BIOMARKERS

SERIES UK 2020

Pre-Event Newsletter Dec 2019

MANCHESTER CENTRAL
18 - 20 FEBRUARY 2020 | MANCHESTER, UK

OXFORD GLOBAL CONFERENCES

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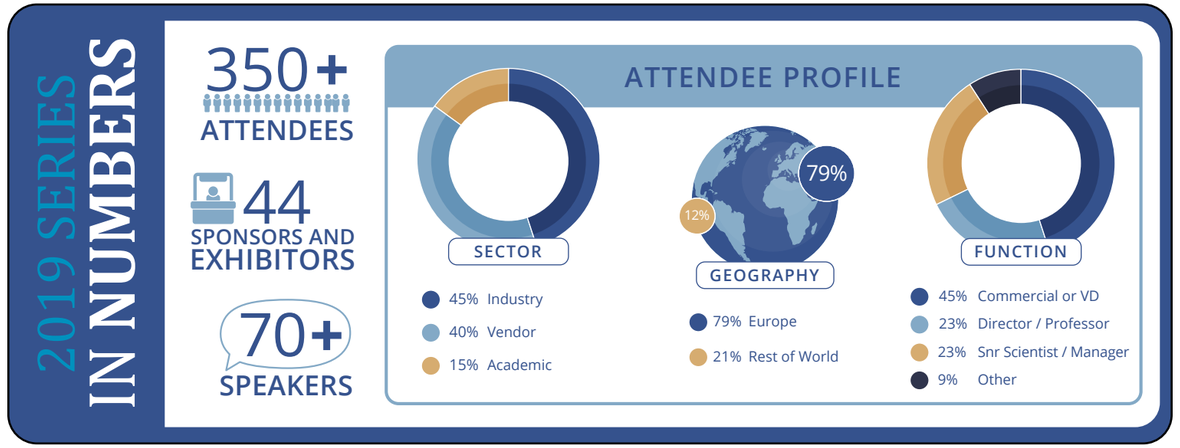

WELCOME TO OXFORD GLOBAL'S ANNUAL BIOMARKERS SERIES UK PRE-EVENT NEWSLETTER!

With the the 15th Biomarkers Congress taking place in February 2020 in Manchester, I am delighted to look back at some of the highlights of the 2019 event and provide some details on a few of the key features & exciting additions for the 2020 congress.

The 2019 congress brought together over 350 attendees in Manchester to discover collaborative solutions to Biomarker Discovery & Development challenges and discuss the latest developments in Innovative Biology & Genomic Markers. The programme featured over 60 + presentations, workshops and roundtables, with numerous comments received regarding the diverse and innovative options available. The complimentary gala dinner was also a hit, with attendees relishing the chance to kick back and relax with peers whilst enjoying a three-course meal and wine.

For 2020, the event will feature 70+ presentations on key topics within Biomarkers In Drug Discovery & Development, Biomarkers for Detection, Monitoring & Diagnosis, Biomarkers for Clinical & Pre-Clinical Development and New Biomarker Technologies & Data. 2020 will also see the introduction of two highly anticipated streams focusing on Genomic Biomarkers in Drug Discovery & Development, Data Analysis of large Genomic Samples and Genomic Biomarkers for Precision Medicine & Clinical Practice. If that wasn't enough, Oxford Global are very excited to launch a new feature and added day to the congress in the form of our pre-event workshops. On the 18th February, attendees of the congress will have the opportunity to take part in half-day, in depth workshops on focused topics within the field. Choosing between topics such as Discovering Novel Biomarkers For Neurodegenerative Conditions, Novel Biomarkers For Cardiovascular Conditions, Multi-Modal Biomarkers For Cancer Detection & Treatment and Designing And Applying A Biomarker Plan In Drug Development, attendees will be spoilt for choice!

Of course the ever popular Breakfast Roundtables, Gala Dinner and networking drinks will be returning for 2020. These features will be even bigger and better for 2020 so stay tuned!

Read on for a range of interesting interviews and insights with some of the Biomarker Series 2019 & 2020's industry-leading speakers and participating sponsors, and I look forward to welcoming you to the 2020 Congress in February.

- Hayley Watson, Portfolio Director

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WHO IS ATTENDING?

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

- **450+ 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:

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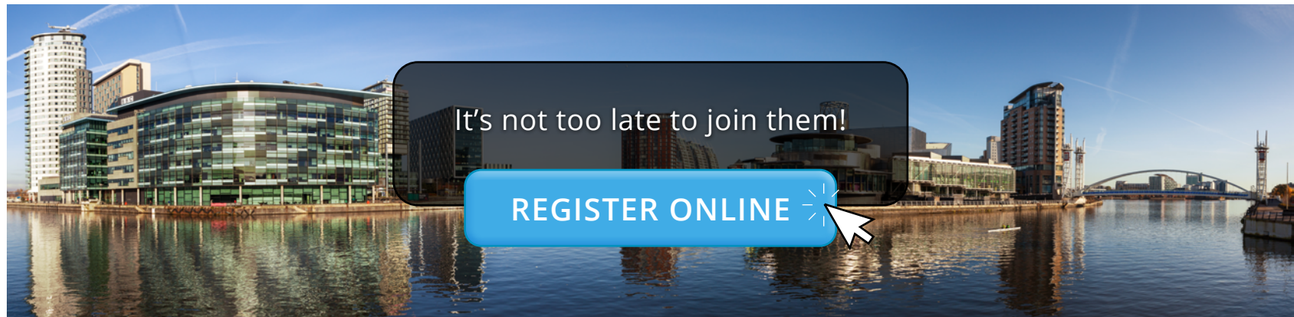


SEIZING THE OPPORTUNITY OF THE DECODED HUMAN GENOME

JANE WILKINSON

Jane Wilkinson,
Senior Director, Broad Institute

Jane is a Senior Director at the Broad Institute where she leads the Broad Genomics Alliance Management team.

Jane has over 20 years of high-throughput genomics experience from the Wellcome Trust Sanger Genome Center, UK where she was a key leader on the Human Genome Project and at Monsanto Company, USA where she led a new directive in plant genomics. Jane has been at the Broad Institute for fifteen years and has worked on various initiatives including Cancer, Mendelian, Infectious and Common Diseases.

Tell me a little about the Broad Genomics team and their mission

The Broad Institute was founded to seize the opportunity that arose from the Human Genome Project -- the international effort that successfully deciphered the entire human genetic code. Despite that accomplishment, scientists knew they still lacked a clear understanding of the genetic basis of disease, and how to translate that understanding into more effective prevention, diagnosis, and treatment.

Since the Human Genome Project, the Broad Genomics Platform has played a leadership role in the design, data generation, and methods development in support of major genomic resource projects including: the HapMap, the 1000 Genomes Project, The Cancer Genome Atlas (TCGA), Comparative Reference Genomes, ENCODE, Genotype-tissue Expression Project (GTEx), Human Microbiome Project, Exome Sequencing Program Center for Mendelian Genomics, Human Cell Atlas (HCA) Exome Aggregation Consortium (ExAC) and Genome Aggregation Database (gnomAD) projects and All Of Us.

Over the past ten years, we have been one of the largest producers of human genomic information in the world. Currently, the group produces approximately 500 terabases of genomic data per month - a rate equivalent to a 30x human whole genome every 10 minutes. The group has processed more than 3 million samples from more than 1,400 groups in more than 50 countries.

Thinking about the challenges of genomics - what have been the key developments of the Broad Genomics within the past few years?

Over the past 20 years, the wave of genomic innovation and development has been incredible. The introduction of the first 'next-generation' sequencing machines (454 and Solexa) in 2005 and 2006 led the way to whole exome sequencing and the <$1000 whole genome. Applying lean manufacturing work design has allowed us to scale-up to handling over 10,000 samples per week - we completed our 100,000th whole human genome on the 15th anniversary of the completion of the Human Genome in 2018. And recently we have launched half a dozen new services, including Clinical Whole Genome Sequencing, Liquid Biopsy, and Single Cell Sequencing. We have also redesigned our Whole Exome which has resulted in an increase in capacity and more importantly - a significant drop in price.

You mentioned the new Whole Exome - can you tell me more how this was developed and the biggest impact it has made?

As sequencing costs continue to drop, the utility of whole genome sequencing for common disease research is beginning to be realized. However, even with cheaper whole genomes, complex common disease studies still often require larger case-control cohorts in the 10s of thousands and greater. Even with a $1000 genome, achieving the necessary power to find meaningful association is expensive. This realization has driven us to redevelop our germline whole exome product and workflow to reduce cost and simultaneously increase quality. The new Broad Custom Exome developed with Twist BioSciences leverages our custom hyb capture workflow, extremely even coverage, and a high on target percentage (~90%) to allow us to offer a high quality exome at ~USD$200. In addition to a high quality exome and lower price, we have re-engineered our automated workflow to enable a 3-fold increase in capacity in the past year, and are now capable of processing >300,000 exomes per year to better support the internal research needs of the Broad Community as well as external customers.

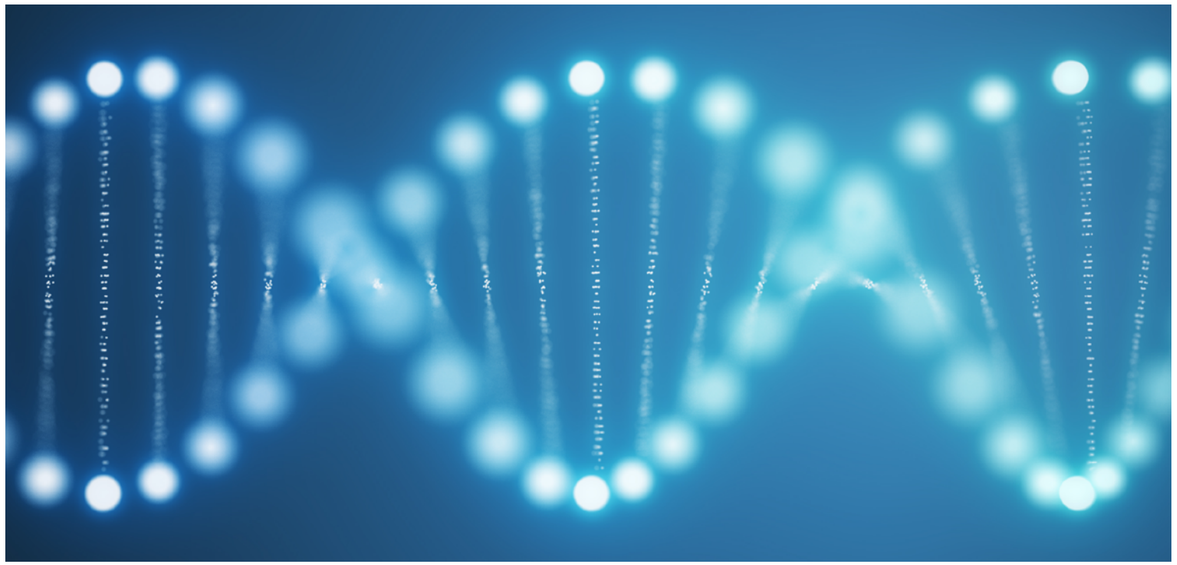
There's a lot of interest in Liquid Biopsy in the community - tell me more about how Broad Genomics has implemented this and how it's being used.

We have developed a custom unified target enrichment workflow to support a broad suite of somatic studies that require high sensitivity and specificity for low allele fraction variants. This method incorporates extremely stringent error correction using duplex UMIs and ultra deep targeted sequencing. Using array-synthesized custom panels from Twist BioScience, we can now rapidly and in a cost effective manner target disease and study-specific genes to high depth. With Twist custom panels and our workflow, panel sizes can range from 10's of kilobases to multiple megabases in size and routinely achieve greater than 90% of sequenced bases on or near target, maximally utilizing gigabases of sequencing purchased. With cheaper cost of entry into a custom panel synthesis, investigators can now sequence only their regions of interest to extreme depth (20,000-50,000X raw coverage) to maximize the likelihood of detecting variants of importance at very low allele fractions. This allows the investigator to decide whether a larger fixed pan-cancer panel or a more targeted small panel is best suited to their study regardless of sample/ patient number. This method and workflow is particularly well suited for blood biopsy cfDNA as well as bone marrow aspirate clonal hematopoiesis studies.

Just recently The Multiple Myeloma Research Foundation announced that it is launching the MMRF CureCloud™, a data hub that generates, aggregates and visualizes data to accelerate the delivery of precision medicine to multiple myeloma patients. Broad Gennomics will be providing our liquid biopsy capabilities as part of this initiative.

Connecting this large scale genomic data generation to translational analysis can be a pinch point for many researchers - can you tell me more about how Broad Genomics has tackled this?

We have tackled this issue in two specific ways. 1. Through the creation of a cloud-platform, Terra, we have enabled researchers to retrieve, analyse, and share their data in a scalable, accessible, and secure environment. We have further created repositories of open-source, best-practice methods in that platform so that researchers can use the same tools as we do to analyze these datasets. 2. For groups who do not have a fleet of bioinformaticians sitting around, we have created the Translational Analysis Group or TAG. TAG is comprised of 3 PhD-level computational scientists, an associate computational biologist, and a variant curation scientist. This group uses best-practice pipelines developed at Broad and beyond, to analyse our users data in a fee-for-service model. The group is fully cloud-native and all data and analytical outputs are made available through our cloud-platform. The team has run >15,000 analyses on samples ranging from whole genome sequencing for germline variant calling to somatic analysis of tumor variants from liquid biopsy. The team can validate analytical pipelines for use in clinical trials, clinical diagnostics, or therapeutic development.



NOVEL MARKERS FOR ALZHEIMER'S DISEASE

RAWAN TARAWNEK

Rawan Tarawnek, Assistant Professor of Neurology and Director of the Neuroscience Biomarker Laboratory, Ohio State University

Dr Rawan Tarawneh is an Assistant Professor of Neurology, and Leader of the Biomarker Laboratory in the Ohio State University. She completed her neurology residency and fellowship training in Washington University in St. Louis, including a post-doctoral research fellowship in the laboratory of Dr David Holtzman and a clinical fellowship in Dementia and Behavioral Neurology with Dr John Morris. Her research focuses on the use of bioinformatics to identify novel biomarkers for Alzheimer disease and neurodegenerative disorders, including new targets for potential therapeutics. Her research has led to the identification of VILIP-1 and neurogranin as novel biomarkers of neuronal and synaptic injury in AD, both of which have been recognized among the largest advances of AD biomarker research over the last decade by the Alzheimer's Association. She is also the primary investigator of several clinical trials and biomarker studies in OSU.

Why is it so important to identify novel markers, Alzheimer's disease?

The clinical trials for Alzheimer's Disease (AD) Therapeutics have unfortunately failed, all of them have had disappointing results. One of the main reasons we think this is the case is that clinical trials enroll patients based on their clinical diagnosis. They stratify patients based on whether or not they have clinical symptoms of memory loss or cognitive impairment. However, we now know that if we wait that long, it's too late to get patients into trials because by the time they come in with their first signs of cognitive impairment, they've already developed significant neuronal loss in the brain, in addition to already having a substantial amount of amyloid and tau pathology - so biomarkers will significantly improve our chances of identifying patients who have preclinical Alzheimer's disease - that is before they develop clinical symptoms, - and enroll them in clinical trials at a time when they are the most likely to benefit from disease modifying treatments. It will also enrich trials with patients who are at the highest risk for imminent cognitive decline, so that we don't have to enroll patients for 10, 15 or 20 years before we notice a decline – we're actually enriching trials with patients who are the high risk patients so to speak. Biomarkers would also provide us with alternative secondary and tertiary outcome measures that we can use to assess the benefits of disease modifying treatments. Most of the outcomes are based on clinical measures or functional measures. The short duration of the clinical trials may be inadequate to assess these effects. If we have a measurable, fluid or dynamic imaging marker that would allow us to better assess response to disease modifying treatment. I think biomarkers are the future of Alzheimer's research, and this has been translated into the updated research framework for Alzheimer's as proposed by the NIA-AA, which now is shifting our focus from thinking of Alzheimer's as a disease or a clinical diagnosis, instead thinking of it as a clinical pathological spectrum, so that we can use biomarkers to identify and characterise the disease regardless of clinical symptoms.

Why has it been so challenging to develop biomarkers for the neurodegenerative condition?

I think there are several reasons for that. One is these are highly complex diseases that span 15 to 20 years. We think still don't fully understand a lot of these diseases from a mechanistic standpoint. For example, in conditions where we have a clear understanding of the disease pathogenesis or we have a disease causing mutation, and we can identify the main pathway that's involved in that disease, it is relatively easy to come up with biomarkers using that pathway. Unfortunately, with Alzheimer's, I think that biomarkers are going to help us understand the disease rather than reflect our understanding of the disease, because our understanding of disease right now is limited. We've spent the last 20 years probably chasing the wrong target or maybe a process that is not as key or as critical as we thought it was, or maybe (I'm referring to the amyloid deposition) it is not pathogenic, it may be a response from the brain to other more important pathways that are impaired. I think there is a great degree of heterogeneity in the disease from a clinical and pathological perspective, as a result it will be extremely difficult to find one single biomarker that will be able to capture all of these elements. However, I think that we should keep an open approach to this and use biomarkers to look at different disease mechanisms so that hopefully, we will be able to better understand the disease and then maybe that will lead to a better diagnostic test for it or hopefully, a more effective treatment.

Biomarkers are also difficult - or the immunoassays used for biomarker assessment - they've been difficult to standardise across different labs - that's also another challenge. However, I think our biggest challenge really is in our understanding of the disease itself.

What are the next steps for your research?

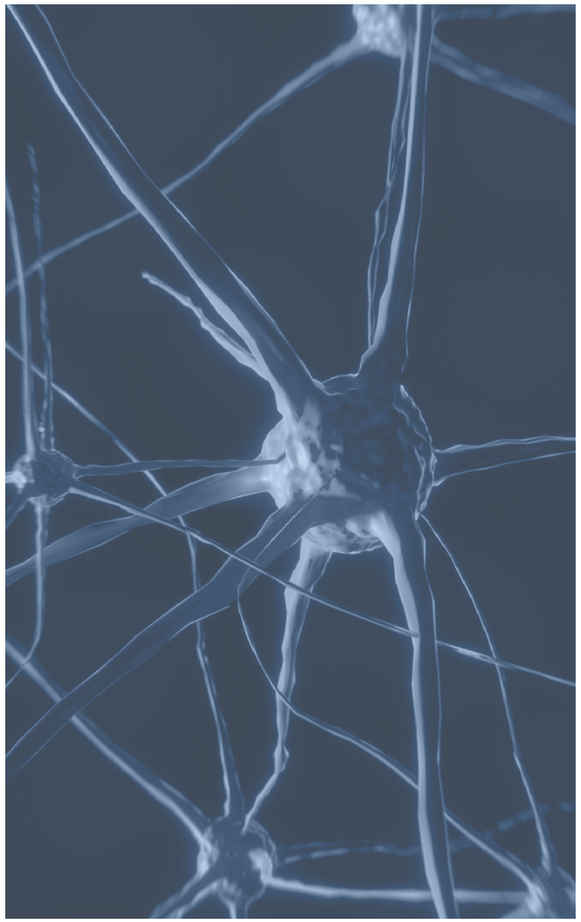
Most of my work so far has been on markers of neuronal and synaptic injury because that is the main driver of the cognitive decline in Alzheimer's disease and other neurodegenerative disorders. My thought process was that they would be better predictors of disease progression and better indicators of disease severity, and they would be more closely correlated with the cognitive outcomes so they would potentially be helpful in clinical trials. However, they are not specific for any particular disease, even though there may be some relative importance for them in Alzheimer's, compared to other diseases. However, we still don't know much about these markers to be able to make that comment with certainty. Now I'm moving towards looking at biomarkers that reflect other disease mechanisms. I'm interested in looking for markers for mitochondrial dysfunction in disease specific manner and also markers of vascular injury and markers of inflammation. I think we need to extend our thinking beyond the amyloid plaque model of Alzheimer's, at least for now.

Are there any particularly important technologies on the approaches that you think are really impacting the biomarker space currently?

Yes, absolutely. I think there are a couple in terms of fluid biomarkers, the single molecule counting technology has revolutionised our ability to measure different types of proteins and body fluids. What were previously undetectable levels of proteins in the blood can now be detected. There are several of these companies and technologies that are based on the single molecule counting. I think that's been tremendous effort and it's an excellent collaboration, or an example of collaboration, between industry and academia. I think that's been very helpful. Also, I think - what would be probably be equally as important - is identifying imaging markers that are ligand based. If we can, it would be beneficial to not only measure the level of a protein in the body fluid, but also image it, in terms of looking at its regional distribution in the brain, and we can use that through ligand based PET scans. I think usually with this kind of research, it starts on the fluid basis, and then we can develop these ligands for PET scans. I think the future of AD research is a combination of fluid and imaging markers that are based on specific mechanisms.

What you hoped the top three takeaways from your presentation would be for the audience?

Number one is as much as we would like to say that we understand Alzheimer's disease, we still do not. Number two is I think we need to expand our thinking, look at additional disease mechanisms and how they interact with amyloid and tau pathology and really try to understand the fact that a lot of these pathologies are not static in time, but they are a dynamic and they change, and the relative importance may change in different stages of disease. I think that intra individual markers, or changes in intra individual levels of markers is going to be more helpful than an arbitrary standard or reference value that we come up with. The last point would be that biomarkers are not just tests to help with diagnosis, but I think they will have a crucial role in finding a cure for Alzheimer's disease.



END-TO-END DRUG & DIAGNOSTIC DEVELOPMENT SUPPORT FOR A NEW IMMUNO-ONCOLOGY AGENT: A CASE STUDY

Immuno-oncology drug development is inherently complex and requires special considerations across the entire spectrum, from preclinical to commercial support for the approved product. In this example, a prominent pharmaceutical company was developing an innovative new programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC). This company selected Covance / LabCorp for support at multiple junctures—from manufacturing to biomarker evaluation to market access—to enable a faster and more effective launch.

Key Highlights of This Case Study:

- Speed to market was crucial—rival companies were pursuing the same or similar indications with therapies having a similar mechanism of action, creating deadline pressure without compromising trial success.
- The molecule required the co-development of a diagnostic laboratory assay, which requires a distinct set of capabilities and CRO / diagnostic company collaboration.

The Common Denominator

Multiple functions touch the drug development path. At Covance, our relationship with LabCorp gives us a unique capability to perform end-to-end services to support trials, starting as early as nonclinical work. In this case, our diverse early development services group—including BioPharm CMC—was engaged to assist in the manufacture and qualification of drug lots that went out to trial use.

Moving from Early Development to Central Laboratory services, Covance provided biomarker evaluation to enroll patients in pivotal clinical trials, enabling patient stratification and selection for trial participation which were critical to the therapies' approval. In addition work was done with an *in vitro* diagnostic company in the co-development of the diagnostic laboratory assay, so that it could be available at the same time as the therapy. This was facilitated through the extensive experience LabCorp has in supporting such test development and then commercially launching the test to coincide with the drug's launch.

The immunotherapeutic launched with great success for patients, but still encountered some market access challenges. Its proposed buy-and-bill model—along with high product costs—required careful understanding and communication about payer policy and coding. Covance Market Access was selected to provide post-launch commercial support—specifically a robust reimbursement strategy to: 1) fend off a rival's encroachment with a similar oncology product; 2) handle access-related issues unique to each oncology provider to facilitate more efficient reimbursement and build stronger provider relationships; and 3) improve overall market access in an increasingly competitive space.

Covance's reimbursement team educated healthcare providers on the client's access services so that they could easily obtain billing and coding support, co-pay assistance and handle underpaid or denied claims. By providing crucial insights, maintaining provider relationships and quickly responding to case-specific concerns, Covance was recognized as an integral part of the client's oncology field team that helped strengthen market presence.

Lastly, for post-approval, Covance CMC in Harrogate (UK) was retained for release and stability testing to verify quality of the manufactured product for its intended audience.

Value to the Client

Most of the FDA-approved diagnostics used to guide therapy decisions are primarily for oncology indications. In addition, most oncology drug development initiatives are biomarker-driven. With so many of these new therapeutics earning a Breakthrough Designation and/or fast-track approval, there can be a significant benefit to having a single partner efficiently support multiple steps in the drug development and diagnostic co-development process. This consolidation of service outsourcing could result in a higher probability of success and accelerated speed to market.

In immuno-oncology, a variety of biomarkers and corresponding assays are being considered to help assess the efficacy of a therapeutic approach, and these include a variety of proteomic and genomic approaches that require specific expertise. As this vibrant area of research continues to expand the options for oncology treatments, Covance's combination of highly specialized expertise and comprehensive end-to-end drug development enables sponsors to better inform patient decision-making and advance the field of personalized medicine.

Covance and LabCorp have supported more than 60% of all FDA-approved diagnostic assays included in drug labels, involving both companion and complementary designations.

PARTNERSHIP AND COLLABORATION IN THE BIOMARKERS SPACE

STEVEN C. HOFFMANN

Steven C. Hoffmann, Director, Inflammation and Immunity, FNIH

Steve Hoffmann is the Director, Inflammation and Immunity in Research Partnerships at the Foundation for the National Institutes of Health (FNIH). In this role, he provides strategic planning, programmatic management and research administration of a broad portfolio of established and emerging projects in inflammation, toxicity, infectious disease and other autoimmune diseases.

Steve has worked for over 20 years in the field of translational biomarkers, molecular immunology and precision medicine with a focus on multi-stakeholder partnerships and project development.

Please explain your work in the field.

The FNIH builds, manages and facilitates pre-competitive alliances and partnerships that helped transform the research landscape. It is focused on areas where there's specific need for input from the private sector to convert biomarker discovery into confident and evidence-based decision-making, fit for regulatory endorsement. The FNIH and our Biomarker Consortium staff are really programme and project managers in our day to day work - But in the same vein, we are marketers, fundraisers, negotiators or contract and relationship managers. We sell; we buy; we do science; we do budgets; we do grants management; we have to be masters of collaboration and dealing with all types of personalities. It is essential for these partnerships that we have a keen understanding of stakeholder perspectives, the return of investment that different partners may need to have, limitations that they may have, and understand what's important for them and continually gauge their interest in how to bring the individual and collective expertise together for the common good, and for patients and treatments.

What are the main challenges you face in your work?

Finding individual champions to lead and help design the development of appropriate and impactful projects can be a continual issue. We want to continue to create a community of understanding in the regulatory biomarker qualification process and the need for regulatory tools and decision making will most directly impact drug development approvals and have immediate patient benefits. When seeking commitment or financial support from the same sources for multiple disease areas, often going to the very same people or organizations can be very challenging. You're going back and asking them for support and their input, and everyone only has a certain amount of bandwidth or dollars. Therefore, prioritising and scoping these projects is what needs to get done first - what might be done vs. what needs to be done - is really challenging day to day.

How do you think the Biomarkers Consortium can be utilized more effectively for Biomarker development?

I think it's about continuing early engagement with our cross sectional, cross functional partners, forming well-structured projects that have clear achievable aims and deliverables that impact and produce clinical tools and accelerate while limit costs of clinical trials. Regulatory guidance and regulatory decision points are key. Expanding our outreach and collaboration, on a more global basis, will really help align us with parallel efforts that are ongoing internationally and may enable greater opportunity to impact and affect more patient populations.

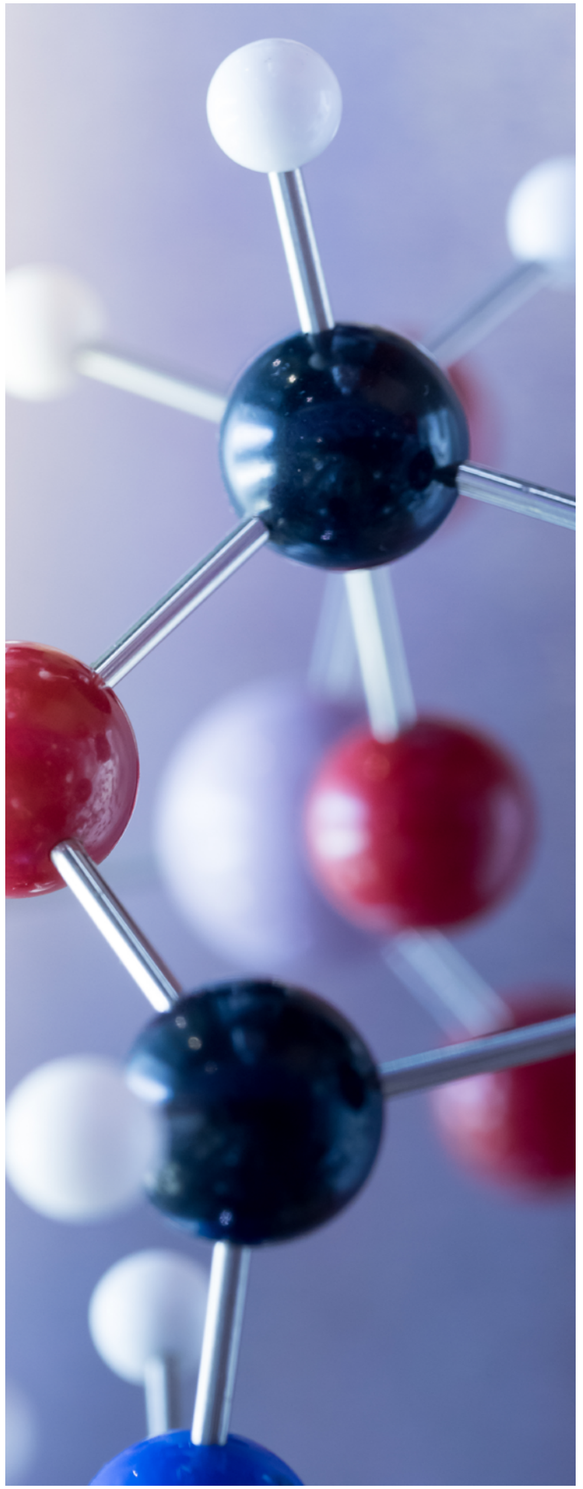
What are your main priorities across the next year?

The Biomarker Consortium and our Inflammation and Immunity Steering Committee has outlined key areas that are ripe with the need for biomarker development and novel clinical tools to move drugs through the regulatory process. This includes projects we are developing in inflammatory bowel disease, Sjögren's syndrome, spondyloarthritis, scleroderma and a better understanding of the rheumatological impacts of immune-oncology in cancer patients . So engaging our academic, industry and advocacy leaders, and moving these initiatives from the concept phase to the plan phase and execution in a well-staged, well managed fashion, within the bandwidth of our team and within the bandwidth of those providing the financial support we need from the private sector is really the priority in the coming year.

You recently spoke at our US sister event. What were the top three takeaways from your presentation?

The efficient and effective validation of biomarkers for the broad use and the development of regulatory medicines and clinical care is a complex process. It requires a breadth of data, a breadth of expertise, and scientific consensus that is typically beyond the means of a single group or single entity and really requires the partnership that we can bring together and make occur. The second would be that not all biomarkers need to be qualified and need to go through the regulatory qualification process, which can be challenging and onerous at times. Success is more likely following a framework of project development that describes unmet medical need, defines the context of use or how these biomarkers will be used in drug development. It considers the potential benefits of successful use of the biomarker and assesses and limits the risks obviously associated with its intended use for various populations. Then finally, to determine the level of evidential criteria, the amount of analytical or clinical validation that's really needed to support that context of use for those biomarkers is the rule of thumb for all projects and it is sound practice for implementing biomarkers and trials in regulatory decision making. The third one is kind of the ad for FNIH, in that we are very effective in third party, neutral programmatic management and administration with a well-documented history of success in biomarker development, validation, utilisation and qualification. Working in these public private partnerships with organisations like the FNIH and with partnerships such as the Biomarker Consortium, is a strategic and impactful step to help share costs, expertise, minimize risk and maximize success across multiple sectors - so please engage with us, work with us and make a difference in patient treatments and patient lives.

Collaboration is vital for successful biomarker development, with the Biomarkers Congress providing a key forum to network and make valuable connections with the leading biomarker experts. Join our Day 2 roundtable discussions to collaborate on some of the key challenges the industry faces, including improvement of robustness through industry & academic partnerships, and strategies to prevent past mistakes.



RNA EXPRESSION IN THE DIAGNOSIS & TREATMENT OF STROKE

JEFF JUNE

Jeff June,
Chief Executive Officer,
Ischemia Care

Jeff June, CEO, founder, investor, and board member for Ischemia Care, a molecular diagnostic company commercializing blood tests for cause of stroke, across the stroke care continuum, including atrial fibrillation and point of care. Background includes founding and investing in multiple early stage companies, including life sciences and IT. Investment experiences spans seed stage venture capital and large private equity firms. As a company founder, participated in establishing clinical, operational, sales, and financial foundations; from seed stage to exit, including a $600M IPO, and a separate $95M exit.

Could you explain a bit more about your company's Stroke diagnostic?

We use RNA expression in the diagnosis and treatment of stroke. In the US every year there are two million visits to emergency rooms for stroke and stroke like symptoms that results in about 800,000 actual strokes and about 250,000 strokes where the cause is never determined. We use RNA expression as a workflow tool to help clinicians get to the right answers more effectively.

What are the challenges you face in this work?

There are a lot of challenges. When we started about 15 years ago, there was very limited RNA expression data and definitely no clinical trials of the size that would be required in bringing a test to the market. We had a challenge with the size of the clinical trial recruitment required and RNA expression was in its infancy. When you look at the business side, early stage for stroke and diagnostic companies in the US is difficult. We turned all these things into positives. We ran the largest, most successful stroke biomarker trial that's ever been conducted. 1700 patients over 20 sites. It was led by the Chairman of the Stroke Committee for the American Heart Association and first author on the 2013 AHA Stroke Guidelines. We couldn't have a more dedicated and prominent clinical base to run the BASE (Biomarkers of Acute Stroke NCT02014896) clinical trial effectively.

The next issue was thinking about RNA expression in stroke. We work with the clinical researchers that are credited with inventing RNA expression in stroke. When I think about our collaboration and pioneering the field of stroke reseach, I think of a globe. The land as being 25% of the mass of the world and this represents the early clinical research when we started. Ischemia Care is the water. We bridge the other 75% by the size of our clinical trial and the amount of data we have contributed to the science. The third piece is, when you think about funding and creating companies, the way we were able to overcome those barriers is that early investment in the company was led by myself, the board members, and then we selectively partnered with companies that were very strong in cardiovascular, neurovascular, and RNA expression in the sciences.

In summary Ischemia Care is pioneering the field of RNA expression in stroke building on ground breaking clinical research, clinically validating discovering in robust clinical trials led by prominent figures in stroke, and creating a capital efficient model to commercialize innovation.

How do you think this will impact treatment for stroke patients?

I think the most important takeaway is when you when you know the cause of stroke, you can change the outcomes through precision medicine. Stroke basically hasn't changed its treatment protocols in over 20 years dating back to the TOAST criteria and there are no blood tests for stroke prior to our launching the first in 2019. If you have a workflow tool, you can effectively guide the diagnosis and treatment of these patients more effectively. For the financial perspective in the US, Ischemia Care testing can reduce the cost of care by about $23,000 per patient. Most importantly, I think stroke is where cardiac care was in the 50s. It was thought that once you had a heart attack, there was there was no cure, it was out of the blue and there was no treatment – and your life was effectively over. I believe that the incredibly dedicated professionals in stroke are ready to apply more precision medicine approaches and biomarkers in the care of these patients, and really make quantum leaps in the care of these patients. Most importantly, when you've had a stroke, it is vital to prevent a secondary stroke, which is a far more massive, debilitating and costly. If we are able to improve the care of those patients, they have another opportunity to get their lives back - to hug their kids and never worried about recurrent stroke.

Why do you think genomic markers, such as RNA expression, are particularly effective for this? How do they facilitate precision?

RNA is expressed before other markers in the blood. When you think about the important clinical decisions that are made across the stroke care continuum - they include some decisions that need to be made right away, and they also include decisions that are made within a 30 day window. This is a broad window of care. I think by looking at RNA expression, we've demonstrated, on the science side, that we can identify markers that are expressed both very early on and consistently across the care of that stroke patient, to really provide clinicians biological insight into the patient. Today, the stroke is diagnosed by imaging and looking at your clinical history, there are no blood test for stroke and its causes. By getting a look at what's going on within the body, you get a more complete view of that patient, to treat them more effectively.

You recently spoke at our US sister event. What were the top three takeaways from your presentation?

When you think about what we've accomplished as a company, we've been the pioneers in the field of biomarkers and stroke, so we're very thankful to be invited to speak on this topic. First and foremost, since this primarily might not have been an audience that's familiar with stroke, biomarkers and RNA expression, it was important to really educate leaders in the field of precision medicine, both from a clinical perspective and advances in sciences - so when they left there, they had a much better understanding of stroke and biomarkers. Another important message was that the field of stroke is ready for precision medicine. In particular, what I talked about is in the US there are 2 million emergency room visits, 800,000 strokes, we have 250,000 strokes every year that never have a cause determine. Now imagine if you were in any cancer presentation at a conference, and they were talking about in 250,000 cases, where clinicians did not have the tools to determine the cause of cancer - there would be outrage. I think that's an important message to take away, looking at how precision medicine can apply to solve clinical needs in stroke. Also, conferences like the Biomarkers Series provide a great opportunity to look at some of the other great science and research that's going on in oncology and neuroscience fields. They are a great opportunity to inspire people to look towards the neurosciences as the next frontier of where precision medicine will have a significant impact on the care of patients.

The themes considered in this piece will be further explored at the Biomarkers Congress through our Day 2 Stream 1 on Biomarkers in Discovery & Development for Neuroscience, as well as our exclusive pre-event deep dive session

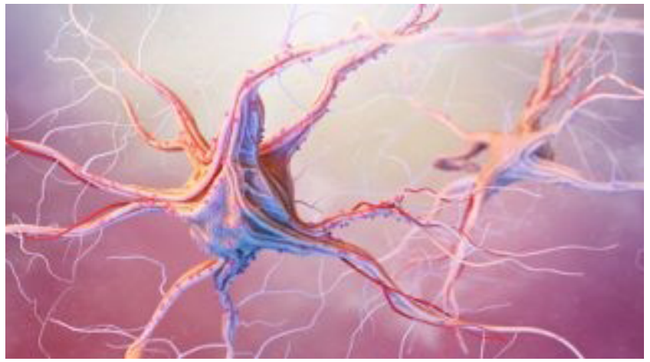
CELL POPULATION ANALYSIS AS A BIOMARKER

TUULIA HUHTALA & CHRISTOPH EBERLE

Flow cytometric technology has been around for 50 years. As we learn more about the immune system's role in incurable diseases, flow cytometry is suddenly popular again.

Since the first instruments using fluorescence-based detection came to market flow cytometry has been widely utilized. Nowadays its support reaches from clinical diagnostics to food safety testing to basic research and drug development. Essentially, it is used to separate, count and characterize particles in a fluid – simultaneously and with high speed. For most applications these particles are variably heterogenous populations of cells. Any sample collected, for example from a patient or an animal model, is processed as single-cell suspension, and cell targets are typically identified by fluorochromes linked to primary antibodies directed against a preselected set of antigens. For analytical interrogation these tagged cells are forced into a line by hydrodynamic focusing (this can be done even more efficiently with the help of sound waves), so that one by one each cell passes the laser beam in a flow cytometer. Thereby the fluorophores conjugated to bound antibodies get excited and emit fluorescence, which is detected and ultimately converted to an electronic file.

Light-scatter properties reveal cell size and complexity, whereas molecular details can be determined based on the pattern, in which antigenic markers are expressed on the surface and intracellularly. Datasets generated with all this stored information can be enormous. A common analytical method is to gate cell populations in two-dimensional dot plots displaying the fluorescence intensity of extracted subsets. As a result, disease-specific phenotypes of immune responses can be identified. The occurrence of such phenotypes with potential changes in immune cell composition and frequency can serve as a translational biomarker in drug development.



How Immune Responses Harm Our CNS

As immunophenotyping may reveal not only inflammatory processes, but also the activation status of immune cell subsets, it can guide selecting individual immunomodulatory therapies. In central nervous system (CNS) animal models this provides insight in the dynamics of peripheral and resident cells. Understanding the innate and adaptive immune cell status within the CNS and in the periphery during disease progression can be applied to monitor biomarker expression profiles as well possible pharmacodynamic changes related to treatment.

Diseases affecting the CNS originate from various sources including tumors, degeneration, trauma, blood circulation interruptions, traumas, structural defects, infection and autoimmune disorders. In these pathogeneses the immune and nervous systems are closely related to either disease origin or progression of disease. Homeostasis and regulation of inflammatory markers is an active process in the brain, and if they malfunction it turns pathological. Both acute and chronic inflammation responses in CNS have been identified with regards to various diseases. Acute inflammation response starts and becomes severe rapidly. Symptoms are typically only present for a few days. In the CNS acute inflammation usually follows an injury, e.g. in traumatic brain injury, spinal cord injury or stroke. Contrary to acute symptoms, chronic inflammation can last from several months to years and is present in diseases such as Alzheimer's, Parkinson's, Huntington's and multiple sclerosis. Increased T-cell numbers have been associated with the mentioned disorders contributing both to inflammation and neuronal dysfunction as well as to deferring inflammatory responses leading to neurodegeneration.

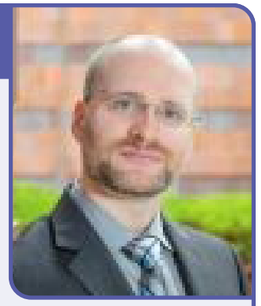
How Immune Responses Fight Cancer

On the other hand, T-lymphocytes join the fight against cancer. They and other immune cells like macrophages, neutrophils or myeloid-derived suppressor cells (MDSC) accumulate in the microenvironment, which surrounds a tumor and nurtures it to promote or suppress its growth. In general, this physiologically abnormal arrangement keeps an immune response down. Novel treatments explore how to put the tumor on the immune system's radar and thus initiate a directed attack. Phenotyping of tumor-infiltrating lymphocytes (TIL) by flow cytometry is a common readout from animal models used in oncology discovery. Experimental studies assess whether and how immune cells within this disguising microenvironment may change under various dosing regimen. Measurable changes in their frequency, composition, distribution and function may help determining a possible therapeutic outcome. Ultimately, the same information can be of prognostic and predictive value down the drug development journey.

Recruiting the body's own immune system as ally to fight cancer is the paradigm of a set of new immunotherapies. This approach has been emerging as the "fourth pillar" of tumor treatment, most notably recognized by this year's Nobel Prize in Physiology or Medicine. Both defense lines, the innate and the adaptive, are utilized for creating an anti-tumor immune response. This form of immunization may be done either actively by targeting selected lymphoid cells (e.g. checkpoint inhibitors) or passively by stimulating the whole immune system (e.g. adoptive cell transfer), both of which depends on the actual therapeutic concept.

Hopes remain high that among these new strategies one or more will be our decisive move in the battle against the "emperor of all maladies". For now, this one has yet to meet his Waterloo.

Christoph Eberle



Trained in biochemistry at the University of Bayreuth (Bavaria, Germany), Christoph graduated with a bachelor's and master's degree. Subsequently, he moved onto the University of Bremen (Bremen, Germany) for a PhD in organic chemistry under the tutelage of Professor Franz-Peter Montforts, synthesizing novel porphyrin and porphyrin-fullerene derivatives for immobilization on gold surfaces. Following postdoctoral research at Dartmouth College (NH, USA), he began his career in laboratory medicine at the University Medical Center Göttingen (Lower Saxony, Germany). He later transitioned into private industry, holding lead scientific positions at the Eurofins Central Laboratory (USA) and Envigo (USA), where he focused on fit-for-purpose validation of multiple cell-based assay formats, preclinical and clinical trial sample testing and reporting. Dr. Eberle joined Charles River (USA) in 2017 to provide immunology testing expertise in support of the company's integrated oncology drug discovery services. As a member of the local pharmacology team at the Worcester Discovery site (MA, USA), he oversees assay development and ex-vivo analysis using flow cytometry.

Tuulia Huhtala

As head of biomarkers and molecular imaging at Charles River Discovery Services, Finland, Tuulia Huhtala works to discover and advance applications of nuclear imaging solutions in drug development, specifically in the fields of CNS and oncological research. With broad experience in imaging, disease models, and ex vivo biomolecule analysis, she has contributed to 20 publications in peer-reviewed journals. After establishing Charles River's nuclear imaging unit, her team merged with the site's biomarker team. Studying bioscientific chemistry, Tuulia received her MSc and PhD in the University of Eastern Finland.

OXFORD GLOBAL CONFERENCES

FORTHCOMING EVENTS

OXFORD GLOBAL CONFERENCES

Biologics Series

UK

13th Annual Proteins & Antibodies Congress
27 - 29 April 2020 | London, UK

7th Annual Peptides & Oligonucleotides Congress
27 - 29 April 2020 | London, UK

2nd Annual Bispecifics in Discovery & Development Congress
27 - 29 April 2020 | London, UK

Co-located Events

Biomarkers Series

UK

15th Annual Biomarkers Congress
18 - 20 February 2020 | Manchester, UK

Genomic Markers Congress
18 - 20 February 2020 | Manchester, UK

Co-located Events

US

5th Annual Biomarkers & Precision Medicine USA Congress
15 - 16 October 2020 | San Diego, USA

Cell Series

UK

9th Annual Cell Culture & Bioprocessing Congress
06 - 07 October 2020 | London, UK

7th Annual Regenerative Medicine & Advanced Therapy Development Congress
06 - 07 October 2020 | London, UK

6th Annual Cell & Gene Therapy Manufacturing Congress
06 - 07 October 2020 | London, UK

Co-located Events

Formulation & Delivery Series

UK

6th Annual Formulation & Drug Delivery Congress
22 - 23 April 2020 | London, UK

5th Annual Inhalation & Respiratory Drug Delivery Congress
22 - 23 April 2020 | London, UK

Biomanufacturing Congress
22 - 23 April 2020 | London, UK

Co-located Events

US

3rd Annual Formulation & Drug Delivery USA Congress
17 - 18 March 2020 | San Diego, USA

3rd Annual Inhalation & Respiratory Drug Delivery USA Congress
17 - 18 March 2020 | San Diego, USA

Co-located Events

Immuno Series

UK

5th Annual Advances in Immuno-Oncology Congress
21 - 22 May 2020 | London, UK

Autoimmunity & Immunology Congress
21 - 22 May 2020 | London, UK

Co-located Events

US

3rd Annual Advances in Immuno-Oncology USA Congress
15 - 16 October 2020 | San Diego, USA

PharmaTec Series

UK

18th Annual Pharmaceutical IT & Data Congress
24 - 25 September 2020 | London, UK

4th Annual Artificial Intelligence in Drug Development Congress
24 - 25 September 2020 | London, UK

2nd Annual SmartLabs & Laboratory Informatics Congress
24 - 25 September 2020 | London, UK

Co-located Events

R&D Series

EU

21st Annual Drug Discovery Summit
26 - 27 May 2020 | Berlin, Germany

8th Annual Drug Design and Medicinal Chemistry Congress
26 - 27 May 2020 | Berlin, Germany

2nd Annual Neuroscience Drug Discovery Congress
26 - 27 May 2020 | Berlin, Germany

Co-located Events

NextGen Omics Series

UK

12th Annual Next Generation Sequencing & Clinical Diagnostics Congress
05 - 06 November 2020 | London, UK

8th Annual Single Cell Analysis Congress
05 - 06 November 2020 | London, UK

6th Annual Genome Editing Congress
05 - 06 November 2020 | London, UK

2nd Annual Digital PCR Congress
05 - 06 November 2020 | London, UK

Co-located Events

US

6th Annual Next Generation Sequencing USA Congress
07 - 08 April 2020 | Boston, USA

6th Annual Single Cell Analysis USA Congress
07 - 08 April 2020 | Boston, USA

4th Annual Genome Editing USA Congress
07 - 08 April 2020 | Boston, USA

Co-located Events

Register your interest, e-mail us:
info@oxfordglobal.co.uk