R&D SERIES

JUNE 2018 NEWSLETTER

Technologies, Tools and Advances
in Drug Discovery, Design & Chemistry

Innovation, Development & Commercialisation
in Microbiome Research

Revolutionary Optogenetic Technology

Daniel Zwilling, Circuit Therapeutics

Improving The Translation Of Disease Biology Through Phenomics

Paul Andrews, National Phenotypic Screening Centre, University of Dundee

Tackling The Antimicrobial Resistance Crisis

Sheila Connelly, Synthetic Biologics, Inc.

HOTEL PALACE BERLIN
6 - 8 JUNE 2018 | BERLIN, GERMANY

OXFORD GLOBAL CONFERENCES

Contents

This is an Interactive Newsletter.
You can click on elements such as website links or the contents below.

Meet the Team

Chris Davies
General Manager and Portfolio Directior

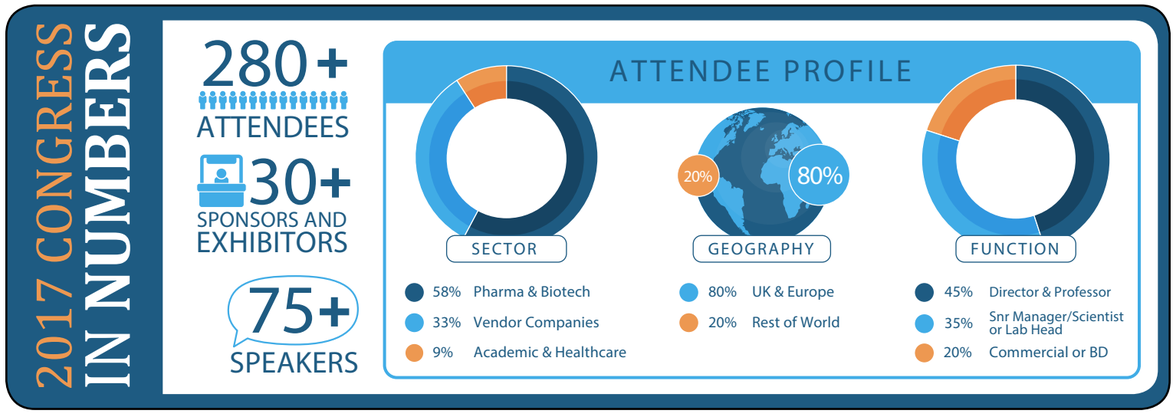
Lydia Millett
Head of Business Operations & HR

Jamie Morris
Delegate Sales Executive

Tim Richters
Portfolio Manager

Stefanie Castellanos
Conference Producer

Guillaume Alonso
Marketing Campaign Manager



WELCOME TO OXFORD GLOBAL'S R&D SERIES JUNE 2018 NEWSLETTER!

With the 19th Annual Drug Discovery Summit, 6th Annual Discovery Chemistry & Drug Design Congress and 2nd Annual Microbiome Discovery & Development Congress returning to Berlin over June 7th & 8th, I'm delighted to look back at the highlights of our 2017 event and offer some details on a few of the key features and new additions coming this year.

In 2017 the event bought together over 270 attendees to discuss and review leading drug discovery innovations and strategies, enabling technologies, novel drug targets and the latest developments in medicinal chemistry and drug design. Our inaugural Microbiome programme focused on exciting issues in the microbiome field, with topics including regulatory and commercial issues, dermatology, computational biology, probiotics and bacteriophages.

The 2018 event will welcome over 300 senior level attendees and will once again cover these 'hot topic' areas with over 60 presentations over two days, **bringing you the latest in drug discovery innovations and strategies, discovery enabling technologies and novel drug targets for key therapeutic areas**. We will be covering critical areas such as **new modalities in drug discovery, artificial intelligence driven target identification, drug target kinetics in drug discovery and ADMET strategies in drug discovery.**

New for 2018, we'll be including **deep dive sessions on DNA encoded libraries as well as presentations on data visualisation, protein-protein interactions, data visualisation and drug design**.

Our Microbiome programme will again focus on **novel strategies in microbiome research and the latest therapeutic trends, challenges and opportunities involved in commercialising microbiome therapeutics**. Further sessions will focus on subjects including **bioinformatics, translational modelling, genomic approaches, IP concerns, investment in the microbiome, the gut-brain axis and autoimmune disorders**.

There will also be opportunities to discuss the latest challenges, advancements and opportunities across the Discovery sector in our **Breakfast Briefing Roundtable Discussions**, and 2018 will once again include our '**Directors club' initiative**, offering leaders within the industry a range of benefits, both pre-event and onsite.

This year's event also sees the inclusion of a pre-event workshop hosted by the Chemical Computing Group on the 6th June. For further details please refer to the advert included later in this newsletter.

After a full day of learning, knowledge sharing and meeting new people, what better way to unwind after the first day of the congress than with a glass of wine (or two) at our official Drinks Reception, which will be followed by our Networking Dinner. The evening promises good food, good wine and great company!

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 Summit in June.

- Chris Davies, Portfolio Director

WHO IS ATTENDING?

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

- **350+ senior level delegates** representing leading biotech companies, global pharmaceutical organisations and internationally renowned academic institutions.
- **Directors, VPs, CEOs and Heads** of Drug Discovery, Drug Development, Drug Design and Medicinal Chemistry.
- **Highly esteemed members** of academic and government institutions.

These companies and many more:

AstraZeneca, abbvie, NOVARTIS, Lilly, UCB, Roche, BAYER, GlaxoSmithKline, MERCK, AMGEN, janssen, LEO, Johnson & Johnson, SANOFI GENZYME, Takeda

Sponsors 2018

GOLD

ELSEVIER

SILVER

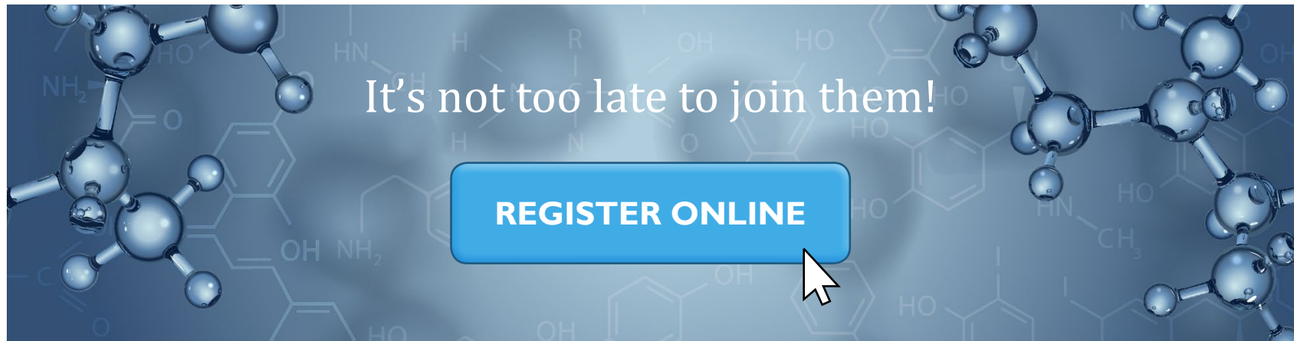
Chemotargets

BRONZE

CHEMICAL COMPUTING GROUP, discngine, CellSine, pivotpark screeningcentre, Onco design BIOTECHNOLOGY, QuayPharma

NETWORK AND PROGRAMME SPONSORS

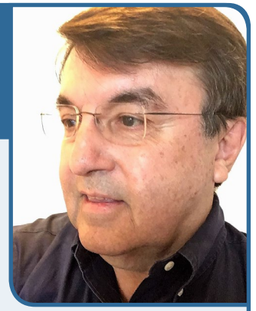
admescope, AnalytiCon discovery, FUJIFILM Cellular Dynamics, ChemAxon, domainex, dotmatics knowledge solutions, evotec, GalChimia, LABCYTE, Luminex complexity simplified., LYSANDO, MercachemSyncom, METABOLON, MIMETAS the organ-on-a-chip company, PALL FortéBio, PELAGO BIOSCIENCE, Recipharm good for business, SCHRÖDINGER, SYGNATURE DISCOVERY, WILEY, 药明康德 WuXi AppTec, ZYMO RESEARCH The Beauty of Science is to Make Things Simple



A UNIVERSAL BIOASSAY FOR IDENTIFYING ENZYME INHIBITORS

ERNESTO FREIRE

Henry Walters Professor, Johns Hopkins University



Ernesto Freire,
Henry Walters Professor,
Johns Hopkins University

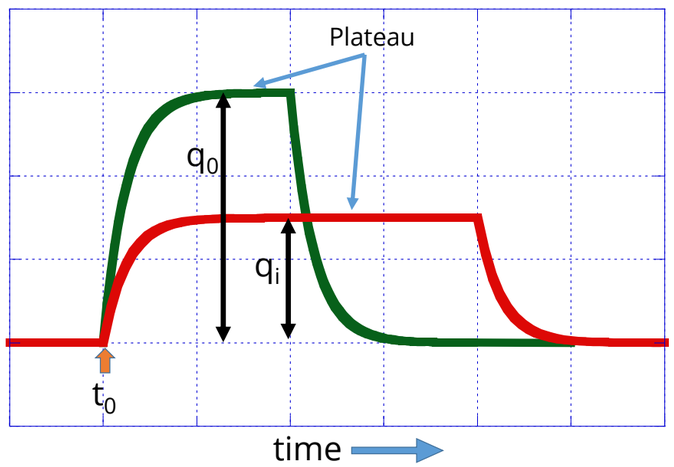
ERNESTO FREIRE is the Henry Walters Professor at the Johns Hopkins University. He is a member of the Department of Biology and Biophysics. He also holds a joint appointment in the Department of Biophysics and Biophysical Chemistry at the Johns Hopkins Medical School. Dr. Freire obtained his doctorate in Biophysics from the University of Virginia.

Dr. Freire is a world recognized expert in biological thermodynamics. He performs research in the thermodynamics of protein stability, protein-protein interactions, and protein-ligand binding. Dr. Freire has pioneered the development of drug design and optimization strategies using thermodynamic techniques. Dr. Freire is the author or co-author of over 260 publications and several patents. Dr. Freire is an Honor Member of the Spanish Society of Biochemistry and Molecular Biology, and a member of the Academy of Sciences of Latin America.

Most targets for drug development are enzymes and the search for small molecule inhibitors is a continuous and major endeavor in the pharmaceutical industry. Developing assays to measure enzyme activity and their inhibition by small molecules is often cumbersome, involving significant development time and investment. Often, developing an enzymatic assay requires the design of fluorescent substrates and sometimes the use of coupled reactions.

There is, however, a universal test for enzymatic reactions. It is well known that enzymatic reactions release energy in the form of heat and that this heat can be measured calorimetrically. The calorimetric test is universal and does not require an optically clear sample. It does not require especially designed substrates and utilizes the same amounts of enzyme as conventional assays.

In brief, if substrate is placed into the calorimeter reaction cell and at time zero a small amount of enzyme is added, the enzymatic reaction will begin and a curve like the green curve in the figure is observed. The calorimeter measures the rate of heat production as a function of time. Since the rate of heat production is proportional to the enzyme velocity or rate of substrate depletion (or product formation), at high substrate concentrations the plateau corresponds to V_{max}. If desired, the experiment can be performed at different substrate concentrations in order to determine K_m. Once the substrate concentration diminishes the signal also decreases until it reaches zero when the substrate is depleted. Under the same conditions but in the presence of an inhibitor the red curve is obtained. Note that the amplitude of the plateau (q_i) is smaller than the one observed in the absence of inhibitor (q_0). However, the area under both curves is the same since it is proportional to the total amount of substrate depleted. The degree of inhibition is simply ($1 - q_i/q_0$) thus providing a very easy way of evaluating the inhibitory potency of small molecules. Of course, more sophisticated analysis can be performed in order to determine the K_i. Calorimetric screening of small molecules at identical concentrations provides a fast and easy way of ranking a library of compounds in terms of their inhibitory potency ■

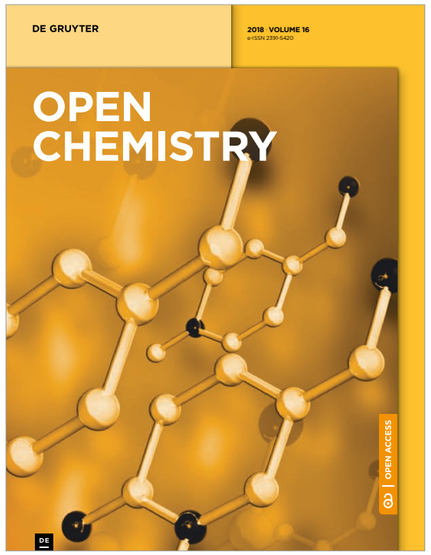


Ernesto Freire will be speaking at our 19th Annual Drug Discovery Summit.

Hear his presentation '*Thermodynamic-Based Selection And Optimization Of Lead Compounds*' on Day Two in the stream 'Lead Identification, Optimisation And Discovery Admet'.

OPEN CHEMISTRY is a peer-reviewed, open access journal that publishes original research, reviews and short communications in the fields of chemistry in an ongoing way. Our central goal is to provide a hub for researchers working across all subjects to present their discoveries, and to be a forum for the discussion of the important issues in the field.

Our journal is the premier source for cutting edge research in fundamental chemistry and it provides high quality peer review services for its authors across the world. Moreover, it allows for libraries everywhere to avoid subscribing to multiple local publications, and to receive instead all the necessary chemistry research from a single source available to the entire scientific community.



ISSN: 2391-5420

Impact Factor: 1.027

JOURNAL COVERS E.G.:

- Medicinal and Clinical Chemistry
- Natural Product Chemistry
- Organic and Inorganic Chemistry
- Materials and Biomaterials
- Catalysis
- Spectroscopy
- Analytical Chemistry
- Biochemistry and Biological Chemistry
- Environmental Chemistry
- Macromolecules and Polymers
- Electrochemistry
- Supramolecular Chemistry and Nanochemistry
- Radiochemistry & Nuclear Chemistry
- Surface Chemistry and Colloids
- Theoretical and Computational Chemistry

SPECIAL ISSUES:

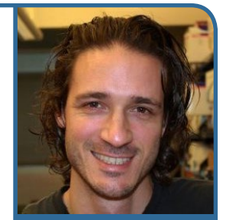
- Secial Issue on the 10th Polish Conference on Analytical Chemistry (POKOCHA 2018)
- Special Issue on the 2nd International Conference on Chemistry, Chemical Process and Engineering (IC3PE)
- Special Issue on the 13th Joint Conference on Chemistry (13th JCC)
- Special Issue on the 4th International Conference on Computational and Experimental Science and Engineering (ICCESEN-2017)
- Topical Issue on Environmental Chemistry
- Special Issue on the International Symposium on Materials Chemistry (ISyMC'18)
- Special Issue on the International Conference on Applied Biochemistry and Biotechnology (ABB 2018)
- Topical Issue on Bond Activation
- Topical Issue on Research for Natural Bioactive Products
- Topical Issue on Agriculture
- Topical Issue on Recent Advances in Marine Natural Products Chemistry

Speaker Q&A

REVOLUTIONARY OPTOGENETIC TECHNOLOGY

DANIEL ZWILLING

Modulating the nervous system with light to transform disease treatment



dzwilling@circuittx.com
www.circuittx.com

The need for novel approaches in CNS drug discovery for psychiatric and neurological diseases

There is a large unmet need worldwide for novel therapies in CNS diseases. Neuropsychiatrict diseases such as major depressive disorder, schizophrenia, autism, and anxiety impose a huge socio-economic burden on society and millions of affected patients are suffering from the debilitating symptoms of these conditions. However, the underlying disease mechanisms are still not well understood and current treatments provide limited relief. The three major classes of psychiatric drugs (anti-psychotic D2 antagonists, anxiolytic GABA receptor agonists and antidepressant monoamine reuptake inhibitors), have limited efficacy in reducing and controlling symptoms, and are often accompanied by significant side effects. Very few new treatments for neuropsychiatric conditions have entered the market during the last few decades and none have transformed treatment in any meaningful way. It is also becoming apparent that psychiatric diseases might be best viewed as spectrum disorders with defined combinations of symptom domains, rather than as monotonic disease states. Moreover, classical preclinical models of neuropsychiatric symptoms have not proven to be predictive of clinical outcomes. Using a combination of in vivo optogenetics, behavioral profiling and a proprietary single cell transcriptomics platform, Circuit Therapeutics has been able to dissect the neural circuitry that underlies specific symptoms and identify specific novel therapeutic targets that modulate those circuits.

What is optogenetics?

Optogenetics is a transformational technology that enables exquisite control of specific neurons and modulate their activity using a directed light source. With optogenetics, we can selectively control neuronal firing patterns in awake and behaving animals and gain insights into how a neuronal circuit influences behavior in normal and disease states. Optogenetics requires two key components: A light-sensitive protein, or opsin, and a light source. Depending on the wavelength, light can either activate neurons with excitatory opsins (e.g., channelrhodopsin), silence neurons with inhibitory opsins (e.g., halorhodopsin), or initiate cellular signaling cascades (e.g., OptoXR). Adjusting the location, strength and wavelength of the light allows for exacting control of the opsin activity. Furthermore, opsins can be selectively delivered to specific cell types. For example, cells with defined expression patterns within a given brain region can be targeted using localized delivery along with discerning expression strategies that harness cell type-specific promoters or transgenes. The opsin toolbox thus provides great flexibility and high specificity for modulating neuronal activity in vivo. By activating or inhibiting individual circuits in the central and peripheral nervous systems, we can alter neuronal activity, animal behavior, and model a specific disease symptom. This unique insight into how individual circuits contribute to symptoms or disease states enables the discovery of novel therapeutics.

Optogenetic Drug Discovery

Using optogenetics, we can identify the neuronal circuits that are responsible for behavioral symptoms of specific neuropsychiatric disease. Combining optogenetics with single-cell transcriptomics enables us to characterize the gene expression profiles of the neurons that are responsible for a given neuropsychiatric symptom. Finally, using the insights we gain into the symptomatic etiology of the disease and the molecular targets that associate with with symptoms, we can develop unique therapies with unprecedented efficacy. Optogenetics facilitates new ways to approach drug discovery and development for the treatment of brain disorders ■

Fig. 1 - What is optogenetics?

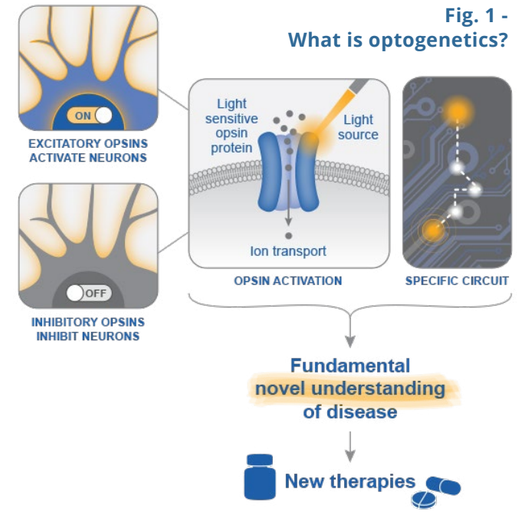
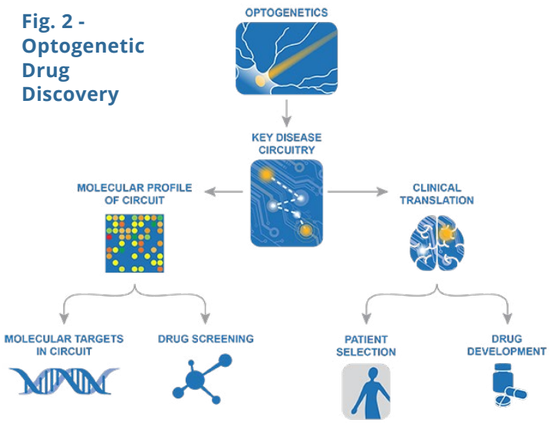


Fig. 2 - Optogenetic Drug Discovery



IMPROVING THE TRANSLATION OF DISEASE BIOLOGY THROUGH PHENOMICS

PAUL ANDREWS

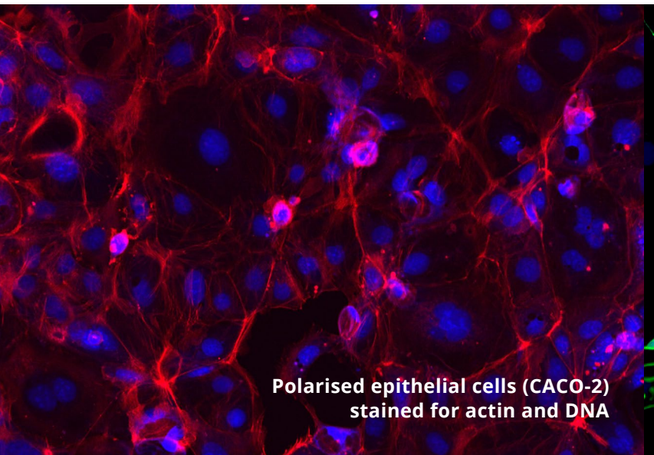
Director of Operations and Dundee Lab Head, National Phenotypic Screening Centre (NPSC), University of Dundee

Paul Andrews
Director of Operations and Dundee Lab Head, National Phenotypic Screening Centre (NPSC), University of Dundee

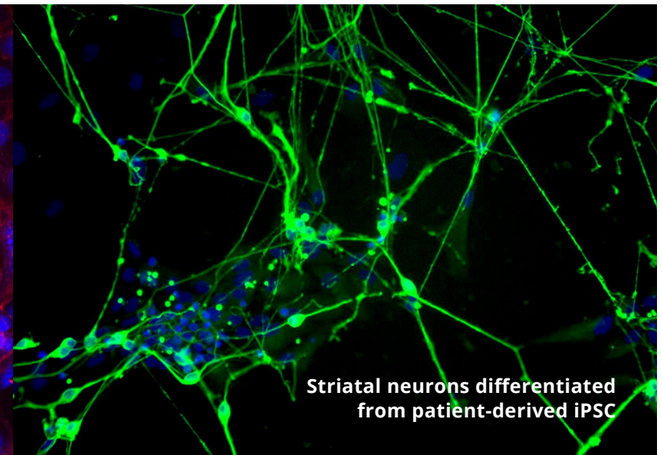
Paul holds an Honours Degree in Biochemistry and a Ph.D. in Molecular Biology from the University of Sheffield, UK and has over 25 years post-doctoral research experience encompassing biochemistry, molecular genetics, cell biology, quantitative imaging and since 2007 phenotypic drug discovery using stem cells. Paul has been working closely with the Scottish Universities Life Science Alliance and University of Oxford since 2013 to create the National Phenotypic Screening Centre, where he is now Director of Operations.

The National Phenotypic Screening Centre (NPSC) launched in 2015 after £10M of Scottish Government investment – with labs in three UK Universities renowned for their life sciences research: Dundee, Edinburgh and Oxford. NPSC's overall aim is to redress the balance in drug discovery by moving away from target-centric approaches, developing highly predictive assays and advance phenomics technologies. The driver for this is the persistent inefficiency in the drug discovery process: on average 90% of drugs fail to reach market due to failures in phase II/III clinical trials. A major contributing factor in this failure is that the traditional target-centric preclinical part of the pipeline is largely patient free, and relies on animal models of disease and toxicology, which often correlate poorly with human outcomes. The re-emergence of the phenotypic approach in drug discovery has been driven by these acknowledged shortcomings, coupled with the realisation that phenotypic approaches have historically been more successful in finding first-in-class medicines, and that before recombinant DNA technology led to target-based drug discovery domination in the 1980s, it was the way most drugs were identified. Despite great leaps in our understanding of fundamental processes in biology, we still struggle when it comes establishing the causative relationships and systems dynamics in more complex human diseases. A reductionist approach to pinpoint targets often fails to deliver when tested in the context of tissues, organs and living breathing humans. The renewed interest in more empirical strategies is partly due of the explosion in the availability of new biological tools including single cell -omics, stem cells and precision genome editing, alongside new imaging technologies and computation including machine learning and AI. The time has come for high throughput phenotypic biology to take centre stage in the hunt for new drugs.

There is a deep well of academic biology in the research community that remains somewhat untapped, for want of translational direction. We founded an industrial consortium framework called the Phenomics Discovery Initiative (PDi) that has successfully begun to address this problem by sourcing the best biology from academia and de-risking the development of more complex phenotypic assays for the industrial partner. The founding industrial partner is Janssen who have being working closely with NPSC staff on a wide range of assays from a highly complex air-liquid interface model of the human bronchus, to cancer stemness and immuno-oncology. PDi leverages NPSC's world class facilities, industry-standard operation and extensive global networks to either crowdsource or seek-out world-leading labs, working together to develop the best predictive biology platforms.



Polarised epithelial cells (CACO-2) stained for actin and DNA



Striatal neurons differentiated from patient-derived iPSC

Developing the most patho/physiologically-relevant assay possible is often non-trivial – sometimes it may be sufficient to have a cell model growing as a homogenous monolayer but in other circumstances 3D spheroids or multicellular co-culture models, or organoids are more appropriate (though very challenging with throughput); some assays involve cancer cells, some primary cells and others iPSC/stem cell-derived with extended differentiation times, and increasingly we find assays that have used CRISPR/Cas9 engineering. At NPSC around half of our assays are image-based and "high content" whilst the other half uses flow cytometry. High content analysis (HCS) is especially powerful because it unlocks a rich source of quantitative information about single cells, groups of cells and tissues that describes their properties and responses to intrinsic cues and extrinsic perturbations. When HCS is applied to good biological assays, this so-called phenomics approach represents a powerful and highly informative first step in the drug discovery process, that should deliver more information, earlier, for medchem and safety-oriented decision-making. Phenomics is also valuable because it can extract multiscale and multiplexed data (eg probing heterogeneous cell-level behaviour and subcellular processes, or even single molecules, simultaneously) and can quantitatively measure endpoints or live events on timescales ranging from milliseconds to several days. A phenotype can be molecular or pathway-centric – examining the changes in specific proteins – or more holistically probing a multitude of readouts of cell physiology. Both approaches have value. Historically, the majority of phenotypic screens were carried out using one or two parameters, which is not as informative and risks bias towards a narrow hypothesis at the expense of understanding the wider effects that a compound has on cell behaviour. In contrast, a much more powerful approach is to extract hundreds or thousands of parameters from each experimental condition and build a phenotypic fingerprint or "phenoprint" that describes the complex responses cells have when exposed to different perturbing agents. The significance of many of these parameters may not be comprehensible to the screening scientist, but nonetheless act as signatures of underlying alterations in biology. By assembling data on the way drugs or chemical tool compounds of known target specificity perturb phenoprints, we can use machine or deep learning approaches to infer the mode of action of hits from chemical library screens. Indeed, a remarkable recent study (Semm et al, 2018), demonstrated machine learning can predict the activities of compounds in hundreds of biochemical assays from a single image-based screen. The future of phenotypic drug discovery promises to be an exciting one ■

Hear Paul's presentation '*The Phenomics Discovery Initiative: Priming The Industrial Drug Discovery Pipeline With The Best Disease-Relevant Biology*' on Day Two, in the stream 'Successful Phenotypic Drug Discovery And Other High Content Screening Tools'.

MaaT Pharma - **M**icrobiota **a**s **a** **T**herapy

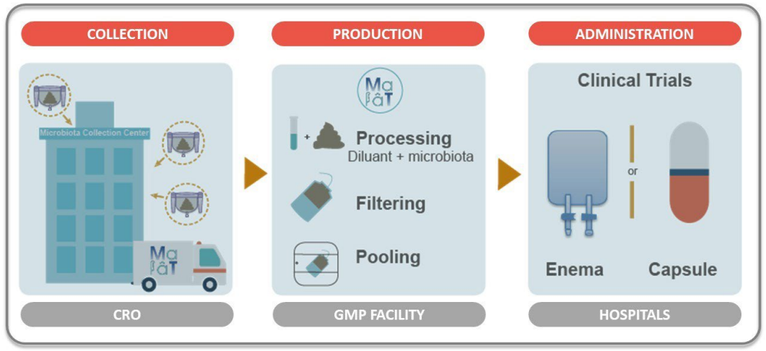
Our Vision:

Be the industry leader for the treatment of Gut Microbiota alteration (so-called dysbiosis) using patient-specific microbiotherapy in patients with serious medical conditions.

We believe that another approach is possible when it comes to treating gut microbiota alteration. Microbiome-based products are the new generation of treatment and will be a critical addition to the current therapeutic arsenal. In this context, **Fecal Microbiota Transfer (FMT)** is a unique technology that allows to restore a beneficial microbiota but also acts at once on all features of host-microbes symbiosis. It has been demonstrated that FMT can successfully treat recurrent Clostridium difficile infection, but it may also have **therapeutic potential** for other diseases.

1st EU GMP Platform

MaaT Pharma **has established the first GMP platform in Europe** supporting the development and manufacturing of FMT-based drugs. MaaT Pharma has developed patented **devices** (collection device, storage bag and administration system), and industrialized a **manufacturing process**, in order to preserve the viability, diversity and original profile of the microbiota at all stages, from collection of raw faeces to administration of the FMT. MaaT Pharma is able to provide an **active, safe, standardized and ready-to-use FMT**, manufactured according to the **Good Manufacturing Practices (GMP)**. The current IMP is an **Enema** but we are currently developing patient-friendly solutions **(Capsule)** as an alternative to rectal administration for appropriate patients.



Our Mission:

Our initial goal is to develop a series of microbiome-based drugs targeting mortality and comorbidities associated with **blood cancer** treatments. Our revolutionary and rapid approach will contribute to the **evolution of treatment therapies** in oncology.

Our initial goal is to develop drugs targeting mortality and comorbidities associated with blood cancer treatments. **Acute Graft-versus-Host Disease (aGvHD)** is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT), occurring in about one out of two patients, and **leading to a one-year death rate of 70-80% in the corticosteroid-refractory population.**

MaaT013, our main drug candidate is developed to treat acute GvHD through the correction of gut microbiota disturbance allowing restoration of immune tolerance, metabolic balance and the barrier function effect for protection against infections. **MaaT Pharma** received authorization from competent authorities to **launch its phase II prospective multicenter clinical trial in France.** This clinical trial is planned to be extended rapidly to Germany, Poland and Italy.

COLD SPRING HARBOR

Molecular Case Studies

A New Journal in Precision Medicine

Cold Spring Harbor Molecular Case Studies is an open-access, peer-reviewed, international journal in the field of precision medicine. Articles in the journal present genomic and molecular analyses of individuals or cohorts alongside their clinical presentations and phenotypic information. The journal's purpose is to rapidly share insights into disease development and treatment gained by application of genomics, proteomics, metabolomics, biomarker analysis, and other approaches.

The journal covers the fields of cancer, complex diseases, monogenic disorders, neurological conditions, orphan diseases, infectious disease, gene therapy, and pharmacogenomics. It has a rapid peer-review process that is based on technical evaluation of the analyses performed, not the novelty of findings, and offers a swift, clear path to publication. Articles types include Research Reports that present detailed case studies of individuals and small cohorts, Research Articles that describe more extensive work using larger cohorts and/or functional analyses, Rapid Communications presenting the discovery of a novel variant and/or novel phenotype associated with a known disease gene, Rapid Cancer Communications presenting the discovery of a novel variant or combination of variants in a cancer type, Follow-up Reports linked to previous observations published in the journal, and Variant Discrepancy Resolutions describing efforts to resolve differences or update variant interpretations in ClinVar through case-level data sharing.

Why submit to *Cold Spring Harbor Molecular Case Studies*?

- Rapidly share insights into disease development and treatment
- Open Access to ensure your manuscript is seen by researchers, clinicians, and patients
- Specializes in individual (n=1) and small cohort studies utilizing genomics and biomarker analyses in cancer and other fields
- Rapid peer review evaluating technical merits of the study
- Immediate online publication upon acceptance

Visit *CSH Molecular Case Studies* for additional information about the journal or https://submit.molecularcasestudies.org/ to submit your case report.

TACKLING THE ANTIMICROBIAL RESISTANCE CRISIS

SHEILA CONNELLY, PHD

Vice President Research, Synthetic Biologics, Inc.

Sheila Connelly, PhD,
Vice President Research,
Synthetic Biologics, Inc.

Dr. Connelly is Vice President, Research, at Synthetic Biologics, Inc., a clinical-stage company focused on gut microbiome therapeutics to protect and restore patient health. She has over 20 years of experience in the biotechnology and pharmaceutical industries ranging from start-ups to large pharma. She served as VP Research at GrayBug Vision, Inc., a Johns Hopkins University spinout and cofounded Advanced Vision Therapies, Inc., both ocular therapeutic startups. Dr. Connelly served as Senior Director of Translational Research with Intrexon, Corp., and as Group Leader at Genetic Therapy, Inc., a Novartis Company. She published over 40 peer-reviewed scientific articles and has numerous research grant awards and issued patents. Dr. Connelly earned her PhD in Molecular Biology from Columbia University and completed postdoctoral training under an awarded NSF fellowship at the Friedrich Miescher Institute for Biomedical Research in Basel, Switzerland.

Antimicrobial resistance (AMR), declared by the World Health Organization (WHO) to be "a global health emergency seriously jeopardizing progress in modern medicine", is responsible for 700,000 deaths per year. Widespread use of antibiotics in agriculture and healthcare has contributed to this AMR crisis resulting in the rampant emergence of multidrug resistant pathogens, aptly described as "nightmare bacteria" by the Centers for Disease Control and Prevention. Such "superbugs" are frequently capable of transferring resistance genes to other species, further complicating this serious and escalating threat. Development of urgently needed new antibiotics has decreased precipitously since 2000, due to steep capital commitments, reduced economic incentives, and onerous regulatory requirements. Consequently, focus has shifted to preserving the efficacy of currently marketed antibiotics to counter resistant microorganisms. Not surprisingly, the single most important factor inducing AMR is exposure to antibiotics.

A pragmatic approach to mitigate AMR is to reduce microbial antibiotic exposure without compromising therapeutic benefit. To this end, nontherapeutic use of medically important antibiotics in agriculture was banned in the United States and European Union, and national antibiotic stewardship polices were adopted to guide prescribers on prudent antibiotic use. Despite the intent of these measures to reduce per capita antibiotic consumption, the Center for Disease Dynamics, Economics & Policy reported a 65% increase in worldwide antibiotic use from 2000 to 2015 and projected consumption to rise an additional 200% from 2015 to 2030 [1]. Especially disturbing was the observed sharp upsurge in use of last-resort compounds such as carbapenems and polymyxins [1]. Therefore, an urgent need exists for the development of new tactics to maintain antibiotic efficacy to preclude the apocalyptic scenario predicted by the WHO of "a post-antibiotic era in which common infections and minor injuries, which have been treatable for decades, can once again kill".

An innovative strategy in the war against AMR, complementary to judicious antibiotic use, is to limit antibiotic exposure within the gut, a site of high microbial density and a known reservoir of resistance genes. Many antibiotics, including parenterally administered agents, are excreted at high concentrations into the GI tract where they damage the gut microbiome, provide selective pressure for AMR evolution, and can lead to overgrowth of opportunistic pathogens such as *Clostridium difficile*. A novel therapeutic, SYN-004 (ribaxamase), being developed by Synthetic Biologics, Inc., is an orally-delivered beta-lactamase enzyme intended to selectively inactivate antibiotics in the GI tract to protect the microbiome and to reduce emergence of AMR.

Beta-lactamases, generally considered the "enemy", are natural, bacterial-derived enzymes that degrade beta-lactam antibiotics, confer antibiotic resistance, and dramatically complicate the treatment of bacterial infections. Synthetic Biologics, Inc. has harnessed the potent antibiotic hydrolyzing power of this enzyme class to develop a prophylactic intervention intended to inactivate selected beta-lactam antibiotics in the GI tract prior to reaching and harming the colonic microbiota. Ribaxamase was engineered from the *Bacillus licheniformis* PenP enzyme, a penicillinase, to broaden its antibiotic degradation spectrum to include most cephalosporins and is intended for use with intravenously administered penicillins and cephalosporins. Ribaxamase is manufactured in *E. coli* and is formulated for oral delivery into enteric-coated pellets to protect the enzyme from stomach acid. Upon reaching a pH of 5.5 or greater in the upper small intestine, the enzyme pellets dissolve and release ribaxamase. Animal studies evaluating ribaxamase verified that antibiotic inactivation in the upper GI tract protected the gut microbiome and reduced emergence of AMR without affecting systemic antibiotic levels. Further examination of this prevention approach in a phase 2b clinical study demonstrated that ribaxamase significantly reduced *Clostridium difficile* infection in high-risk patients who were receiving ceftriaxone for treatment of a lower respiratory tract infection without compromising pulmonary infection control. Ribaxamase protected the patients' gut microbiomes from antibiotic damage and diminished emergence of AMR.

To broaden the utility of this beta-lactamase technology, pipeline products are being developed by Synthetic Biologics, Inc. to expand microbiome protection to oral antibiotics and carbapenems. For use with oral beta-lactams, a ribaxamase formulation, SYN-007, was engineered for release in the lower small intestine distal to the site of antibiotic absorption. Evaluation of SYN-007 in a canine model of oral amoxicillin-mediated gut microbiome dysbiosis demonstrated that SYN-007 protected the microbiome from antibiotic damage and reduced AMR emergence. SYN-007 did not significantly affect amoxicillin blood levels indicating that the beta-lactamase was not released prematurely and did not degrade the antibiotic prior to its systemic absorption. To expand microbiome protection to carbapenem antibiotics, a novel carbapenemase, SYN-006, was identified. SYN-006 is a metallo-beta-lactamase derived from *Bacillus cereus* that hydrolyzes all classes of beta-lactam antibiotics including penicillins, cephalosporins, and carbapenems. SYN-006 was formulated into enteric-coated pellets intended for oral delivery and release in the upper small intestine. Evaluation of SYN-006 in pigs that received an intravenous carbapenem antibiotic, ertapenem, demonstrated diminished antibiotic-mediated microbiome damage and reduced AMR gene propagation in the presence of SYN-006. These data demonstrate that ribaxamase, SYN-007, and SYN-006 have the potential to protect the gut microbiome from antibiotic-mediated damage and to diminish evolution, emergence, and spread of AMR.

Reducing microbial antibiotic exposure is a promising strategy to mitigate AMR that has the potential to contribute to solutions for the global AMR crisis. Antibiotic inactivation represents a new intervention paradigm to preserve the gut microbiome by limiting antibiotic collateral damage and is complementary to other AMR initiatives, such as antibiotic stewardship, intended to prolong the utility of life-saving antibiotics. Ribaxamase represents an innovative approach envisioned for use in conjunction with ongoing interventions to provide another weapon in war against AMR ■

1. Klein, Eili Y et al., "Global increase and geographic convergence in antibiotic consumption between 2000 and 2015". Proc Natl Acad Sci USA. 2018 Mar 26. doi: 10.1073/pnas.1717295115.

COMPLIMENTARY PRE-CONGRESS WORKSHOP

Computational Ligand and Structure-Based Drug Design

Chemical Computing Group
Complimentary Pre-Congress Workshop

Sponsored by

CHEMICAL COMPUTING GROUP

Date: June 6th 2018

Venue: Hotel Palace, Budapesterstr. 45, 10787 Berlin

Aim of the Workshop

To aid the progression of drug design and discovery projects computationally, with or without protein-ligand structural knowledge.

Workshop Summary

Computational methods for aiding drug discovery are now widely available and applied in situations where there is the presence (Structure-Based Drug Design) or absence (Ligand-Based Drug Design) of crystal structure information about the bound states of active molecules with their targets. The workshop will illustrate a range of computational techniques through demonstration using the MOE software. Trial copies of MOE can be provided by contacting info@chemcomp.com

WORKSHOP PROGRAMME

12:30	**Registration and Lunch**
13:30	**Ligand-Based Drug Design and SAR Analysis** R-Group Profiles and Analysis / MOEsaic / MMP Analysis / Descriptor Calculations / Conformational Searching / Molecular Alignments / Pharmacophore Modeling and Searching / Diversity Analysis
15:00	**Refreshment Break**
15:30	**Structure-Based Drug Design** Pharmacophore Modeling / Docking / Fragment-based Design / Scaffold Replacement / R-Group Screening / Project Search / Protein-Ligand Interaction Fingerprints
17:00	

This complimentary workshop is part of the 19th Annual Drug Discovery Summit.

To sign up, please be sure to select it when making your booking. Contact **operations@oxfordglobal.co.uk** for more details.

5TH ANNUAL DRUG DISCOVERY USA CONGRESS

If you are looking for a US-based Drug Discovery event, look no further than our **5th Annual Drug Discovery USA Congress**, taking placing 11 - 12 October 2018 in San Diego, USA.

More details can be found at:

www.discoveryusa-congress.com

You don't need to wait until future events to get involved!

Our LinkedIn and Twitter groups are an excellent way of keeping up to date on the industry and with your peers.

Follow @DrugDiscovery1 on **Twitter** and join the conversation with #DDSummit18

>> Follow @DrugDiscovery1

Connect and network with industry and academic peers through our Drug Discovery & Development Network **LinkedIn** group.

>> Join our LinkedIn group

Listen to our complimentary webinar recordings, in which our expert speakers shared their insights in the lead up to this year's event.

>> Drug Discovery Webinars

>> Microbiome Webinar

FORTHCOMING EVENTS

OXFORD GLOBAL

Biologics Series

APR 2019	12th Annual Proteins & Antibodies Congress	London, UK
	6th Annual Peptides Congress	London, UK
	6th Biennial Biosimilars & Biobetters Congress	London, UK

Co-located Events

Genomics Series

MAY 2019	2nd Annual Genome Editing USA Congress	Boston, USA
	2nd Annual Advances in Transgenic Technology USA Congress	Boston, USA
	Synthetic Biology USA Congress	Boston, USA
OCT	4th Annual Next Generation Sequencing & Clinical Diagnostics USA Congress	Boston, USA
	4th Annual Single Cell Analysis USA Congress	Boston, USA
	Industrial Synthetic Biology Congress	Munich, Germany
NOV	10th Annual Next Generation Sequencing & Clinical Diagnostics Congress	London, UK
	6th Annual Single Cell Analysis Congress	London, UK
	4th Annual Genome Editing Congress	London, UK
	Synthetic Biology Congress	London, UK

Co-located Events

Cell Series

OCT	4th Annual Cell & Gene Therapy Congress	London, UK
	7th Annual Cell Culture & Bioprocessing Congress	London, UK
	5th Annual Stem Cell & Regenerative Medicine Congress	London, UK
	Biobanking Congress	London, UK

Co-located Events

R & D Series

FEB 2019	14th Annual Biomarkers Congress	Manchester, UK
MAR 2019	2nd Annual Formulation & Drug Delivery USA Congress	San Diego, USA
	2nd Annual Inhalation & Respiratory Drug Delivery USA Congress	San Diego, USA
MAY 2019	4th Annual Formulation & Drug Delivery Congress	London, UK
	3rd Annual Inhalation & Respiratory Drug Delivery Congress	London, UK
	3rd Annual Advances in Immuno-Oncology Congress	London, UK
JUN	19th Annual Drug Discovery Summit	Berlin, Germany
	6th Annual Discovery Chemistry & Drug Design Congress	Berlin, Germany
	2nd Annual Microbiome Discovery & Development Congress	Berlin, Germany
	2nd Annual Precision Medicine Congress	Munich, Germany
OCT	5th Annual Drug Discovery USA Congress	San Diego, USA
	3rd Annual Biomarkers & Precision Medicine USA Congress	San Diego, USA
	Advances in Immuno-Oncology USA Congress	San Diego, USA

Co-located Events

PharmaTec Series

SEP	16th Annual Pharmaceutical IT Congress	London, UK
	2nd Annual Artificial Intelligence in Drug Development Congress	London, UK
	Digital Health and Digital Technologies Congress	London, UK

Co-located Events

Biotech Investment Series

MAY 2019	Biotech Investment Showcase & Start Up Slam	London, UK

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