14TH ANNUAL

BIOMARKERS

CONGRESS

Pre-Event Newsletter Jan 2019

MANCHESTER CENTRAL

21 - 22 FEBRUARY 2019 | MANCHESTER, UK

OXFORD GLOBAL CONFERENCES

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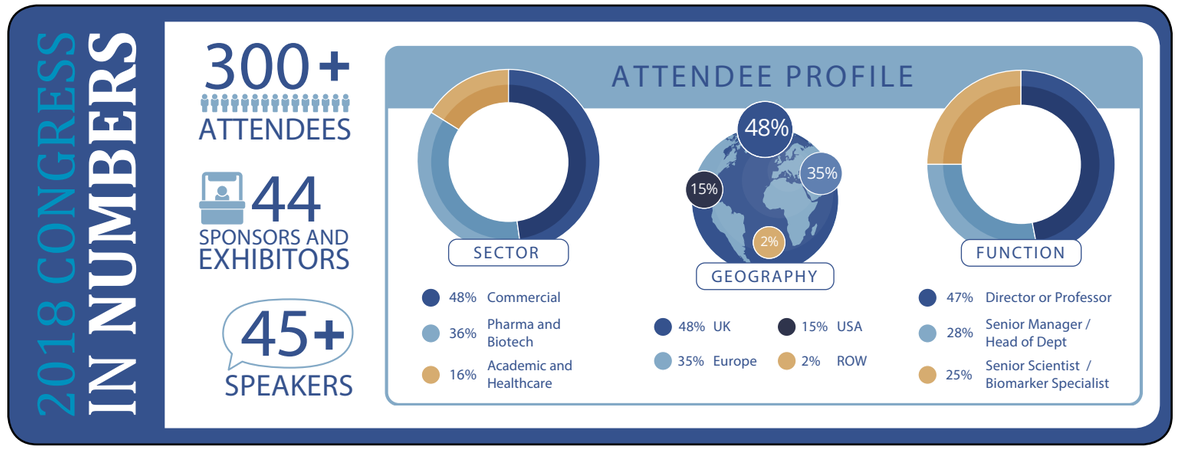


WELCOME TO OXFORD GLOBAL'S ANNUAL BIOMARKERS UK CONGRESS PRE-EVENT NEWSLETTER!

With the 14th Biomarkers Congress taking place in February 2019 in Manchester, I am delighted to look back at some of the highlights of the 2018 event and provide some details on a few of the key features & exciting additions for the 2019 congress.

The 2018 congress brought together over 300 attendees in Manchester to discover collaborative solutions to biomarker discovery & development challenges and discuss the latest developments in innovative biology & genomic markers.

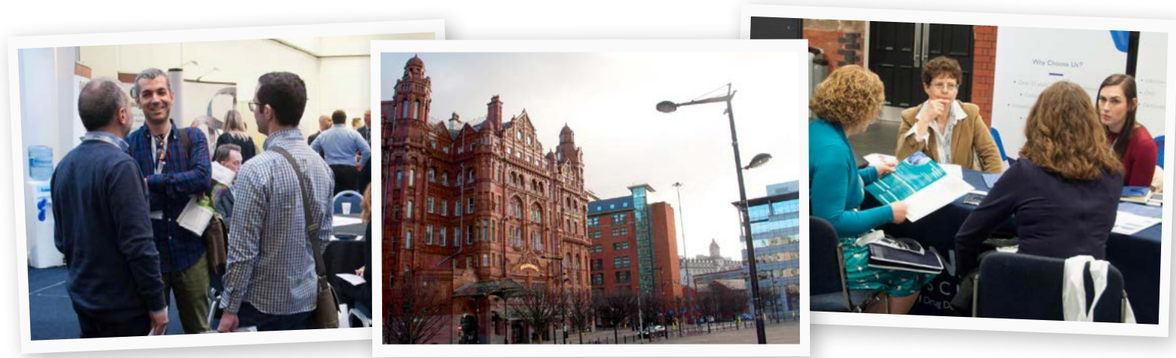
Alongside the exciting talks and extensive networking opportunities, 2018 saw the launch of the breakfast roundtables, with attendees advising the opportunity to discuss key challenges and knowledge share with their peers was invaluable.

The 2019 event will feature 60+ presentations on key topics within Biomarkers In Drug Discovery & Development, Personalised Medicine, Precision Medicine & Companion Diagnostics, Innovations In Biomarker Research and Biomarkers In Clinical Development & Clinical Trials from industry leaders. 2019 will also see the introduction of a new stream discussing & tackling challenges in Biomarkers for early detection & prognosis and Digital Biomarkers.

Due to the popularity of the 2018 Breakfast Roundtables and Gala Dinner, these features will be returning in 2019. The Gala Dinner will be even bigger and better, offering attendees a chance to relax over a glass of wine and a sit down dinner, enjoying the company of their peers.

Read on for a range of interesting interviews and insights with some of 2018's industry-leading speakers and participating sponsors, and I look forward to welcoming you to the 2019 Congress in February

- Hayley Watson, Portfolio Director



14TH ANNUAL BIOMARKERS CONGRESS

MANCHESTER CENTRAL

21 - 22 FEBRUARY 2019 | MANCHESTER, UK

WHO IS ATTENDING?

For the full attendee list please contact
marketing@oxfordglobal.co.uk

- **350+ senior level delegates** from leading pharmaceutical, biotechnology, diagnostics, CRO and solution provider companies.
- **Directors, VPs, CEOs and Heads** of biomarker identification & development, translational medicine, precision medicine, companion diganostics and biomarker safety.
- **Highly esteemed members** of academic institutions.

These companies and many more:

abbvie · AstraZeneca · AMGEN · janssen · Bristol-Myers Squibb · Celgene · ucb · Biogen · BAYER · gsk · SANOFI GENZYME · Genentech A Member of the Roche Group · NOVARTIS · Boehringer Ingelheim · MedImmune

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NETWORK AND PROGRAMME

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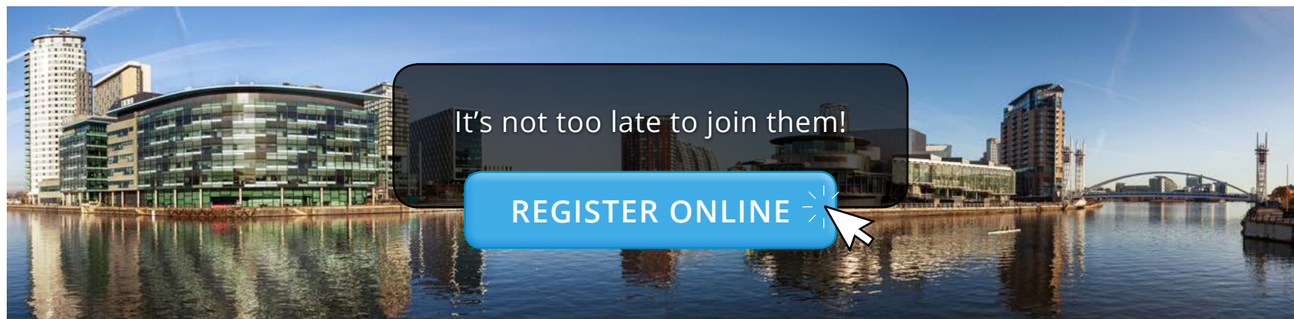


2019 is Going to be an Exciting Time for Genomic Medicine

The UK is very committed to using genomic medicine to offer patients improvements in the diagnosis of their disease and to provide treatments that are more effective. The 100,000 Genome project has successfully whole genome sequenced patients with rare diseases and cancers. Many of these patients had no diagnosis so were very difficult to treat, however, comparing the patient's genomic data with that of their immediate family provided an insight into the molecular basis of their condition and identified family members at high risk of disease. The data collected during this project held in a central repository is an invaluable resource for both academic and industry scientists to access through Genomics England Clinical Interpretation Partnerships (GeCIP) to develop novel drugs and treatments of the future. Following on from this project the National Health Service (NHS) is launching the Genomic Medicine Service In March 2019 to screen patients for known genetic variants that both cause disease and affect the choice of drug to treat disease.

To deliver genomic medicine to patients in the clinic requires collaborative support from across academic, clinical, industrial and regulatory organisations, plus support from patients. For example, academic and industrial innovators are working together to continually improve sequencing technologies and develop novel diagnostic genetic tests. Multidisciplinary partners are developing artificial Intelligence (AI) programmes that handle the big data generated, and deliver it in a format to enable clinicians use the patient's genomic information to improve healthcare. Entrepreneurs' support for innovators is essential to move new technologies and novel diagnostics for use in the clinic forward.

Professor Sir Munir Pirmohamed founded the UK Pharmacogenetics and Stratified Medicine Network in 2010 to develop collaborative partnerships across all sectors to support the delivery of personalised genomic medicine to patients in the clinic. Since 2014, the Network has attracted ~1,000 members from across all disciplines and is currently collaborating with similar international organisations to develop a global consortium. The Network website http://www.uk-pgx-stratmed.co.uk/ attracts global interest, as it is a valuable resource for news on all the latest developments in the field, events taking place, details of funding and educational opportunities. Membership of the Network is free and provides the opportunity for individuals to advertise their expertise and develop cross-sector research partnerships through the web-based collaborators database. The Network brings together major academic institutions, large Pharma, SMEs and government organisations NHS, National Institute Health Research-Clinical Research Network (NIHR-CRN), Academic Health Science Network (AHSN), Innovate UK, Medicines and Healthcare products Regulatory Agency (MHRA) and National Institute for Health and Care Excellence. A steering committee made up of thought leaders from Association of the British Pharmaceutical Industry, British in Vitro Diagnostics Association, Department of Health, Genomics England, Innovate UK, NHS, large pharma and academic institutions support the activities of the Network. The Network is a not-for-profit organisation that relies on donations for financial support.

Changing the practice of medicine from basing a diagnosis on the signs and symptoms of disease to using genomics to offer patients a more precise diagnosis and treatment is not without it challenges.

UK Pharmacogenetics & Stratified Medicine Network

The Network identifies the challenges and brings thought leaders from across all sectors together in focused workshops to provide solutions to overcome the challenges. The workshops have defined drug response for stratified medicine, reviewed patient engagement and the development of biobanks, and debated health economics of personalised medicine. The Network has partnered with government organisations to investigate NIHR-CRN role in promoting clinical trials, supported MHRA develop genomic diagnostic testing regulations, debated how to introduce genomics into NHS clinical practice, reviewed how to encourage entrepreneurs and innovators to develop new technologies required, and the educational support primary care require to introduce genomic medicine into primary care. Presentations from these workshops, and publications on the findings, are all available on our website.

In March every year, the Network holds an Annual Open Meeting. The quality of speakers attracts ~250 delegates from across all sectors to attend, providing excellent opportunities to meet colleagues from different backgrounds and develop multidisciplinary research partnerships. The excellent talks on the latest topics presented by experts at the meeting are available on our website. At this year's meeting, on 6th March at the Royal College of Physicians London, there will be presentations on implementing pharmacogenomics in paediatrics / rare disease and in the role of membrane transporters in regulating drug disposition / distribution, value of biobanks and electronic health records to precision medicine, and how partnerships with pharmaceutical companies accelerate pioneer treatments. Experts in AI will show how the advances in health informatics are offering personalised medicine treatment, and how AI in radiology / pathology is improving the diagnosis of disease. A patient will give an account of their experience of personalised medicine and details of NHS Genomic Medicine Service announced. Registration for the event is via the Network website, and there are opportunities to exhibit the expertise of your organisation.

Using genomic data to diagnose disease and pharmacogenomics (study of drug-gene interactions) to offer patients optimised treatments is the basis of offering personalised medicine in the clinic. Personalised medicine, also described as stratified or precision medicine, delivers patients the most effective treatment, at the correct dose in combination with other medications, at the start of their treatment. Personalised genomic medicine optimises drug efficacy and improves drug safety by identifying patients likely to experience adverse drug reactions, which are often life threatening. Furthermore, genomic medicine predicts disease risks and allows clinicians to offer the patients most at risk of disease monitoring, changes in lifestyle to minimise the risk or preventative treatment to reduce the risk or impact of disease. The Pharmacogenetics and Stratified Medicine Network is proud to be supporting the development of personalised genomic medicine. Contact Christine at cjmcn@liv.ac.uk or visit www.uk-pgx-stratmed.co.uk for more information.

PRESENTATION PREVIEW FROM **LAUREN STEVENSON**

Lauren Stevenson,
Senior Director & Head,
Development Biomarkers and
Bioanalytical Sciences,
Biogen

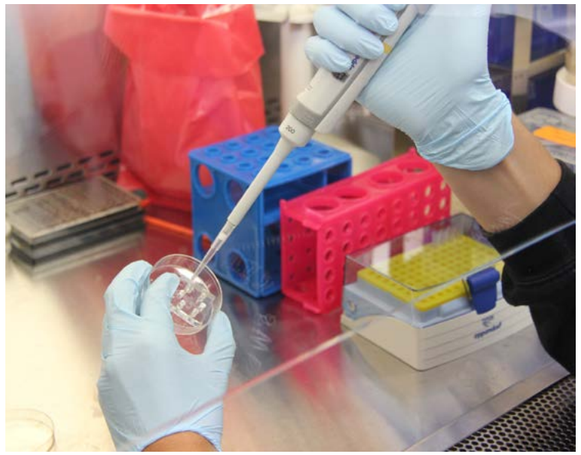
Lauren received her BA and MA in Biology from Boston University and earned her Ph.D. in Biomedical Sciences from Harvard University in 2001. Following a postdoctoral fellowship in molecular oncology at the University of Dundee, Scotland, she joined Biogen in 2006 where she has leveraged her 20+ years' experience in molecular biology, biochemistry, cell-based and ligand-binding assay development to lead a team of talented scientists, setting bioanalytical and biomarker strategies and developing PK, immunogenicity and biomarker assays in support of programs at all stages of development, from discovery to post-marketing.

The title of my talk is "**Perspective and Recommendations for Biomarker Assays in Drug Development**".

The real driver behind this talk is that every time we come to different forums and we talk about the analytical validation for the qualification of biomarkers, inevitably the questions that arise tend to be in the form of "but what does this mean for me every day? What about the biomarker assays that I am developing for my drug development programs for exploratory purposes? You've explained to us that the evidentiary criteria papers are really for biomarkers for the highest level of qualification, and we feel like we don't necessarily have clarity about what we should do the rest of the time." So, this is what this talk is really supposed to address.

I will start with a bit of a disclaimer up front that this talk is probably not going to provide you with as many answers as you may like. Instead, I think it may provoke some thought. We really end up framing it internally at Biogen within my team more in this way, which is, "So you want to be a biomarker scientist?" This talk is about framing what it takes to be a biomarker scientist and what biomarkers demand of us as scientists.

You will be glad to hear however, that I am going to start with recommendations. There are three simple recommendations that we're going to review over the course of this talk. These recommendations are applicable whether or not formal guidance is available.



The first one is kind of obvious. It is, "be a scientist". That may seem a bit simplified to you, but I will expand upon that later in the presentation. The second recommendation is, "embrace and own fit for purpose". I think that I've seen a lot of discomfort with people really embracing fit for purpose. They're looking for rules, as opposed to just figuring out what is the right thing to do. I also think that fit for purpose has gotten a bit of a bad rap in that it's been associated with "you're not going to do everything you should do". But in fact, fit for purpose really does mean "do good science". And I'll talk quite a bit about that later.

And the last piece is tied to fit for purpose, and that is, "demand your context of use". Always start with the question 'why'. We get bombarded with requests to develop biomarker assays and the first question we always ask is, 'why'? Why do you need this assay? What is it you need to learn? How do you need to use your biomarker? All of that is to understand context of use, because if you don't have context of use, then how can you develop an assay that's fit for its purpose? ■

Lauren Stevenson will be presenting *'Perspective and Recommendations for Biomarker Assays in Drug Development'* on Day One of the 14th Annual Biomarkers Congress, as part of a special extended workshop: *'Scientific And Regulatory Considerations For The Analytical Validation Of Assays For The Qualification Of Biomarkers'*

SPEAKER INSIGHT FROM **JOHN SMERAGLIA**

John Smeraglia,
Senior Director,
Bioanalytic Sciences,
UCB Pharma

John is Senior Director of Bioanalytical Sciences in Non-Clinical Development at UCB with laboratories in the UK and Belgium. He has responsibilities for bioanalytical sciences to enhance and revolutionise the way that the quantitative bioanalysis and biomarker assays are performed from pre-clinical development to post marketing for NBE's and NCE's. He is also responsible for providing bioanalytical leadership for the quantification of mechanistic biochemical biomarkers to advance drug development. John has held bioanalytical leadership positions in the US and EU with innovator drug development companies and CROs. Achieving his first degree in Medical Technology (B.Sc.) and his second degree in Biomedical Sciences (M.Sc.). His has developed his experience in bioanalytical sciences for the last 26 years.

What issues faced the biomarkers industry in 2017?

Recently there has been a big push by the agencies around the c-path initiative and what is required to develop and validate biomarker assays. I think that's a key element to how we think about these assays and how we link them to clinical efficacy and clinical utility, so we truly understand both the context of use and how the analytical tools will be able to match up closely to that context of use.

So, the focus has been very much on that in 2017, effectively responding to the regulatory agency and their expectations, to ensure that the analytical tools link very closely to the clinical development paradigm and ultimately getting out biomarkers that are appropriate for disease modification and disease progression.

What will be the biggest technology impact for 2018?

In the area that I work in, which is targeted protein quantitation, there are a couple of key developments that have come through. One is on the utility of mass spectrometry in targeted protein quantitation and effectively it's a progression of the technology, specifically to look at low-abundance proteins and using tools such as nanoflow LC along with antibody capture techniques. One of the challenges is to do with how fast that's moving in the pharma industry. Secondly, I'd say the advancement of low-abundance immune-analytical tools and there are a range of platforms that focus on very low-level sensitivities.

Why did you choose to work within this industry?

I think this industry really links up the interests I have in analytical technology, but then also linking that up closely to what it means from a patient value perspective and when you then develop clinical designs and clinical strategies, along with biomarker strategies that truly help us to either aid our knowledge about disease progression or disease modification, that's where the interest lies for me.

What inspires you within your current role?

Currently, we are merging a lot of the clinical development strategies with analytical tools and therefore, working with our clinical staff to understand what the actual context of use is, to help develop the analytical tools to get to more appropriate markers and characterisation of disease. I think that's what inspires me, the link between analytics and what patient value really looks like ■

This interview is an excerpt from our Speaker Insight videos, in which experts at our events answer questions on the state of the industry. Follow the link below to hear from:

- Claire Huguet, Head of Biomarkers, Randox
- John Allinson, Vice President, Biomarker Services, Biologics Development Services
- David Henderson, Director - Statistical Genetics, Axio Reach
- Oliver Poetz, Head of Protein Analytics, University of Tuebingen
- Erik Bennink, Key Account Manager, Luminex
- Daniel Garcia West, Biomarker & Protein Specialist, Merck
- Ben Chaffey, Scientific Business Development Manager, Newgene

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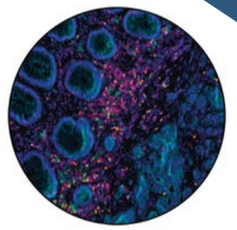

Histalim is a service provider company in histology, immunohistochemistry (IHC), in situ hybridization (ISH), and image analysis. Our laboratory located in Montpellier was founded in 2005. This positioning shows our willingness to meet the increasing demand to design, develop, and validate protocols based on standard and/or innovative techniques.

Our specialized services take part in research and development projects for pharmaceutic products, medical devices, and diagnostic tools… and in other areas like dermo-cosmetic, ecotoxicity, food industry… We are particularly engaged in the development of new therapies in the fields of oncology and chronic diseases i.e. therapeutic antibody, and new generation diagnostic tools i.e. circulating biomarkers. Histalim positions its strategic growth specifically in the development of therapeutic antibodies issues.

Our activities are conformed to Good Laboratory Practices (GLP) and our laboratory is authorized to perform studies with human tissue samples. Histalim can also offer to perform in-house research and development projects. This particularity allows us to provide some customized services to our customers, with innovative technologies.
Therefore we can provide a large range of expert services like Tissue Cross Reactivity (TCR) studies, Tissue MicroArray (TMA), and Fluorescent ISH (FISH)…

CERBA

5.4000
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250.000
Patients per day

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Laboratoires

OUR MISSION

Image analysis, immunohistochemistry and molecular biology techniques have never brought as much innovation and possibilities as they do today for the study of tissues and cells.
Histology, which was until now a method of identification of lesions or cancer, now offers us a range of opportunities for life sciences, allowing both the study of structure and integrity and the spatial organization of tissues and cells.

In recent years, the nature of the results produced by histological methods has increased progressively from qualitative to semi-quantitative then to quantitative methods. Due to the changes occurring in this discipline, it is now necessary to ensure the reliability of results, to adopt working methods within the meteorology laboratory, where to date the only evidence by the image was satisfactory.
The more an innovative method provides a precisely formulated result, the more the risk of errors intensifies. This implies that specific provisions have to be made for the production of reliable results.

Histalim is clearly positioned in this field, integrating new methods concerning histology and re-designing them so that they fit the strictest quality charts. As a result, we offer to our customers a quality of service that might satisfy the most demanding of them… And we believe that only this requirement will allow them to succeed (Jean-Philippe COTON – CEO of Histalim)

SINCE 2018 : A BRANCH OF CERBA Healthcare

CERBA HealthCare an international medical biology group acquires HISTALIM in January 2018, of which it becomes a subsidiary.

Cerba HealthCare is a European leader in clinical pathology ranging from first intention to highly specialized tests including central laboratory facilities for clinical trials.

CERBA HealthCare had also acquired BARC Global Central Lab in 2007. BARC LAB provides the pharmaceutical and biotech industry with central lab services in routine and specialized testing in a wide range of fields including Oncology, immuno-oncology, hematology, virology, microbiology, clinical pathology, genetics…

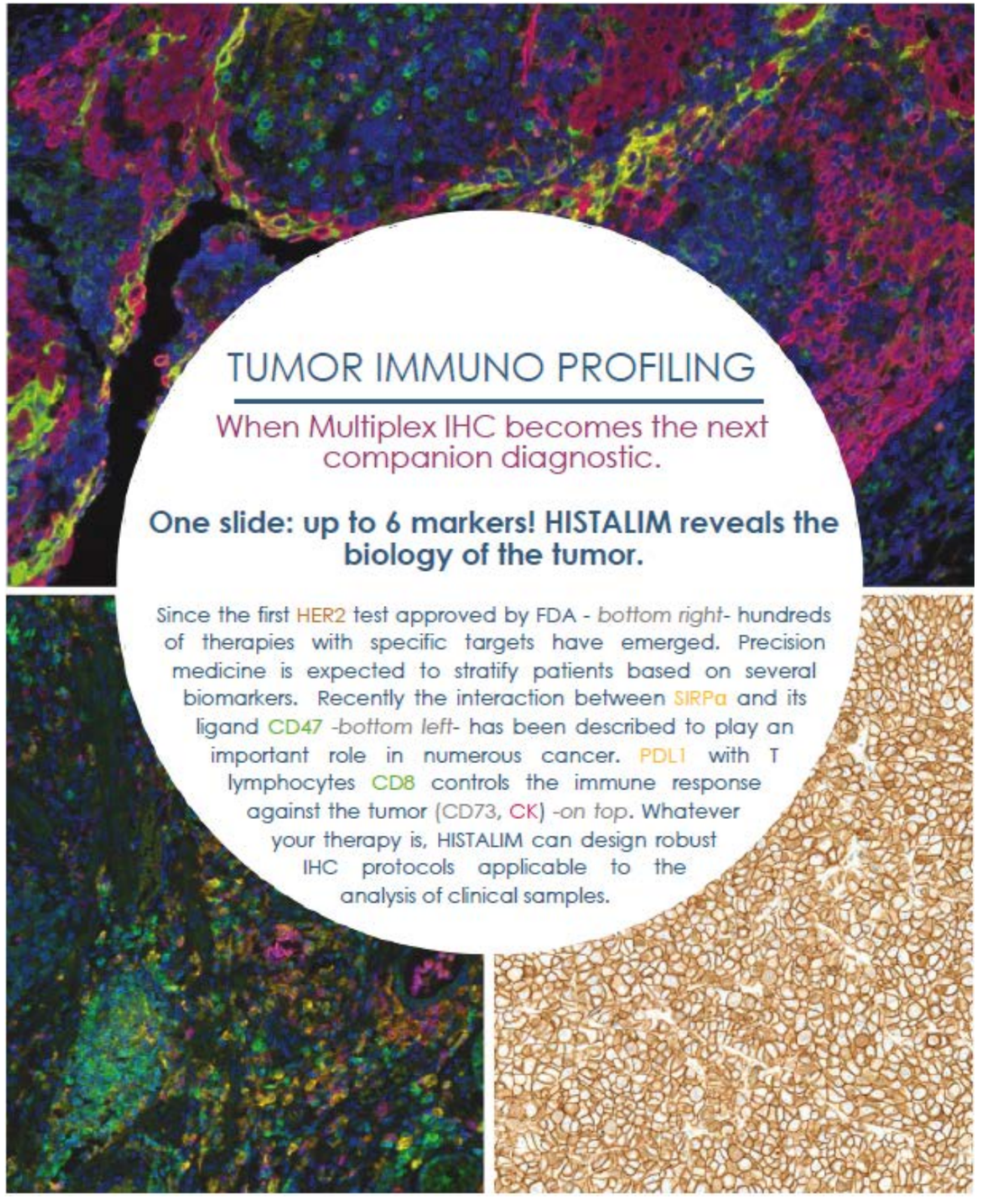
As Histalim's strategic development progressed, it became clear that the work developed for our clients led us to become more and more involved in clinical trials. For its part, CERBA healthcare has gone the other way, supporting customers who increasingly need an upstream technological lead and to anticipate tomorrow's biomarkers. It therefore seemed only natural that we should join the CERBA Healthcare group which gives us the opportunity to:

· be involved in a large number of clinical trials in Europe, United States (biotech companies and large pharmaceutical companies),
· Access to all services developed by the group with strong international recognition,
· Access to impressive logistics and exceptional analytical capacity.
· Strengthen our mutual commercial offers
· Access to new markets and new customers
· Acceleration of Corporate and Group Development

For BARC and CERBA Healthcare, HISTALIM offers strong expertise in the fields of Histology, Immunohistochemistry (IHC), In-Situ Hybridation (ISH), Tissue Cross Reactivity (TCR), Tissue Micro Array (TMA), Biomarkers, Companion Diagnostic (CDx), Biobanking, …

Cerba Research

HISTALIM



CSO VIEWPOINT: **STEVE ANDERSON**

Steve Anderson
Senior VP and
Chief Scientific Officer,
Covance, Inc.

Significant advances have been made in the identification and utilization of biomarkers to guide clinical development of new therapies. Most pharmaceutical trials today are biomarker-driven. Drug developers recognize that incorporating a predictive biomarker into trial design results in about a threefold greater likelihood of success advancing from early stage trials to approval of the therapy.

Biomarkers may be exploratory in nature, or they can be used to stratify patient populations, or be used as an inclusion or selection criteria in specific trials. Biomarkers might be genomic or proteomic in nature, ranging from tissue-based biomarkers in oncology to soluble biomarkers in neuro-degenerative disease, like Alzheimer's disease.

Biopharma companies are moving away from simpler SNP analysis to identify more complex genetic alterations such as gene amplification and deletions that have implications on disease progression and drug resistance. Similarly, in proteomics, interest is shifting from single proteins / receptor immunohistochemistry (IHC) to next generation IHC using multiple tags to look at post-translational modifications. Metabolic technologies are gaining traction, particularly in immuno-oncology where the microbiome may have a major influence on disease progression and metabolites may act as surrogate biomarkers.

In oncology today, many drugs have received accelerated or breakthrough therapy designation; and the registration of trials that have been traditionally a Phase 2 trial, so we're seeing approvals based on smaller populations, and then often a commitment to do a follow-on trial. By selecting the population using a specific biomarker, you're actually potentially decreasing the population size that would be needed to power your trial. Moreover, not all patients respond to immuno-oncology drugs, but there's a series of biomarkers like deficiencies in mismatch repair, micro satellite instability or tumor mutation burden, that will potentially help differentiate and be more directive in a personalized approach in a tumor-agnostic fashion.

The trend in biomarker assays is increasingly less invasive, from traditional tissue biopsy approaches to today's liquid biopsy and circulating tumor cell applications – requiring smaller patient samples and sample sizes, enabling serial sampling for early detection, disease monitoring and drug resistance, and in some cases, are less costly to run. At the same time, we're seeing a paradigm shift from one assay / one drug to multi-analyte assays / multiple drugs, such as multiple gene mutations as measured by NGS. These new technologies and assay validation studies have been more complex for both test developers and the FDA but they hold great promise.

Taken together, advances in technology and biomarker identification help to provide a better categorization of disease and a more targeted approach to therapy, to achieve better patient outcomes.

COMPANION DIAGNOSTICS

The clinical and financial implications of utilizing biomarkers are profound – demanding a deep knowledge of disease biology, relevant targets, a drug candidate's mechanism of action and the ability to determine the appropriateness of a companion diagnostic (CDx) co-development approach. In 2018 we observed the 20th anniversary of the first companion diagnostic, which coincided with the launch of Herceptin. Now there are more than 40 CDx available across some 25 therapies.

Companion diagnostics offer significant benefits and value, helping streamline clinical studies and enabling clinicians to identify patients most likely to respond to treatment (and thereby increase patient response rates), helping to avoid unwanted side effects and minimizing wastage in non-responsive patients. These are important tools for pharma companies to differentiate their medicines and facilitate access to them via favorable pricing and reimbursement.

At LabCorp / Covance, we view the path from exploratory biomarker to CDx as a continuum, rather than discrete, sequential steps. Regulatory considerations for what might ultimately become a CDx inform early stage trial design. Drug developers can't afford to get to the tail end of a long, expensive clinical development process only to learn that a key regulatory step is missing, delaying the launch and getting the Rx / Dx combination to the patients who need it.

Access to the CDx – simultaneous with drug launch – is essential. It needs to be on a platform that laboratories routinely use. Value and cost are important factors, as well as scientific and clinical evidence, for the uptake of the technology. Currently, in vitro diagnostic regulations, product requirements and quality management systems vary across Europe, North America and Asia-Pacific, but many regulators are working to align guidance and approval processes.

Precision medicine is both the present and the future of our approach to drug development. There will be an increasing appreciation for other types of biomarker assays that may not be predictive but still add value as complementary diagnostics, which help clinicians understand the potential benefits and/or risks to the patient of a given therapy. We are at the cusp of an entirely new cascade of biomarkers that will be useful in managing a patient's disease.

Q&A SESSION WITH MATTIAS BERQVIST

Mattias Berqvist,
VP Clinical Development,
Biovica International

Mattias Bergqvist is Vice President Clinical Development at Biovica and has over 20 years of experience from the pharmaceutical and biotechnology industry. He has global responsibility for clinical development programs focused on providing proliferation markers in the evaluation of novel oncology drugs. Mattias has authored a number of publications in peer-review journals and studies presented at global scientific conferences.

What are your biggest priorities in the biomarker field at the moment?

Our main objective is to contribute to better patient outcome and provide solid documentation demonstrating clinical value. All biomarkers need to be documented for valuable applications and the appropriate intended use for an unmet medical need. Hence our priorities lie on study collaborations with well renowned cancer institutes to document the DiviTum technology as a useful tool in evaluating early treatment efficacy in specific solid tumors. Focus is a biomarker for selecting and evaluating patients with hormone receptor positive metastatic breast cancer treated with standard therapy with or without the new cyclin dependent 4/6 inhibitors (CDK4/6) for optimal outcome.

Your talk at the event is on liquid biomarkers. How do you think liquid biomarkers will impact oncology drug development?

I believe every new technology that contributes to more effective drug development needs to be embraced in order to increase probability to be successful. Steps forward in the evaluation process of new compounds can lead to big results, maximize information for gate-keeper decisions and be the difference between approval or failure. A valuable liquid biomarker can contribute throughout the development continuum; provide candidate drug dose-response information, select appropriate tumor types & patients and translate early pre-clinical findings to potential clinical efficacy benefits.

What do you think the future will hold for biomarker assay development?

The use of liquid biomarkers will grow since they hold benefits for patient clinical use; they are more flexible and can provide important information during adjuvant therapy that tissue markers cannot. With knowledge building from banked material in many studies, information and the use of liquid biomarkers will increase and certainly new combinations of biomarkers with other risk factors will improve foundations for decision making when selecting and evaluating therapies. DNA-testing will be combined with other liquid techniques providing "decision panels" for better risk assessment and early therapy evaluation.

What are the main challenges researchers are facing in this field?

Developing new drugs is time consuming and requires a lot of resources. For Pharma it's important to gain information as early as possible in the development process on Mode of action effects, dose-response and preclinical data that can be translated into clinical value. The majority of drugs entering phase 3 fail - using biomarkers for patient selection and optimal evaluation can increase success rates to 50-60%. For companies developing biomarkers, access to, and the time it takes to access samples is a limiting factor. It is also important that small companies and new innovations are supported and financially endorsed (grants etc.) to develop and validate new products

What do you think are the most important technologies impacting biomarker research currently?

Since so many new candidate compounds target the cell cycle, biomarkers that can evaluate and match those drugs to patients will become increasingly important. Uncontrolled cell growth is a fundament for cancer and new available solutions can impact R&D. Technologies that provide patient-specific treatment information and new tools available to extract information from DNA-tests, matching mutations will assist in selecting optimal therapy. In the growing area of immunotherapy there are significant advances of treating cancer, but that also increase the need for biomarkers to select patients and evaluate therapies ■

Mattias Berqvist will be presenting on Day Two of the 14th Annual Biomarkers Congress with his talk *'Liquid Biomarkers In Oncology Drug Development And Clinical Validation'* in the stream Biomarkers In Clinical Development & Clinical Trials

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Application Note

Detection Of Anti-Drug Antibody (ADA) Using Single Molecule Counting (SMC™) Technology

Introduction to Immunogenicity

All biological therapeutics have the potential to induce an immune mediated response ranging from benign to severe adverse effects. These effects can encompass diminished clinical efficacy of the biotherapeutic being administered to hypersensitivity, allergic reaction or even cytokine storms.

Consequently, regulatory agencies are looking to understand the implications of immunogenicity and are directing the industry to integrate programs for immunogenicity risk management starting in early phase drug development in clinical and pre-clinical.

The Federal Drug Administration (FDA) and pharmaceutical experts in the area of immunogenicity testing have recently published guidelines for the design and optimization of immunoassays used in the detection of antibodies against biopharmaceutical drug products in patient samples in the absence of drug and more importantly, when drug is present. FDA recommends that screening and confirmatory IgG and IgM assays achieve a sensitivity of 100–500 ng/mL (FDA Guidance 2016).

The increased sensitivity recommended is based on the current state of the science observed in the FDA's filings as well as publicly available studies.

A more sensitive detection method may lead to earlier detection of a primary immune response or detection of IgG4 which the FDA can request on a case by case basis.

It has been seen that patients develop persistent ADA responses having levels lower than 100 ng/mL (AAPS Journal, Vol. 15, No. 1, January 2013).

Traditionally ELISAs or Electrochemiluminescence (ECL) have been used to identify the presence of anti-drug antibodies (ADA). Though effective for detection, ELISA

methods often fail to adequately measure specific antibody response in the presence of circulating protein therapeutic due to the limitation on sensitivity and problems presented on a plate-based format.

Multivalent IgM ADA binding to the antigen on a plate surface or in a microwell (spatial restriction) can prevent binding of the detecting reagent. This could lead to loss of early detection of the primary ADA response as IgM is the first isotype generated.

According to the FDA: 'ADA assays need to be sufficiently sensitive to detect low levels of ADA before the amount of ADA impact the PK, PD, safety, or efficacy.' The SMC™ technology offers a magnitude fold increase in sensitivity over current existing technologies.

Immunogenicity and SMC™ Technology

SMC™ technology enables the development of ADA assays by the labelling of the drug with capture & detection reagents, and utilization of buffer reagents to develop and optimize the assays. The technology allows the ability to develop a homogenous species-independent assay format that is simple, easy to design and validate. The reduced number of wash steps aids in the detection of low affinity antibodies and decreases assay time. This assay format is often referred to as a "bridging assay" since the ADA acts as a bridge between the drug labelled capture & detection.

SMC™ technology, employing the SMCxPRO™ high sensitivity instrument, uses digital counting for low level protein detection and offers several advantages with a unique platform design, in addition to specialized chemistry for enhanced specificity.

Controlling the SMCxPRO™ system is an integrated software package that is 21 CFR part II interface coupled with easy to use, flexible command and data interpretation functions.

By using a 642 nm laser focused 250 µm above the base of an Aurora plate, a rotating objective scans through the free-floating suspension exciting fluorochromes as they pass through the interrogation space.

A low noise Avalanche Photodiode (APD) counts individual photons as they are emitted. The focused interrogation space of acquisition reduces cross talk from well to well, flare from meniscus diffusion of light, as well as inherent interference from turbid solutions.

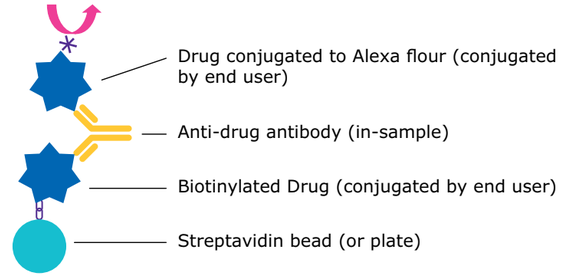


Figure 1. Bridging assay format for ADA detection in sample. immunocomplex Drug is Alexa and Biotin conjugated, and the is captured on a magnetic streptavidin bead.

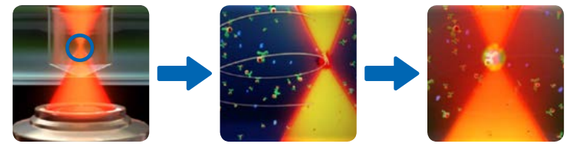
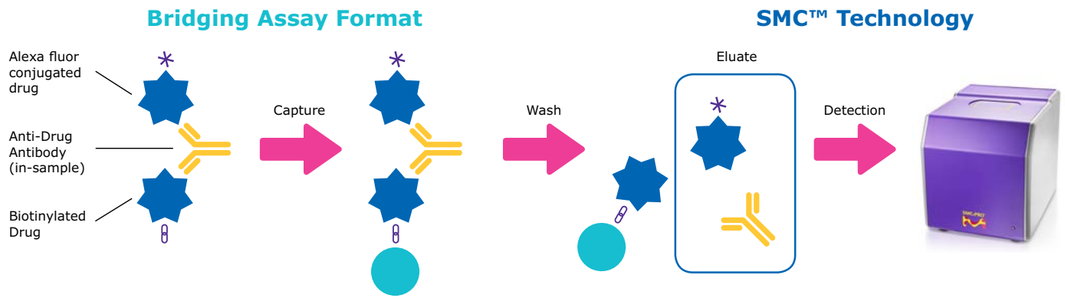


Figure 2. Counting of Alexa conjugated detection antibody as it traverses through interrogation window.

Simple Workflow

Upon completion of the derivatization of the drug for use as capture and detection, the workflow for assay development is as follows:



Offline Sample Incubation

- ADA in sample is incubated for 2hr or overnight

Complex Capture

- Complex is captured onto blocked beads
- Wash to remove unbound antibodies

Elution

- Complex is dissociated, beads are magnetically separated and eluate transferred to read plate.

Single Molecule Counting

- Rotating laser scans sample
- Alexa-conjugated Antibody is excited and photons generated is counted by an APD

MERCK

In developing an immunogenicity assay, optimization is required to fully validate for the immunological system being studied. Considerations such as those listed below can be easily studied with the SMC technology platform:

- Drug tolerance
- Cut point/Matrix Tolerance
- Sensitivity/Dynamic range of the assay
- Reproducibility

Further Optimization

Further optimization of different variables can take place to produce the most sensitive assay. These include:

- Drug concentration (capture and detection reagent)
- Assay Diluents (to mitigate HAMA or other interfering factors)
- Sample volume
- Number of wash steps
- Incubation time
- Standard / sample diluent
- Determination of minimum required dilution (MRD)
- Evaluation of Drug interference / tolerance

Drug Tolerance

In bridging assays of this type, it is important to minimize the amount of free (unlabelled capture or detection reagent) drug to quantify and drive the equilibrium in favour of quantifying ADA's in samples.

Drug tolerance is an important consideration in immunogenicity and is a challenge faced where the ability to quantify ADA in matrix is reduced in the presence of high drug concentration as result of competition. Several methods have been used to overcome this challenge, which include acid dissociation.

By using a platform such as SMC™, with better sensitivity, may help overcome this by simple dilution, thereby eliminating the need for acid dissociation.

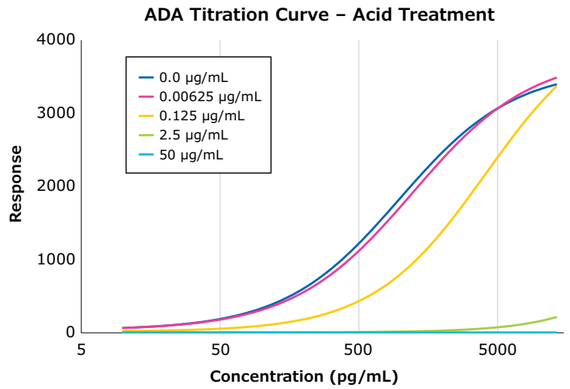


Figure 4. Example of drug tolerance on SMC Technology.

Further Implications of Immunogenicity — Adaptive Immune Response Assessment

Screening assays do not necessarily need to identify isotypes but need to be capable of binding multiple relevant classes or sub-classes. A number of isotypes play a major role in the immunogenic response. For instance:

- IgE-specific assays may be informative for products with a history of high risk of anaphylaxis.
- IgG4-specific assays may be informative for products that are chronically administered, or on erythropoietin-treated patients with pure-red cell aplasia.
- IgE and IgG4-specific assays may be requested on a case-by-case basis by the FDA due to hypersensitivity. The Compliment cascade can also be mediated by IgM and IgG.

These responses ultimately leads to generation of an inflammatory response through the formation of anaphylatoxins, such as C1q, C4a, C3a, and C5a.

Engagement of FcR or CR (Complement receptor) on cells, through immune complex cross-linking, results in the production of chemokines and growth factors that have a cascade effect on trafficking and growth of T and B cells.

This leads to release of cytokines and chemokines (IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, IL-21, IFN-g) which ultimately leads to tissue damage.

We have several products that can assist in the assessment of these responses and are available for the Luminex® platform using MILLIPLEX® kits.

Human High Sensitivity T Cell

◉ (Cat. No. HSTCMAG-28SK)
(Cat. No. HSTCMAG28SPMX13)♦
(Bulk Cat. No. HSTCMAG28PMX13BK)♦
(Cat. No. HSTCMAG28SPMX21)
(Bulk Cat. No. HSTCMAG28PMX21BK)

Fractalkine/CX3CL1	IL-12 (p70)♦
GM-CSF♦	IL-13♦
IFNγ♦	IL-17A/CTLA8
IL-1β♦	IL-21
IL-2♦	IL-23
IL-4♦	I-TAC/CXCL11
IL-5♦	MIP-1α/CCL3
IL-6♦	MIP-1β/CCL4
IL-7♦	MIP-3α/CCL20
IL-8/CXCL8♦	TNFα♦
IL-10♦	

Human Immunoglobulin Isotyping

◉ (Cat. No. HGAMMAG-301K)

IgA	IgG3
IgG1	IgG4
IgG2	IgM

Human IgE – Singleplex

(Cat. No. HGAMMAG-303E)

IgE

Human Complement Panel 1

(Cat. No. HCMP1MAG-19K)

Adipsin/Factor D	C5a
C2	C9
C4b	Factor I
C5	Mannose-binding Lectin (MBL)

Human Complement Panel 2

(Cat. No. HCMP2MAG-19K)

C1q	Factor B
C3	Factor H
C3b/iC3b	Factor P/Properdin
C4	

Legend key for MILLIPLEX® MAP kits

♦ Available in Cat. No. listed
◉ Available for custom premix

Mouse High Sensitivity T Cell

(Cat. No. MHSTCMAG-70K)
(Cat. No. MHSTCMAG-70KPMX)
(Bulk Cat. No. MHSTCMAG-70KPXBK)

GM-CSF	IL-10
IFNγ	IL-12 (p70)
IL-1α	IL-13
IL-1β	IL17A/CTLA8
IL-2	KC/GROα/CXCL1
IL-4	LIX
IL-5	MCP-1/CCL2
IL-6	MIP-2/CXCL2
IL-7	TNFα

Mouse Immunoglobulin Isotyping

◉ (Cat. No. MGAMMAG-300K)

IgA	IgG2b
IgG1	IgG3
IgG2a	IgM

Mouse IgE – Singleplex

(Cat. No. MGAMMAG-300E)

IgE

SMC™ Immunogenicity Assay Development Kit (Cat. No. 03-0175-00)

Combining our Immunoassay portfolio to study the impact on the immunogenicity of a therapeutic can provide great insight into the mechanism of the response. The SMC™ technology can offer increased sensitivity which may assist in the detection of low affinity antibodies and lead to earlier detection of primary ADA response, overcome matrix effects and may reduce drug tolerance.

The MILLIPLEX® kits can offer insight into the mechanism of the response and also help understand the immune complex mediated responses to the ADA.

To place an order or receive technical assistance

In Europe, please call Customer Service:
France: 0825 045 645
Germany: 069 86798021
Italy: 848 845 645
Spain: 901 516 645 Option 1
Switzerland: 0848 645 645
United Kingdom: 0870 900 4645

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Or visit: **MerckMillipore.com/offices**
For Technical Service visit: **MerckMillipore.com/techservice**

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OXFORD GLOBAL CONFERENCES

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12th Annual Proteins & Antibodies Congress
24 - 25 April 2019 | London, UK

6th Annual Peptides Congress
24 - 25 April 2019 | London, UK

6th Annual Biosimilars & Biobetters Congress
24 - 25 April 2019 | London, UK

Biomanufacturing Congress
17 - 18 September 2019 | London, UK

Co-located Events

US

Proteins & Antibodies USA Congress
18 - 19 November 2019 | Boston, USA

Peptides USA Congress
18 - 19 November 2019 | Boston, USA

Co-located Events

Biomarkers Series

UK

14th Annual Biomarkers Congress
21 - 22 February 2019 | Manchester, UK

US

4th Annual Biomarkers & Precision Medicine USA Congress
October 2019 | San Diego, USA

Cell Series

UK

8th Annual Cell Culture & Bioprocessing Congress
24 - 25 October 2019 | London, UK

6th Annual Stem Cell & Regenerative Medicine Congress
24 - 25 October 2019 | London, UK

5th Annual Cell & Gene Therapy Congress
24 - 25 October 2019 | London, UK

2nd Annual Biobanking & Cell Banking Congress
24 - 25 October 2019 | London, UK

Co-located Events

US

Cell Culture & Bioprocessing USA Congress
14 - 15 May 2019 | Boston, USA

Cell & Gene Therapy USA Congress
14 - 15 May 2019 | Boston, USA

Co-located Events

Formulation & Delivery Series

UK

5th Annual Formulation & Drug Delivery Congress
29 - 30 April 2019 | London, UK

4th Annual Inhalation & Respiratory Drug Delivery Congress
29 - 30 April 2019 | London, UK

Co-located Events

US

2nd Annual Formulation & Drug Delivery USA Congress
18 - 19 March 2019 | San Diego, USA

2nd Annual Inhalation & Respiratory Drug Delivery USA Congress
18 - 19 March 2019 | San Diego, USA

Co-located Events

Immuno-Oncology Series

UK

4th Annual Advances in Immuno-Oncology Congress
20 - 21 May 2019 | London, UK

US

2nd Annual Advances in Immuno-Oncology USA Congress
October 2019 | San Diego, USA

PharmaTec Series

UK

17th Annual Pharmaceutical IT Congress
25 - 26 September 2019 | London, UK

3rd Annual Artificial Intelligence in Drug Development Congress
25 - 26 September 2019 | London, UK

Pharma Cybersecurity Congress
25 - 26 September 2019 | London, UK

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11 - 12 June 2019 | Berlin, Germany

7th Annual Discovery Chemistry & Drug Design Congress
11 - 12 June 2019 | Berlin, Germany

Neuroscience in Discovery & Development Congress
11 - 12 June 2019 | Berlin, Germany

Bispecifics in Discovery & Development Congress
11 - 12 June 2019 | Berlin, Germany

Co-located Events

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UK

11th Annual Next Generation Sequencing & Clinical Diagnostics Congress
07 - 08 November 2019 | London, UK

7th Annual Single Cell Analysis Congress
07 - 08 November 2019 | London, UK

5th Annual Genome Editing Congress
07 - 08 November 2019 | London, UK

2nd Annual Synthetic Biology Congress
07 - 08 November 2019 | London, UK

Digital PCR Congress
07 - 08 November 2019 | London, UK

Co-located Events

US

5th Annual Next Generation Sequencing & Clinical Diagnostics USA Congress
14 - 15 May 2019 | Boston, USA

5th Annual Single Cell Analysis USA Congress
14 - 15 May 2019 | Boston, USA

3rd Annual Genome Editing USA Congress
14 - 15 May 2019 | Boston, USA

2nd Annual Synthetic Biology USA Congress
14 - 15 May 2019 | Boston, USA

Co-located Events

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info@oxfordglobal.co.uk