The British Toxicology Society awards bursaries to individuals in non-profit making educational or research organisations to support their attendance at EUROTOX and IUTOX meetings in addition to bursaries for domestic **bts** meetings, such as the annual Congress. Priority is given to students and Early Career Toxicologists. For more information on how **bts** bursaries are awarded and the eligibility criteria visit: http://www.thebts.org/Meetings/Bursaries.aspx

OVERALL CONGRESS PERSPECTIVE

The 2018 BTS Congress took place in Newcastle Gateshead, at the Hilton hotel which provided scenic vistas over the Tyne bridge and most of the city. After an introduction by Dr. Ernie Harpur, Syril Pettit gave a motivating plenary lecture on the need of toxicologists to focus on the 'last mile problem'. This was followed by the first two symposia in parallel. During the first coffee and refreshment break, there was a jovial atmosphere of people reconnecting with each other and new introductions being made. The AGM, my first, followed and the effort and dedication by the volunteers who keep the BTS running was apparent. The formal part of the day was finished off with a wine and canape reception, kindly support by ForthTox.

The first evening ended with BTS Specialty Section Networking and the Early Career Networking session. The latter of these was very well attended with enough young career scientists to form 5 teams for a competitive yet friendly pub quiz. Our collective creative limits were hit with the winning team name "intoxicated". The evening concluded with an agreeable trip across with river to sample the delights of Newcastle's restaurant scene.

By the next day, Tuesday 17th April, the congress was well under way. The introductions from previous day led to both serious and more light-hearted conversations during the coffee and lunch breaks. Discussions based off the talks, oral reports and posters led to mixing of both industry and academia, with the promise of further collaboration in the future.

The social highlight of the Congress, the Gala Dinner, started with drinks provided by ApconiX. Coinciding with the delicious food, the prizes were awarded and a speech from the new BTS President, Dr. Chris Powell, which was well received. Sadly, the evening's entertainment, the band Gotcha!, raised the roof a little too much – with a power cut caused by breaching noise levels. The evening was far from ruined, with networking continuing until late in the night at the hotel bar.

The Congress ended on Wednesday afternoon, leaving many of the attendees looking forward to the next one, in Cambridge in 2019.

Ben Alexander-Dann, University of Cambridge

PLENARY LECTURE

The Plenary of this year's BTS Annual Congress was delivered by Mrs Syril Pettit, Executive Director of the Health and Environmental Sciences Institute (HESI) at Washington DC. This, the first talk of the conference, gave an overview of HESI's work, as well as ideas and advice about how to improve the outcomes of collaborative scientific research to better solve problems in toxicology and public health overall.

Mrs Pettit described a problem in current toxicological research which may broadly be summarised as poor implementation of the outcomes of research data. While today's resources and technology may enable researchers to investigate ever more challenging topics in science and health, the translation of this knowledge into genuine solutions to global issues is less than often achieved.

This 'translation problem' was loosely compared to the 'Last Mile problem' in the energy industry, in which the greatest challenge to the supply of electricity is overcoming difficulties encountered during the final stage of distribution to the consumer. In this analogy, the Last Mile of public health research would presumably be the use of novel scientific understanding to positively impact global health. While the Last Mile of the energy industry is typically described as a problem of logistics and efficiency, Mrs Pettit argues that our Last Mile can be overcome with carefully planned collaboration between government, private companies, and academic institutions.

Central to this concept is the workflow that HESI has adopted, which responds to matters affecting public health and the environment with a structured, outcome-oriented approach to collaboration between interested parties and policymakers. In this way, it was explained that collaboration may be regarded as a tool to solving big problems, but only when organised and managed sensibly, with a final outcome in mind from the beginning.

One of HESI's success stories that was mentioned is RISK21. Notably, as the congress progressed, a number of speakers made of use of the RISK21 graphic to illustrate their research. This visualisation tool produced by HESI in 2014 displays toxicological data on universal axes to simplify risk assessment, and it was encouraging to see it being used in context.

The plenary lecture provided a thought-provoking start to the congress, and Mrs Pettit's message was particularly relevant to later sessions on advanced in-vitro models for toxicology, as well as the cautionary lecture from Prof Lewis Smith (Paton Prize Lecture) – Will the investment of time and resources into emerging technologies for novel in-vitro assessment of toxicity yield results that prove translatable to the clinic, or public health policy, in the long term?

Thomas Mulroney, MRC Toxicology Unit, University of Cambridge

SYMPOSIUM 1

Symposium 1: Liver disease and environmental cause of liver disease The first symposium was chaired by Dr Sarah Judge (Newcastle University) and Dr Dominic Williams (AstraZeneca, UK).

The first talk by Professor Fiona Oakley (Newcastle university) was entitled “Introduction to liver disease”. She started with the impact of liver disease on economy as it cost the NHS 2.4 billion pounds annually and it is the 5th highest cause of death in the UK with predictably increasing prevalence. Inflammation is the common pathway in liver disease which is caused by inherited disease, alcohol, viruses, obesity, autoimmune disease and drug induced liver disease. She added that until today there is no proven treatment for liver fibrosis which is the result of any liver injury from any aetiology apart from liver transplantation. Then she explained the strategy of any fibrotic drugs and the potential drug targets through limiting tissue damage, supressing inflammation and inhibiting/reversing fibrogenesis. Finally she explained how to study liver disease and the models of approach, through extraction of fibroblasts and exposing them to different stimuli, but there are limitations for using this model. In addition she went through the animal studies used, for example CCl4 model in rat and chemical model of biliary disease in mice and rats and described the advantages and disadvantages of each model.

The second talk was hosted by Dr Patricia Lalor (University of Birmingham) whose talk was titled “Hepatic response to injury in liver disease”. Dr Lalor started by describing the types of liver injury and highlighted the importance of liver disease and the need of efficient diagnostic measures and treatment in the UK. Then she showed how liver injury happens, how the liver can regenerate to a point and how the mechanism behind the irreversible damages due to paracetamol or acute alcohol exposure are still not fully understood. Dr Lalor research focuses on trying to understand the measure to control inflammatory disease and she developed human tissue model to uncover the spatial localisation. Also using human liver samples to permit ex-vivo perfusion assays, but this model is useful for 24 hours only and it is useful in cases of paracetamol toxicity. She was able to isolate different liver cells like STAB2 and LYVE1. Moreover, she also developed a murine model to consider the role of the immune system in paracetamol and alcohol –induced hepatotoxicity and highlighted the role platelets play in liver disease that is ‘time localisation’ dependent. Finally she concluded that the strategies to interfere with interactions between platelets and immune system might have a therapeutic benefits.

The third talk was “Immunological mechanisms underlying drug- induced liver diseases” presented by Professor Guru Aithal (University of Nottingham). Prof Aithal started by defining the term drug induced liver disease ‘DILD’ which is acute onset liver injury attributed to a medication taken in a therapeutic dose that is not predictable by its pharmacological action and it is usually acute and not related to overdose. Then he presented several cases where liver injury raised from using medications. In addition, he explained the mechanism of pathogenesis that lead to formation of reactive metabolites which in turn initiate an immune response causing DILD.

Prof Matt Wright (Newcastle University) finished the session with a talk entitled “looking for toxins in the environment that could be associated with triggering the liver disease PBC” he started by defining primary biliary cholangitis (PBC) that could be triggered by environmental factors such as xenobiotic exposure. He added that more than 90-95% of patients have high levels of serum anti- mitochondrial antibodies (AMA) and it is more common in female than male (10:1). PBC is an autoimmune disease caused by multifactorial causes with environmental factors having an important role, like chemicals, hair dyes and cosmetic use. Prof Wright addressed a question “what were we supposed to be doing?” Then he hypothesised that there are chemicals in the environment (soil) that could trigger PBC. In addition, he explained how they successfully identified chemicals from soil, such as M8OI, which have the ability to inhibit mitochondrial enzymes and induce apoptosis. Finally he suggested that their studies could be a cost-effective approach to screen the presences of xenobiotic in the environment.

Israa Al-Banaa, Newcastle University

SYMPOSIUM 2

Symposium 2 with the theme “Respiratory toxicity and lung pathology” was held on the first day of The British Toxicology Society (BTS) Annual Congress 2018 (16th – 18th April). It was chaired by Dr. Jo Kilgour from Regulatory Science Associates, UK and Dr. Catherine Ross from Covance, UK.

The symposium was kicked off with Dr. Colin Fish’s presentation which entitled “Responses of the respiratory tract to toxic injury: adverse vs non-adverse findings and impact on drug development”. Dr. Colin fish heads a world-wide group of non-clinical safety and disposition project team members in GSK. Using animal models and STP guidance, the speaker discussed “adverse” and “non-adverse” toxic injury in the respiratory tract. The speaker also illustrated real but anonymised examples to show the process of translating toxicology findings in the respiratory tract to risk assessment for clinical trials of pharmaceuticals. These examples included cases where progression has been possible despite “adverse” findings and “non-adverse” findings that has delayed development.

The second talk which entitled “Nanoparticle toxicology” was presented by Dr. Rodger Duffin who is currently a Senior Lecturer in Respiratory Medicine within the Centre for Inflammation Research at the University of Edinburgh. According to Dr. Rodger Duffin, combustion-derived nanoparticles (CDNP), which originate from a number of sources and pose a hazard to the lung, can generate free radicals and induce oxidative stress and inflammation. Nevertheless, the adverse effects of NP are much less understood. Thus, it is a considerable challenge to understand the potential toxicology surrounding environmental and occupational NP exposures.

Professor Frank Kelly who is the Director of the NIHR HPRU on the Health Impact of Environmental Hazards at King’s College London, presented the third talk which entitled “Air pollution and public health: emerging hazards and improved understanding of risk”. Air pollution such as smog may cause susceptible individuals undergo an acute exacerbation requiring increased medication or admission to hospital. Of greater concern, however, is the modern day air pollutants particulate matter (PM) which is invisible at ground level but is linked with a wide range of chronic health effects. The speaker also highlighted that over the past ten years public awareness and understanding of the problem has improved.

The symposium was ended with Dr. Kev Dhaliwal’s presentation which entitled “Optical molecular sensing and imaging of human disease in situ”. He is the Professor of Molecular Imaging and Healthcare Technology at the MRC Centre for Inflammation Research in the Queen’s Medical Research Institute (QMRI) and Consultant Physician in Respiratory Medicine. The speaker pointed out that advances in sensing infection, inflammation and fibrogenesis and in developing sensing technology can help to better understand distal lung pathology. For further information, readers may log on to www.proteus.ac.uk to find out the work to date and approaches being taken by the Proteus team in Edinburgh to develop optical molecular imaging for pulmonary pathology.

Cheong poi Yee, Monash University Malaysia

EARLY CAREER PRIZE LECTURE

The talk entitled "Role of Nrf2 in protection against drug-induced disease" by Dr Ian Copple was very interesting and motivating. It was inspirational to hear what an early career scientist can achieve with enough effort and dedication to his career.

Topics like how drugs or their metabolites can alter homeostasis or even be the cause of diseases are highly important as several current therapies can have risks due to side effects. An example is cisplatin-induced nephrotoxicity or ototoxicity. Other relevant drugs can be toxic in different kinds of tissue, for example bleomycin to the lung or paracetamol to the liver.

In this talk Dr Copple explained how the nature of the Nrf2 system can be used in a better way than currently using markers for drug toxicity detection and there is a possibility to use or modulate it to reduce drug toxicity.

Dr Copple emphasized the importance of understanding the transcription factor Nrf2 for therapeutic purpose. It can be involved in the efficacy and toxicity of drugs and it might determine the drug-induced stress susceptibility of an individual. Furthermore, a controlled and safe activation of Nrf2 can be of therapeutic use against diverse diseases, even if they are not drug induced.

During the talk, the use of different models (human cells and whole animals) to help address the challenges in drug safety for existing or new therapies was also shown.

I left the Congress with a very good impression of the BTS. I was able to expand my knowledge on a several different areas of toxicology. Having the opportunity to see how different kinds of research are performed is very useful as it has inspired me to introduce new perspectives into my own research. Meeting importantly personalities coming from different fields presented the opportunity to increase my network of contacts which is very important for pre-doctoral and early career scientists. I am very grateful for the opportunity to talk about the research conducted in our laboratory through the poster session, where I received encouraging feedback and several good suggestions for future work.

Misael Corral, University of Aberdeen

SYMPOSIUM 3

This symposium was a joint session between the BTS and the In Vitro Toxicology Society (IVTS) and focused completely of the cellular models and their uses for toxicology testing.

The first talk was presented by Professor Barbara Rothen-Rutishauser and was entitled “In vitro systems to study the toxicology of particles and drugs at the epithelial lung tissue barrier”. This talk focused on 3D lung models that have been developed and characterised to represent in vivo as close as possible. Using air-liquid interface cultures to represent a realistic exposure route to investigate the potential health effects of drugs, particles and nanoparticles. However, as good as these models are becoming they also have their own individual limitations.

Next was “Synthetic lung lining fluid model for testing inhaled pharmaceuticals” presented by Dr Ben Forbes and focused on the development of lung lining fluid. This is a very under developed field when compared to GI fluid synthesis and use and the aim of this presentation was to discuss the development and potential production of a synthetic biocompatible lung lining fluid that could be stored without degradation for a short period of time. The message from the presentation is that there is no optimal model for the components of this fluid and the contents depends on what is being investigated. The addition of lung lining fluid will be important in future advanced lung model development as the interaction between particles and the fluid will have an impact on the particle surface and the contact within the lung and the immune system.

The third talk was entitled “Complex organ-on-chip technology meets routine laboratory work. A breathing human alveolus-on-chip model for in-vitro drug transport and safety studies.” and was presented by Dr Nina Hobi. This presentation focused on the development of a lung on a chip. The majority of companies have focused on liver and gut models with lungs on a chip being slightly neglected to date. The model being developed incorporates mechanical strain (through negative pressure) and breathing cycles. There is no tubing in this system, which means there is no potential for air bubbles to enter the system, but still ports that can be used to take samples of the medium flowing through the system. One of the main findings was that the breathing motion affects the cell phenotype, but the cell number, tight junctions, and TEER remained constant throughout.

The final talk of this symposium was presented by Mrs Kinga Balogh Sivars and was entitled “Use of air-liquid interface models in the pharma space”. This presentation focused on the use of a commercially available 3D model of the lung and development of a protocol for 11 days repeated exposure of potential toxic compounds. A panel of drug candidates were used to assess the potential for in vitro models to replicate the predicted toxicology shown in vivo. With this panel, it was found that the in vivo toxicology could be predicted by studying the TEER and cytotoxicity and this allowed a tiered screening approach that can be used for drug discovery and potentially save money and time in the pharmaceutical industry. This symposium demonstrated that even with the development of new 3D lung models, further work is required to try and replicate the in vivo system as close as possible. This has commenced now with the addition of advanced systems such as lung lining fluid, stretch and movements, flow and addition of immune cells to monocultures.

Kirst Meldrum, Imperial College London

SYMPOSIUM 4

The Symposium 4 on Ageing, Frailty and multi-morbidity opened with the presentation of Professor Thomas von Zglinicki from the University of Newcastle who described aging as the most important risk factor for disease. He envisaged senolytic treatments as a way to improve multi-age disease, since senescence is involved in telomere shortening and mitochondrial disorders. The frailty index has demonstrated a strong correlation with aging associated multi-morbidity, and senolysis in mouse models decreases frailty. Therefore, existent senolytics could be considered as potential therapeutics for age related diseases using the frailty index as a relevant evaluation tool.

Professor Susan Howlett from Dalhousie University in Canada further elaborated on the frailty index and its application to translate research findings from aged animal models into the clinic. Her research on cardiac function led her to inquire on the implications of aging in heart conditions. Interestingly, and despite the ample heterogeneity of individual responses to aging, frailty scores are able to predict mortality both in mice and humans by quantifying accumulated deficits. In addition, factors linked to deteriorated cardiac function such as contractile dysfunction and lower cardiac expression of specific calcium channels also correlates with the frailty index. These results stress the importance of ageing animal models in basic research to study age-related conditions in humans.

Dr Andreas Simm from the University Hospital Halle (Saale) approached the problem of human age from a broader position through the results of the MARK-AGE project. This collaborative European study looked to find a set of biomarkers that could better define biological age using a large population sample. Several ensembles that include oxidative stress, protein modifications and immunological makers among others have been considered. Dr Simm's interest specifically focuses on advanced glycation end- products (AGEs) involved in pathophysiological mechanisms. Individuals with increased AGEs seemed to have increased survival, although the effect appears to be organ specific. From this collaborative work, ten candidate biomarkers, many of them involved in methylation, showed an important correlation with the biological age.

Professor Ilaria Bellantuono from the University of Sheffield proposed geroprotectors to tackle common ageing mechanism such as inflammation, oxidative stress or autophagy so as to prevent multi-morbidity associated with aging, thus increasing health span. Their work showed that Zoledronate delayed senescence and extended life span in mesenchymal stem cells, making it a good candidate for this holistic approach. However, the translation of geroprotectors to the clinic faces several obstacles. Agreement in a common metric of frailty, the use of adequate animal models, and a focus on health span rather than life span by screening across different tissues need to be urgently addressed.

Sara Gómez-Arnaiz, University of Strathclyde

PATTON PRICE LECTURE

The lecture delivered by professor Lewis Smith, the Paton prize winner, at the 2018 BTS annual conference, titled “the importance of balance in toxicological decision making”, was highly informative. While being introduced as an outstanding researcher with vast research experience, professor smith’s sense of humour during his lecture was first class. In his lecture, he emphasized the importance of arriving at a balance judgement in extrapolating potential hazard in experimental system to human population. In humans with paraquat poisoning as an example cited in his lecture, prof smith provided experimental data to show the mechanism of paraquat accumulation into cells using the polyamines transport system, however, he suggested that the cysteamine transporter rather than polyamines transporter might be responsible for paraquat transport into human cells. This was particularly relevant to my research which focus on polyamines metabolism, transport and functions in human breast cancer cells.

Prof Smith also stressed the need to apply the increasing experimental and intellectual knowledge to improving the welfare of humans exposed to toxic substances, however, he noted that this must be done without under- or over - emphasizing the nature of the hazard and indirect measures of exposure. Thus, there must be a balance in the characterisation of toxicity and the susceptibility of human exposure, as balance is the prerequisite between knowledge and wisdom.

Overall, the 2018 BTS annual congress was an educative, informative event and I must admit I came back with great memories about the proceedings and excellent lectures delivered in each session. The conference also provided excellent networking opportunities to meet academics from different disciplines especially an opportunity to chat with prof smith after his lecture. The conference also allowed me to present and receive feedback about my own research which was presented during the poster session and I am enthused to pursue my research and attend future conferences.

Oluwaseun Akinyele

ORAL COMMUNICATIONS

The first session on Oral Communications encompassed a range of *in vitro, in vivo* and *in silico* studies on toxicity and risk assessment as well as the development of investigative techniques and predictive models. The first session on Oral Communications of the BTS Congress was chaired by Dr Dominic Williams (Imperial College London) and Dr Patricia Parris (AstraZeneca). **Mr Alistair Leitch** opened the session with his presentation on the metabolism of the ionic liquid M8OI in primary human hepatocytes. He demonstrated the appearance of COOH7IM metabolite following treatment with recently identified environmental chemical, M8OI, and provided evidence of the involvement of CYP3A4 in this metabolic pathway. Since COOH7IM is structurally similar to lipoic acid, Mr Leitch highlighted that it could potentially serve as the environmental trigger for the development of primary biliary cholangitis, an autoimmune chronic liver disease. Next, **Mrs Arathi Kizhedath** gave a general overview of parabens and discussed its hepatotoxic and dermal toxicity effects using human hepatocarcinoma cell line (HepG2) and human dermal fibroblasts, neonatal (HDFN) as *in vitro* models. In her study, cell viability assay revealed concentration-dependant toxicity of butyl paraben, but not methyl paraben, in both cell lines. This seemed to be mediated by ATP depletion due to inhibitory effect on mitochondrial function, and reduction in glutathione levels, suggesting the involvement of oxidative stress. Following on, **Mr Ben Alexander-Dann** outlined his research on toxicogenomics, seeking to predict and understand compound-induced toxicity using gene co-expression network methods. As an example he discussed the use of DrugMatrix database in conjunction with a system biology analysis to generate co-expression modules and identify compounds associated with cellular infiltrate in liver. This approach has a potential to identify early-stage biomarkers and elucidate molecular mechanisms of compound toxicity, predicting the late-stage histopathological changes. **Miss Kirsty Meldrum** gave an insight into health impact of air pollution constituents, focussing on the cerium dioxide nanoparticles (CeO2NPs) that are emitted with the diesel exhaust particles (DEP) and have a potential to alter the development of asthma and allergic airway disease. Her preliminary investigations in an *in vivo* mouse model of airway allergen exposure suggested that the addition of CeO2NPs increased the number of immune cells and different immune mediators and, therefore, potentiated the pulmonary response to DEP. Further research is, however, needed to characterise this response.

Miss Kayleigh Frame followed with a talk about the established galactose-conditioned HepG2 *in vitro* model, which is routinely utilised for detecting unknown drug-induced mitotoxicity. She discussed the benefits and limitations of this model, emphasising that little is known about the role of metabolic reprogramming in the cellular response. Kayleigh, therefore, used multiple endpoints in her study, including the analysis of mitochondrial dynamics and regulators of cell death, in order to identify additional mechanisms of mitochondrial toxicity. Then, **Mrs Israa Al-banaa** discussed the neurotoxicological analysis of synthetic cannabinoids (SC) using human neuronal stem cells. In addition to cell toxicity assays, where exposure to SC resulted in a significant reduction in cell viability in immature neurones, she demonstrated proteomic changes induced by repeated exposure to SCs. Therefore, her investigations may contribute to our understanding of the molecular mechanisms underlying the adverse effects of SC, such as behavioural disturbances, reduced level of consciousness and seizures. **Dr Emma Marczylo's** talk highlighted the importance to study the environmental mycobiome and its potential health effects and stressed the need for methods to uncover microbial diversity and abundance. Dr Marczylo described the recently published next generation sequencing method for analysing fungal DNA and demonstrated its application using a range of experimental sample sets, including environmental (soil, compost, bathroom) and human (dental/oral) samples. The final presentation of this session was held by **Dr Alex Charlton**, who explained how a 3D *in vitro* cell model of human airway epithelium, MucilAir™, could be used in risk assessment of an irritant aerosol. This model mimics the structure of respiratory tract and uses various irritancy endpoints as markers of membrane and cell damage as well as metabolic competence. Dr Charlton focussed on the dose-response data obtained from MucilAir™ following exposure to respiratory irritant, chlorothalonil, and discussed the benchmark dose approach for risk assessment purpose.

Elizabeth Zhuikova, Public Health England

SYMPOSIUM 5

The symposium started with a talk entitled “Assessing bioenergetic health in cells isolated from human subjects” presented by Professor Victor Darley-Usmar. He spoke about isolating a small number of cells from human blood and using high-throughput assays to measure a bioenergetic profile from these. This profile was combined into a single value – the Bioenergetic Health Index. Professor Darley-Usmar spoke about the applications of this to toxicology in human populations, including how to adapt this approach for different populations and genetic backgrounds.

Professor John Hayes presented the second talk on “NRF2 and antioxidant response”, sharing his latest research on the therapeutic effects of targeting NRF2. Although the exact mechanisms involved have not been clearly elucidated, drugs which limit the half-life of the NRF2 protein seem to have many potential benefits. While the claim of possibly reversing early stages of fibrosis lead to much discussion, it was clear that NRF2 will continue to be a target of much interest in the future.

The next talk was on “Biomarkers of oxidative stress”, given by Professor Pietro Ghezzi. Professor Ghezzi provided a fresh perspective for most toxicologists, talking about the philosophy of signs. Does seeing smoke necessarily mean there is a fire? Does seeing a fire engine necessarily mean there is a fire? He went on to apply these ideas to oxidative stress. Reactive oxygen species have too short half-lives to be measured directly, so we must instead measure biomarkers – the traces left by their reactions with biological molecules. Does seeing one of these biomarkers necessarily mean there is oxidative stress? Professor Ghezzi addressed this question, suggesting measurement of multiple biomarkers and a statistical approach to using a combination of biomarkers measurements.

The session was concluded by Dr Alistair Middleton, talking about “Redox and cellular stress in relation to consumer risk assessments”. A mechanistic-based tiered approach was presented, incorporating computational and experimental models at each tier. Dr Middleton focused on how in vitro models for stress responses would be used in this approach and, using oxidative stress as an example, discussed the challenges faced. This final talk provided some particularly interesting perspectives on toxicology without animal testing, and will likely be of increasing interest to all branches of toxicology as the models continue to be developed.

Andrew Wedlake, University of Cambridge

SYMPOSIUM 6

The session on **Stem cells and toxicology testing** explored different application of stem cell technologies in the fields of cardiotoxicity, neurotoxicity, pulmonary toxicity as well as screening model.

Dr Jason Gill (Newcastle University) spoke on how advances in cancer therapy has brought in increase therapy associated cardiotoxicity. Though routinely used in vitro models, primary cardiomyocytes and cardiac tissue have limitations revolving around clinical translation, sub optimal screening qualities, and limited utility for in vitro culture. Recent advances in human induced pluripotent stem cell derived cardiomyocytes and their ability to form function syncytium with synchronous beating. Progress in microelectrode technology and electrical impedance measurement such as xCELLigence Cardio real time analyzer, permits label free evaluation of cell viability as well as drug induced effect on cardiac contractility. These technologies allow for simultaneous measurement of multiple cardiotoxicity endpoints, are noninvasive and provide a human derived cell system. Thus, they form an invaluable avenue for developing pharmacological strategies as well as safety testing with an ease for clinical translation.

Dr Lia Panman (MRC Toxicology Unit) spoke on how human embryonic stem technology has opened opportunities to explore selective toxicity of chemical compounds in selective neuronal populations to elicit neurodegenerative disease. The differentiation of human ES cell can be directed to study the sensitivity of neuronal populations to various toxic insults as well as their mode of action. Thus, their platform provides a human relevant model that can explore the selective nature of toxic insults elicited by different environment compounds in the development of neurodegenerative diseases.

Dr Karijn Wilschut (University of Utrecht) touch on further advances including 3D human stem cell based Organ on a chip models such as OrganoPlate® consisting of human iPSC derived neurons and astrocytes can predict multiple toxicity endpoints such as cell death, neurite integrity, mitochondrial toxicity and neuronal physiology. This can be further advanced by integration of perfused blood brain barrier tissue which could be valuable for studying metabolism and transport of compounds through the blood brain barrier.

Dr Mark Holbrook, (VAST Pharma Solutions) spoke about addressing the limitations and challenges posed by screening models could aid in extrapolation or interpolations of the probabilistic prediction to real life scenarios. The key aspects of the model should revolve around relevance (sensitivity, specificity and predictive power) reproducibility (variance and consistency) and should meet practical requirements regarding cost, turnaround time as well as reliability.

Arathi Kizhedath, Newcastle University

HOT TOPIC LECTURE

The hot topic lecture at the BTS annual congress 2018 was from Dr Lolke de Haan (MedImmune, UK) titled **'Challenges in the Assessment of Nonclinical Pharmacology and Safety of monoclonal antibody (mAb) based immune-oncology products'**

Over the past decade immune modulatory mAbs against programmed cell death 1 (PD1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte – associated protein 4(CTL-4) have shown to be effective at harnessing the immune system to combat a variety of cancers in response patients. Immuno-oncology products can be receptor agonists or antagonists eliciting either a direct response or a co stimulatory response. With a move towards combination therapy i.e. combination of chemical small molecules and biological drugs, there is a need to consider the landscape of small molecules and mAbs that brings about a new paradigm for safety testing. The principles for these pharmacological and safety testing mAbs are derived from ICH S8, S9 and S6 which lays down the requirements such as minimum testing in 2 pharmacological relevant species, species chosen must be closest to humans etc. However, the current paradigm has limitations as seen in the case of TGN1412 as well formation of anti-drug antibodies. Clinical toxicities associated with mAbs are usually immune related adverse effect (IAERs) and recent studies indicate a correlation between haplotypes and IAER. These IAERs include cytokine storms, immunogenicity, anaphylactic release etc. Therefore, there are multiple strategies outlined for the safety testing of MAbs such as repeat dosing, different duration GLP studies, TXR study etc.
The key challenges revolved around non- clinical pharmacology, tradition rodent models are deemed inadequate as efficacy requires a fully function immune system. Furthermore, surrogate reagents are often required to demonstrate pharmacological activity as there is limited species cross reactivity in mice models. For nonclinical safety testing there are challenges such as regulatory requirements around in vitro testing and cross reactivity of MAbs only to non-human primates. This is again selective as seen in the case of the TGN412 non- reactivity in cynomolgus monkeys but elicited a cytokine storm in healthy volunteers. With the advent of MABEL dosing there is the advantage of reducing an adverse effect but a disadvantage of not reaching a pharmacologically effective dosage for humans. Additionally, species cross reactivity, Antidrug Antibodies formation, time frame of testing for eliciting these response remain areas of concern.

Thus, there is a need for more complex, hybrid and comprehensive testing strategies that include in vitro, in vivo and in silico aspects to fill the gaps in non-clinical pharmacology and safety testing of mAbs especially since the age of biosimilars is just around the corner.

Arathi Kizhedath, Newcastle University