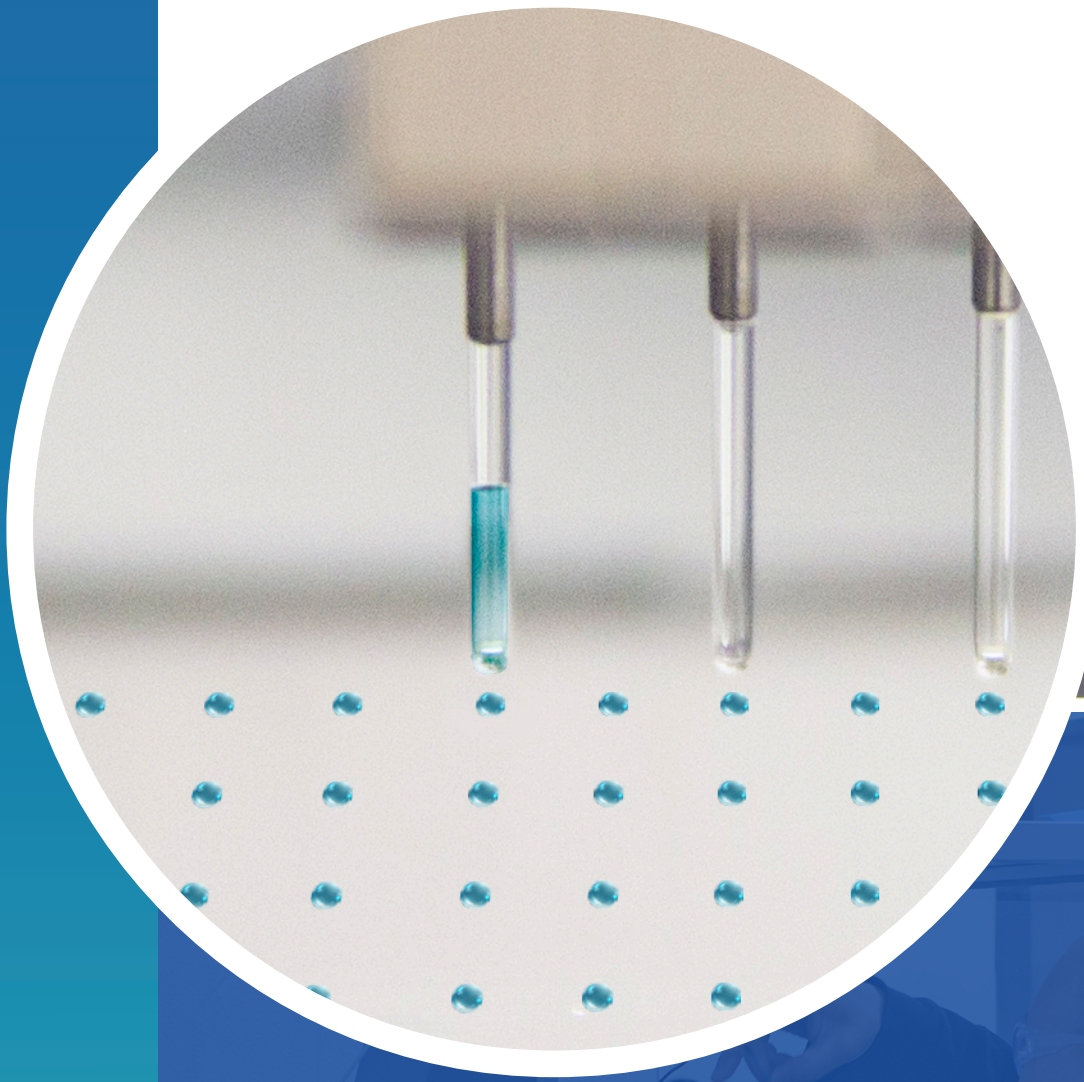
THE DOT

30 Years of Discrete Droplet Dispensing™ Innovation



Welcome to The Dot

Celebrating 30 years of groundbreaking science

Welcome to the inaugural edition of The Dot, a special publication marking BioDot's 30th anniversary. Over the past three decades, laboratory science has changed almost beyond recognition, driving us to evolve in parallel with the industries we serve, as well as expanding into others. This journal showcases just a snapshot of this journey, taking a glimpse at how some of our customers are implementing BioDot technologies, and the positive impacts they continue to have for lab technicians, researchers or clinicians and, in many cases, healthcare systems and their patients.

As we celebrate this milestone, we reflect on how our innovative solutions have helped customers pioneer discoveries in the past, and how they will continue to do so into the future, driven by a collaborative mindset and our dedication to advancing technology and improving lives. From our heritage in supporting lateral flow immunoassay development to solving unique dispensing challenges for life sciences and diagnostic companies, we are delighted to be celebrating our origins, highlighting recent developments, and looking ahead to a future filled with more scientific breakthroughs. We also want to thank our customers and applaud their successes. Our story is written through their work, and we will continue to support them as we strive towards our vision, to create a world where every scientist's vision is met with the precision it deserves.

I hope you enjoy reading the first edition of The Dot,
Debbie Bowers, General Manager at BioDot

Three Decades of Making a Difference: a Moment with Shane Gunsalus

Before we delve into all these wonderful customer stories, we took a moment to talk with Shane Gunsalus, one of the longest-serving BioDot employees, to get his perspectives on the recent growth of the company and the changes he has seen over the course of his long-standing career.

Shane Gunsalus,
Senior R&D Manager at BioDot

With a near 30-year tenure, you must've seen some incredible changes within BioDot and the industries you serve. Could you please give us an insight into what the early years were like at the company?
I started with the company in 1996, approximately two years after it was formed. The founders had a really clear vision about how our technologies – which were centered around lateral flow tests (LFTs) and liquid dispensing – could make a difference in the diagnostics market, and had the connections and market insights to bring their dream to life. This created a really strong company from the outset, with a relatively small and agile team that was driven by the collective excitement and belief in our products making a positive impact in the clinic and, ultimately, improving patient outcomes.

You mentioned that LFTs were a focus of the company at the beginning. How much has this changed over time? And how do you decide which fields to venture into?
To answer your last question, keeping an open communication channel with our customers has always given us a clear indication as to what the market needs. I used to travel a lot for the company, meeting new customers and getting to know their products and pain points, how we could support their work in the lab, and what was essentially missing.

In the early days, we primarily supported developers and manufacturers of LFTs. Our first systems were based on two technologies – BioJet™ and AirJet™ – which produced non-quantifiable droplets at that time. This was clearly not suitable for applications requiring more precision, such as those in many medical fields, leading us to develop quantitative dispensing technologies and systems amenable to proteins and biologics, as well as fine tuning the different components that affected final droplet performance. For example, we performed a lot of R&D on improving dispense tips, looking at products in the semiconductor industry and adapting them for the diagnostics market.

LFTs are still one of our key areas, but we have matured in several markets since the beginning, based on the knowledge that our fluid dispensing systems could also be employed for other applications. We started by expanding to microarrays and biosensors using droplets down to the nanoliter range, which was impressive at the time. Now, dispensing volumes can go as low as a few picoliters, making these systems ideal for high throughput microarray spotting. We have even ventured into devices used for manufacturing the physical components of lateral flow assays and other materials, including guillotine cutters, assembly rollers and lamination systems.

What's the secret behind the ability to dispense down to the picoliter range? And what were some of the challenges you had to overcome in product development?
The development of our own proprietary non-contact piezoelectric dispensing technology has allowed us to achieve such low volumes. We are essentially working at the very limits of what can be accurately dispensed, which obviously comes with many challenges, from defining manufacturing tolerances to being able to qualify the performance of the dispensers and quantify the volumes. The latter especially came with many difficulties because, by the time the drop lands on a surface, it's already evaporating. We therefore developed horizontal drop cameras to quantify the liquid on the fly before it settles, as well as onboard QC methods that adjust and steer dispensers to target locations in real time.

Has the company culture changed since BioDot was acquired by ATS?
Of course there have been some big changes since we were acquired. We are no longer a family-run business, but we have maintained the 'laugh together, cry together' mentality, and have a large, public organization to support us and help us grow. I have been particularly impressed with the life sciences division of ATS, and we are learning a lot from each other. Overall, we share a strong belief in our technologies, and we are working together to ensure our founders' vision remains at the core of everything we do.

Enhancing Autoimmune Disease Diagnostics with

Advanced Dispensing Technology

Accurate diagnosis of autoimmune diseases is critical for effective disease management and positive patient outcomes. Advanced immunodiagnostic tests – from ELISAs to microarrays – are essential for detecting autoimmune markers with the required accuracy and precision. D-tek, a leader in autoimmune diagnostics, is using BioDot instrumentation to manufacture high quality diagnostic kits that accurately detect these markers for reliable and consistent patient results.

Autoimmune diseases – such as lupus and multiple sclerosis – occur when the immune system mistakenly attacks the body's own tissues, leading to chronic inflammation and tissue damage. Diagnosing these diseases involves the detection of specific autoantibodies in the blood as indicators of an autoimmune response. The availability of accurate, reliable and efficient diagnostic tools is therefore essential for the early detection, appropriate treatment and effective management of autoimmune conditions, ultimately improving patient outcomes.

D-tek is a Belgian biotechnology company founded in 1995 that specializes in diagnostic products for autoimmune disorders. Thanks to its strong R&D capabilities, the company has become a pioneer in this space, including the development of the world's first kit for detecting anti-nucleosome antibodies for the diagnosis of lupus. Today, D-tek offers a comprehensive range of diagnostic kits – including ELISAs, ImmunoDOT assays and microarrays – as well as an automated platform, the BlueDiver Instrument, designed to process nitrocellulose strips in ready-to-use assay cartridges.

Accurate dispensing of very small reagent volumes during manufacture is crucial for ensuring the precision and sensitivity of diagnostic assays, which directly affect the reliability and cost effectiveness of the tests. Creation of high quality diagnostic kits therefore hinges on liquid dispensers capable of handling picoliter to nanoliter volumes in a precise and reproducible manner. D-tek relies on BioDot instrumentation to ensure consistent and accurate assay production, as Benoît Autem, Managing Director at D-tek, explained: "D-tek was founded with the goal of developing a multiplexing project that would allow us to create strips on a nitrocellulose membrane containing different biomarkers, enabling more comprehensive and precise diagnosis of autoimmune diseases. These strips were initially produced manually, but this method proved to be unsustainable due to its tedious and time-consuming nature, so we incorporated BioDot's AD3220™ with BioJet Elite™ dispensing technology into our workflow to streamline the process. The BioDot team assisted us in evaluating, testing and validating the coating process on the system, helping to ensure that everything ran smoothly. The instrument's software makes it easy to set up the production of different assay strips, allowing us to vary the number of strips and quantities of specific reagents according to our needs."

The D-tek team employs BioDot technology to streamline its processes.

> "BioDot's automated solution allows our scientists to set up a run, then walk away and focus on other activities, such as preparing antigens or performing quality control testing."

Automating this part of the manufacturing process has allowed D-tek to save time and free up its production team to undertake other skilled tasks. Benoît continued: "BioDot's automated solution allows our scientists to set up a run, then walk away and focus on other activities, such as preparing antigens or performing quality control testing. This is especially important in a production environment, as it offers flexibility and greatly increases our overall productivity and efficiency."

"We have been working with BioDot for over 20 years, and have a very good relationship with the team. Throughout this time, BioDot has continuously improved its systems to offer even better low volume dispensing capabilities, and we have consistently upgraded our instruments to benefit from these advancements. We have tried other brands, but always returned to BioDot, as its systems are more robust and reliable, making it easier to coat many strips on the same membrane. As we have extensive experience with its equipment, BioDot often refers new or potential customers to us, so that we can highlight all of the instrumentation's capabilities, acting as a showcase for what can be achieved. We certainly plan to build on our successful collaboration and the significant enhancements we've experienced by making further investments in BioDot products in the future," Benoît concluded.

To find out more about BioDot, visit **www.biodot.com**

To discover more about D-tek, go to **www.d-tek.be**

Blotting a Course to Rapid Allergy Diagnostic Test Manufacturing

Allergy testing is an important part of medical care, especially with the increasing prevalence of life-threatening reactions to some allergens. Immunoblot diagnostic assays are widely used to help screen patients and diagnose allergies, with modern tests capable of analyzing a whole range of allergens in one test strip. German manufacturer MEDIWISS ANALYTIC GmbH has been a pioneer of allergy testing for over two decades, and employs a number of instruments from BioDot to accelerate the production of customized tests for its clients.

An allergic response occurs when an individual's immune system reacts to a foreign substance – such as pollen, animal dander or medication – that is otherwise harmless to most people. Although the majority of allergies cause mild symptoms and are generally self-limiting, some can lead to severe consequences and even death. Anaphylaxis, for example, is a potentially life-threatening allergic reaction most commonly caused by food, with about 30,000 cases presenting to emergency departments in the USA each year.[1] It is therefore vital to identify potential allergens – often even in asymptomatic individuals – to mitigate risk and enable implementation of appropriate lifestyle choices.

Type 1 allergic reactions – also known as immediate hypersensitivity – are the most common form of immune response, in which immunoglobulin E (IgE) plays a central role, binding to allergens and triggering the release of histamine and other biochemicals that manifest as symptoms. Small quantities of IgEs are normal in human blood, but elevated levels typically indicate an allergic response or hypersensitivity, making this protein an obvious choice as a biomarker. Using this knowledge, MEDIWISS ANALYTIC GmbH has developed two immunoblot test kits for the semi-quantitative determination of circulating allergen-specific IgEs in human blood, which are capable of testing for a wide range of allergens. Dr Bianca Lux, Head of Membrane Production at MEDIWISS ANALYTIC GmbH, commented: "We have 25 years of experience producing test strips for the detection of IgEs in blood. We extract raw protein allergens from a variety of sources – from animals to pollens to foods – that our customers are interested in testing for, then lyophilize the extracts and dissolve them into a special solvent that we can print onto a nitrocellulose membrane. We have a library of around 450 different allergens for our customers to choose from, and can include up to 30 options on one test strip, plus a control line. This provides a clear advantage over a single allergen testing system, as our assays can identify a whole range of allergens from only 300 µl of serum."

MEDIWISS ANALYTIC GmbH is a long-standing customer of BioDot, and relies on the company's instrumentation daily to ensure the manufacture of accurate and reliable tests. It now manufactures hundreds of thousands of tests per year, with ever-increasing demand prompting the company to extend its portfolio of BioDot systems. Peer von Wahl, CEO, said: "We first started working with BioDot 20 years ago, and were actually the first company in the world to purchase an XYZ1688™ Dispense System. We now have three XYZ3200™ Dispense Systems – plus one XYZ3210™ – in the lab, which have either 31 or 23 micro-dispenser pumps. We use these contact dispensers to print the allergen solutions onto the nitrocellulose strips, using pumps that are specifically designed for protein extracts. The set-up can easily be adjusted to change the distance between the testing strips, while specially designed dispenser tips ensure that we produce distinct lines that don't bleed into each other. Producing one large membrane takes around 30 minutes by hand, but this can be achieved in just one minute using the BioDot systems, significantly increasing our productivity. We currently produce approximately 100 membranes per day, each containing 140 individual test strips – which we cut using one of the BioDot CM4000™ or CM5000™ Guillotine Cutters we have – equating to around 14,000 tests per day."

Peer continued: "The systems are incredibly straightforward to use, and we generally do most of the troubleshooting ourselves. However, if we do require support with something more technical, the team at BioDot is always very responsive. We've had some of our instruments for more than 10 years, so parts will naturally need replacing over this time. The service team always responds on the same day – with either a resolution or a clear timeline for when an engineer will be available – meaning we can plan ahead. This is vital to minimize downtime in our lab and to ensure optimal productivity. Of course, since first partnering with BioDot, we have been approached by various other suppliers, but the company's support over this time has ensured we never look anywhere else."

> "The systems are incredibly straightforward to use, and we generally do most of the troubleshooting ourselves."

References

1. Dribin TE, Motosue MS, Campbell RL. Overview of Allergy and Anaphylaxis. *Emerg Med Clin North Am*. 2022;40(1):1-17. doi:10.1016/j.emc.2021.08.007

To find out more about BioDot's immunoblot solutions, visit **www.biodot.com/immunoblot**

To discover more about MEDIWISS ANALYTIC GmbH, go to **www.mediwiss-analytic.de**

The Power of Multiplex Testing in Animal Health

Monitoring the spread of infectious diseases is an essential process for industries and situations that rely on animal husbandry, whether it's screening agricultural herds that will enter the food chain, testing animals involved in zoo breeding programs, or countrywide surveillance of wildlife populations. Irish veterinary technology company Enfer Scientific is at the forefront of this testing, supplying a wide range of diagnostic assays to help control disease and safeguard animal and human health. The company relies on BioDot instrumentation to manufacture its multiplex arrays, taking advantage of the accuracy and flexibility on offer to produce assays for use in a multitude of species.

The Enfer Scientific team relies on BioDot instrumentation to develop its diagnostic assays.

Early detection of infections is crucial in agriculture to prevent outbreaks that can devastate livestock and impact food safety and security. Vets, farmers, researchers and even wildlife conservationists therefore perform comprehensive testing to follow the evolution and spread of prevalent microbial strains in both wild and domesticated animal populations. The diversity of species under scrutiny, and the environments in which they live, represent significant challenges, especially as some diseases can easily spread from wild populations to livestock, even across species. Tracking, catching and testing wild animals, although logistically difficult, is an important element in preventing the infection of farm animals, as well as in identifying zoonotic diseases that could cross into human populations.

Rapid and accurate testing is a critical tool in this battle, and Irish veterinary technology company Enfer Scientific – part of the Enfer Group – develops and manufactures diagnostic assays and kits for numerous veterinary testing applications at its site in County Kildare. Dr Amanda O'Brien, Research and Development Supervisor, explained: "Enfer Scientific was initially founded to develop tests for identifying illegal growth hormone promoters in cattle and, from there, it naturally progressed to similar technologies for livestock diseases, such as tuberculosis (TB), bovine spongiform encephalitis (BSE) and scrapie."

"The company has continued to diversify, and we now develop diagnostic assays for a whole range of animals. We have worked with camelids, like alpacas, llamas and camels; bovines, from bison to everyday cattle; other farm animals, such as sheep and goats; and even deer, lions and monkeys. We manufacture standard kits for common diseases such as TB, but also develop custom assays for customers with more unusual requirements, including testing animals transferring between zoos, or monitoring the spread of a disease in a wild population. In addition, we collaborate with many companies, institutes and universities around the world to understand important diseases and develop relevant tests."

"We have now been working with BioDot for over 15 years. The company's instruments have been real workhorses for the lab throughout this time."

Many of Enfer Scientific's diagnostic assays use multiplex ELISAs that allow the simultaneous detection of multiple pathogens or biomarkers in a single sample. By using a series of different antigens, each specific to a different target, these diagnostic arrays provide comprehensive and efficient identification of complex diseases, or multiple diseases at the same time. Amanda continued: "When a customer asks us to develop a test, we start by searching the literature to understand the disease and its complexity, and see if its whole genome has been previously published. This helps us to identify target biomarkers that are specific to that disease, and to confirm if they are suitable for ELISAs, as that is not always the case. The multiplex format is a real advantage for identifying complex diseases and multiple strains of a pathogen. We can use several markers in one well to improve accuracy, so each assay has a different number of antigens. For example, our bovine kit has 11, while others only have three or four. Many of our goat and sheep kits are also customizable; one customer may have four diseases that they want to test for, while another might have six, so we adapt each ELISA to their individual needs."

"When we first started to develop multiplex assays, we tried lots of different companies that provided microarray printers, but quickly settled on BioDot dispensers, because they did exactly what they were meant to do; reliably printing 50 nanoliter dots of several antigens into a single well of a microplate. After validating a loan system, we eventually purchased an AD6000™, and later added an AD3420™ to give us extra capacity. We create a unique program for each specific assay, load up the machine with the necessary reagents and plates, then just press go; it does all the work."

While most of Enfer Scientific's current tests are based on multiplex ELISAs, attention is now turning to the development of LFTs as an alternative technology that can be more readily used in the field. LFTs provide immediate results from a small biological sample, and can also include several antigens on a single test strip. Enfer Scientific is using a BioDot XYZ3210R™ to develop new lateral flow formats that will be a significant step forward for field veterinary diagnostics. Amanda added: "So far, not many LFTs have been developed for veterinary use, but BioDot is already a renowned expert in this field, and has been able to give us a lot of assistance and support in what we are trying to achieve."

"We have now been working with BioDot for over 15 years. The company's instruments have been real workhorses for the lab throughout this time; they are very robust, while still offering the precision to handle liquids on such small scales. The printers are also very adaptable, allowing us to offer the level of customization that our customers need; they work very well for our needs," she concluded.

For more information about the BioDot systems, see **www.biodot.com/products**

Read more about Enfer Scientific at **www.enfergroup.com/services/diagnostic-solutions**

Our History

1994

BioDot, Inc., founded by Dr Thomas Tisone and Michael Surmanian, enters the diagnostics laboratory and manufacturing market, providing automation and liquid handling systems for LFTs and POC devices.

1996

Schleicher & Schuell, a membrane provider for LFTs and partner in BioDot's Lateral Flow Workshop, invests in the company.

Cartesian Technologies is formed and granted an exclusive cross-license to apply BioDot dispensing technologies to the life sciences market.

BioDot, Inc. holds its first Lateral Flow Workshop, an annual meeting to teach the nuances of developing and manufacturing lateral flow devices, which continues today.

1998

BioDot, Inc. receives its second dispensing technology patent.

2000

One Step One Solution, an in-house assay development and training platform for LFTs, is launched.

2001

BioDot, Inc. expands by acquiring BioDot Ltd, a UK company.

2010

BioDot, Inc. establishes a legal entity in Shanghai, China.

2014

BioDot, Inc. regains access to the life sciences market when Cartesian Technologies is dissolved.

2016

BioDot, Inc. forms alliance with Symbolics LLC to develop technology for multiplex lateral flow devices.

2019

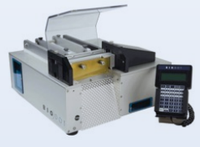
CellWriterS™ platform and FISHArray slides introduced for cytogenetics applications.

BioDot, Inc. receives its 29th patent.

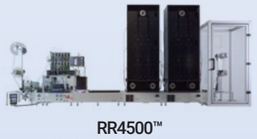
2021

BioDot, Inc. is acquired by ATS Automation.

XYZ3000™
Dispense System



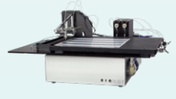
CM3000™ Cutter



RR4500™
Web Handling System

LM5000
Auto Lamination System

AD6000 Aspirate
Dispense System



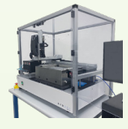
GlucoDot™ Dispense System

ZX1000™
Dispense System

AD1500™
Aspirate Dispense System

CellWriter™ 960

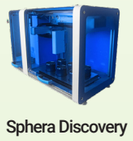
CellWriter S



Sphera™

Omina™

MODULIS™



Sphera Discovery

1st Decade (1994–2004)

2nd Decade (2004–2014)

3rd Decade (2014–2024)

30 Years of Innovation at BioDot

Debbie Bowers, General Manager at BioDot

BioDot is a company that never rests on its laurels, as demonstrated by our transformation from a family-run business firmly rooted in the lateral flow testing sector to a global powerhouse of the scientific community. Our founders dedicated their tenure to developing the technologies that would shape the lateral flow industry, setting the stage for what was to come. We are proud to see our precision fluid dispensing technology and automation solutions now supporting a broad range of applications, including the development of biosensors for point-of-care (POC) devices and the miniaturization of a variety of assays in life sciences discovery laboratories all over the world.

Where it all began – lateral flow testing

BioDot has always been synonymous with lateral flow testing, supporting developers and manufacturers in this field since 1994. LFTs have long been employed for a number of applications, from identifying toxins in crops and diagnosing diseases in domesticated animals to home pregnancy and fertility tests. During the COVID-19 pandemic, governments and international healthcare organizations turned to LFTs for a reliable, deployable and cost-effective device that gave individuals the information they needed to keep themselves and their families safe. They were paramount to curbing the flow of infection, and we were proud to support the global scale-up during a moment of crisis.

The broad potential of LFTs is still under the microscope, and developers are now looking for the next 'blockbuster' application. Their benefits are being explored to potentially take the diagnosis of common pathogens – such as influenza and RSV – to the clinical bedside and even to the patient's home, with cancer screening being investigated as well, which could lead to earlier diagnoses and improved prognoses for many patients. The ongoing evolution of LFTs is a beautiful story; we've been fortunate

> "We were proud to support the global scale-up during a moment of crisis."

to be at the forefront from the outset – certainly with their application in modern medicine – and we will continue to support the hundreds of global developers and manufacturers who rely on our technologies for this purpose.

LFTs and beyond – much more than a one-trick pony

Our proprietary ultra-low volume dispensing technology is a fundamental factor to why LFT developers and manufacturers continue to turn to us. That said, many are surprised to learn that our instruments have been enabling the miniaturization of science in every aspect of healthcare – from clinical diagnostics and next generation biosensors to drug development and discovery – since the early 2000s. It is well known that precision nanoliter – or even picoliter – volumes are vital for LFT development, but working with such low quantities has also had a profound impact on the number of reactions that can be performed on a single multiplex device, transforming the scale at which researchers can develop common assays, including qPCR, mass spectrometry and ELISA. For example, we have worked with one customer on biosensors for a multiplexing application, which involved dispensing around 100 drops of up to 40 different reagents at 5 nl volumes onto a substrate with a surface area of only 4 cm^2. Accuracy and precision in these applications are more vital than ever, especially as medicine shifts towards telehealth and non-invasive, remote monitoring.

Another expanding field that we have ventured into, which also has perfect synergy with our skillset, is the miniaturization of assays in clinical diagnostics. For this purpose, many global clinical labs use our technologies and know-how to support automating fluorescence *in situ* hybridization (FISH) techniques used for the diagnosis of certain cancers, as well as for monitoring treatment response. The typical volumes of the traditional method were about 10 µl of both probe and sample, which we can reduce to approximately 500 nl, saving valuable probes and significant costs. This is done using our FISHArray™ slides, which can be multiplexed with up to eight unique assays on a single slide – with just a fraction of the testing materials – and automated on our CellWriter S robotic workstation.

> "These and many more innovations have supported impressive scientific breakthroughs in the 30 years since our inception."

We also have customers working on the lyophilization of products or reagents, which can help to make them less sensitive to temperature changes and remain bioactive for more extended periods. This has exciting opportunities in the development of novel vaccines, improving stability to make them more accessible to remote populations without the need for refrigeration. Lyobeads – small, bead-like spheres of lyophilized materials – are one of the main constituents being investigated, for which our non-contact dispensing technologies, such as the Sphera Lyobead Dispensing Platform, can dispense precise droplets of the exact dose into an onboard liquid nitrogen bath. A single tip can create up to 10,000 beads per hour, which is too high for many customers, so we'll soon be launching a lower throughput solution to make this technology accessible to more labs in this field.

Syncing growth with market demand

These and many more innovations have supported impressive scientific breakthroughs in the 30 years since our inception, during which time we have undergone an equally incredible internal evolution. The recent acquisition by ATS perhaps marked the biggest shift in our culture, effectively transitioning the company from a privately held business into a global corporation. This saw the conversion – for the better – of many internal processes, harnessing the 'no change, no growth' ethos that allows us to continue supporting our ever-evolving customer base. The ATS business model (ABM) focuses on people first, then process and performance, with the customer always at the center of the conversation. We think about strategy and success, recognition and growth through adversity, quickly pivoting when something isn't working as it should. Being an affiliate of ATS gives us unprecedented access to multidisciplinary experts – both in and out of the lab – allowing us to grow in existing niches, as well as venture into and flourish in new applications.

It's the customer who ultimately benefits from this new direction, as enhancing internal quality and performance translates to product and process improvements, including better support and reduced lead times. Our customer support team has grown sevenfold, specializing in various applications and serving a global customer base. The COVID-19 pandemic also made us rethink our supply chain strategy, meaning we now have contingencies of critical components, more airtight contracts in place with vendors, and warehouses located in different locations worldwide. This means the customer receives more robust products and quicker turnaround times, as well as more documentation, quick start guides and manuals, which have all been recently updated to improve the user experience and help with compliance.

Building on solid foundations

Our continuous evolution has allowed us to rapidly progress into new fields. We've proven ourselves in lateral flow, and have now diversified into areas where miniaturization matters, listening to our customers and developing the tools that enable them to address the ever-shifting challenges facing humankind. We will continue to honor our founders' entrepreneurial and tenacious spirit in POC diagnostics, and be proud as a company that thrives in making tomorrow better than today.

Keeping Things Flowing from End to End

California-based DCN Dx began life as a consultancy service with a focus on lateral flow. The company has since evolved to offer end-to-end services – from assay development and validation to manufacturing and clinical research services – and relies on BioDot equipment for its deposition needs.

Dr Pat Vaughan, Chief Operating Officer at DCN Dx

DCN Dx, based in Carlsbad, USA, is a globally recognized provider of contract research, development and manufacturing (CRDMO) services for *in vitro* diagnostics. Spun out from BioDot in 2006, the company initially offered consultancy services focusing on the development of POC assays, particularly lateral flow. Since then, DCN Dx has expanded considerably, as Chief Operating Officer Dr Pat Vaughan explained: "The company's original emphasis was on lateral flow – plus some flow-through assays and ELISAs – but we have expanded our scope substantially over the years. Today, we are a fully fledged CRDMO, offering everything from assay development and manufacture to consumables and reader customization, as well as clinical trials for all types of *in vitro* diagnostics."

LFTs came to the fore in everyone's mind during the COVID-19 pandemic, leading to a surge of interest in POC testing formats for a wide range of indications. However, manufacturers looking to make the leap from laboratory testing to POC settings face a number of challenges. Pat continued: "An immunoassay based on ELISA technology, for example, will not necessarily transfer directly to a lateral flow format. It requires a great deal of expertise to achieve a smooth transition; you can't assume that it will simply work as intended. The antibodies and conjugates often need to be manipulated and optimized, and it might be necessary to experiment with different ways of striping and spraying to successfully print the assay onto a device. This is where our many combined years of experience are beneficial, helping to accelerate development and time to market."

> "We use BioDot equipment for all our deposition needs, and these systems are central to our services, from assay development right through to product manufacture."

"Our customers range from start-ups to established IVD companies, each with different requirements," said Pat. "Start-ups may prefer to use end-to-end services to get their first assay to market as quickly as possible without major investment in infrastructure, while longer-standing companies may have some capacity themselves, and just need support for one aspect of their assay development. We can therefore act in varying capacities: as an extension of an in-house R&D team to speed up development of an assay, as an independent party to undertake validation studies, or as a solutions provider that can scale up a manufacturing process to high throughput at either our own or the customer's facility. We might also be involved in refining an assay prior to high throughput production, and offer full clinical research services, with extensive experience in obtaining regulatory approval for a wide range of diagnostic assays, from simple POC tests to laboratory instrument-based applications."

"We use BioDot equipment for all our deposition needs, and these systems are central to our services, from assay development right through to product manufacture. We have seven benchtop XYZ Dispense Systems – including the XYZ3210 and XYZ3060™ platforms – that we use for striping and spraying on a small scale, as well as two large RR120™ reel-to-reel deposition systems for high throughput production. This enables us to scale up processes efficiently, and gives us enormous capacity for high quality product manufacturing. A key advantage of the BioDot instruments is that the core components – FrontLine™ technology, pumps and spray heads – on the benchtop XYZ Dispense Systems are the same as those on the reel-to-reel systems, making the technology transfer from development to manufacturing much easier. This gives us the reassurance that an assay produced on the lab bench platforms will perform predictably when transferring to high throughput production."

Chief Revenue Officer Mitzi Rettinger added: "Alongside our CRDMO services, we offer hands-on lateral flow training for people wanting to set up their own lab or develop assays in house. Essentially, we teach people how to develop an assay. A basic course will include examples, but sometimes an organization will have a specific assay in mind, but not know how to develop it. We start with the basic chemistry, then teach them how to stripe and spray on a BioDot instrument, so that they gain practical experience. When they go back to their own lab and need to invest in equipment, they tend to replicate what they've learned during training."

Science doesn't stand still though, and it has been important for DCN Dx to continue to innovate. Pat commented: "We are routinely applying our experience to multiplexed assays, using the BioDot equipment to stripe multiple test lines per strip. The challenge here is to ensure that the assays are compatible with each other, so that you still have optimal sensitivity and specificity for each one. The same formulation must be used for each assay, they must work individually initially and eventually all together with no cross-reaction, and the dynamic ranges must be compatible. If the assays are not fully compatible and cannot be applied to the same test strip, we look for ways around this. For example, we might design a sample handling cassette to accommodate two test strips side by side, with a shared sample port. We have also developed a lateral flow reader, the miniDxR, that can be customized to a specific assay to deliver a quantitative result and, importantly, removes the subjectivity of interpreting results. The reader can even be integrated with a hospital LIMS to provide a permanent record of the result."

> "Technology continues to move forward, with improvements in sensitivity and increasingly complex assays being introduced into POC devices."

Lateral flow has come a long way since the introduction of the first pregnancy tests, and it's important to keep up to date with the latest developments. To this end, DCN Dx hosts the annual Advanced Lateral Flow Conference, a BioDot-sponsored global event for assay developers, manufacturers and others working in the sector to learn about the latest developments in the field. "Technology continues to move forward, with improvements in sensitivity and increasingly complex assays being introduced into POC devices. The way that science changes is really impressive, and it is enabling us to do more and more," Mitzi concluded.

To find out more about BioDot, visit **www.biodot.com**

To discover more about DCN Dx, go to **www.dcndx.com**

Partners in Quality:
Supporting 20 Years of Point-of-Care Test Manufacturing

Lateral flow testing is increasingly being used in POC settings to provide rapid results and increase access to diagnostics, particularly in remote locations and low income countries. The fundamental immunochemistries underpinning these assays are well established and understood, but cost-effective manufacturing of reliable and robust tests to a specific price point can be challenging. As a result, many providers turn to contract development and manufacturing organizations (CDMOs) for the large-scale production of lateral flow kits. IVD Research, Inc. has been manufacturing LFTs for POC applications for over 20 years, and relies on benchtop and inline dispensers and laminators from BioDot to meets its customers varied needs.

IVD Research is a CDMO based in Carlsbad, California, specializing in the development and production of LFTs for a wide range of screening and diagnostic applications. Founded in 1996 alongside sister company SafePath® Laboratories, LLC – which caters to the veterinary diagnostics market – this family-run business has grown into a global supplier of high quality immunoassay products, with a strong track record in both ELISA and lateral flow formats. Chief Operating Officer Chris Lambillotte explained: "IVD Research and SafePath were originally created with the aim of developing new, high quality ELISA formats for a variety of human and veterinary diagnostic applications. I joined the company in 2001 and, not long after, we used our understanding of immunoassay technologies to expand into the production of LFTs for POC applications. We currently manufacture a range of assays focusing on rare diseases, waterborne infections and neglected tropical diseases – as well as having an established portfolio of fertility tests – but, as a CDMO, we can produce LFTs for whatever indication a client needs."

Lateral flow approaches offer a number of benefits for POC settings, as Denise Glascock, Director of Business Development, outlined: "Lateral flow testing has been around for decades, and has always been popular for the speed at which you can get an actionable result, but the COVID-19 pandemic has really brought the format to the attention of the general public. ELISA testing is great if you're in a lab running 50, 100 or 1,000 tests at a time, but lateral flow can be used in a doctor's office, rural clinic or a patient's own home to provide a result in as little as 10 minutes. For example, women can use the fertility tests we manufacture – in combination with a mobile phone app – to get an accurate reading of their hormone cycles in almost real time, avoiding the need to go to a lab or clinic and wait several hours for their results. This ease of use is crucial in low resource settings, particularly in low- and middle-income countries with patchy healthcare provision. It allows testing to be performed there and then, enabling better informed, more immediate treatment decisions."

Quality is a central tenet of the company ethos, and IVD Research is an ISO 13485 certified facility and FDA Registered Manufacturer operating under cGMP guidelines. Chris continued: "As sister companies, IVD Research and SafePath Laboratories are housed under the same roof, but we manufacture every test we make according to ISO 13485 and FDA regulations, regardless of the intended application. We take pride in upholding this standard as, even though our name may not be on the final product, we want to support our partners in achieving their goals by producing the very best quality assays on their behalf. The equipment we use in our manufacturing processes is a key part of that quality standard, and we have been working with BioDot since we began manufacturing LFTs. We now have both benchtop and inline dispensers and laminators from BioDot, and this not only ensures reliable and reproducible production at the bench scale, but also allows an easy transition to high volume production without the need to reoptimize workflows or reagents."

Denise commented: "The BioDot brand has made a real mark in the industry, as it was basically the first company offering products specifically designed for lateral flow manufacturing and, in our experience, its machines have remained the first and foremost devices capable of reliably performing this type of work. I come from a background in high throughput, high-end manufacturing – working with large kit providers in India and across Asia – and all these companies use BioDot equipment. The company's strong reputation means that, when talking to customers, the fact that we use BioDot equipment is actually a strong selling point for us."

"The concept behind lateral flow testing may be well established, but the industry hasn't been standing still," Chris added. "BioDot has been very supportive as we've developed our capabilities and product offerings over the last two decades, and we have a good working relationship with the company, especially as it's based only an hour away. For example, when we first introduced our inline dispensers, the team worked closely with us to ensure that the production process for our four line multiplex tests – which are quite complex, with a lot of different layers printed on a single card – would seamlessly transfer from the bench scale. This required one of the largest BioDot laminators ever built, and we're scientists here at IVD Research – not engineers – so we were dependent on the BioDot team to design a system that could meet our needs. We are also working with BioDot on developing immunoassay arrays based on dots instead of strips, which is technically complex, but would allow numerous analytes to be tested in a single cartridge from a small sample. This approach would be particularly beneficial in rural communities and countries with limited healthcare provision, cutting the cost of diagnostics and simplifying the care pathway for those who need it most."

> "The BioDot brand has made a real mark in the industry, as it was basically the first company offering products specifically designed for lateral flow manufacturing."

To find out more about BioDot, visit **www.biodot.com**

Read more about IVD Research at **www.ivdresearch.com**

Bringing Flexibility and Scalability to Enzymatic DNA Synthesis

Gene editing and protein engineering technologies are rapidly evolving, with the potential to substantially improve patient outcomes across a wide range of medical conditions. The provision of accurate and long DNA for R&D is crucial to move these technologies forward, and Molecular Assemblies, Inc. – a leader in enzymatic DNA synthesis – is combining BioDot instrumentation with its own proprietary enzymatic synthesis technology to manufacture high quality oligonucleotides precisely for this purpose at a commercial scale.

Molecular Assemblies is a pioneering biotechnology company based in San Diego, California, USA, which produces custom oligonucleotides and genes. Founded in 2013, the company specializes in novel methods of DNA synthesis for applications such as protein engineering, CRISPR gene editing, molecular cloning and gene assembly, as well as other applications outside medical fields that also require synthetic DNA. As such, Molecular Assemblies has developed the first Fully Enzymatic Synthesis™ (FES™) technology for synthetic DNA production. The company's enzymatic approach allows the production of the longest and most complex DNA sequences, which is not feasible with most current methods, and is more efficient compared with traditional chemical methods, allowing the rapid delivery of DNA to speed up R&D cycles for its customers.

A key requirement for Molecular Assemblies when developing its FES commercial platform was flexibility, as Phil Paik, Chief Technology Officer, explained: "When we started to think about the development of our platform, we had clear intentions for the type of architecture it should have. BioDot really came to the surface for us because its technology is focused on nanoliter-scale microfluidics but also gives us the flexibility to seamlessly dispense all the way up to microliters with minimal reprogramming. This was essential for our customers, because different applications have different input DNA requirements. For example, customers in the protein engineering space or assembling genes require very little input, femtomoles or less, while those who are working in areas such as CRISPR require at least an order of magnitude more. We wanted a system that could cope with a wide range of volumes, but was also small, compact and modular. The dispensing technology and available deck space on the BioDot instrument meet those needs. For example, our thermal, evacuation and mixing module – which dictates throughput – is small enough to fit up to three onto the deck, allowing us to scale production up and down as required."

The rapid development timeline for the FES technology platform was a challenge, as Phil described: "As a start-up company, we need to move fast and be nimble. Our target – from locking down the biochemistry to developing the commercial platform – was less than a year, and the partnership we developed with BioDot was an important factor in achieving this timeline. It was most definitely a real partnership; we engaged with BioDot's architects and engineers and developed the system in a very collaborative way. While the microfluidic delivery system was from BioDot, other aspects of the system were being worked on by our teams in house, so we needed that 'back and forth' working model to be in sync, and make sure that each party had the right requirements going forward. This is especially important for something that's being developed at such a rapid pace and, once the prototype instrument was built, it continued with our team going to the BioDot site and working together through the factory acceptance, performance and verification tests." The BioDot software was also integral to this: "The software architecture allowed our development engineers to modify recipes very quickly and easily, which was also a crucial feature that helped us to meet our deadline."

Unsurprisingly, reliability was a significant reason for choosing BioDot as a partner. Phil continued: "Reliability is of the utmost importance when synthesizing custom oligonucleotides, to ensure that the product has the correct sequence, purity and functional properties required for the intended applications. Precise microfluidic delivery is a core aspect of ensuring reliability, and we set very high and stringent requirements for this from the start. When you're printing thousands of oligos, your reliability needs to be far above 99 percent – a challenge for any instrumentation – and we're continually working with BioDot to improve this."

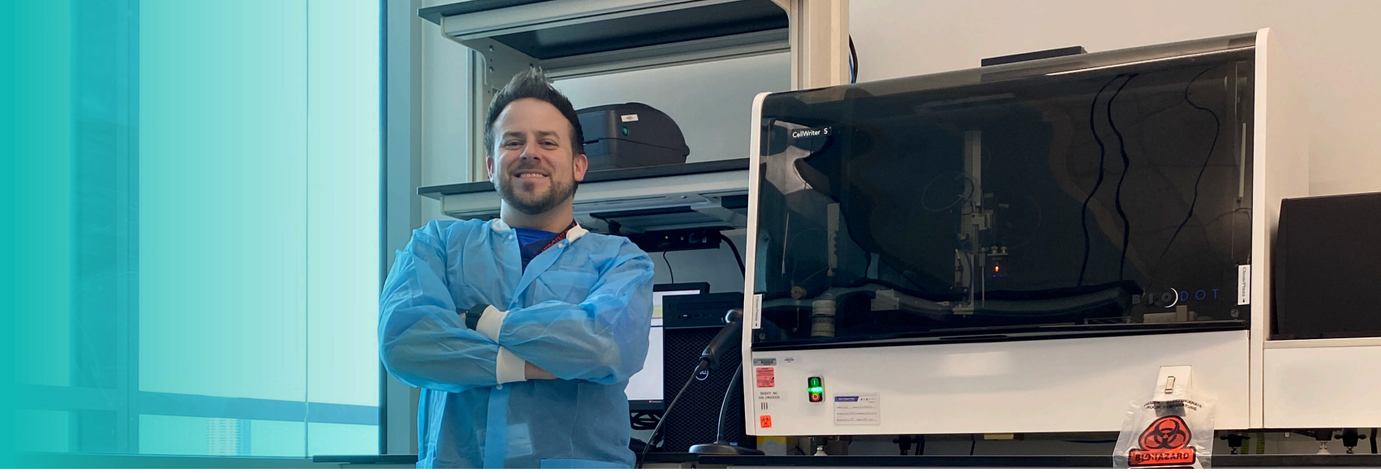
> "Our partnership continues to evolve, and this largely comes down to the BioDot team, which truly feels like an extension of our own team."

"Our partnership continues to evolve, and this largely comes down to the BioDot team, which truly feels like an extension of our own team. We have constant open access to development engineers, and talk freely about how we can continue to improve the platforms in the next iteration of instrument design. There is no friction or barrier there; the response time and availability of personnel – even just for brainstorming – is excellent. This is absolutely crucial, especially as we're trying to move very, very quickly and, of course, the state-of-the-art technology is a given part of that too," Phil concluded.

To find out more about BioDot, visit **www.biodot.com**

To discover more about Molecular Assemblies Ltd., go to **www.molecularassemblies.com**

FISH-ing for Chromosomal Anomalies in Cancer Diagnosis



Cytogenetics has become a crucial tool for identifying and monitoring changes in cancer cells. Unfortunately, the variability and inefficiency of manually dispensing cell suspensions onto slides can place enormous pressure on scientists, and cause delays for patients waiting for their diagnosis. The MD Anderson Cancer Center has introduced CellWriter S systems from BioDot to automate its chromosome metaphase analysis and fluorescence in situ *hybridization (FISH) processes, leading to better quality and a smoother workflow, as well as helping the lab to cope with greater demand.*

The MD Anderson Cancer Center in Texas is the top-rated cancer center in the US and, as such, faces a high demand for cytogenetic analysis of patient samples for the diagnosis and management of all types of cancer. Until 2020, the 50-strong cytogenetics team at MD Anderson relied on a rather cumbersome and inefficient semi-automated workflow for its routine sample analysis, as Andrew McCoy, laboratory supervisor of the department, explained: "When I joined the lab in 2019, there would be four to five people preparing around eight slides per patient sample, and we would need to stagger who could use our small slide-dropping instruments because we only had three. This took up a lot of staff time and required careful scheduling, especially during busier times of the week, when we could have an influx of anything up to 80-100 patients; we really had to plan out the whole day, from start to finish."

The team also found that the variation between users led to a lot of inconsistency with manual dispensing, and even slight environmental or handling factors – like the proximity to air conditioning, or the distance between the pipette tip and the slide – could make a significant difference to results. Similarly, judging cellularity by eye was very imprecise, as Andrew described: "We used to gauge cellularity by using the human eye to look at the turbidity of the sample, which is very variable, depending largely on the skill and experience of the staff members. We found that, if the cells were over-diluted, there might not be enough to analyze. Conversely, if they were crowded and overlapping, they were difficult to distinguish. In the worst cases, the analyst was sometimes unable to reach a clear diagnosis on a patient sample, and repeat slides would need to be prepared, delaying the time the results reached the pathologist and potentially affecting the timeliness of treatment plans."

> "We used to gauge cellularity by using the human eye to look at the turbidity of the sample, which is very variable, depending largely on the skill and experience of the staff members."

Andrew continued: "My priorities throughout my long career in cytogenetics have been to maximize time, improve workflows and standardize the quality of results across everyone in a lab who handles and processes patient samples, so I was happy to hear that the department was already looking at BioDot instruments for a better solution. In 2020, we introduced three CellWriter S dispensers: two for routine chromosome metaphase analysis, and one for bone marrow interphase FISH analysis. These robotic workstations automate the dropping process with nanoliter precision, and are also humidity- and temperature-controlled to minimize inter-operator variability. The CellWriter S allows us to use much smaller amounts of the cell suspension, spaced evenly and economically across the whole surface area of the slide, and it automatically calculates the cellularity of each cell suspension."

Two years after the initial implementation, the lab purchased two more CellWriter S workstations to handle the increase in demand that it saw immediately after the pandemic. The instruments have significantly reduced time-consuming manual work, allowing the scientists and technologists to focus on other important tasks within the department: "We can be doing other things in the wet lab, knowing that we can load up a CellWriter S, literally walk away from it for an hour, and come back to 12 processed patient samples," said Andrew. In addition, the efficiency of slide preparation has meant going from eight slides per patient down to just two, saving on the cost of consumables and reducing the time needed to analyze the slides. "Our five systems have helped to make analysis far more straightforward, which also speeds up the workflow. We're not dropping anywhere near as many slides, so there aren't so many to scan, and we can spend more time on the ones we do have, finding those cells that we want to analyze. It's definitely noticeable that we get a lot more cases to our pathologist within the first seven to 10 days than we used to."

> "We can be doing other things in the wet lab, knowing that we can load up a CellWriter S, literally walk away from it for an hour and come back to 12 processed patient samples."

The lab team has quickly adapted to the CellWriter S, and BioDot has been available to give support when it has been necessary. "The instruments are really easy to learn how to use, and there are two people located here in Houston, Texas, who we can call on – or helpful specialists at the end of the phone – with rapid attendance afterwards if required. We've had these instruments in our lab for four years now, and we really love them. They're just amazing for our workflow," Andrew concluded.

To find out more about BioDot, visit **www.biodot.com**

To discover more about the MD Anderson Cancer Center, go to **www.mdanderson.org**

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