ToxBank
public forum

TOXBANK
PUBLIC FORUM

26 – 27 October 2015
WELLCOME COLLECTION
LONDON, UK

ADVANCES
>> TOWARD >>
REPLACING OF ANIMAL TESTING

Welcome to Public Forum

DEAR DELEGATES,

We are pleased to offer the opportunity to present results from the SEURAT-1 Program and ToxBank project, at this meeting in London at the Wellcome Collection building 26th October.

This will provide an opportunity for stakeholders interested in replacement of animals in toxicology testing to see the advances made in ToxBank.

On 27th October we will in addition, have the privilege to present a series of talks by key EC-funded programmes relating to the use of stem cells in supporting such research.

I hope you will take this unique opportunity to talk to representatives of these projects when all in one location.

I believe you will enjoy the meeting and look forward to welcoming you in London on 26th October.

Regards

Glyn Stacey,
ToxBank

Table of Contents

Public Forum Chairs

Dr Glyn Stacey, National Institute for Biological Standards and Control (NIBSC)
Dr Barry Hardy, Douglas Connect, Switzerland

TO REGISTER GO TO

www.toxbank.net/toxbank-public-forum

About the Forum

ToxBank
public forum

Advances toward
REPLACEMENT OF ANIMAL TESTING
25 - 26 October 2015

In this forum we will discuss the results of the recent research and development of alternative testing methods aimed to replace animal testing, and the potential impact this work has on our society.
To make a good decision on safety we need to bring both expertise and relevant human scientific information together to form the basis for a structured well-informed discussion leading to best judgement based on available evidence and opinions formed on it.

Such a knowledge integration is required in many areas of toxicology and safety assessment based on scientific knowledge generated by a growing number of alternative testing research methods and initiatives. Integration may include evidence from in vitro or in silico methods, biology or chemistry, science and engineering, human health or environment-oriented, and requires both effective organisation of knowledge and communications to reach common understandings.

All alternative testing applications require a sound reproducible scientific basis and the use of good practices in characterising experiments, organising data and describing concepts in our knowledge framework.

We also need community frameworks to bring different disciplines together for fruitful interactions and discussions to progress the introduction of new alternatives to replace animal testing.

In this session we will explore the emerging opportunities for innovation in safety research and assessment based on a set of diverse contributing perspectives from current initiatives in this area.

We will complete the session with a forum with interactive audience participation on questions and suggestions from audience members.

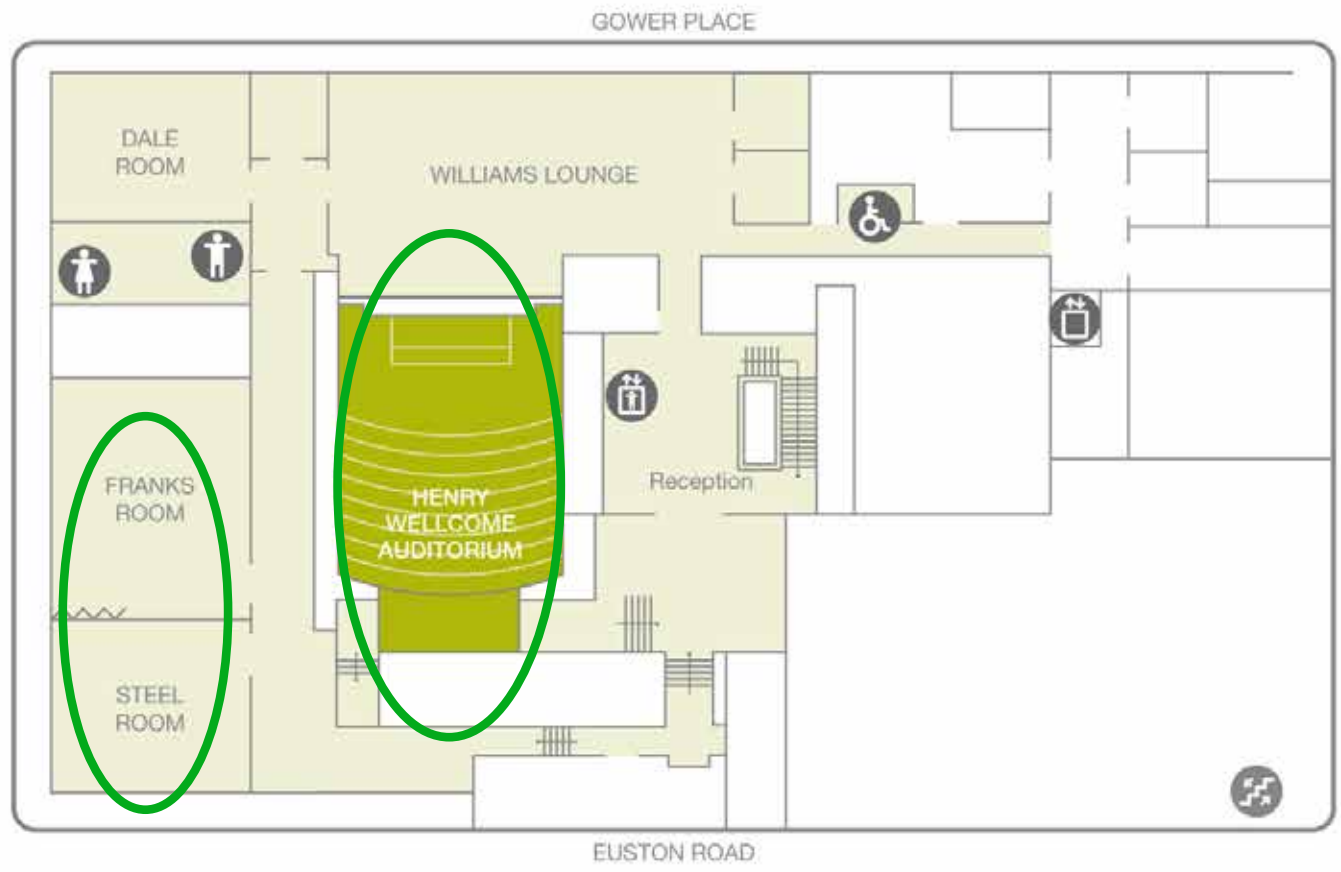
Forum Venue

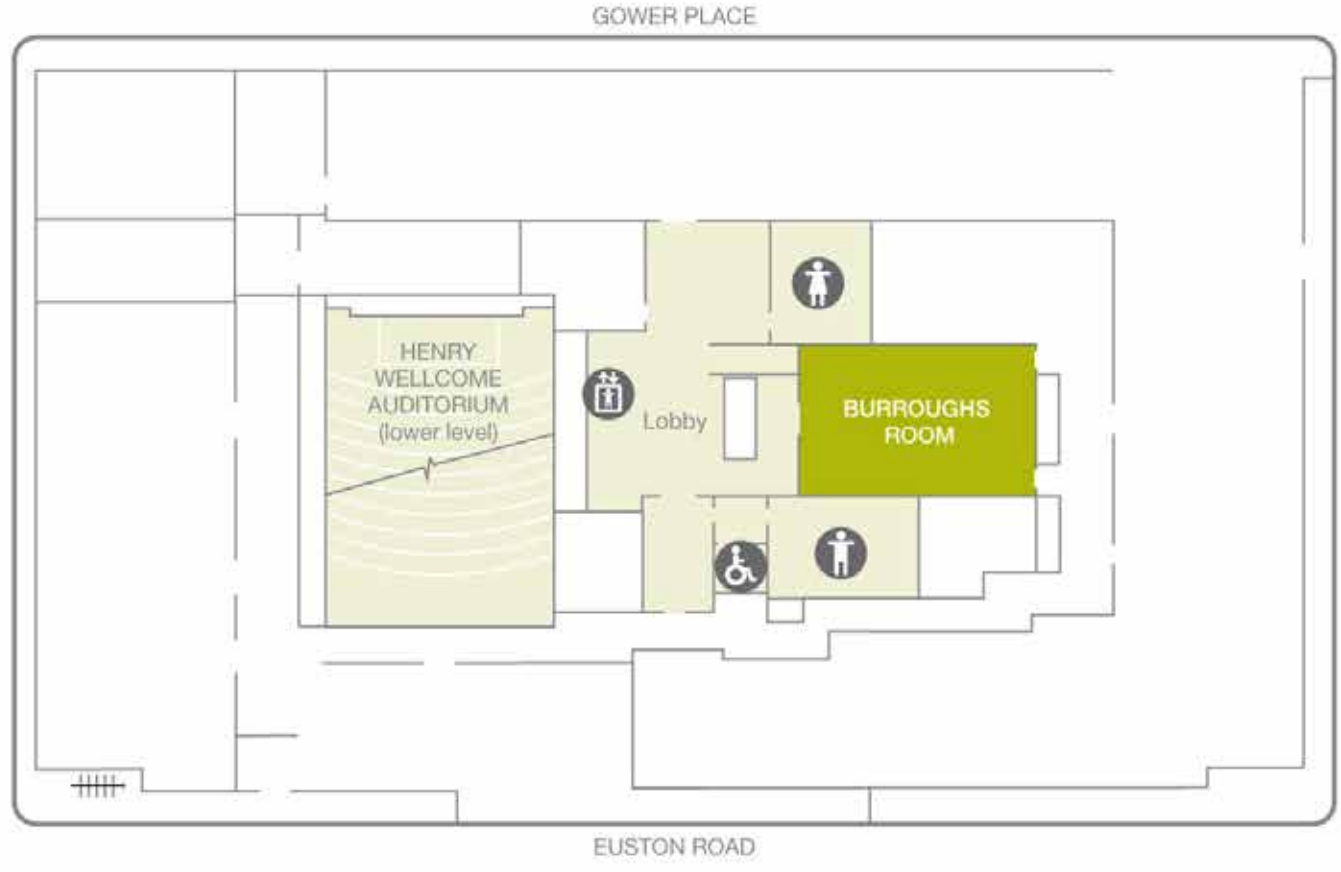
THE WELLCOME COLLECTION
LONDON, UK

DAY 1: Franks and Steel Rooms
DAY 2: Henry Wellcome Auditorium

Wellcome Collection
183 Euston Road
London NW1 2BE, UK
tel: +44 (0)20 7611 2222

Forum Map


GOWER PLACE
DALE ROOM
WILLIAMS LOUNGE
FRANKS ROOM
HENRY WELLCOME AUDITORIUM
Reception
STEEL ROOM
EUSTON ROAD


GOWER PLACE
HENRY WELLCOME AUDITORIUM (lower level)
Lobby
BURROUGHS ROOM
EUSTON ROAD

Poster Session

HENRY WELLCOME AUDITORIUM
WELLCOME COLLECTION

ON TUESDAY, 27 OCTOBER 2015, AT 12:00

Posters explaining the work carried out by ToxBank will be available throughout the event.

Public Forum Schedule

DAY 1, 26th OCTOBER 2015

INDUSTRY AND REGULATORY COORDINATION

Chair: BARRY HARDY

FRANKS AND STEEL ROOMS

Time	Topic	Speakers
12:00	Buffet Lunch: Arrival & Registration	!
13:00	Chair's Introduction	• Barry Hardy, Douglas Connect
13:05	Case Studies from the SEURAT-1 projects • HeMiBio: A hepatic microfluidic Bioreactor • Platform for Chemical Safety Assessment • DETECTIVE	 • Catherine Verfailie, University of Leuven • Bob van de Water, Leiden University • Jos Kleinjans, University of Maastricht
14:05	Defining adverse outcome pathways from omics-driven bioinformatics and modeling approaches	• Roland Grafström / Pekka Konnen, Karolinska Institutet
14:25	• A Path to Validation – SEURAT-1 case studies and the role of ECVAM • Industrial application of alternative testing methods for risk assessment	• Elisabet Berggren, EU Joint Research Centre • Andrew White, Unilever
15:00	Key learning and advances obtained from alternatives programs on the Translation of new technologies in validated safety testing methods to industrial application and regulatory acceptance: • An ethical perspective • Development of new toxicity assays	 • Emily McIvor, Humane Society • J Malcolm Wilkinson, Kirkstall Ltd
15:30	Coffee break	!
16:00	The ToxBank infrastructure project to support the replacement for repeated dose toxicity	• Glenn J. Myatt, Leadscope
16:20	A ToxBank Integrated Data Analysis of SEURAT-1 Reference Compounds	• Barry Hardy, Douglas Connect
16:40	Question & Answer forum	!
17:30	End Session	!

DAY 2, 27th OCTOBER 2015

APPLICATION OF PLURIPOTENT STEM CELLS FOR SAFETY TESTING AND DISEASE STUDIES

Chair: GLYN STACEY

HENRY WELLCOME AUDITORIUM

Time	Topic	Speakers
09:00	Arrival and registration	!
09:15	Welcome Coffee, Tea	!
09:30	Chair's Introduction	• Glyn Stacey, NIBSC
09:35	New iPSC based modeling of normal and diseased states – StemBANCC	• Jim Ross, University of Edinburgh - MRC Centre for Regenerative Medicine
10:10	EU Funding of research-A need for Ethical Governance	• Joana Namorado, European Commission
10:45	Coffee break	!
11:15	Scientific and ethical qualification of pluripotent stem cells for European research - hPSCreg	• Andreas Kurtz, Charité
12:00	Lunch – Poster session	!
13:00	EBiSC: Access to HIPSc Line Acquisition via the EBiSC	• Paul de Sousa, Roslin Cells
13.40	End Session	!

ToxBank Abstracts

DAY 1:
Research progress supporting industrial application and regulatory acceptance

Session Chair:
Dr Barry Hardy, Managing Director,
Douglas Connect, Switzerland

Dr. Barry Hardy has coordinated the OpenTox project in predictive toxicology and the ToxBank infrastructure development project. He currently leads the infrastructure development for the IMI EBiSC stem cell banking project and eNanoMapper supporting nanotechnology safety assessment.

He has led the development of research and best practice activities in drug design and toxicology through founding the eCheminfo Community of Practice, InnovationWell and Scientists Against Malaria project.

Currently he is developing Douglas Connect and its Collaboration Pools supporting new business area development and growth.

Dr. Hardy obtained his Ph.D. in 1990 from Syracuse University working in computational science. He was a National Research Fellow at the FDA Center for Biologics and Evaluation, a Hitchings-Elion Fellow at Oxford University and CEO of Virtual Environments International.

He was a pioneer in the early 1990s in the development of Web technology applied to virtual scientific communities and conferences. He has developed technology solutions for internet-based communications, tutor-supported e-learning, laboratory automation systems, and computational science and informatics.

In recent years he has been active in the field of knowledge management as applied to supporting innovation, communities of practice, and collaboration.

SESSION 1 SCHEDULE

Monday, 26th October 2015, from 12.00 to 17:30
Franks and Steel Rooms

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12:00	Buffet Lunch: Arrival & Registration	!
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HeMiBio:
A hepatic microfluidic Bioreactor

In HeMiBio, we proposed to generate a liver-simulating device mimicking the complex structure and function of the human liver. The device will reproduce the interactions between hepatocytes and non-parenchymal liver cells (hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSECs) for over 1 month *in vitro*.

Such a Hepatic Microfluidic Bioreactor could serve to test the effects of repeated exposure to chemicals, including cosmetic ingredients. To create such a device, the cellular components of the liver need to be viable for over 1 month, with *in vivo*-like metabolic and transport function, and physiology.

Microsensors were created to monitor cell culture conditions and to measure at specific interrogation times relevant parameters of the state of the cells.

In addition, stem cells were used to create the different cell population, and were equipped with molecular sensors to provide information not only on the state of the cells, such as differentiation to mature cell types, but also on toxic effects on specific cell types.

Finally, we developed self- assembled organoid systems of hepatocytes and HSCs to enable modeling of repeat dose toxicity causing liver fibrosis as the clinical endpoint.

AUTHORS: Joris Braspenningen, Toni Cathomen, Philip Collas, Claus Duschl , Silvia Generelli, Marcus Heimann Aernout Luttun, Yaakov Nahmias, Vera Rogiers, Pau Sancho-Bru, Bard Smedsrod. Leo van Grunsven, Jan Vanfleteren, Catherine Verfaillie, Mathieu Vinken

ABOUT THE SPEAKER

Prof Catherine Verfaillie

Director of Stem Cell Institute, Head of Stem Cell Biology and Embryology Unit, KU Leuven

Catherine Verfaillie received her Medical degree from the KU Leuven in 1982. She then trained as an internist/hematologist at the KU Leuven between 1982 and 1987. She went to the U. of Minnesota in 1987 for a postdoctoral fellowship. After completing her post-doctoral fellowship, she was appointed consecutively as Instructor, assistant professor, associate professor and finally full professor of Medicine in 1998. In 2001, she became the Director of the University of Minnesota's Stem Cell Institute.

In 2006, she accepted to become the director of the Interdepartementeel Stamcel Instituut at the KU Leuven. She has a long-standing career in stem cell biology, initially focusing on normal hematopoietic stem cells and leukemic stem cells, and the role played by the microenvironment in regulating their selfrenewal and differentiation ability. Since 1997 she has also focused extensively on more pluripotent stem cells. Her group described in 2002 a novel cell population culture from rodent and human bone marrow samples with greater expansion and differentiation potency, named multipotent adult progenitor cells or MAPC.

The current research of the Verfaillie lab is focused on understanding what regulates selfrenewal and (de)differentiation of adult as well as embryonic/induced pluripotent stem cells, and testing the possible use of stem cell based and stem cell derived therapies in animal models of hematopoietic, liver, and CNS disorders. In 2014, she created the KUL-STEM platform, for the generation and differentiation of induced pluripotent stem cells as disease models and for drug discovery.

Towards a High Throughput Microscopy Pathway of Toxicity Reporter Platform for Chemical Safety Assessment

Adaptive cellular stress responses are paramount in the healthy control of cell and tissue homeostasis after cell injury during hypoxia, oxidative stress or unanticipated side-effect of medications and other chemical exposures.

To increase our understanding of chemically-induced adaptive stress response pathway activation and its contribution to safety assessment a time-resolved, sensitive and multiplex readout of chemical-induced toxicological relevant cellular stress responses is essential.

For this we develop a unique innovative platform containing a broad panel of distinct adaptive stress response fluorescent protein reporter HepG2 cell lines that can represent both upstream as well as downstream components in the respective toxicity pathways.

These are used for automated high content live cell imaging and quantitative multi-parameter image analysis to elucidate critical adaptive stress response pathway activation that can contribute to human chemical safety assessment.

To conserve the endogenous gene regulatory programs, we tag selected reporter target genes with GFP using BAC-transgenomics approaches. Here we demonstrate the functionality of individual BAC-GFP pathway in toxicity reporter cell lines to their respective specific model compounds in HepG2 2D as well as 3D spheroid culture in 384 well format.

The application of these reporters in chemical safety assessment in relation to drug-induced liver injury will be discussed. We anticipate that ultimately a phenotypic adaptive stress response profiling platform will allow a high throughput and time-resolved classification of chemical-induced stress responses assisting in the safety assessment of chemicals.

This work is part of the MIP-DILI project supported by the Innovative Medicines Initiative (grant agreement n° 115336), and the FP7 SEURAT-1 DETECTIVE project (grant agreement 266838).

ABOUT THE SPEAKER

Prof Bob van de Water
Universiteit Leiden, Netherlands

Professor Van de Water studied bio-pharmaceutical sciences at Leiden University where he graduated in 1990 (specialization: toxicology). He obtained his PhD (cum laude) from the Leiden/Amsterdam Center for Drug Research (LACDR) from Leiden University in 1995 and performed a postdoctoral training in the USA in the lab of Dr James Stevens.

After a postdoctoral position in the USA in the lab of Dr James L Stevens, he rejoined the Division of Toxicology of the LACDR in 1997.

In 1999 he received a fellowship from the Royal Netherlands Academy of Arts and Sciences (KNAW).

In 2006, he was appointed as professor of drug safety sciences and head of the division of Toxicology. His research interest is on identifying molecular mechanisms of xenobiotic-induced cytotoxicity using a systems toxicology approach by integrating both gene expression profiling, phospho-proteomics and large scale RNAi-based functional genomics.

A central theme is the control of cellular signaling by cell-matrix and cell-cell interactions in the context of molecular mechanisms of cytotoxicity and cancer progression.

These studies provide fundamental insight on the consequences of cellular stress conditions on cell adhesion, migration, differentiation and survival in context of both xenobiotic-induced acute tissue injury and repair as well as cancer treatment.

He is heading the high throughput and high resolution imaging facility of the institute and applying this technology to better understand and predict cytotoxicity. In DETECTIVE he is project leader for the organelle morphometry/function reporter cell lines and automated imaging analysis.

Case Studies from the SEURAT-1 projects: DETECTIVE

DETECTIVE is part of an integrated research strategy towards the replacement of animal testing set up by the European Commission (EC) within the FP7 Health Programme and supported by the Cosmetics Europe – The Personal Care Association. The project's main focus refers to the systematic exploitation of a battery of complementary functional and 'omics readouts to identify in relevant human cellular models *in vitro* predictive biomarkers for repeated dose toxicity in humans. Endpoints of toxicity under investigation are liver toxicity, heart toxicity and kidney toxicity. Importantly, DETECTIVE performs for the first time an in-depth investigation of repeated dose effects on epigenetics and microRNA expression thus exploring whether such analyses deepen our understanding of toxic modes of action. Check http://www.detect-iv-e.eu/.

Within this context, we investigated cross-omics and functional responses to several well-known human liver toxicants in primary human hepatocytes taken from three donors. Liver cells were pooled in order to bypass the issue of large inter-individual differences in toxic responses. Liver toxicants were administered daily over a 5 day period, at sub-cytotoxic incubation concentrations. Sub-types of liver injury evaluated to date, refer to necrosis and steatosis. Relevant functional tests were applied in order to ascertain that these particular toxic phenotypes were actually induced. After 5 days of treatment, samples were taken and subjected to analyses by multiple 'omics platforms enabling the capturing of responses to liver toxicants on the gene expression, microRNA and epigenetics level. Advanced bioinformatics approaches were applied for combining and visualizing cross-omics results into integrated response networks. This could successfully be linked to the observed functional characteristics of induced toxicity, thus enabling the discovery of new molecular biomarkers for these types of liver toxicity.

In order to evaluate whether repeated dosing of liver toxicants is capable of inducing toxic responses also on longer term, e.g. after exposure has stopped, some hepatocyte cultures were maintained only in incubation medium for a further 3 days. Samples were subjected to the same cross-omics analyses as described above. Persistent molecular response networks were identified which indeed are still indicative for these particular endpoints of liver toxicity despite the earlier termination of the toxic challenge. It is thus suggested that genes involved in these persistent modifications, represent most promising biomarkers for assessing repeated dose toxicity in the human liver *in vitro*.

AUTHORS: Jos Kleinjans, Linda Rieswijk,Theo de Kok, Simone van Breda (Department of Toxicogenomics, Maastricht University, the Netherlands)

ABOUT THE SPEAKER

Prof Jos Kleinjans

Maastricht University, Netherlands

Professor Jos Kleinjans studied biology at the Catholic University of Nijmegen and took a training in general biology and further trainings in physiological psychology, pharmacology, neuro-anatomy, and chemical cytology. Immediately after his graduation in 1979, he started working as a PhD student at the Department of Pharmacology of the Faculty of Medicine of Maastricht University.

In 1983, he obtained his PhD degree for his thesis 'Stimulation of renal adrenergic mechanisms as a model for the development of hypertension'. A few months before, he had started to work as a Postdoctoral Research Fellow at the Department of Biological Health Science of the Faculty of Health Sciences of the same University. His research interests were project development in relation to human nutrition and project development and project management concerning nutritional toxicology. In addition, he was involved in the development of curricula and training courses in biological health.

In 1986, he was appointed Associate Professor at the Department of Biological Health Science, where he performed research tasks of programme management in nutritional toxicology and programme development regarding environmental health sciences as well as educational tasks described earlier extended with the development of curricula concerning environmental health sciences.

In 1991, he was appointed Full Professor of Environmental Health Science, head of the Department of Health Risk Analysis and Toxicology, and director of the interfaculty research programme Health and Environment of the Faculties of Health Sciences and Medicine.

Prof. Kleinjans was acknowledged as a pharmacologist by the Concilium Pharmacologicum on behalf of the Foundation for the training of Medical-Biological Scientific Researchers (SMBWO) in 1985 and as a toxicologist in 1988. He is a member of the Netherlands Society of Toxicology (Genetic Toxicology Section and In Vitro Toxicology Section), the Netherlands Society of Environmental Medicine, the Netherlands Society of Environmental Sciences, the Belgian Society of Toxicology, the European Environmental Mutagen Society, the Interuniversity Commission for Environmental Sciences of the Society of Cooperating Dutch Universities, and the Commission on Criteria Documents of the Dutch Health Council. Prof. Kleinjans, furthermore, is a consultant for governmental and non-governmental organizations on an incidental basis and author of national and international training courses in toxicology.

Defining adverse outcome pathways from omics-driven bioinformatics and modeling approaches

Knowledge integration of data from *in vitro* and *in silico* methods are increasingly being used in safety testing relative to traditional costly animal testing, including for evaluation of chemicals, nanomaterials and diverse consumer products.

Stimulating this development, the European Chemicals Agency now advocates for a flexible and extensible "conceptual framework for evaluating chemicals safety", built on combining results generated from new predictive tools with existing data.

The Grafström laboratory has for many years analyzed numerous formaldehyde effects *in vitro* as a case study for adverse outcome pathways, involving a set of complex interactions that associate with toxicity, DNA damage, mutagenicity, cell transformation and carcinogenicity.

We demonstrate under the theme of "knowledge integration supporting decision making" that:

1) toxicogenomics results serve excellently to explore modes of action and adverse outcome pathways,

2) bioinformatics-driven analysis versus large data repositories is key to generating the mechanism-based predictions, and that

3) omics-driven toxicity modeling is a complementary and useful exercise relative other methods.

We conclude on this basis that the omics-driven bioinformatics and modeling approaches overall is able to address toxicity pathways, threshold of toxicological concern ranking, coupling of *in vivo* pathology to *in vitro* data, dose response estimation of NOEL/LOEL results, as well as the grouping and read across between different agents.

Consistent and systematic warehousing of the toxicity data types and analysis now presented promises to handle future *ab initio* "*in vitro*-based only" toxicity predictions.

To this end, we foresee the application of possibly different variants of the "adverse outcome pathways framework".

AUTHORS: Roland Grafström, Pekka Kohonen, Penny Nymark (Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden), Vesa Hongisto (Toxicology Department, Misvik Biology Corporation, Turku, Finland), Ola Spjuth (Department of Pharmaceutical Biosciences and Science for Life Laboratory, Uppsala University, Uppsala, Sweden) and Barry Hardy (Douglas Connect, Switzerland)

ABOUT THE SPEAKER

Prof Roland Grafström
Karolinska Institutet, Stockholm, Sweden

Winner of over 80 international competitive research grants, including from US and European sources. Current grants from the Scientific Research Council, the Cancer and Allergy Fund and the Fund for Research without Animal Experiments in Sweden. Partner/team member 2011-2016 in EU projects: FP7-HEALTH-2010-Alternative-Testing, through "SEURAT/ToxBank" - Integrated data analysis and servicing", NMP-2012- "NANoREG" "Regulatory testing of nanomaterials", NMP-2012-NANOSOLUTIONS "Systematic investigations of the mechanisms and effects of engineered nanomaterial interactions with living systems and/or the environment", and NMP-2013-eNanoMapper "A Database and ontology framework for nanomaterials design and safety assessment".

Of special relevance to this lecture is the coordination of safety and nanotechnology development studies for a lead group of 12 professors/senior scientists and 400+ persons at diverse VTT sites in Finland. Leading this work has included handling of internal projects and customer offerings according to a "safe by design strategy" as well as the promotion of methods development, research concepts and cross-disciplinary interactions.

CURRENT EMPLOYMENT: Full Professor in Biochemical Toxicology, Institute of Environmental Medicine, Karolinska Institutet (KI), Stockholm, Sweden, 2000- (60% time effort, research time: 50% of the 60%)

A Path to Validation: SEURAT-1 case studies and the role of ECVAM

The SEURAT-1 * vision is to fundamentally change the way we assess the safety of chemicals, by superseding traditional animal experiments with a predictive toxicology that is based on a comprehensive understanding of how chemicals can cause adverse effects in humans (**2.**). The SEURAT strategy is to adopt a toxicological mode-of-action framework to describe how any substance may adversely affect human health, and to use this knowledge to develop complementary theoretical, computational and experimental (in vitro) models that predict quantitative points of departure needed for safety assessment. One of the SEURAT-1 objectives is to demonstrate a multiple level proof-of-concept (theoretical, methodological, and application)(**3.**) for repeated dose systemic toxicity but in principle also applicable to other endpoints.

The results of testing strategies based on combinations of *in vitro*, *in silico* and *in chemico* data in combination with already existing data (physical chemical information, animal or human *in vivo* data or other) and biokinetic modelling, could provide sufficient evidence to support chemical safety assessment. This is the basic idea for the safety assessment case studies currently developed within the SEURAT-1 framework.

This is also the basic idea for how to substitute traditional animal testing with alternative methods of the European Union Reference Laboratory for Alternatives to Animal testing (EURL ECVAM) established by the European Commission at the Joint Research Centre based on Directive 2010/EU/63. The aim of EURL ECVAM is basically to promote the scientific and regulatory acceptance of non-animal tests which are of importance to biomedical sciences, through research, test development and validation and the establishment of a specialised database service. In addition EURL ECVAM co-ordinates at the European level the independent evaluation of the relevance and reliability of tests for specific purposes, so that chemicals and products of various kinds, including medicines, vaccines, medical devices, cosmetics, household products and agricultural products, can be manufactured, transported and used more economically and more safely, whilst the current reliance on animal test procedures is progressively reduced.

** The SEURAT-1 homepage. http://www.seurat-1.eu/*

2. *Whelan M, Schwarz M. 2011. SEURAT-1 Annual Report, Vol 1, 47-51. http://www.seurat-1.eu/pages/library/seurat-1-annual-report.php.* **3.** *Whelan M, Schwarz M. 2012. SEURAT-1 Annual Report, Vol 2, 7-63. http://www.seurat-1.eu/pages/library/seurat-1-annual-report.php.* **4.** *The EURL ECVAM homepage. https://eurl-ecvam.jrc.ec.europa.eu/*

ABOUT THE SPEAKER

Dr Elisabet Berggren
Eurl ECVAM

Elisabet Berggren currently works at the Systems Toxicology Unit and the European Reference Laboratory for Alternatives to Animal Testing (Eurl ECVAM). The Systems Toxicology Unit assists in the development of a new and more efficient safety assessment of chemicals based on in vitro, in silico and in chemico methods. The aim is to develop new predictive methodologies more relevant to human health, encouraging innovation and avoiding animal testing. Elisabet is also contributing to the coordination action COACH of SEURAT-1, the largest EU initiative ever on alternative testing, focussing on toxicity testing for repeated dose toxicity and funded by European Commission (FP7) and Cosmetics Europe.

Elisabet started to work for the European Commission in 1996, and she was responsible for the Technical Committee of Classification and Labelling of Dangerous Chemicals at the European Chemicals Bureau during many years. She was involved in the negotiations of the Globally Harmonised System, its implementation within the EU through the CLP Regulation and development of the CLP guidance document. She also contributed to the negotiations of the Rotterdam Convention and its EU regulatory implementation.

Elisabet made her PhD in physical chemistry at Stockholm University in 1991. In her academic career she primarily focused on the development of theoretical dynamic models for liquid crystals and biological relevant systems.

Industrial application of alternative testing methods for risk assessment

The development of novel ingredients that can provide innovative new benefits is a central theme across a range of industries, including the chemical, pharmaceutical and consumer product sectors. It is essential however that robust scientific based assessments are used to assure the safety of these new ingredients; for consumers who will use them, the workers who manufacture them, and the environment into which they may ultimately be disposed.

For more than 10 years, we have been working with others to develop novel ways of assuring consumer safety that are human-relevant and do not rely on animal data. There has been a great deal of progress in realising this goal and, for many areas of consumer safety, prototype case study risk assessments are being developed.

These are based on the initial framework described by the US NRC and the Adverse Outcome Pathway framework currently being explored by the OECD. In part these reflect the application of new technologies both in data generation, and also in data integration and analysis that have taken place within the biological sphere but also the desire to improve on the current process and respond to the demands of a modern society.

The scientific challenges and opportunities presented to Industry by these new approaches and their place in a framework for exposure- and pathways-based safety assessments will be discussed alongside the need for new mechanisms to capture, store and integrate data for decision making.

ABOUT THE SPEAKER

Dr Andrew White
Unilever

Dr Andrew White's current role is science leader in computational toxicology within the Safety and Environment Assurance Centre at Unilever.

The focus for his work since 2008 has been in the integration of *in vitro* and *in silico* approaches to drive the development of mechanistically relevant pathway based approaches for human risk assessment.

Andy has a PhD from Newcastle University and prior to his current role has held previous roles in Unilever as a research biochemist, and as lead scientist of an internal genomics facility involved in the development of parallel assay design and analysis for 'omic technologies.

He has previously represented Unilever as a partner for several European and international projects and currently represents Unilever on several external forums including the Industry forum for the European Bioinformatics Institute, as a partner in the EuToxRisk project, and as a Unilever/Cosmetic Industry representative (CosmeticsEurope), for the Seurat 1 FP7 Research Initiative aimed at the development of solutions for the replacement of current repeated dose systemic toxicity testing *in vivo*.

An ethical perspective

Acknowledgement that replacement of animal testing is desirable for scientific reasons has created a momentum of its own, but ethical arguments are still identified by many as the central motivation for change. This creates both advantages and disadvantages: animal welfare can be seen as a distraction, and important aspects of the debate can be missed.

Implementation of the European Union's REACH Regulation demonstrates that failure to reconcile these differing perspectives produces unsatisfactory results, and while industry is often keen to promote development of new methods changes that force uptake can be resisted.

The ethical arguments are complex: we know it is not just test animals whose welfare is relevant and that changes can affect patients, consumers and the environment. Measuring the cost of a procedure in terms of animal suffering against potential advantages that may result now forms a crucial mechanism within the new "animal experiments" EU Directive 2010/63.

Arguments against testing cosmetics on animals are different from those about testing drugs, but what about household products, pesticides or nanomaterials?

And whichever way one argues, the past 15 years has seen the animal welfare debate overtaken by science. With 95% of new drugs deemed safe and effective in animal studies failing when they reach clinical trials, patient protection is certainly not guaranteed by rigid adherence to the old ways.

This presentation will highlight ways in which differing ethical viewpoints influence implementation of alternative methods, and examine shifts in public opinion as well as the rapidly changing scientific debate.

ABOUT THE SPEAKER

Emily McIvor, Policy Director
Research and Toxicology Department, Humane Society International

Emily McIvor is Policy Director of Humane Society International's Research and Toxicology Department, having worked on EU animal welfare issues for many years, and specialising in those concerning the use of animals in research and testing. Ms. McIvor is a member of the EPAA (European Partnership on Alternatives to Animal Testing) Mirror Group, a former Partner of the 7th Framework Programme project AXLR8 (www.axlr8.eu), and a member of the ECVAM Stakeholder Forum.

Emily contributed to several processes during preparation and negotiation of Directive 2010/63 EU on the protection of animals used for research, and coordinated the 'Make Animal Testing History' campaign which focused on promoting measures to replace animals used in research and testing. As a regular contributor to several REACH (Registration, Evaluation and Authorisation of Chemicals) committees and processes, and through HSI's global 'Be Cruelty Free' campaign to end animal testing for cosmetics, Emily continues to work for both immediate term reductions in animal use as well as the longer term goal of full replacement.

Emily received the prestigious Henry Spira Award for her outstanding contribution to Animal Welfare in 2011, and the LUSH Special Prize in 2013 to celebrate implementation of the EU ban on cosmetics animal testing and sale of newly animal tested cosmetics ingredients.

Development and validation of new toxicity assays for industrial application and regulatory acceptance

The challenges involved in the development of a new in vitro method of assessing cardiotoxicity of drug candidates are highlighted in this short presentation.

The first stage is the building of a sound scientific basis for the new method.

However that is just the start because many other hurdles exist before an easy to use test method is accepted by industry, especially if the new method has to displace an established one.

Economic, scientific and ethical motivations can all play their part.

ABOUT THE SPEAKER

Dr J Malcolm Wilkinson, Chief Executive Officer
Kirkstall Ltd.

Dr Wilkinson is the Chief Executive Officer of Kirkstall Ltd.

Prior to founding Kirkstall Ltd., he managed a high technology consulting company after having had a career in high technology product development both in large corporations as well as start-ups.

He has had senior roles in most important functions from R&D through to sales and marketing. In the consulting company he supported spin-outs from Universities and raised over $15 million from Venture capital and regional development funds.

He has a BA from Oxford University, MSc from Southampton and did his PhD research at Middlesex University.

He has been a visiting Lecturer for FSRM, Neuchatel, Switzerland, on the subject of Micro and Nanotechnology in Biomedical Engineering for over 10 years.

Dr Wilkinson is co-author on several papers on in-vitro models of toxicity and a contributing editor of a recently published book on In-Vitro Testing. He is a champion for the use of leading edge technology to replace animal testing for the development of safe drugs, nutraceuticals, chemicals and cosmetics.

The ToxBank infrastructure project to support the replacement for repeated dose toxicity

The SEURAT-1 (Safety Evaluation Ultimately Replacing Animal Testing-1) research cluster is comprised of seven EU FP7 Health projects and is co-financed by Cosmetics Europe. The SEURAT-1 strategy is to adopt a mode-of-action framework to describe repeated dose toxicity to derive predictions of in vivo toxicity responses.

ToxBank is the cross-cluster infrastructure project which provides a web-accessible shared repository of research data and protocols.

Experiments generate dose response data over multiple timepoints using different omics platforms including transcriptomics, proteomics, metabolomics, and epigenetics over different cell lines and a common set of reference compounds (details available at wiki.toxbank.net).

Data is also generated from functional assays and bioreactors and supplemented with in silico approaches. This complex and heterogeneous data is consolidated and harmonized through the ToxBank data warehouse in order to perform an integrated data analysis.

This presentation will outline the development of the ToxBank data warehouse from the initial requirements gathering, through implementation which included the adoption and extension of the ISA-tab universal data exchange format.

ABOUT THE SPEAKER

Dr Glenn Myatt, Chief Scientific Officer
Leadscope Inc, USA

Dr. Myatt is one of the founders and currently chief scientific officer of Leadscope, Inc.

He has over 25 years' experience researching, building, and managing in silico solutions for the life sciences.

He has been principal investigator on a number of projects, including significant international research collaborations.

A ToxBank Integrated Data Analysis of SEURAT-1 Reference Compounds

The SEURAT-1 (Safety Evaluation Ultimately Replacing Animal Testing-1) research cluster is comprised of seven EU FP7 Health projects and is co-financed by Cosmetics Europe. The SEURAT-1 strategy is to adopt a mode-of-action framework to describe repeated dose toxicity to derive predictions of in vivo toxicity responses.

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Data is also generated from functional assays and bioreactors and supplemented with in silico approaches. This complex and heterogeneous data is consolidated and harmonized through the ToxBank data warehouse. The approach includes the use of the ISA-Tab standard to describe experimental metadata and OpenTox services supporting interoperable data integration and analysis.

We describe for 14 reference compounds the meta-analysis of multiple types of time-dependent dose response omics and functional data combined with in vitro and in vivo background knowledge including consideration of modeling variations in biokinetic responses.

Open TG-GATEs human in vitro liver data of the reference compounds includes reactive compounds (e.g., acetaminophen, CCl4), mitochondrial disruptors (e.g., Rotenone), promiscuous binders (e.g., valproic acid, amiadarone), nuclear hormone receptor ligands (e.g., tamoxifen, WY14643), selective binders (e.g. fluoxetine) and cardiotoxins (e.g., Doxorubicin, Nifedipine).

Adverse events of interest that are represented include cytotoxicity, fibrosis, steatosis, cholestasis and phospholipidosis.

Overall we obtained 31,717 differential expression results with 14 compounds from the 45 comparisons, with Doxorubicin for example providing over 5000 results. We evaluate the use of ToxCast and PubChem data in the enrichment analysis, read across and interpretation of the evidence on reference compounds as mapped to biological pathways.

AUTHORS: Barry Hardy, Thomas Exner, Lucian Farcal and Markus Hegi (Douglas Connect), Glenn Myatt (Leadscope), Nina Jeliazkova (Ideaconsult), Micha Rautenburg (in silico toxicology), Pekka Kohonen and Roland Grafstrom (Karolinska Institute)

ABOUT THE SPEAKER

Dr Barry Hardy, Managing Director
Douglas Connect, Switzerland

Dr. Barry Hardy is the Managing Director of Douglas Connect, Switzerland.

He has coordinated the OpenTox project in predictive toxicology and the ToxBank infrastructure development project. He currently leads the infrastructure development for the IMI EBiSC stem cell banking project and eNanoMapper supporting nanotechnology safety assessment.

He has led the development of research and best practice activities in drug design and toxicology through founding the eCheminfo Community of Practice, InnovationWell and Scientists Against Malaria project.

Currently he is developing Douglas Connect and its Collaboration Pools supporting new business area development and growth.

Dr. Hardy obtained his Ph.D. in 1990 from Syracuse University working in computational science. He was a National Research Fellow at the FDA Center for Biologics and Evaluation, a Hitchings-Elion Fellow at Oxford University and CEO of Virtual Environments International.

He was a pioneer in the early 1990s in the development of Web technology applied to virtual scientific communities and conferences. He has developed technology solutions for internet-based communications, tutor-supported e-learning, laboratory automation systems, and computational science and informatics.

In recent years he has been active in the field of knowledge management as applied to supporting innovation, communities of practice, and collaboration.

ToxBank Abstracts

DAY 2:
Application of Pluripotent Stem Cells for safety testing and disease studies

Session Chair:
Dr Glyn Stacey, Principal Scientist and Head of Cell Biology,
National Institute for Biological Standards and Control (NIBSC), UK

Glyn Stacey has a background in microbiology and cancer research and has worked on the development of cell substrates for manufacture of biological medicines for over fifteen years. He is currently at the National Institute for Biological Standards and Control which is a part of the Medicines and Healthcare Products Regulatory Agency.

He is Head of Division of Cell Biology and Imaging and Director for the UK Stem Cell Bank (UKSCB). The UKSCB has been a licensed clinical tissue bank since 2004. The work of his group covers safety and quality issues in cell therapy, cells used for manufacturing purposes, development of novel cell-based assays and the development of reference materials for tissue typing and diagnosis of genetic disorders. This work includes the need for scale up of preservation techniques and long term storage of DNA and cell lines of various types including human stem cell lines and cells used in bioassays and vaccine production.

Glyn has served on numerous steering groups for organisations promoting and funding regenerative medicine. He has also chaired the UK National Clinical hESC Forum and the scientific advisory board for a Public Private Partnership not-for-profit company called Stem Cells for Safer Medicine.

His academic roles include member of faculty for postgraduate courses in regenerative medicine at Kings College London and University College London, and he is a visiting Professor at the University of Bedfordshire in the UK.

SESSION 2 SCHEDULE

Tuesday, 27th October 2015, from 09.00 to 13:40
Henry Wellcome Auditorium

Time	TITLE	SPEAKERS
09:00	Arrival and registration	!
09:15	Welcome Coffee, Tea	!
09:30	Chair's Introduction	• Glyn Stacey, NIBSC
09:35	New iPSC based modeling of normal and diseased states – StemBANCC	• Jim Ross, University of Edinburgh - MRC Centre for Regenerative Medicine
10:10	EU Funding of research-A need for Ethical Governance	• Joana Namorado, European Commission
10:45	Coffee break	!
11:15	Scientific and ethical qualification of pluripotent stem cells for European research - hPSCreg	• Andreas Kurtz, Charité
12:00	Lunch – Poster session	!
13:00	EBiSC: Access to HIPSc Line Acquisition via the EBiSC	• Paul de Sousa, Roslin Cells
13.40	End Session	!

iPSC Models for Drug Discovery & Safety Assessment

StemBANCC (Stem cells for biological assays of novel drugs and predictive toxicology) is a large-scale, 5 year academic-industry partnership in the area of stem cell research.

It brings together a consortium of 35 partners who share their expertise in 12 work packages. It is a collaborative project between pharmaceutical companies, research institutions and small and medium enterprises (SMEs) to exploit the rich body of experience across sectors and enhance knowledge transfer between academia and industry for patient benefit.

The goal of StemBANCC is to generate 1,500 induced pluripotent stem cell (iPSC) lines from 500 individuals, including individuals without disease and those with known diseases, characterise the cells in terms of their genetic, proteomic and metabolic profiles, and make them available to researchers.

All cell lines also undergo a rigorous quality check. A key component of the consortium is to assess the derived induced pluripotent cells for drug safety studies.

The toxicology workpackage deals with the differentiation and characterisation of hepatocytes, cardiomyocytes, renal cells and brain aggregates from the derived iPSCs and their use in toxicological assays. See StemBancc's website for further information.

ABOUT THE SPEAKER

Professor Jim Ross, Prof. of Liver Cell Biology and director of the Tissue Injury & Repair Group University of Edinburgh/MRC for Regenerative Medicine

James Ross is Professor of Liver Cell Biology and director of the Tissue Injury & Repair Group. The group are an integral part of the University of Edinburgh/MRC for Regenerative Medicine and have developed particular expertise in the isolation and functional characterisation of adult and foetal human hepatocytes and both embryonic stem cell-derived and foetal liver stem cell-derived populations including hepatocytes.

Professor Ross has published extensively in the area of liver cell biology, liver involvement in inflammatory processes, cancer and stem cell biology. In recent years he has broadened his interests to include imaging and has developed a novel ultrasound contrast agent for targeted imaging.

Current projects involve the extension of this work to other imaging modalities and the development of methods for drug and gene delivery.

Professor Ross is also an active participant in the Centre for Cardiovascular Studies, the Centre for Translational and Chemical Biology and the recently formed Centre for Biomedical Engineering within the University of Edinburgh.

The group have active research interests in liver, pancreas, muscle, prostate and eye development and disease.

EU Funding of research-A need for Ethical Governance

There are two visions of Ethics Review:

- A Burden, burocratic distraction
- Risk anticipation and mitigation

Ex-ante process used in the EU was pioneered by Health. Has been followed by ERC, Marie Curie, will be taken up more and more by other agencies and services.

Many Member States are taking it up, and increasingly, in the US, particularly since law-suits have reaches the proportions they have. An Ex-ante ER Identifies the issues, the risks,

Offers processes/solutions to mitigate them, Protects the researcher, the project and the funding bodies, Minimizes adverse impact, to the patient, for a very small investment.

Internal review processes have NO VALUE in court. Risk for researchers of being blocked by third parties – even at publication stage (cf. avian flu case). Results of the EU Experience – out of thousands of Projects (basic research to the Product, huge Cooperative Projects+ Translational+Funding Vaccination Clinical Trials).Only one critical case, resolved out of court; thanks to the Ethical Review process, both the Researchers and the Commission could offer satisfactory answers and safeguards to the EP.

However, there are ways to make this effort work for you. If a product results from research, with an ethics review that was conducted vigorously, All products can have traceable regulatory “ID Card”.

ABOUT THE SPEAKER

Dr. Joana NAMORADO MD, Scientific Officer
European Commission, DG Research & Innovation

Official of the EU Commission, RTD

First in the Cancer sector, and since 2006, in charge of Ethics Review and management of Health Projects.

PreviouslyOfficial of the Council of Ministers of the EU drafting legislation as Desk Officer. And namely, Blood, Tissues Directives

Doctor in Medicine, MD, (Cytopath.) , Master Phil (Ethics)

Consultant in Cytopathology, Lecturer in Histopathology, in charge of Cytopathology and Aids unit– Lisbon – Portugal

Research Fellowship in Cytolopathology –(Ludwig Inst, UK and Charing Cross), research into gynaecological and urinary cytology, HPV and diagnosis of tumours and of P. Carinii in Aids patients– London

Consultant in clinical cytopathology– India

Assistant-Professor at the Institute of Histology and Embryology of the Faculty of Medicine Lisbon – Portugal;

Research Fellowship and MSc (Clinical Cytopathology and Oncology) - USSR Academy of Sciences –

Afiliations:

Medical Associations (Pt, Be, UK, India) European Biochemistry Society, Société Française de Colposcopie, Sociedade Portuguesa de Bioquímica, Society for Stem Cell Research (Pt)

Scientific and ethical qualification of pluripotent stem cells for European research

Human embryonic and induced pluripotent stem cells are powerful tools that allow for a broad range of research including the development of personalized toxicity testing.

It is therefore important to have access to available lines and implement strict and transparent scientific and ethical qualification for these lines.

The human pluripotent stem cell registry (hPSCreg), originally established to provide clarity on the human embryonic stem cell (hESC) landscape, provides access to diverse pluripotent stem cell lines available from multiple resources on a global scale.

The hPSCreg annotates registered lines with scientific information and data in a user-friendly way. To register, a set of minimal criteria must be fulfilled in order to assess the scientific and ethical provenance of a line.

Specifications and inclusion of new and additional annotations is an ongoing process, which has to anticipate the directions, in which the field and the application of the lines grow.

Thus, feedback with the community and close user-interaction are essential to maintain value of the stem cell resource.

ABOUT THE SPEAKER

Dr Andreas Kurtz
Charité - Universitätsmedizin Berlin

A stem cell biologist with a broad range of experience in cell-focused databases, ethics, translational medicine and teaching, Andreas is participating in and co-ordinating several related projects.

He is head of the Laboratory for Stem Cell Research and Knowledge Management at BCRT and holds a faculty position at Seoul National University.

EBiSC - European Bank for Induced Stem Cells

Under joint Innovative Medicines Initiative (IMI) funding from the European Commission and a consortium of European Federation of Pharmaceutical Industries and Associations (EFPIA) members (AstraZeneca AB, H Lundbeck A/S, Janssen Pharmaceutica AB, Novonordisk A/S, Pfizer Ltd, UCB Biopharma SPRL), the European Bank for Induced Stem Cells (www.ebisc.org) has been established to provide standardised access to disease representative human induced pluripotent stem cells for discovery to benefit both industry and the broader community.

This includes detailed scrutiny of ethical provenance, safety screening, scientific characteristics and intellectual property issues.

EBiSC has established acceptability criteria and a management process to evaluate and approve new lines, and assure consistency of stem cell lines at an early phase of accession.

These procedures are captured in a Quality Manual designed to assure consistent delivery of high quality cell lines to users. To launch the bank a fast track "Hot Start" process was implemented with EBiSC project partners at the Universities of Bonn, Cologne, Hubrecht, Newcastle, Instituto de Salud Carlos III, Bioneer and Roslin Cells, to provide early release of established iPSC lines.

Data characterising these lines supplied by the depositors directly will be available via the hESCreg database (www.hescreg.eu/).

Cell lines will be stored at central and mirror banking facilities at Roslin Cells in Edinburgh and Babraham UK, and Fraunhofer IBMT, in Sulzbach Germany and Babraham, UK, and distributed via the European Collection of Cell Cultures, Public Health England, UK) with certificates of analysis for each lot of cells.

Here we present the experience of the bank to date and discuss scientific and technological challenges for the field in the procurement, processing and use of this resource in discovery.

ABOUT THE SPEAKER

Dr Paul De Sousa, Reader, School of Clinical Sciences, University of Edinburgh, Chief Scientific Officer, Roslin Cells Ltd.

Following graduate and postdoctoral training in Canada and the US as a developmental biologist, Dr De Sousa joined the Roslin Institute in 1998 as a group leader in embryo biotechnology focused on development of animal cloning and transgenesis by somatic cell nuclear transfer and associated technologies such as egg and embryo culture, parthenogenesis and pregnancy maintenance across diverse species including mouse, pig, cow, sheep and human.

In 2001 he shifted and narrowed his focus to human embryo stem cells, specifically development of culture environments to support their isolation and growth for human clinical applications.

Dr De Sousa joined the University of Edinburgh in 2005, at which time he also co-founded Roslin Cells Ltd, a not-for-profit company serving to translate stem cell research into quality assured Good Manufacturing Practice (GMP) for advanced cellular therapies.

His academic research concerns advancing knowledge and tools to enable the isolation, growth, and qualification of induced and embryo derived pluripotent stem cells for their safe and efficacious use in therapy and discovery, notably for the treatment of neurodegenerative diseases.

Dr De Sousa currently serves as an Executive Director and Chief Scientist for Roslin Cells Ltd, and leads work-packages to establish foundational collections for the EU Innovative Medicines Initiative European Bank for Induced Stem Cells, GMP translation of a human pluripotent stem cell based therapy for Huntington's Disease (EU FP7 Repair HD) and automated developmental toxicity screening (EU FP7 Droptech).

He is also an executive director of Roslin Cellab Ltd, and on the scientific advisory board of the UK government Department of Health Advisory Committee for Safety of Blood Tissues and Organs.

About **ToxBank Project**

ToxBank is the cross-cluster infrastructure project whose activities include the development of the ToxBank Data Warehouse (TBDW), the selection of reference gold compounds to support the mode-of-action framework, a physical compounds repository, and resources to support the reliable use of qualified biomaterials and protocols.

TOXBANK DATA WAREHOUSE

The ToxBank data warehouse provides a web-accessible shared repository of know-how and experimental results to support predictive toxicology (eg. as carried out by the SEURAT-1 Program). The information within the data warehouse is uploaded from the research activities of the cluster partners as well as relevant data and protocols from other sources, such as public databases containing toxicogenomics data. You can apply for access by contacting the **ToxBank support**.

GOLD COMPOUNDS WIKI

The underlying assumption is that we can identify Modes of Action (MOAs) that are demonstrably relevant to human toxicity based on existing knowledge such as from adverse events of marketed drugs in humans. The goal then becomes to establish *in vitro* assays to characterize and represent these MOAs. A limitation of an MOA-based strategy is that our understanding of MOAs for even the best-known toxicants is incomplete. The challenge and the opportunity are to select compounds that will enable us to increase our understanding of MOAs. Approved compound-related information is made publically available through the **ToxBank wiki** (wiki.toxbank.net).

BIOMATERIALS RESOURCES

The ToxBank cell and tissue bank provides an important open source service to identify suitable sources of cell lines that will meet scientific criteria, ensure compliance with EU and national regulations and provide assays which can be taken up by industry without delays or blocks due to adverse constraints on commercial exploitation. This work utilizes standards recently developed as consensus amongst stem cell scientists and biobanks. The standards established are used in ToxBank to develop evaluation criteria for suppliers of stem cell lines. Data from these suppliers are used to demonstrate compliance with best practices.

ToxBank Provides

Research, Discovery, Product Development,
Safety Assessment, Regulatory Managers...

- Science & Technology
- OpenTox Solutions
- ToxBank Consulting
- Research Project Coordination
- Safety Assessment
- Data Management & Integration
- Integrated Analysis
- Alternative Evidence Reporting

OPENTOX

In developing infrastructure, such as the data warehouse, the project is taking advantage of existing open standards, particularly the **OpenTox project** (www.opentox.net). OpenTox developed a standard framework for interoperable predictive toxicology support. It makes extensive use of web services for interaction with different geographically distributed services necessary to support predictive toxicology data management, algorithms, modeling, validation, and reporting.

Extensions were made to the OpenTox framework to support additional activities needing services by ToxBank representing 'omics datasets.

OPEN STANDARDS AND THE SEMANTIC WEB

ToxBank uses the Investigation/Study/Assay (ISA) representation of experiments. Ontologies and a domain-specific ToxBank keyword hierarchy are used to enrich datasets by adding enough experimental metadata to make the archives comprehensible and reusable.

The ISA2RDF tool developed by ToxBank builds on the ISA-Tab framework and facilitates conversion of investigation metadata into the semantic web standard RDF format.

INTEGRATED DATA ANALYSIS

The ToxBank data is being collected to enable a cross-cluster integrated data analysis leading to the prediction of repeated dose toxicity within an MOA framework, based on a detailed understanding of the technologies, requirements and work practices developed. Semantic web technologies are useful for integration of internal information from SEURAT-1 with external information from database resources around the world.

TOXBANK PUBLIC FORUM

The meeting will take place in London, UK, at the
Wellcome Collection,
183 Euston Rd, London NW1 2BE.

In this forum we will discuss the results of the recent research and development of alternative testing methods aimed to replace animal testing, and the potential impact this work has on our society.

To make a good decision on safety we need to bring both expertise and relevant human scientific information together to form the basis for a structured well-informed discussion leading to best judgement based on available evidence and opinions formed on it.

Conference Chairs

The forum will be co-chaired by **Dr. Barry Hardy** (Douglas Connect) and **Glyn Stacey** (NIBSC).

www.toxbank.net