed that those without a genetic link could benefit from the discovery. One woman's rare genetic mutation could be the key to helping many who experience symptoms, whether early or in their 70s and 80s.

Paving the Way

It's estimated that, in the United States alone, 13.8 million people will be diagnosed with Alzheimer's disease by 2050. Understanding the biological relationship between genetics and disease progression will help researchers develop more targeted drugs. The hope is that new treatment options can, at the very least, extend the time between the onset of disease and the presentation of symptoms.

> It's estimated that, in the United States alone, 13.8 million people will be diagnosed with Alzheimer's disease by 2050.

Although this study is based on the experience of one person, it shows that amyloid alone does not cause dementia. It highlights a biological flaw in the disease that we may one day be able to overcome.

As researchers learn more from clinical trials and additional studies, this Colombian family might help them make critical scientific connections.

Note: The woman's exact age and name were omitted from the Nature Medicine study for privacy purposes.

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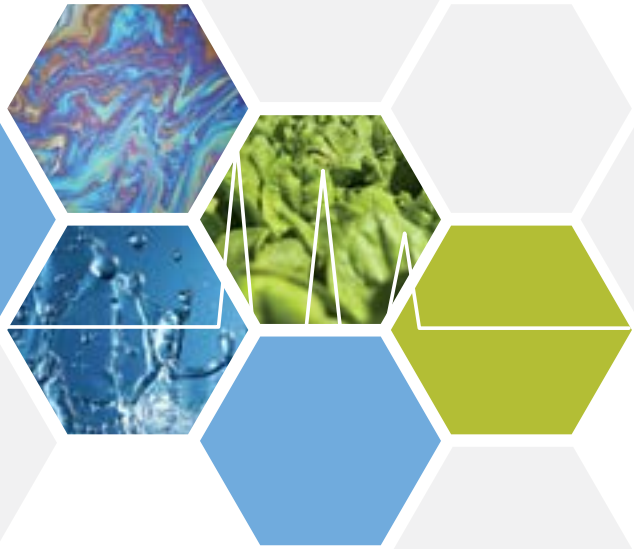

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Common Blood Test May Help Heart Failure Patients

By Christina Phillis

A widely used blood test is being evaluated as part of a potentially life-saving treatment for heart failure patients with hypothyroidism.

Blood levels of brain natriuretic peptide (BNP) may help to determine the correct dosage of a thyroid hormone given to improve heart function, according to a new study by researchers at New York Institute of Technology College of Osteopathic Medicine (NYITCOM) and FuWai Heart Hospital, Beijing, China.

Matters of the Heart

Heart failure occurs when your heart muscle doesn't pump blood as efficiently as it should, according to the Mayo Clinic. Conditions including coronary artery disease (narrowed arteries) and high blood pressure can gradually cause the heart muscle to weaken or stiffen over time. Shortness of breath, fatigue, swollen legs, and rapid heartbeat are common symptoms of heart failure.

Recent research has shown the possibility of a connection between thyroid hormones and cardiac function. Clinical studies suggest that low thyroid hormone levels may contribute to death in heart failure patients. According to a study published in February 2020 in *Clinical Thyroidology for the Public*, "Thyroid hormone has direct effects on heart function, blood vessels, and cholesterol levels."

Symptoms related to low levels of the thyroid hormone triiodothyronine (T3) are very similar to those in other conditions that can lead to heart failure. Some experts believe that half of heart failure patients have low levels of T3 in their cardiac tissue.

Animal studies have shown that restoring cardiac thyroid levels can significantly improve heart function. While treating patients for T3 hormone imbalance is relatively easy, too much of the hormone could trigger irregular heartbeats and no method to safely restore T3 levels has been developed to date. Practitioners have therefore been hesitant to prescribe T3 to heart patients.

A Delicate Balance

That's where the biomarker BNP comes in. Biomarkers found in blood, fluid, or tissue can be used to track the presence of a disease or other condition. Doctors measure BNP in the blood to determine if one's heart disease is worsening. The authors of the study thought if they could measure the level of BNP in a patient's blood in response to added T3, they might be able to titrate to a safe dosage.

The team used rat models to measure changes in BNP, cardiac function, and heart failure genes after T3 treatment. The results showed an inverse relationship between T3 and BNP, meaning reducing serum BNP could potentially be used to monitor T3 dosing.

"The results were remarkable, suggesting that serum BNP levels can be used to titrate the volume of T3 required," said Martin Gerdes, PhD, chair and professor of biomedical sciences at NYITCOM. "When T3 treatment led to a reduction in serum BNP levels, this was associated with improved cardiac function and reversal of these heart failure genes." Gerdes was a researcher for the study according to the NYIT article "Widely Used Blood Test Could Advance Heart Failure Treatment" by Kim Tucker Campo.

> "The results were remarkable, suggesting that serum BNP levels can be used to titrate the volume of T3 required."

Using BNP to adjust T3 levels to restore cardiac hormone balance is not only non-invasive, it's a fairly routine test for cardiac patients. The team hopes to demonstrate efficacy with future investigations and believes that evidence can be gathered rather quickly, given the widespread use of this biomarker. That's a positive assessment we can all take to heart.

Disease Research

Filtering Samples Prior to FLOW/FACS Analysis Without Sample Loss

An Interview with the Inventor of Flowmi Cell Strainers

Dr. Steve Zatechka, inventor of the Flowmi Cell Strainer, has focused on gene targeting technologies, genetic engineering, and developing new biotechnology-based protocols. Since much of this research involved flow cytometry, Zatechka became more aware of the inefficiency of available filtration methods, which often meant the loss of precious samples. A natural born problem-solver and solution seeker, he developed a quick, easy, and reliable filtration method to minimize sample loss and reduce the likelihood of clogging instruments.

Why Should Samples Be Filtered Prior to FLOW/FACS Analysis?

Sample filtration is critical for removing cellular and sample debris before performing fluorescence-assisted cell sorting (FACS) or flow cytometry analysis (FLOW). Only clarified and individual cellular particles should enter flow cells for detection analysis. Disregarding this filtering step can lead to flow cell clogging, impeded flow of aligned cells, and, ultimately, the loss of precious sample.

In addition to sample waste, clogged flow cells require instrument maintenance and recalibration, which can result in both expensive repairs and the loss of useful instrument time. It is a universally accepted practice to filter samples using membranes with pore sizes from 40 to 70 µm before FACS/FLOW analyses.

What Is Flowmi?

These simple-to-use cell strainers easily and quickly press-fit onto the end of standard 1000 mL pipette tips to allow one-handed sample clarification by filtering out cellular debris. Flowmi strainers are as simple as aspirating or dispensing with a pipettor.

What Are the Limitations of Traditional Filtration Methods?

Traditional filtration has been performed with cell strainers that work with gravity or “home-made” filters that use cut mesh. These methods can be cumbersome and may require additional pressure from a pestle, which can

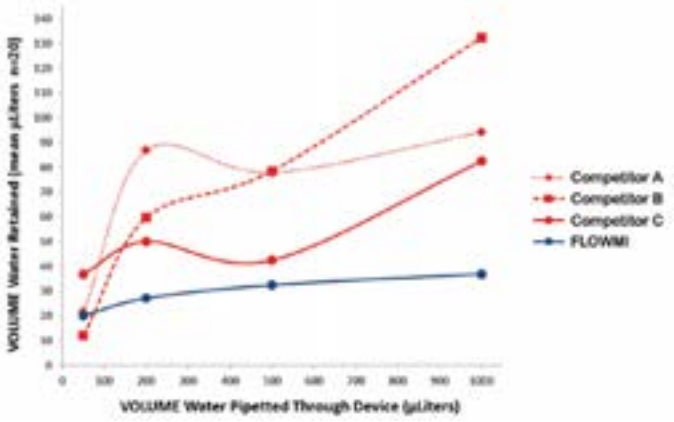

Figure 1: Flowmi and three competing strainers were examined at four different pipetted volumes. The volume of water retained is represented by the mean difference in weight before and after pipetting.

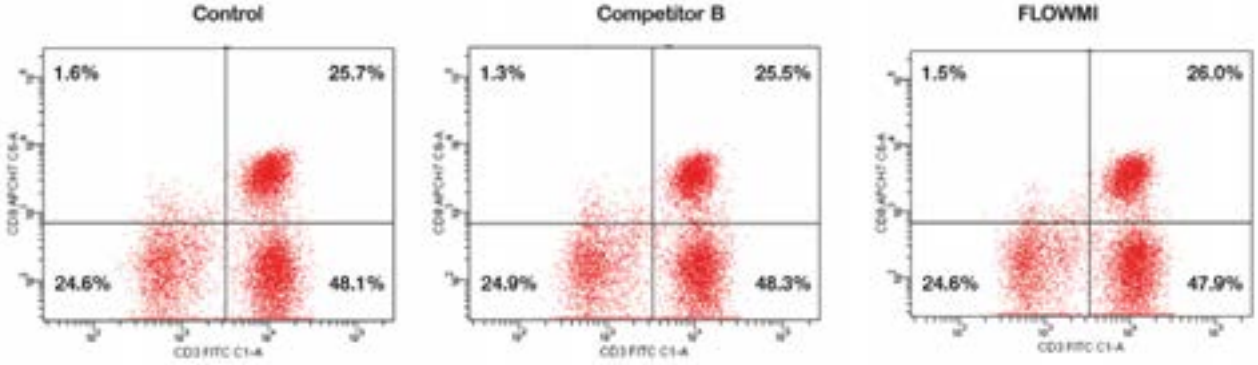

Figure 2: Cytograms of CD-CHEX™ Plus Cells; Cytograms and “Percent of Parent” data demonstrate no loss of specific cells using Flowmi vs. competing filter

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potentially damage the cells and affect cell recovery. Due to retained volume across the filtering surface area, there is also often a loss of sample associated with the use of these products. Since many of the samples being processed yield low volume recovery or exist as rare cell populations, researchers may be reluctant to pre-filter samples for FACS or FLOW analysis since they may lose sample volume.

Why Is Flowmi a Better Alternative?

Flowmi performs fast and efficient filtration and avoids wasted time and costly delays. Using a pipettor to push the crude sample preps through a filter on the pipette tip offers more controlled, rapid, and gentle filtration than gravity alone. The Flowmi filter's small size minimizes fluid retention for very little sample loss (see Figure 1). Field tests have demonstrated minimal fluid retention with filtration passage, enhanced sample volume recovery, and minimal loss of desired specific cell types when compared to competitive products (see Figure 2).

How Are Flowmi Strainers Made and What Sizes Are Available?

Flowmi cell strainers are constructed from high-quality, low-density polyethylene (LDPE) using a proprietary manufacturing process. They are pre-sterilized using gamma irradiation and available in 40 and 70 µm sizes to meet your specific needs.

About the Interviewee

Dr. Steve Zatechka earned his PhD in biochemistry and molecular biology from the University of Nebraska Medical Center and his MBA from the University of Memphis. He completed his postdoctoral fellowship with the Howard Hughes Medical Institute at St. Jude Children's Research Hospital. Dr. Zatechka's research and training focused on gene targeting technologies for genetically engineering biological models of disease and the development of novel applied biotechnology-based protocols.

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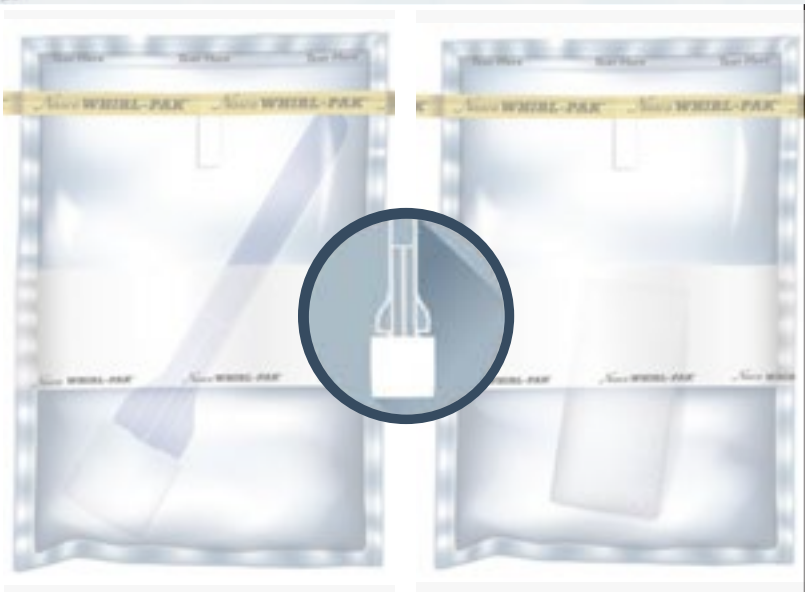

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Critical Medicines Reformulated Using AI

By Iva Fedorka

As new drugs emerge to treat COVID-19 infections, demand is likely to exceed supply. Researchers are now using artificial intelligence (AI) software to help develop new methods for synthesizing medications with proprietary formulas.

Patents and Limitations

One medicine, the antiviral drug remdesivir, has been shown to decrease critical hospital days for COVID-19 patients, although it does not reduce the number of deaths. As a result, attorneys general from 34 states sent a letter on August 4, 2020 stating that supplies of remdesivir were "dangerously limited." They even proposed that the ownership rights of Gilead Science be set aside so that third-party manufacturers could produce more of the drug.

Patents give pharmaceutical companies the rights to be the sole producers of new drugs. These laws vary by country, but patents last for 20 years in the United States. After a drug goes "off patent," it can be produced and sold as "generic" by other companies.

Manufacturing formulations are confidential to discourage competition even after patents expire. But COVID-19 has changed all that, says Danielle Schultz, a chemist at Merck. "We are at a time when it's all hands on deck."

Finding New Formulas

Chemist Timothy Cernak and colleagues at the University of Michigan Ann Arbor have been using a commercial drug synthesis program called Synthia, released by MilliporeSigma.

The software helps to find efficient and cost-effective pathways for synthesizing medicines, many of which contain molecules that can be produced in more than one way. "It's more options than the human mind can comprehend," Cernak says.

Because these new methods are also designed to be made from readily available raw materials, manufacturers could more quickly ramp up the production of any promising therapies.

"If you are going to supply a drug to the world, your starting materials have to be cheap and as available as sugar," says Schultz. The new method, posted as a preprint this week, "is really solid," she says. "I am impressed by the speed at which [the researchers] were able to find new solutions for making existing drugs."

Cernak and his colleagues reviewed patents and other literature for 12 specific medications (including remdesivir) being tested as COVID-19 therapies and programmed Synthia to find new synthetic solutions. Their search was limited based on the cost and availability of starting materials, requirements for catalysts or equipment, and methods that could produce large amounts of the drug.

Synthesis Success

The software ultimately found novel solutions for nearly all of the compounds, although not for remdesivir. It did find new generic formulas for several other antivirals. In fact, Synthia found four different ways to synthesize one compound, including a formulation that used less expensive materials than are currently used. "For the same amount of money [or less], we can make these drugs from different starting materials," Cernak says.

Cernak and his team reported their findings in a non–peer-reviewed preprint on ChemRxiv. They have also filed patents on all of the new synthetic routes but aren't primarily interested in making a profit. Instead, they hope to license their formulas to one or more pharmaceutical manufacturers to help maintain adequate supplies and lower prices. Now, he adds, they wait and see whether any of the drugs prove effective in clinical trials.

> "We are at a time when it's all hands on deck."

Navigating the complex matrix of drug discovery possibilities while taking into consideration what has already been done, what could be done, and what starting materials are available is definitely a challenge. The Synthia retrosynthesis software helps chemists apply search criteria to tens of thousands of possibilities to quickly transition from imagination to probability to actuality.

This new AI software is proving to be an effective tool for chemists to refine drug discovery and save time and costs while opening new synthetic pathways.

Damaging Ecosystems Can Aid Wildlife in Spread of Disease

By Kevin Ritchart

A recent study has found that the human destruction of natural ecosystems increases the number of animals that carry diseases responsible for pandemics like COVID-19.

Research published earlier this year in *Nature* assessing nearly 7,000 animal communities on six continents found that the conversion of wild lands into farms or settlements often tends to wipe out larger species of animals. But the damage to the landscape actually benefits smaller, more adaptive animals like rats and bats that carry pathogens more likely to be passed along to humans.

The study found that the populations of animals hosting zoonotic diseases were up to two-and-a-half times larger in areas where their established habitat had been degraded and that the proportion of those animals who carry pathogens increased by as much as 70 percent compared with those who continued to reside in undamaged areas.

The Human Problem

Human populations are becoming increasingly vulnerable to diseases that originate in wild animals like HIV, Zika, Sars, and others. Since the outset of the COVID-19 pandemic earlier this year, the United Nations and World Health Organization have warned the public about the importance of tackling the cause of the outbreaks — the destruction of ecosystems — rather than merely addressing health and economic systems.

While the conversation surrounding the current COVID-19 pandemic continues to evolve, there's one aspect where biodiversity experts agree: Unless we take further steps to protect the environment, more deadly disease outbreaks are likely.

This new study is the first to outline how the destruction of wild places, in concert with the world's population and consumption growth, leads to changes in animal populations that increase the risk of outbreaks. And the best way to respond in areas already affected is to ramp up disease monitoring efforts and offer medical assistance to residents.

"As people go in and, for example, turn a forest into farmland, what they're doing inadvertently is making it more likely for them to be in contact with an animal that carries disease," said David Redding of the Zoological Society of London, who was part of the research team.

Redding also points out that the costs of disease were not taken into account when deciding to convert natural ecosystems into farmland or clear them for other uses. A recent report in the journal *Science* estimated that the cost of preventing further pandemics in the next decade would equate to just two percent of the money that's already been spent fighting COVID-19 in 2020.

Small Animals, Big Impact

The main reason that smaller animal species like rodents and bats are both thriving in ecosystems damaged by humans and carrying the most pathogens is likely because they're small, mobile, adaptable, and reproduce rapidly.

"The ultimate example is the brown rat," Redding said.

> Unless we take further steps to protect the environment, more deadly disease outbreaks are likely.

Brown rats have an evolutionary strategy that favors large numbers of offspring ahead of a high survival rate, which means they invest relatively little in their immune systems.

"In contrast, an elephant has a calf every couple of years," Redding said. "It has to make sure that offspring survives, so it is born with a very strong and adaptive immune system."

The study also found that small, perching birds thrive as disease hosts in habitats suffering from the impact of human activities. Such birds can be carriers of viruses like West Nile and others.

What Happens Next?

Humans have already affected more than half of the Earth's habitable land, and there's no sign of that slowing down anytime soon.

"As agricultural and urban lands are predicted to continue expanding in the coming decades, we should be strengthening disease surveillance and healthcare provision in those areas that are undergoing a lot of land disturbance," said Professor Kate Jones of the University College London, who was also part of the research team. "They are increasingly likely to have animals that could be hosting harmful pathogens."

Disease Research

Selecting Smart Hand Protection for Laboratories

Working with the chemicals and specialized equipment found in laboratory environments requires specific hand protection. This also applies to laboratory process integrity and test results that are at higher risk of contamination or cross-contamination.

Whether hands need to be protected from chemical or bacterial hazards or from cuts and temperature extremes, the choice of hand protection can provide optimal safety, comfort, and efficiency.

Laboratory Hazards

Every laboratory task presents its own challenges, along with pathways to achieve the best results. Researchers must often wear gloves for extended periods, so it's important that glove materials are allergen-free and keep hands dry and comfortable.

Consider whether the application requires:

- Tactility
- Dexterity
- Grip in wet or dry conditions
- Protection from fluid splash or permeation
- Protection from biohazard or bacterial exposure
- Protection against cuts and abrasions

Chemical Protection

Chemical exposure to spills or splashes is the most prevalent hazard in laboratory environments. Typically, lab procedures include the use of acids, bases, inorganic and organic chemicals, and various solvents. A wide range of protection is needed for this variety of chemicals as well as new chemical entities for which complete toxicological testing has not been performed.

To choose the right protection from chemical exposure:

- Recognize that gloves deliver different levels of protection based on construction materials, length, thickness, and other factors
- Conduct a hazard assessment, review chemical labels, and consider all substances that the wearer may contact
- Assess whether the wearer requires chemical splash or immersion protection
- Determine the duration of exposure to specific chemicals

Biological Hazard Protection

Laboratory workers can be exposed to biological hazards through microbiological or DNA research and analysis of biological fluids. This work may involve contact with bacteria, viruses, insects, plants, birds, animals, and humans, which can cause skin irritation, allergies, infections (such as tuberculosis and AIDS), and other detrimental health effects.

Some test procedures may also require that samples be protected against potential contamination from human skin, dust, and microorganisms or from cross-contamination between samples.

Select hand protection that allows you to perform tasks efficiently while offering a positive sensory experience combined with high-level barrier protection. Consider whether the glove can provide a positive grip and easy donning and doffing between tasks. Glove length may be a factor, along with dexterity and tactility demands.

Materials Research

Research into materials and manufacturing techniques has produced ongoing improvements and many new options to help researchers and lab workers derive maximum value from their gloves. The most common laboratory glove materials are natural rubber latex, nitrile, and neoprene.

Natural rubber latex offers a comfortable fit but provides less chemical splash protection than nitrile and neoprene. Recent innovations have increased the comfort of wearing neoprene gloves.

Natural rubber latex can pose a health risk for people with Type I allergies

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(immediate hypersensitivity or anaphylactic reactions). Those who suffer from Type IV allergies (cell-mediated or delayed hypersensitivity) may benefit from using nitrile or neoprene gloves that are free from chemical accelerants.

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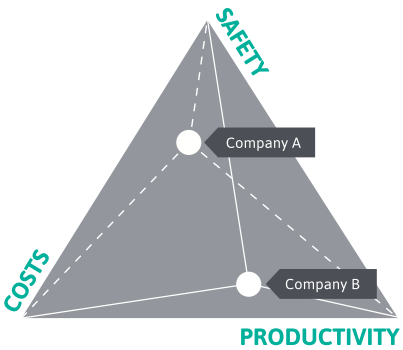

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Adhesive Mats for Contamination Control

By Eric Bookland, Vice President of Product Development & Operations, PURUS International

Never in recent history has there been a greater widespread need for contamination control. The unprecedented global pandemic requires more thought, planning, and precautions to ensure everyone's safety and well-being. With the many hurdles being addressed, we should also consider the impact our solutions have on the environment.

Until recently, contamination control matting has been manufactured for more than 30 years using the same materials and processes. We have now introduced advancements in technology with one thought in mind: Adhesive mats for contamination and infection control can be effective and environmentally friendly at the same time. The result is EnviroTack adhesive contamination control mats, which help meet these goals for workplaces where contamination control is paramount.

The Anti-Microbial Benefits

A series of experiments was conducted to determine the efficacy of EnviroTack mats in preventing bacteria from entering controlled environments. This first-of-its-kind research was conducted in the field and the results showed robust success rates. The adhesive contamination control mats prevented a significant amount of bacteria from entering controlled environments.

Various microbes, including *Staphylococcus aureus*, were tested through various methods. After establishing the test methodology and setting various parameters, results began to reveal meaningful trends. For *S. aureus* bacteria, the adhesive contamination control mats achieved a removal rate of 85% with a prevention rate of 99.7%. Similarly, for *Aspergillus niger*, the removal and prevention rates were 97% and 99.9% respectively.

The test product:

- Removed 85% of *S. aureus* and 97% of *A. niger*
- Prevented 99.7% of *S. aureus* and 99.9% of *A. niger* from entering a protected zone
- Was 82% and 95.7% more effective than the negative control in preventing *S. aureus* and *A. niger* from entering a protected zone, respectively

Contact your Fisher Scientific safety specialist to request more details about the methodology of these tests.

Environmental Impact

What is the environmental impact of your business? Environmental concerns may seem difficult to address in industrial production, but they don't have to be. ISO 14001 has an excellent framework for developing and executing an effective environmental management system (EMS) and specifies requirements to enable organizations to achieve the intended outcomes set for environmental management systems.

Addressing environmental impact is a win-win situation for any business. In addition to providing a great service to the environment, a quality EMS can:

- Help reduce waste
- Drive down costs
- Increase new business opportunities
- Increase stakeholder and customer trust
- Manage environmental obligations with consistency

In 2015, ISO 14001 published a revision that addressed some aspects that are vital to an EMS. One key addition was proactive initiatives to protect the environment from harm and degradation, like sustainable resource use and climate change mitigation. Another update encourages companies to engage in life cycle thinking when considering environmental aspects of activities, products, and services.

> **EMS can bring amazing benefits to the organization. It can help reduce waste and drive down costs.**

One area to consider might be disposable products. Depending on the industry, these can consume a large part of a company's budget. And, although many of these items are used and discarded in the course of day-to-day operations, it's easy to overlook their environmental impact. Choosing an alternative product that is environmentally preferred can make a significant impact on the

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environment with minimal effort.

PURUS recognizes that building sustainable business practices to enhance the value of the company is in the best interest of our company, our associates, our suppliers, our customers, and our community. We also know that you have other initiatives and PURUS is committed to helping you achieve your sustainability goals by providing you with environmentally preferred products.

EnviroTack Contamination Control Mats

EnviroTack, available exclusively from Purus International, Inc., is the first ever contamination control product made with renewable plant-based materials to provide an environmentally friendly alternative.

To better understand this new technology, one must understand the makeup of tacky mats. Each mat consists of 30 or 60 sheets of 1.5 mil low-density film with a 0.3 mil acrylic-based, pressure-sensitive adhesive coating.

Sustainability

Traditionally, tacky mat sheets have been made from 100% low-density polyethylene (LDPE) film, a material that comes from non-renewable resources. EnviroTack uses a special resin called thermoplastic starch (TPS), which is made from renewable and sustainable raw materials. Each EnviroTack sheet contains 20% TPS blended with LDPE.

Our hybrid resin only uses materials that are GMO-free. Each starch has also met various environmental criteria regarding its sourcing.

Carbon Footprint

A major benefit of using renewable resources is the reduction of the product's overall carbon footprint. Using a hybrid resin in these mats has reduced our greenhouse gas emissions by 11%, as verified by the life cycle analysis (LCA) performed by the Centre for Design at RMIT University in Melbourne, Australia. An LCA determines the total amount of greenhouse gases produced to directly support human activities and is usually expressed in equivalent tons of carbon dioxide (CO_2). EnviroTack is projected to reduce annual CO_2 gas emissions by 40 metric tons, an amount that would otherwise take nearly 50 acres of forests to sequester.*

In addition to the carbon sequestered by the material itself, PURUS goes even further to protect the environment. Carbon emitted from incoming freight is offset in the form of carbon credits. By contributing to various forestry, energy efficiency, and renewable energy projects, PURUS will offset an additional 52 tons of CO_2 per year, an amount that would require an additional 60 acres of forests.

Performance

Because the TPS and LDPE behave like the LDPE alone, EnviroTack offers the same performance as its predecessor. The quality of tacky mats lies in the strength of the individual sheets. Each sheet needs to be sturdy enough to endure the abuse of being trod on and flexible enough to not tear under the force required to remove it from the pad. EnviroTack has the tensile strength and elongation properties to meet both requirements.

Environmental initiatives in production can be difficult to manage. EnviroTack from PURUS can be one solution for teams that want to reduce their overall environmental impact without sacrificing the effectiveness and anti-microbial attributes necessary for effective contamination control.

*Emission calculations based on EPA calculator tool: https://www.epa.gov/energy/greenhouse-gas-equivalencies-calculator

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NIH Funding Bringing Genomic Risk Assessments to More Diverse Populations

By Mike Howie

The National Institutes of Health (NIH) will provide $75 million in funding over five years to support genomics research that could ultimately help healthcare providers assess, manage, and even anticipate disease risk. The funding will go to the Electronic Medical Record and Genomics (eMERGE) Genomic Risk Assessment and Management Network, a collection of hospitals and universities spread throughout the United States.

eMERGE was created in 2007 with five biobanks linked to electronic medical records systems to conduct large-scale, high-throughput genetic research to help implement genomic medicine and provide more informed medical care to patients. During the first three phases of its work, the Network used electronic phenotypic algorithms across more than 100,000 participants to electronically determine if a participant had specific diseases or traits. In this new phase of work, the Network aims to develop disease risk scores that are more comprehensive than those currently available and, importantly, applicable to a more diverse population.

Polygenic Risk Scores

While all humans have nearly identical DNA sequences, each of us has genetic variants that make us unique. In the roughly six billion letters that code the human genome, an individual will have four to five million variants, all of which may also occur in others. While some of these variants affect things like physical appearance, others influence our risk for certain diseases, making us more or less likely to get sick. By studying these variants across large populations, researchers can better understand an individual's risk of developing a disease.

Some diseases, like cystic fibrosis, are caused by a single variant on just one chromosome. Others can be caused by hundreds or even thousands of variants across the whole genome. Coronary artery disease, for example, is linked to 60 variants. Most diseases fall somewhere on the spectrum between these single-gene and complex diseases.

By comparing the genomes of people with and without complex diseases, researchers can identify the variants associated with those diseases. They can then calculate which variants are common in groups of people with a single disease. And with statistical analysis, the researchers can create a polygenic risk score for an individual, which estimates how a person's variants affect their relative risk for a certain disease.

A significant shortcoming, however, is that polygenic risk scores were developed and validated in studies that predominantly involved people of European descent. Because of this, the scores may not be accurate for people from other backgrounds. The scores also don't account for other factors that play a role in disease risk, including age, environmental factors, body-mass index, and more, which similarly limits accuracy. The eMERGE Network plans to gather data in these areas to create a more accurate way of scoring risk, which they call a "genomic risk assessment" or "integrated risk score."

Enhancing Diversity

Clinical sites from the eMERGE Network are now aiming to conduct and validate genomic risk assessment and management methods for common diseases, including coronary heart disease, Alzheimer's disease, and diabetes, that can be effective in the general population. To do this, they'll be recruiting patients from diverse populations, including racial or ethnic minority populations, underserved populations, or populations that experience poorer medical outcomes.

A portion of the Network's new funding will go to six enhanced-diversity clinical sites. The goal for these sites — which include the University of Alabama, Icahn School of Medicine at Mount Sinai, Cincinnati Children's Hospital Medical Center, Columbia University, Children's Hospital of Philadelphia, and University of Washington Medical Center — is to recruit 15,000 patients, including 75% or more from diverse ancestries.

> "The work has the potential to transform how we estimate disease risk in clinical practice," said Iftikhar Kullo, MD, of the Mayo Clinic.

Children's Hospital of Philadelphia (CHOP) is an asset to the Network in that it's home to both the world's largest pediatric biorepository and the world's largest biorepository of samples from people of African ancestry.

"CHOP is uniquely placed to specifically address risk factors and outcomes in the African American community," said

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NIH Funding Bringing Genomic Risk Assessments to More Diverse Populations

Hakon Hakonarson, MD, director of the hospital's Center for Applied Genomics, in an interview with the *Philadelphia Business Journal*. "This grant addresses polygenic risk scores in minority populations, which has not been examined before."

"A key component of this effort will be to determine how to integrate clinical data, genomic risk estimates, and family history to deliver disease management recommendations," said James Cimino, MD, professor of medicine and director of the University of Alabama at Birmingham (UAB) Informatics Institute. "We will be able to leverage UAB's strengths in precision medicine and informatics to accomplish this goal."

> "This grant addresses polygenic risk scores in minority populations, which has not been examined before," said Hakon Hakonarson, MD, of Children's Hospital of Philadelphia.

Funding will also go to the Mayo Clinic, Vanderbilt University Medical Center, Brigham and Women's Hospital, and Northwestern University. These clinical sites will recruit about 10,000 patients, including 35% or more from diverse ancestries. Combined, the six enhanced-diversity clinical sites and four clinical sites will receive about $61 million of the funding.

"We are delighted to be part of eMERGE Network phase IV," said Iftikhar Kullo, MD, of the Mayo Clinic. "The work has the potential to transform how we estimate disease risk in clinical practice."

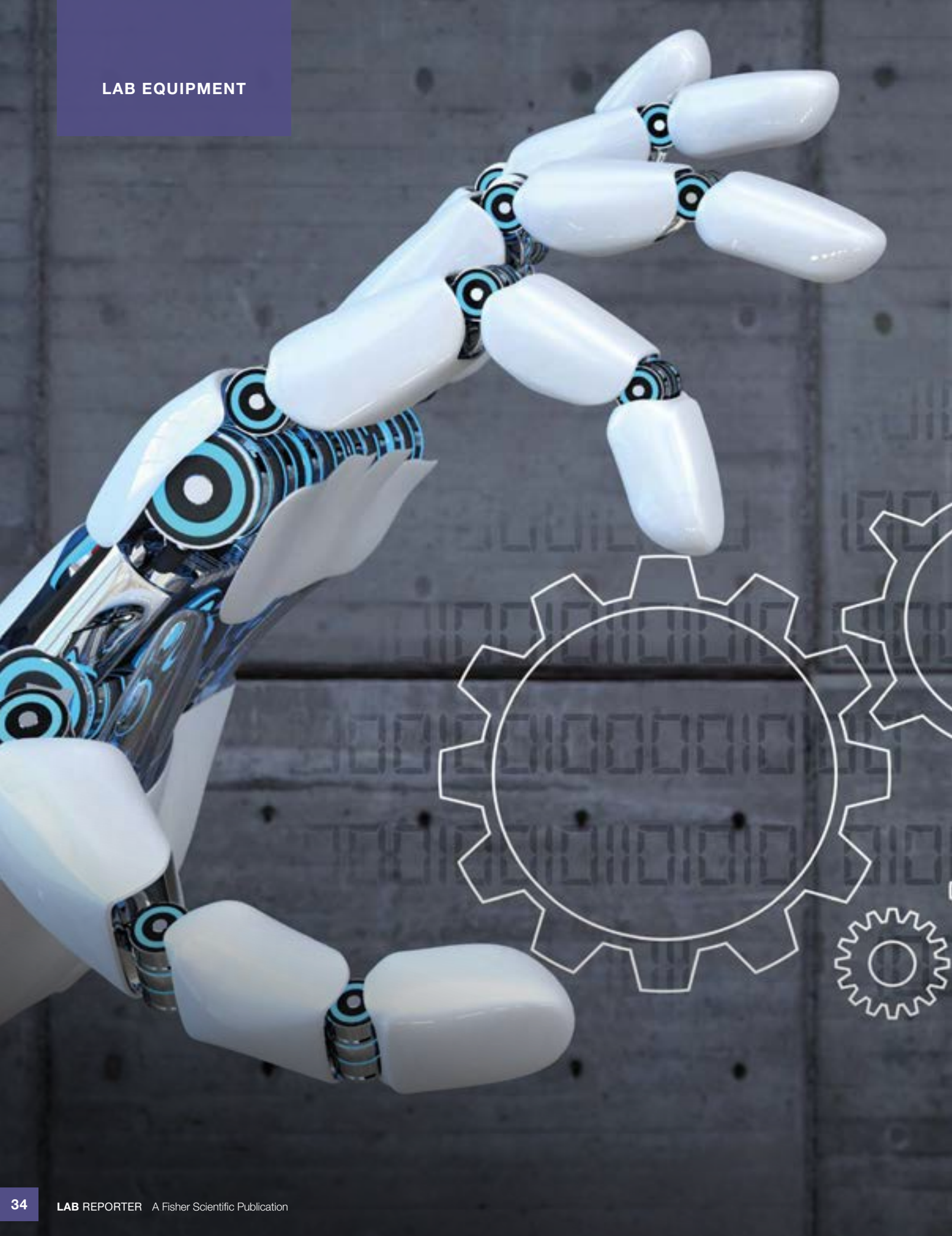
Collectively, the Network will provide a genomic risk assessment to 25,000 pediatric and adult patients. The assessment will include four components: a polygenic risk score, family history, monogenic risk, and clinical risk factors. Through these assessments, they hope to identify people at unusually high risk for common diseases and test the degree to which measurable risk can aid prevention and early treatment of common complex diseases.

A Coordinated Effort

The eMERGE Network's coordinating center at Vanderbilt will receive $13.4 million in funding. As the coordinating center, Vanderbilt will collect risk assessments from participants and process biospecimens for genotyping. They've also invited Duke University to become part of the coordinating center to help with this effort. Duke will use their MeTree tool to collect and interpret family history data. Vanderbilt will also be collaborating with the Broad Institute, which is developing a pipeline for a CLIA-certified polygenic risk score for each of the phenotypes the Network studies.

Vanderbilt plays a key role in bringing research from 10 health systems together. The university develops centralized data and service infrastructure that allows all the sites to communicate and deposit de-identified data into an NIH-funded discovery resource called the Genomic Data Science Analysis, Visualization, and Informatics Lab-space (AnVIL). The coordinating center also organizes workgroups for individual aspects of the project, including interpretation of genetic results, the return-of-results process, ethical and legal implications, integration of electronic health record systems, and outcome assessment.

"We hope to be able to show that a detailed genetic assessment on each of the participants will have a meaningful impact on the participants' preventative care," said Josh Peterson, MD, MPH, professor of Biomedical Informatics at Vanderbilt, "either by impacting the screening and surveillance testing by their physicians, or by modifying their health habits if they are at a particularly high risk of a common complex disease." ❄



Robot Scientist
Could Be Key to Conquering Complex Challenges

By Gina Wynn

University of Liverpool researchers have a new colleague. It works 21.5 hours a day, seven days a week and never gets bored or tired. It's a robot chemist. The first of its kind, it has already discovered a new catalyst.

Andrew Cooper from the University's Department of Chemistry and Materials Innovation Factory led the project to build the intelligent mobile robot. It was featured on the cover of the journal *Nature*.

Built for Science

The 5-foot 8-inch (1.75-meter) tall mechanism uses a robotic arm — similar to those used in car factories — and mimics humans in various ways. Human-like proportions and physical reach enable the manipulation of standard lab equipment and instruments for performing a multitude of tasks.

For independent movement around the lab, the 882-pound (400-kilogram) robot uses a combination of laser scanning and touch feedback for positioning, instead of being programmed to "see."

The robot differs from human scientists in its ability to think in 10 dimensions and its capacity for long stretches of uninterrupted work. Because it needs to charge for only about 2.5 hours a day, it can consistently perform complex tasks at a pace and scale that a human could not possibly match.

"It frees up my time to focus on innovation and new solutions rather than doing the same action over and over again," Benjamin Burger told BBC in a YouTube report. Burger is a University of Liverpool PhD student who built and programmed the robot. "It can easily go through thousands of samples, which would take me a very long time to do by hand."

Bound for Discovery

This new technology could also prove useful for keeping the lab operational when Burger and his colleagues need to socially distance or work from home. While on its own, the robot can measure and dispense liquids, weigh solids, remove air from vessels, run catalytic reactions, and quantify reaction products, according to the University of Liverpool website.

Statistics from the robot's first example of published work show that in eight days, it worked 172 out of 192 hours and conducted 688 chemistry experiments. This entailed cataloging 319 moves, 6,500 manipulations, and over 1 mile and 613 yards (2.17 kilometers) of travel.

Cooper and team designed the robot scientist using artificial intelligence so it would be able to make decisions about what experiment to run next based on previous results. Using a search algorithm, it mines information from the 98 million candidate experiments that exist within the 10-dimensional space of the machine's brain.

This technique already resulted in the robot's discovery of a catalyst that is six times more active, without any assistance from researchers. Another advantage of employing this technology is that robots are able to link with other robots around the world to address global challenges. The robot chemist also makes far fewer mistakes than human operators, according to Burger.

People Still Prevail

Even though it might seem like these intelligent robots could eventually revolutionize the world of science, human researchers needn't worry. The robots will not replace human scientists, according to Deirdre Black of the Royal Society of Chemistry as reported by BBC on YouTube.

"This is about human beings harnessing all of these digital technologies so that they can innovate faster and explore bigger and tackle much more complex problems like decarbonization, preventing and treating disease, making the quality of our air cleaner," said Black. "But we'll always need people." ❄

Disease Research

Equipment Challenges in Scaling Up Cell Therapy Processes

By Mary Kay Bates, Brian McBride, and Molly Love Parrucci

As proteomics, genomics, and cell-based sciences have developed over several decades, the pace of transition for academic discoveries to applied research and eventual commercialization has increased significantly.

It's an exciting time to be part of this unprecedented growth, with new medical applications targeting previously untreatable diseases. As of February 2020, there are nine approved cell or gene therapies,[1] with dozens more in clinical trials. And as of July 2020, 95 monoclonal antibodies are approved by the U.S. Food and Drug Administration (FDA).[2]

Transition from the Bench

Many new therapies use stem cells, immune cells, or other very sensitive cells. Especially precious are cells cultured for autologous therapy, where the patient-specific cells themselves become the treatment. In such treatments, the integrity of methods and equipment for culturing, processing, and storing cells is even more critical. As these methods move to larger-scale production, materials and equipment become key to ensuring cellular integrity, uniformity, yield, and contamination risk control.

Taking a discovery from academia to the commercial market has been a historically difficult process, but new resources can help. By first addressing your procedures, reagents, and equipment, you may ease the transition and reduce some of the many challenges associated with current good manufacturing practices (cGMP) and audited processes. This article offers some guidance on making the transition a success.

Develop Your Process

Choose trusted laboratory suppliers that offer equipment that can help you move from the academic lab to startup and production. There is a lot to consider, so ask the following questions:

- How reliable is the equipment manufacturing and testing?
- Does the factory comply with ISO 13485?
- Do product claims match performance?
- Are critical steps in your process easy to set up, use, maintain, and control?
- Is technical support and service available? Are service personnel trained and qualified for your specific equipment and knowledgeable about your procedures?

A More Holistic Approach

As you transition to production, additional considerations apply. Think about the design and operation of equipment from both a research and a production perspective. Can your equipment make the transition? Will you need to requalify at each step?

For an example of this exercise, consider a CO_2 incubator. In the lab, key features include contamination control, a consistent and uniform environment, and fast open-door recovery. But new factors arise for pilots and production transitions, including cleanability, data management, documentation, capacity, and ergonomics. Can the supplier provide factory acceptance test (FAT) document and validation services? Selecting products that meet your needs throughout the process affords a more rapid transition between stages with lower risk.

Biological safety cabinets (BSCs) pose similar challenges. Their operation is more than just specifications — it's about how well performance meets those specifications. It's not just about HEPA filtration, but also about how the airflow is driven and directed through those HEPA filters to keep you safe and protect the integrity of your work, even over hours of continuous operation and months of filtration. How well your BSCs operate in the working environment and surrounding airflow requirements should also be part of your decision process.

Evaluating centrifuges also illustrates these critical transition concerns. A research lab focuses on ease of use, biocontainment, and rotor choice. In production environments, the focus shifts to capacity, disinfectant compatibility, automation, and data management. Does the supplier offer FAT documentation and installation, operation, and performance qualification (IQ/OQ/PQ) services? Select a centrifuge from a supplier that serves both research and production to help smooth the path to scale up and avoid buyer's remorse.

Controlled cooling and storage of the final cellular product is another key scale-up consideration. Many cell and gene therapy processes require greater control of cellular cooling rates. This may include special manipulation to minimize the detrimental effects of undercooling and the heat liberated during the change from water to ice. The ultimate stability of frozen cells requires their maintenance at temperatures below -130˚C and will affect the storage duration after which the materials can be safely recovered.

Key criteria for cold storage equipment include temperature range, temperature accuracy, and data output. Pilot and production users should also consider programmability, cleanability, and service support. Validation, monitoring, and ready availability of cGMP documents, including FAT and IQ/OQ/PQ protocols, are critical for cold storage equipment compliance.

Supplier cGMP Capabilities

Understanding your suppliers' capabilities is a top priority in this changing environment. These conversations need to occur long before expansion plans are made.

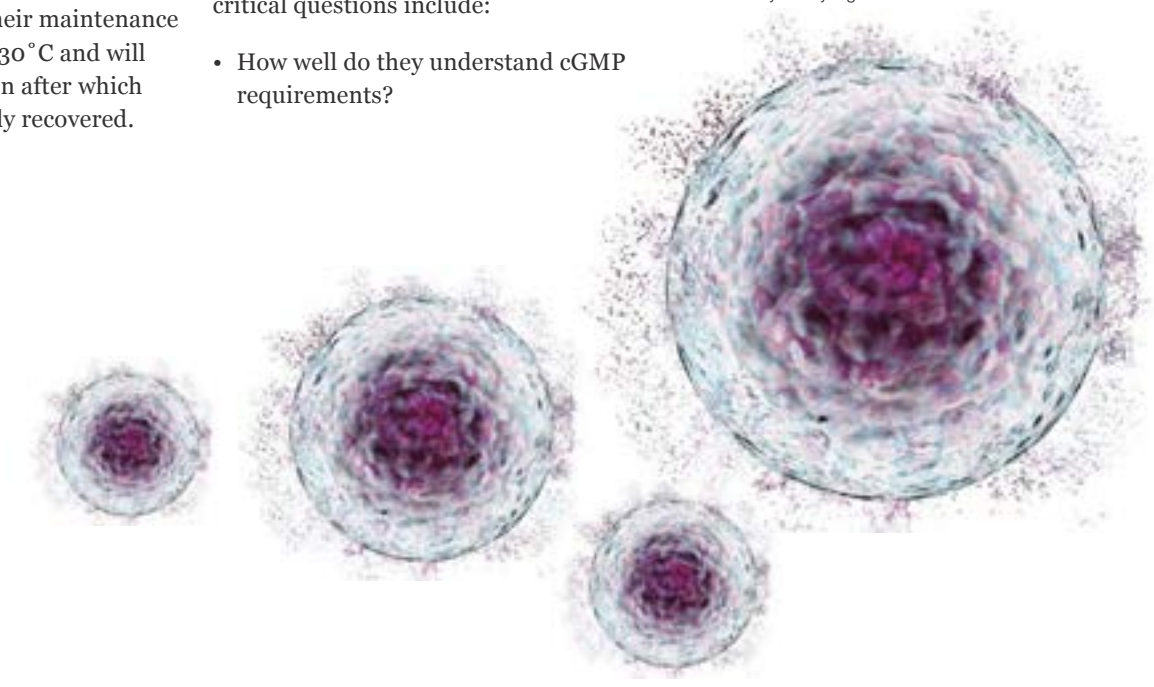
A supplier should be able to help you adapt as you move along the product development path. Their expertise should include bench-scale considerations and production of cells as therapies. More critical questions include:

- How well do they understand cGMP requirements?
- Do they offer the documentation needed for all qualification steps?
- Is technical data readily available?
- Are onsite services an option?

Manufacturers can usually provide IQ/OQ/PQ support because they know their product best. Ask your vendors about service support and onsite validation capabilities to gain insight about the level of support you can expect from them.

Consider the future demands which may be placed upon the laboratory equipment you purchase for your research work. By thinking about the long-term use of equipment, reagents, and other lab products, you can meet regulatory requirements, shorten timelines, and hit every milestone.

Sources
1. phrma.org
2. antibodysociety.org



Disease Research

Centrifuge Solutions for Therapeutic Monoclonal Antibody Research

By Florian Bundis, PhD, and Kate Meola, Eppendorf North America

Antibodies dominate today's biopharmaceutical market, with drugs like Humira (AbbVie) and Avastin (Roche [Genentech]) among the top-selling drugs worldwide.[1] The use of monoclonal antibodies (mAbs) has proven to be effective for treating various types of cancer and autoimmune diseases.

The development and production of mAbs using hybridoma or hybrid cells produced by fusing an antibody-producing lymphocyte with a tumor cell is now widely established and has been extended into SARS-CoV-2 vaccine development research. But rising time and cost pressures along with the demand for higher throughput make the development of therapeutic antibodies challenging.

Rising time and cost pressures along with the demand for higher throughput can make the development of therapeutic antibodies challenging.

Optimizing Results

Factors that affect reproducibility, efficiency, and sample protection must be evaluated and new alternative solutions must be explored to optimize results and meet the high demand. Ergonomically designed equipment can help reduce hands-on time, protect staff from incurring work-associated injuries, and improve overall productivity and performance.

Multiple centrifugation steps occur during the mAb drug discovery process, each with unique speed, vessel, and temperature requirements. Based on in-depth protocol evaluations and customer interviews within the mAb drug discovery community, Eppendorf has developed seven centrifugation options that include the combination of an optimal centrifuge, rotor, and vessel adapters for each stage of the drug discovery workflow.

Eppendorf's seven centrifugation solutions for therapeutic mAb research include:

- Molecular biology, ideal for spin column-based MiniPrep kits for nucleic acid purification, gel extraction, and PCR clean-up
- High speed, ideal for lysate clarification at 20,000 x g in nucleic acid purification protocols for target antigen production and antibody humanization
- Big volume harvesting, ideal for harvesting cells from large volume suspensions to produce antibodies in cell lines and antigens in bacteria
- Versatility, ideal for purifying peripheral blood mononuclear cells (PBMC), FACS/Flow cytometry, and hybridoma technology in multiple vessels
- High-throughput screening, ideal for identifying antibody hits
- Low-throughput screening, ideal for screening assays for selection and characterization of antibody leads
- Classic cell culture, ideal for cultivation and selection of stable cell lines

For example, high-throughput screening to identify antibody "hits" in the supernatants of hybridoma clone cultures is usually performed using microtiter plates (MTPs). Although various methods can be used, all include centrifuging temperature-sensitive samples in MTPs multiple times.

Eppendorf's refrigerated benchtop centrifuge 5920 R, combined with swinging bucket rotor S-4x1000 and plate/tube buckets, can accommodate up to 28 MTPs per run. The Dynamic Compressor Control, a dynamic cooling technology, provides optimal sample protection. Continuous cooling ensures a constant temperature after the run is complete, and its soft-touch lid closure and quiet operation contribute to a comfortable working environment.

Eppendorf knows that your results are critical. Whether you work with therapeutic antibodies or vaccines

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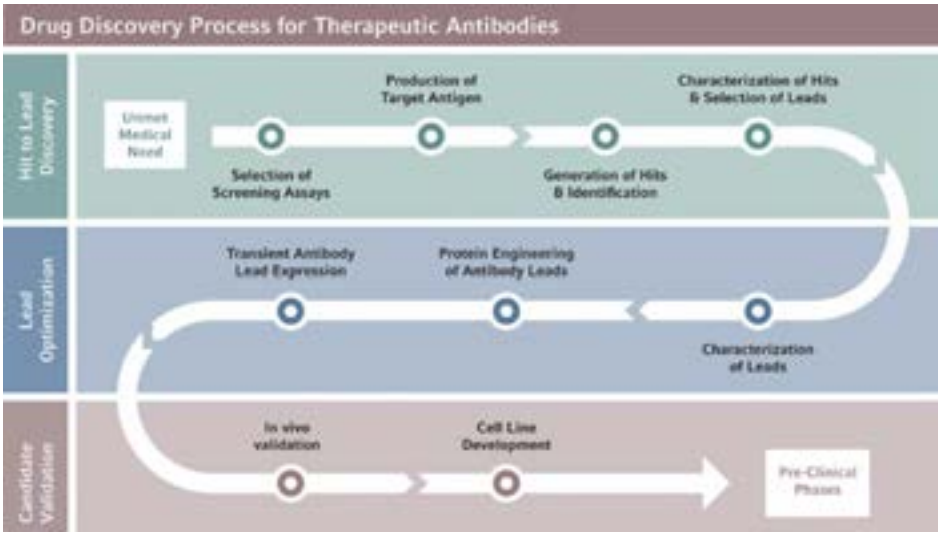
against SARS-CoV-2, Eppendorf centrifuges can help you overcome your challenges and support your demand for sample protection, efficiency, and reproducibility.

Sources
1. Genetic Engineering & Biotechnology News, April 2019. https://www.genengnews.com/wp-content/uploads/2019/03/GEN_Apr19_AList_Table.jpg



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Single Stage	40 L/min.	65 torr	15 psig	⅙ hp	13 x 6.5 x 8.5 in.	**13-880-16**
Two Stage	20 L/min.	6 torr	15 psig	⅙ hp	15 x 6.5 x 8.5 in.	**13-880-18**
Two Stage	35 L/min.	6 torr	15 psig	⅓ hp	16 x 7 x 9 in.	**13-880-20**
Two Stage	35 L/min.	1.5 torr	15 psig	⅓ hp	16 × 7 × 9 in.	**13-880-22**

Disease Research

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Model 505

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705	• Cell Disruption • Protein Extraction • DNA Shearing/ChIP • Nanoparticle Dispersion • Homogenization/Mixing • Sonochemistry	0.2 to 1000 mL	700w	**FB705110**

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MY-PCR, W: 32 in.	MY-PCR32	**15-338-366**
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Peristaltic Pumps Meet the Demands of Biopharma Processes

By Eric Rentsch, Masterflex Product Marketing Manager, Cole-Parmer

The biopharmaceutical industry has grown consistently as new therapies are developed to treat diseases across the globe. This trend requires scale-up production methods for various medications that maintain quality along with agile bioprocess systems that meet the shifting demands of a diversified market.

The increasing demands for scalability and sterility of biopharmaceuticals have led to the integration of truly aseptic options that use peristaltic pump technology.

The Benefits of Peristaltic Pumps

Major steps in biopharmaceutical production include media preparation, fermentation, harvesting, purification, and fill or finish. Other metering pump technologies are being replaced by peristaltic pumps, which can provide more flexible and reliable fluid handling.

Biopharmaceuticals are fermented in bioreactors from biological materials rather than chemically-synthesized molecules. Although these types of medications may offer more effective and specific drug delivery for patients, they are also more sensitive to contamination and the effects of mechanical shear. Here, peristaltic pumps excel. Peristaltic pumps alternately compress and release flexible tubing that contains the fluids. As a roller passes over, the tubing is first occluded (squeezed) and then released.

To grow biologics inside bioreactors, specific conditions must be maintained and media must be injected and recirculated. Peristaltic pumps also work well here — they can move fixed amounts of fluid per motor revolution to produce precise and reproducible dosing. The titer of the product (called target biologic density) increases over time, making it more likely that cells will rupture during recirculation. The gentle squeezing action of peristaltic pumps creates less shear than other pump types.

During harvest and purification, mitigating the risk of cross-contamination is crucial. Peristaltic pumps are ideal here because their flexible tubing can be quickly replaced rather than sterilized, so there are no cleaning methods to validate. And, because the fluid only comes into contact with the tubing, material validation is limited. Most manufacturers will also offer validation packets to verify that their components are safe for biologic production.

The final step is fill/finish. This can take weeks of labor and costly materials. As the product moves downstream, fill/finish is where the product is most valuable and at risk. Peristaltic pumps show their real value at this stage. They can accept various tube sizes, allowing process scalability.

Peristaltic Pump Tubing

Some pump tubing is formulated specifically for cell transfer applications. Formulations like Masterflex Puri-Flex and silicone feature smooth inner surfaces for low protein binding and low leachables and extractables. This maximizes bioreactor cell vitality throughout the growth cycle to produce a higher titer.

It is important to note that peristaltic pump tubing is separate and distinct from tubing for general fluid transfer. Peristaltic pump tubing undergoes significant pressure that could cause spallation or premature rupture of other tubing. Materials from the lining of the inner tubing can also flake off due to wear, which can affect the integrity of the product and change the volume of fluid being delivered each revolution, ultimately affecting pump precision.

When choosing pump tubing, make sure that proper testing was performed with the manufacturer's own peristaltic pump models because each has different magnitudes of mechanical stress. Masterflex tubing is tested with Masterflex pumps to ensure accuracy and meet specifications.

Peristaltic pumps are driving more efficient fluid handling due to their ability to meet the challenges of scalability and sterility demands in biopharmaceutical processing today.

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48 x 29 x 32 in.	63 x 31 x 35 in.	**11-386-002**
60 x 29 x 32 in.	76 x 32 x 35 in.	**11-386-003**

*Outside width includes a 12 in. transfer chamber

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The New Transferpette *S*: A Perfect Fit for Every Hand

Experience how simple, easy, and efficient pipetting can be with the new BRAND Transferpette *S*. Crafted with high-grade materials, precision workmanship, and the quality of German manufacturing, the Transferpette *S* line of air displacement pipettes offers a host of updated features:

- The grip has been designed for a better fit in left and right hands of all sizes
- All functions — volume setting and locking, pipetting, and tip ejection — can be comfortably operated single handedly without shifting position
- Low operating forces, a short pipetting stroke, and easy tip mounting and ejection ensure comfortable pipetting
- Volume setting is quick and easy with a four-digit volume display that is always visible, with an easy-to-operate thumbwheel to rapidly select the desired volume
- The thumb-operated volume change protection mechanism prevents inadvertent volume drift during pipetting for additional reliability and improved reproducibility
- Color-coded pipette accents simplify pipette and tip selection
- Single- and multi-channel models are available, as well as sets with volume ranges from 0.1 µL to 10 mL
- All Transferpette *S* pipettes are made of UV-resistant materials and can be repeatedly autoclaved at 121°C for decontamination

Single-channel models include a three-year warranty and feature a slimmer shaft that fits narrow vessels — including 15 mL conical tubes, housing designed for easy cleaning, and tip cones designed to fit most brands of quality pipette tips. The lower housing can be easily disassembled without tools for cleaning and maintenance. A special "sub-micro" model provides unsurpassed accuracy in the 0.1 to 1 µL range, and 10 adjustable-volume models cover the 0.1 µL to 10 mL range. Ten pipettes in five sizes cover the volume range from 0.5 to 300 µL. Eight different fixed-volume models are also available.

Multichannel pipettes are available in 8- and 12-channel models. The patented tip cone design allows the user to easily remove individual tip cones for cleaning or replacement in the lab, reducing downtime. The advanced O-ring design and stepped tip ejector improve tip fit and reduce tip mounting and ejection forces even further.

In addition to Transferpette *S* pipettes, BrandTech offers a full line of liquid handling products, including the new HandyStep touch repeating pipette. The HandyStep touch features a touchscreen interface with intuitive menu-driven operation and integrated help function. Operating modes include multi-dispensing, auto-dispensing, and pipetting. Automatic tip ejection simplifies use and additional modes — sequential dispensing, multi-aspiration, and titration — are also available.

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BRANDTECH® SCIENTIFIC, INC.

Vaccine Development: Fighting Infectious Diseases

Vaccines have played a huge role in shaping modern society. The notion of acquired immunity was discovered in ancient China centuries ago, but the modern concept of vaccination was born in the 18th century when English scientist Edward Jenner used cowpox infections to protect against smallpox. Today, the global vaccine industry is worth over 50 billion USD.

Vaccine Development

The concept behind vaccines is simple: a weakened pathogen is used to trigger an immune response that helps fight a disease to which a person is exposed. Due to current immunization practices, polio, smallpox, and other devastating diseases that once obliterated communities are nearly eradicated. Many others like measles and mumps can also be controlled.

Vaccine development begins with identifying the disease-causing agent. Then scientists can research and develop live attenuated or inactivated agents from which to produce a vaccine. Genetic engineering technologies are also used to develop modified versions of the agents.

While the antigens in vaccine formulations evoke the immune response, vaccines would not work without adjuvants, emulsifiers, and stabilizers.

Quality Control and Regulation

As biological products, vaccines require strict quality control and quality assurance practices to ensure their safety. Global guidelines provide standards, and various *in vitro* and *in vivo* tests are used to measure the potency of the finished products.

One critical and regulated aspect is constant and accurate temperature monitoring. Data-logging thermometers, like Fisherbrand Traceable products, can help ensure that optimal temperatures are maintained through the entire vaccine creation and production cycle.

Pre-Clinical and Clinical Trials

Before a vaccine can be certified for human use, it needs to be validated through several rounds of pre-clinical and clinical trials.

Pre-Clinical Trial: After a vaccine is developed, it is tested with tissue culture and animal models to determine safety and immunogenicity. These studies help researchers understand the cellular responses they can expect from the candidate vaccine and adjust formulations and dosages for the next round of tests.

Clinical Trial I: Having satisfied any pre-clinical trials, the potential vaccine is ready to be tested on a small group of healthy people. A controlled challenge test, where subjects are exposed to the disease to determine vaccine effectiveness, might also occur at this stage.

Clinical Trial II: This trial is expanded to a larger group that includes at-risk individuals. Tests are randomized and often include a control or placebo group for comparison.

Clinical Trial III: After successful completion of the first two rounds of clinical trials, the vaccine is tested on a group of thousands of individuals. The vaccine is validated with this larger group, as some rare side-effects may not be detected in smaller groups. For example, an adverse event that occurs only once in 10,000 people may only surface after a substantial number of people have been exposed to the vaccine.

Licensing: Regulatory authorities independently verify clinical trial I, II, and III test results before issuing a license for the products to be sold and used.

Clinical Trial IV: Manufacturers may continue to perform other tests for safety, efficacy, and other potential uses for the vaccine after it has been approved for distribution and use.

Storage and Transport

Vaccines will naturally biodegrade over time and can lose efficacy when

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exposed to extreme heat or cold. Poor or inadequate storage and transport conditions may violate the vaccine's license or cause the vaccine to fail. Cold chain temperature ranges for vaccines are typically between +2˚C and +8˚C.

Today, advanced instrumentation can help you monitor and maintain temperatures for safety and traceability during storage and transport. Fisherbrand TraceableLIVE cloud-based dataloggers or Fisherbrand Excursion-Trac USB dataloggers provide the complete temperature recording needed to validate proper vaccine storage. For vaccine transport, use Fisherbrand TraceableGO dataloggers to document that vaccine temperatures are appropriate and uncompromised.

All Fisherbrand Traceable products include a two-year, NIST-accredited calibration certificate to help you comply with CDC, VFC, Joint Commission, CLIA, and other regulatory recommendations and requirements.

Summary

Immunization is one of modern medicine's greatest success stories. It can prevent sickness and death and also supports global education and economic development.

Visit **fishersci.com/traceableresources** or **fishersci.ca/traceableresources** to browse our catalog of Fisherbrand Traceable products and learn how they can help you keep your vaccines safe and compliant.

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Range	Resolution	Accuracy	Data Overwrite	Memory	Probe	Cat. No.
Refrigerator/Freezer						
–50.00 to +70.00°C (–58.00 to +158.00°F)	0.01°	±0.25°C	Yes	525,600 Data Points	1 Bottle	**15-081-123**
					2 Bottles	**15-081-124**
					1 Bottle & 1 Bullet	**15-081-127**
Ultra-Low Temperature						
–90.00 to +105.00°C (–130.00 to +221.00°F)	0.01°	±0.2°C	Yes	525,600 Data Points	1 Stainless Steel	**15-079-624**
					2 Stainless Steel	**15-079-625**

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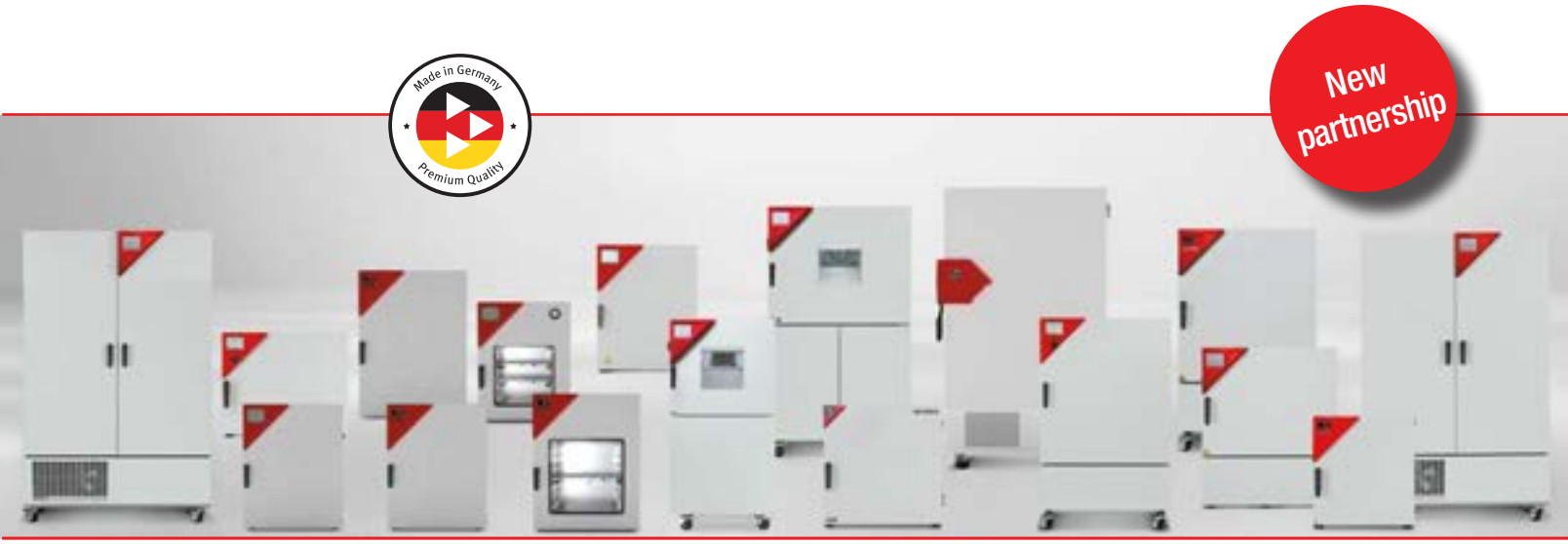

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FB-11203	5.75 L (1.5 gal.)	**FB11203**
FB-11206	6.9 L (1.8 gal.)	**FB11205**
FB-11207	12.75 L (3.3 gal.)	**FB11207**
FB-11209	18 L (4.75 gal.)	**FB11209**
FB-11211	29 L (7.3 gal.)	**FB11211**

Trees Socially Distance to Stay Healthy, Too

By Kylie Wolfe

Gazing out over treetops after a hike or a drive through the mountains, it looks as though the leaves and branches are woven together into one green abyss. But if you observe from the forest floor, some treetops tell a different story.

The truth is, neighboring trees don't always touch. Instead of blending together, some species will leave intentional gaps between the end of one branch and the start of another. This creates openings in the canopy where slivers of blue sky and sunlight slip through, framing each treetop's green leaves. This strategic spacing, also known as crown shyness, helps them avoid disease and share resources with the plants below. And it's something scientists have been studying for decades.

A History of Observation

While social distancing is a relatively new concept for humans, it's something trees have been doing for a long time. There are scientific reports dating back to the 1920s describing this phenomenon and noting lack of light as a potential cause.

But a 1984 study of Costa Rica's black mangroves linked crown shyness to wind. They found a relationship between how much each tree swayed and the resulting distance between their treetops. The more they collided, the greater the gap.

Researchers at Michigan Technological University later found the same to be true of lodgepole pine. Trees of a similar height would collide, damaging nearby branches. Branches found along the edges of each gap were usually broken and held fewer leaves. During the study, researchers secured the swaying trees with nylon ropes, keeping them from interacting. Over time, the canopies grew together, closing the gaps.

Crown shyness doesn't occur with every tree species, but is usually found between trees of the same species.

Branches with Benefits

As scientists study how trees keep their distance, they're also exploring what benefits the resulting spaces may have in nature. For example, fewer leaves gives the sun a chance to reach the ground. This improves photosynthesis for plants on the forest floor.

Gaps can also help trees avoid disease, harmful insects, and invasive vines. This preserves the overall health of the forest.

"Leaves are like a tree's most expensive diamonds — you want to protect them at all costs," Meg Lowman, forest canopy biologist and director of the TREE Foundation, told *National Geographic*. "If a whole bunch get bumped off, that's a terrible disaster for the tree."

Trees that experience a lot of wind may have adapted to avoid damage, not growing into gaps where they could collide with others. They can instead invest their energy elsewhere.

> While social distancing is a relatively new concept for humans, it's something trees have been doing for a long time.

"The minute you start keeping plants from physically touching each other, you can increase productivity. That's the beauty of isolation … The tree is really safeguarding its own health," said Lowman.

Finding Answers in the Treetops

Researchers are still looking for concrete answers about the causes of crown shyness. There's likely a combination of factors at play. Other than wind, it's possible some trees sense chemicals or light as they approach their neighbors. Both experiences could cause branches to stop growing, keeping the tree safe and healthy from a potentially dangerous encounter.

Trees require a balance of nutrients, water, space, and sunlight. And while the benefits they experience from distinct gaps aren't a proven result of crown shyness, it could be their way of meeting their own needs.

It's not easy to find answers dozens, if not hundreds of feet in the sky. But the power of observation is heightened when you approach with a new perspective. There's much more to learn about trees simply hiding in the treetops.

Disease Research

Your Guide to the Cryopreservation of Cells

Cell cryopreservation puts your cell lines in suspended animation, effectively stopping biological time. While it might seem like the stuff of science fiction, cryopreservation is a meticulous and fundamental process in cell culturing that requires the utmost precision and care.

So how does cryopreservation of cells work? Let's break down the process.

Step 1: Select the Cells

Optimal cryopreservation occurs when cells are in the best possible condition and near the end of their logarithmic growth phase.

Carefully examine your cultures for signs of microbial contamination. Growing cultures for several passages in an antibiotic-free medium before testing can bring contaminants that might have gone undetected to a more detectable level.

Examine your samples under a microscope and directly culture for bacteria, yeasts, fungi, and mycoplasma. Mycoplasma presents unique issues because it goes undetected during testing. You'll also need to test culture stocks again after they've been frozen.

Step 2: Harvest the Cells

Harvest the cells using the proper procedure for the cell type — and be as gentle as possible. Once the cells are harvested, wash off or inactivate any dissociating agents that may damage the cells. For this step, use a centrifuge only if absolutely necessary and use a low force — just enough to produce a soft pellet.

Pool the contents of harvested culture vessels to ensure uniformity in the final frozen stock. Dilute or concentrate the cell suspension as needed to achieve twice the desired concentration.

Keep the cells chilled to slow cell metabolism and prevent clumping. Cells can be gassed with carbon dioxide when necessary to prevent alkaline pH shifts.

Step 3: Choose the Container

Selecting the right cryoprotective agents can minimize cell damage during cryopreservation. The right storage vessel is also critical. The wrong storage vessel creates numerous risks, including injury, damage to vessels, and contamination or loss of frozen stock.

Heat-sealable glass ampules and polypropylene screw-capped vials (with internal or external threads) are most commonly used. However, sealing issues with ampules have researchers and industry professionals increasingly preferring cryogenic vials.

Step 4: Cool the Cells

Cooling rates must be uninterrupted, slow enough to give the cells time to dehydrate, and fast enough to prevent dehydration damage. For most animal cell cultures, the ideal cooling rate is a steady drop between 1°C and 3°C per minute. Larger or less-permeable cells might need to cool more slowly because they take longer to dehydrate.

Some labs use programmable electronic cooling units, which provide precise control of the freezing process and yield uniform, reproducible results. Others use mechanical units that offer sufficient process controls at less cost. Ultracold freezers with insulated polystyrene foam boxes are one of the most economical and common methods of cooling cell lines. A Corning CoolCell container, in combination with a -80°C freezer, provides consistent and reproducible freezing profiles.

Step 5: Store the Cells

Once the cells are frozen, you need to move quickly. Use an insulated container filled with dry ice or liquid nitrogen to transfer the frozen stock to permanent storage.

Speed is the key to preventing the vials from warming and damaging the cells. Even a temporary rise in temperature can cause damage. Most cell culture labs use liquid nitrogen freezers, but the most important feature of any permanent storage location is the ability to reliably maintain temperatures below -130°C.

Step 6: Thaw the Cells

While cooling cells must be gradual, the opposite is true when thawing cells. Rapid thawing reduces the formation of damage-causing ice crystals within

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the cells as they rehydrate. Place your container in warm water and stir it gently until it's completely thawed. For most cell cultures, thawing for 60 to 90 seconds at 37°C achieves the best results.

Step 7: Let the Cells Recover

Remove the cryoprotective agents from the cells as quickly and gently as possible to avoid damage from prolonged exposure to these agents. The method of removing cryoprotective agents depends on the type of agent and the type of cells. Cells that are sensitive to cryoprotective agents require gentle centrifugation to remove the agent. When glycerol is the cryoprotectant, cells can be damaged by the sudden addition of a large volume of fresh medium to the thawed cell suspension. Instead, take glycerol-preserved cells through several stepwise dilutions to give the cells time to adjust. Use equal volumes of warm media every 10 minutes.

In general, most cells recover normally if the cryoprotective agent is removed within six to eight hours of thawing via medium change.

When successfully preserved, frozen cells need little maintenance and can be a lifeline if you lose cell cultures to contamination or an accident. Frozen cell cultures are especially useful for long-term experiments because their suspended animation ensures that biological variants are minimal.

Visit **fishersci.com/corning** or **fishersci.ca/corning** to shop a variety of Corning cryopreservation products.

Disease Research

A Dedicated Solution for Microbial Growth Analysis

By JD Herlihy, Product Manager, BioTek Instruments

The global microbiome is composed of the bacteria, algae, fungi, and other microorganisms that surround us and form the foundation of our world. While microbiologists have been studying these organisms for centuries, we are just starting to understand the complexity and diversity of microbes as tools and agents in disease pathophysiology.

The growth characteristics of microbes are some of their most commonly studied phenotypic traits. This information is used for new antibiotic screening, new microbial isolate characterizations, interrogation of clones for the bioremediation of toxic waste or wastewater treatment, and many other applications.

Microbial growth has traditionally been measured using optical density measurements, most often taken at 600 nm as a proxy for turbidity. First, the microbes are grown in an Erlenmeyer flask using a shaking incubator. The changes in optical density of the cell suspension over time are determined spectrophotometrically using a 1 cm cuvette. Such kinetic analyses of microbial growth provide robust data on lag times, log phases, and the time needed to reach the stationary growth phase. But they are also laborious, requiring that each culture be sampled at multiple stages of growth: 6, 12, and 24 hours as well as longer periods.

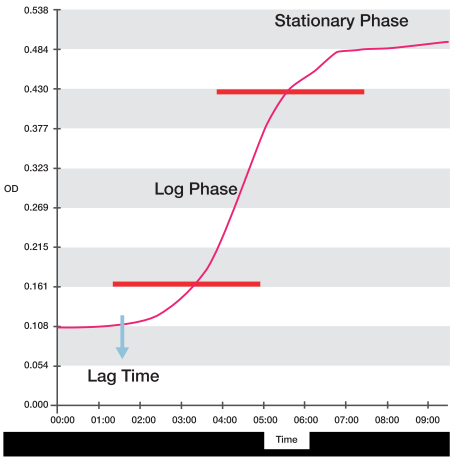

Figure 1. Three phenotypic characteristics used to measure microbial growth and the differences between microbial samples.

The transition to multi-well plates and incubated microplate readers has greatly increased throughput and automated data acquisition. However, microplate readers have some limitations when performing microbial growth analysis.

These limitations have restricted the ability to fully realize the increased throughput and other automation aspects of microplate readers. Under normal aerobic growth conditions, accurate growth measurements require efficient sample mixing and controlled incubation temperatures. And since the plates require constant shaking and incubation, growth analyses have been limited to one plate per instrument.

Mixing is also critical to delivering accurate results in two ways. First, the samples must be properly aerated so that dissolved oxygen is not a limiting growth factor. And second, inconsistently suspended cells can lead to artifacts in turbidity measurements. Surface tension in the small diameters of microtiter plate wells makes it difficult to get proper sample mixing. Also, the mechanics of some microplate readers cannot tolerate the rigorous shaking required to break the surface tension in microwells.

Another critical element of microbial growth is temperature. Microorganisms are highly temperature sensitive, so fluctuations and gradations in incubation temperatures can create inconsistent growth and edge or plate effects. Without proper temperature control, results are variable and unreliable.

The BioTek LogPhase 600 is the first microplate reader dedicated to microbial growth analysis and addresses the earlier

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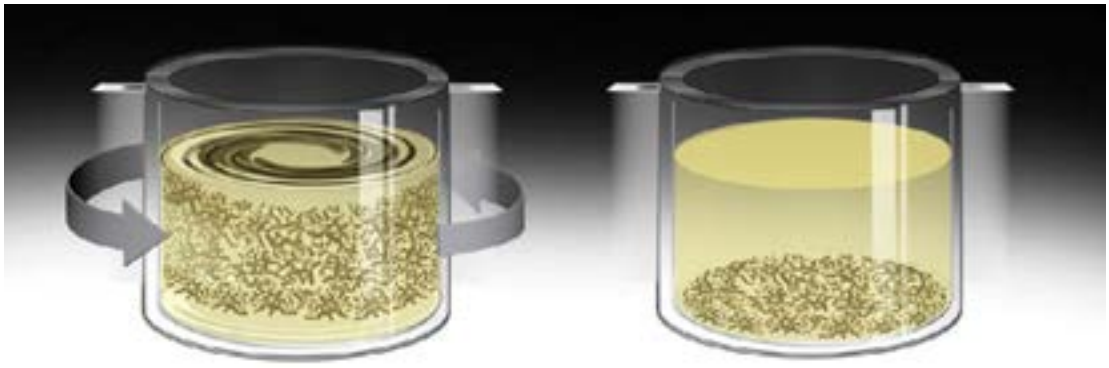
constraints of microplate readers. The shaking speed and amplitude of the LogPhase 600 was designed to rigorously shake samples for proper aeration and sample suspension. The shaking mechanism has limited mechanical connections and a robust motor. It has been painstakingly tested to deliver a lifetime of robust performance.

The incubation chamber has also been carefully designed with 11 independent thermistors that measure and adjust temperatures to maintain consistent conditions. Dedicated to a single application, LogPhase 600 reliably delivers high-quality data and accommodates four microplates at a time.

Keep your cells in solution for optimal growth



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Disease Research

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BioTek LogPhase 600 Microbiology Reader

The LogPhase 600 Microbiology Reader is designed to measure microbial growth curves and can process four standard 96-well microplates simultaneously.

The LogPhase 600 Reader features variable orbital shaking speed, consistent temperature control, and other factors critical for optimal microbial growth and data quality. And the LogPhase App provides convenient control for consistent microbiological analysis and data acquisition.

Description	Wavelength	Cat. No.
LogPhase 600 4-Plate Absorbance Reader to Measure Kinetic Growth Curves at Specific Wavelengths; Orbital Shaking, Incubation to 45°C; Includes LogPhase App for Reader Control, Data Collection, and Analysis	560 nm	**BTLP560**
	580 nm	**BTLP580**
	600 nm	**BTLP600**
	620 nm	**BTLP620**
	640 nm	**BTLP640**

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Description	Cat. No.
Upright Microscope Only (1x, 2x, 4x, 8x); Upgradeable	**BTCYT7U**
Upright Microscope (1x, 2x, 4x, 8x) and Multi-Mode Microplate Reader; Monochromator-Based Fluorescence, Luminescence, and Absorbance	**BTCYT7UM**
Upright Microscope (1x to 8x) and Inverted Fluorescence Microscope (1.25x to 60x) with WFOV Camera; Monochromator-Based Fluorescence Intensity, Luminescence and Absorbance	**BTCYT7UMW**
Upright Microscope (1x to 8x) and Inverted Fluorescence Microscope (1.25x to 60x) with WFOV Camera	**BTCYT7UW**

Disease Research

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