

**Newsletter Editor:
Camilla Pease**

**IVTS website
www.IVTS.org.uk**

The IVTS is
affiliated to the
British Toxicology
Society (BTS)

**BTS website
www.bts.org.uk**

**IVTS Nov 2008
Winter meeting,
invited speakers will talk on**

Safety Pharmacology

Look out for more
information coming soon
on abstract submission
for free selected oral
communications on any
topic of in vitro research
to be included
in the programme

Inside this issue:

Meetings diary	2
IVTS Winter 2007 meeting feedback	3
Report of the IVTS/ BTS symposium	4
News	5
AGM pointers AltTox spotlight	6
Report—NC3Rs/ BBSRC meeting	8
Useful info and How to contact us	10

Letter from the New Chairman

Welcome to the IVTS Spring Newsletter. I am happy to report that the society continues to enjoy a busy and exciting period. I have tried to keep you up to date with the recent changes to the committee, but here is a summary. After making an outstanding contribution by producing the Newsletter and revamping the IVTS website, Pauline Lee is the new IVTS Secretary. Amanda Woodrooffe is continuing in the role of treasurer. Camilla Pease has taken over the role of Newsletter editor. You are now reading her first production – and I am sure you will agree that she has done a brilliant job. We also realise the importance of the IVTS website, and more information about how it will develop will follow soon. Jeffrey Penny has kindly volunteered to take over as membership secretary, so make sure that your subscriptions are up to date! Finally (after a closely fought contest) welcome to Pratibha Mistry as our newest committee member. With George Kass, Robert Guest and Kelly Bérubé, the committee is now at full strength. From the perspective of a new Chairman I would like to pay tribute to my fellow committee members in making the IVTS a successful society.



In April, the BTS Annual Congress was held at the University of Surrey, where the IVTS hosted a symposium on the topic of Drug and Xenobiotic Metabolism: Current Perspectives. I understand that this was a very informative symposium and gave a great overview of the area. On behalf of the society thank you to the speakers for their excellent presentations. Once again the IVTS recognised the contribution of a young scientist to the field of in vitro toxicology by presenting an award for the best student in vitro poster at the conference dinner. The standard of posters was high and the award went to Laura Price from the University of Aberdeen for her work on the action of diquat on kidney cells in vitro. Congratulations to Laura. Maybe next year we should also offer a prize for the best IVTS ceilidh dancer? A more detailed report on the meeting can be found later in the newsletter.

The committee has met several times this year to plan the meetings programme for 2008 and beyond. This will take us in to some areas of in vitro toxicology that have not previously been covered by the society. We are at an advanced stage of planning the Annual Winter IVTS meeting. This will be a one-day event in London in late November and the theme will be Safety Pharmacology and cardiovascular systems. At the last two annual meetings the poster sessions open to all themes of in vitro toxicology have proved popular. We now plan to complement this with a short oral communications session again open to all areas of in vitro toxicology.

Looking further ahead the IVTS hosted symposium at the BTS Annual conference in 2009 will be on in vitro models derived from human tissue. Also in 2009 the IVTS will be supporting a Society of Experimental Biology sponsored meeting on fish and invertebrate in vitro models, this will be held in Glasgow in June. The committee welcomes ideas for future meetings and issues or debates relating to in vitro toxicology. So if you have a suggestion please contact a committee member.

Finally, it just remains for me to wish you a very pleasant and enjoyable summer.

**James Sidaway
Chairman**

Meetings Diary 2008



IVTIP 'In vitro methods to assess respiratory toxicity', 8-9 May, Southampton UK.

NC3Rs Workshop 'Toxicokinetics and the 3R's' - 29 May 2008, London, UK.
contact details events@nc3rs.org.uk

Nanotechnology—towards reducing animal testing—28-29 May 2008, London, UK.
http://www.nano.org.uk/conferences/alt_Animals/prog.htm

World Congress on In Vitro Biology, 14-18 June 2008, Tucson, Arizona, USA
<http://www.sivb.org/meetings.asp>

BTS Autumn meeting, 8-9 September 2008, Liverpool Hope University, UK.

Eurotox 2008, 5-8 October, Rhodes, Greece. www.eurotox2008.org

ESTIV2008 - the 15th International Congress on In Vitro Toxicology will be held in the Stockholm archipelago, Sweden, September 25-28, 2008. The congress is a joint venture organised by ESTIV (European Society of Toxicology In Vitro), SSCT (Scandinavian Society for Cell Toxicology) and Expertrådet ECB Environmental Competence Ltd.

The interest for developing and using non-animal (in vitro) methods for toxicity testing has increased the last couple of years and the former INVITOX, held every second year, have been upgraded to ESTIV Congress. ESTIV2008 will cover the topics such as in vitro models for environmental toxicology, new in vitro models and strategies, in vitro models for tissue-specific toxicity and toxicokinetics. Full details can be found on <http://www.estiv2008.org/>

Have You seen
the latest on
AltTox, the web
forum for
Alternatives

www.alttox.org

Early announcements of 2009 meetings

Society of Experimental Biology symposium, see <http://www.sebiology.org>

In Vitro Techniques Symposium: Can Fish and Invertebrates Methods Replace Mammalian Models? 28-29 June 2009, Glasgow Scottish Exhibition & Conference Centre (SECC) and hosted during the SEB's annual conference 28 June to 1 July 2009.

7th World Congress on Alternatives Rome, Italy from 30 Aug - 3 Sept 2009.

Hot off the Press News Reports in this Issue

**Report from the IVTS/BTS joint symposium
'Drug and Xenobiotic Metabolism'**
Held on 9 April 2008, Guildford, UK.

**Report from the NC3Rs/BBSRC meeting
'Engineering Tissue Alternatives to Animals'**
Held on 30 April 2008, London, UK.



IVTS Winter 2007 Meeting feedback: Your comments thoughts and ideas are always welcome

The IVTS winter 2007 meeting was titled '**New alternatives, current status and regulatory requirements/expectations**' and was held on 20th November 2007 at AstraZeneca, Cheshire, UK. This meeting was well attended and we received 52 feedback forms.

Current validated methods and pipeline of in vitro models Sebastian Hoffman (ECVAM)
Mutagenicity testing post 2008 Stefan Pfuhrer (Proctor & Gamble)
Case study 1: Pharmaceutical industry. Models used to investigate the renal effects of rosuvastatin James Sidaway (Astra Zeneca)
Case study 2: Chemical/consumer industry. Assuring safety without animal testing – skin allergy Gavin Maxwell (Unilever)
Case study 3: Academia. In silico modelling of in vitro screens – the way to improved prediction Nick Plant (University of Surrey)
Regulatory use of data from validated alternative models Ian Indans (UK HSE)

← Six speakers gave presentations

With respect to the length of the meeting and the number of presentations, 46/52 felt the day was about right. Thanks go to all of the speakers who received good to excellent ratings in terms of scientific content of their presentations and relevance to the topic of the meeting.

Good feedback in general was received in relation to the choice of venue and the majority would go back to the Astra Zeneca site for a future IVTS meeting. We noted that attendees would like an area map and some more information re hotels prior to meetings. We received some good suggestions for improvements for future meetings including having more shorter presentations, especially from students or those new to the field of in vitro toxicology, which the committee has taken on board and for the winter meeting in 2008 we will have a new open session of free 15 minute oral communications from selected abstracts.

Students should be encouraged to submit abstracts for this, and we will aim to provide a supportive environment at future IVTS meetings for new researchers.

It was also interesting to note the diversity of subject matter that our members interests represent (on the left below) and we received suggestions for topics of future meetings, which the committee have taken on board in preparing our future meetings.

Suggested topics for future meetings:

Occupational toxicology
Pulmonary/inhalation toxicology
In vitro skin models
Cytotoxicity
Biochemical problem solving
Mechanisms in vitro models
Regulatory toxicology
Neurotoxicology
Developmental toxicology
Alternatives to animal testing
Modelling human airway
New/emerging technologies/
Systems biology
In vitro assays early in drug discovery
Genetic toxicology
Sensitisation
Safety assessment, eye & skin
Developmental neurotoxicology
Screening
Bone marrow toxicology
Immunotoxicology
Hepatotoxicity
Occupational risk assessment
Models for specific organ toxicity
Kidney cell hrpT
Prediction of acute and chronic toxicity

Eye irritation assays
Skin sensitisation
Use of in vitro data for risk assessment
Models of pathologies which can halt drug development
eg idiopathic hepatotox, phospholipidosis etc
A main organ theme such as skin/liver/heart
In vitro methods for problem solving in pharma industry
Differences between regions (US/EU/Asia) in
acceptance of in vitro data for regulatory purposes

Human based models (cell lines etc)
(to be the topic of IVTS/BTS joint symposium in 2009!)

Pulmonary toxicity
Pre-regulatory screens
Adrenal toxicity
Endocrine toxicity

Safety pharmacology

(to be the topic of our IVTS Winter meeting 2008!)

Biomarkers of exposure and harm to aerial toxins
In silico approaches to modelling systems/toxicology
Barriers to implementation of new validated methods

**Contact details for
IVTS committee
members can be
found at the end of
the newsletter**

Please send feedback
to anyone on the
committee at any
time.

Report of the Joint IVTS/BTS symposium April 2008

DRUG AND XENOBIOTIC METABOLISM: CURRENT PERSPECTIVES

The IVTS sponsored symposium took place on the final day of the BTS 2008 Annual Meeting and was chaired jointly by **Brian Lake** (LFI) and **Mark Graham** (AZ). **Brian Lake** introduced the symposium by giving an historical overview of drug metabolism at the University of Surrey, then introduced the first speaker, **Kuresh Youdim** (Pfizer), who summarised current *in vitro* technologies that are available to study the metabolism of new therapeutic agents. Kuresh Youdim started his presentation with an overview of the phase I and II reactions that contribute to drug metabolism. Although these pathways are well understood, the current challenge is the increased need for metabolic profiling, and this calls for efficient HTS platforms to cope with the substantial increase in the number of compounds that are being generated. The current strategy is to make use of the biochemical profiles generated *in vitro* for compounds or family of compounds and develop *in silico* approaches. Currently, several *in silico* models are used in industry. Some based on X-ray crystal structures can predict metabolic sites, statistical models help to get a yes/no answer on physico-chemical properties to predict dosage requirements and compound stability, whereas continuous models help to predict compound clearance. The modelling package SimCyp predicts the likelihood of drug-drug interactions (DDIs) in humans based on *in vitro* data. GastroPlus is PBPK modelling software used to predict compound absorption in gut (based on physico-chemical properties). Kuresh Youdim concluded his presentation by highlighting the current trend to move away from collections of large quantities of *in vitro* data to better develop *in silico* prediction.

Brian Houston (University of Manchester) gave the next talk and focused on the prediction of metabolic clearance and drug-drug interactions (DDIs) from *in vitro* data. This talk highlighted the importance of a strong theoretical basis to enable mechanism-based predictive *in vivo* metabolic clearance. The need is driven by the increasing reliance on HTS. The prediction of *in vivo* metabolic clearance can make use of mechanism-based PK and consider blood flow, drug binding, transporters and CYPs to determine intrinsic clearance. *In vitro* experiments based on human liver microsomes provide a good correlation with human clearance. A similar prediction can be obtained from human hepatocytes. However, the perceived advantage because of the contribution of Phase II metabolism in intact hepatocytes is offset by a lesser degree of precision due to donor liver variability. Data from experiments carried out on 110 reference compounds to see if the use of recombinant CYPs would provide an improved correlation were presented. However, the inefficient metabolism of over 30% of the compounds by the recombinant enzymes limited the overall predictive value of the study even though a good correlation was observed with the compounds that were rapidly metabolised by the recombinant CYPs. In the next part of the talk, Brian Houston demonstrated that *in vitro* data can be used to provide qualitative zoning to predict DDIs. Although this is a good initial screen to identify true negatives and eliminate false negative hits, the downside is that the properties of the compounds are ignored (giving many false positives) and that it is not quantitative, making the predictions relative. Brian Houston concluded his talk by emphasizing future needs to refine the hepatocyte model by building in drug transporters, taking into consideration Phase II metabolism and taking drug transport inhibition into consideration.

The third presentation addressed the role of transporters in drug clearance and toxicology, and was given by **Steve Hood** (GSK). Following an overview of the members of the ABC and SLS transporters and the large degree of complexity resulting from a large number of polymorphisms, the role of the transporters in selective tissue distribution were discussed. Key functions regulated by transporters include intestinal absorption, organ protection (e.g. CNS) and hepatic uptake and biliary clearance. For example, Pgp prevents intestinal absorption and contributes to the blood-brain barrier. The differential accessibility of verapamil to the CNS in Pgp^{-/-} mice versus wild type mice was used to illustrate this point. The next part of the presentation focused on methodologies that are available to study drug transport *in vitro*. The simpler models include polarised cells in transwells (e.g. Caco-2 cells) or primary cultures of hepatocytes. To model biliary transport, more complex models such as sandwiched cultures of hepatocytes that maintain tight junctions are necessary. Drug transport can also be studied *in vivo* thanks to the availability of a large number of transgenic and knockout animal models and surgical models. Steve Hood concluded his talk by emphasizing the importance of transporters in DDI and drug toxicity.

The final talk of the symposium was provided jointly by **Brian Lake** and **Mark Graham**. Brian Lake gave an historical overview of enzyme induction in drug metabolism. In the clinic, enzyme induction is associated with decreased pharmacological efficacy and DDIs. Also, at the preclinical level, enzyme induction must be considered as it may be a cause of reduced exposure, hepatotoxicity and carcinogenicity. Several nuclear receptors, including AhR, CAR, PXR and PPAR α have been identified to regulate enzyme levels although additional factors such as mRNA and protein stabilisation can also contribute to enzyme induction. Finally, the importance of species differences in enzyme induction was highlighted. The last part of Brian's section dealt with the methods used to study enzyme induction, and *in vitro* cell models and *in vivo* knockout and humanised transgenic animal models were discussed. Mark Graham's talk addressed the role of enzyme induction in drug toxicity. It was highlighted that CYP induction not only had toxicological consequences but should be viewed as part of a pleiotropic response that affects not only retinoid, steroid and eicosanoid metabolism but also causes changes in cholesterol homeostasis, cell communication and growth (tumour promotion). For instance, CAR activation leads to the induction of Phase I and II metabolism as well as apoptosis suppression and upregulation of cell cycle proteins. The induction of CYP2B can therefore be used as a measure of the pleiotropic response and hence a predictor of toxicity. As an example for the application of such mechanistic knowledge, the differential effect exerted by phenobarbitone on mouse versus human liver (with no changes in apoptosis or cell cycle in the latter) can be used to conclude that the human liver is not at risk from CAR activation. Mark then went on to discuss the role of CYP induction in extrahepatic tumourigenesis by citing the liver-thyroid and liver-testis axes as examples. The enhanced metabolic clearance of thyroid hormones and testosterone by the liver leads to hyperplasia of the thyroid and Leydig cells, respectively, with the risk of tumour development. The presentation was concluded by a discussion of the role of extrahepatic CYPs in carcinogenesis. The induction of extrahepatic CYP1B1 by dioxin-like PCBs is viewed as a risk factor for carcinogenesis, and evidence supporting the hypothesis that uncoupled CYP1B1 metabolism leads to ROS formation and oxidative DNA damage was presented.

Overall, this was a well attended and successful symposium that gave a thorough overview of contemporary issues in drug metabolism and how *in vitro* approaches can be used to successfully predict *in vivo* metabolism, drug clearance and toxicity.

News from In Vitro Testing Industrial Platform (IVTIP)

IVTIP is an informal forum of European companies with an active interest in *in vitro* testing to be used in regulatory/safety testing or to be used with compound discovery and development processes. They are also supportive of applying where possible the principle of the 3Rs, replacing, reducing and refining animal testing. The members represent companies in the chemical, cosmetics and pharmaceutical sectors.

IVTIP has recently announced dr. Bart de Wever as new Executive Secretary. Bart has always been a very active company representative within IVTIP. Some of you may remember him as a representative for membercompany SkinEthic, others will know him as an external consultant for Phenion/Henkel. Bart will take over the tasks of the previous Executive Secretary, dr. Helma Hermans, in cooperation with the IVTIP Secretariat.

Source: IVTIP website

Visit the website of
IVTIP

at

<http://www.ivtip.org/>

News from ECVAM

The ECVAM Scientific Advisory Committee (ESAC) has endorsed the validation of alternative tests, which take an important step towards ending the practice of using animals in skin and eye irritancy testing and for skin sensitisation.

Skin irritation: The EPIKIN[®] method will completely replace the regulatory Draize skin irritation test, a classic test introduced into safety tests for drugs and chemicals 60 years ago and involves applying the product to a rabbit's skin. The EpiDerm[®] model instead is seen as a constituent of a testing strategy. The two alternative testing methods are using artificial human skin, which is able to identify irritant and non-irritant chemicals and both have undergone a full validation study.

Eye irritation: The two validated organotypic *in vitro* assays [the Bovine Corneal Opacity and Permeability (BCOP) and the Isolated Chicken Eye (ICE) test methods], will identify severe eye irritants using tissues from slaughter-houses, which would otherwise be discarded. The tests will replace the use of animals to identify severe irritants, though some animal testing will still be required for mild irritants.

Skin sensitisation: Following the endorsement of the Local Lymph Node Assay (LLNA) in 2000, a "reduced" version of the LLNA, namely the rLLNA has now scientifically been validated by ESAC.

Source: ECVAM website

For full details and
report downloads visit
the ECVAM website

at

<http://ecvam.jrc.it/>

News from ICCVAM

Plan Expedites Alternatives to Animal Testing

A new plan to further reduce, refine and replace the use of animals in research and regulatory testing commonly referred to as the 3Rs was unveiled in Feb 2008 at a symposium marking the 10-year anniversary of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The plan identifies priority areas for research, development, translation, and validation activities necessary to achieve regulatory acceptance of alternative test methods. A cornerstone of the federal government's five-year plan is the formation of partnerships with industry and other national and international stakeholders to achieve measurable progress.

The five-year plan was developed over a 12-month period with multiple opportunities for input, including a public Town Meeting held in June 2006. The NICEATM-ICCVAM Five-Year Plan is available electronically at web link:

<http://iccvam.niehs.nih.gov/docs/5yearplan.htm>

Read the full NIEHS News Release at web link:

<http://www.niehs.nih.gov/news/releases/2008/animaltest.cfm>

Source: ICCVAM website

Visit the website of
ICCVAM

at

<http://iccvam.niehs.nih.gov/>

The In Vitro
Toxicology Society is
affiliated to the British
Toxicology Society
(BTS)

**20th
Anniversary of
the IVTS
in 2007
Congratulations!**

**See the full
minutes of the
IVTS 2007 AGM
on
www.ivts.org.uk**

Interested in training?

For information about
toxicology training
courses visit the BTS
website:
www.thebts.org

Exiting IVTS 'Chairman's Letter' to the AGM 2007

As 2007 draws to a close, my time as your Chairman also comes to an end, a role which I feel extremely privileged to have held for the last four years. My final duty is to report on behalf of the committee on another very successful year for the Society in all aspects of its affairs.

A year ago we hosted a very successful winter meeting on the subject of *Pulmonary Toxicity* while earlier this year our symposium at the BTS Annual Congress on the topic of *Toxicity and Compatibility Testing of Medical Devices* was a similar success story providing a fascinating insight into the work involved in developing and testing a range of medical devices. Both meetings received some great feedback thanks to the excellent presentations from our invited speakers. Our winter meeting this year on the subject of *In Vitro Models: New Alternatives, Current Status and Regulatory Requirement/Expectations* maintained this high standard, and I would like to express my thanks to all the speakers and poster presenters for their excellent and stimulating presentations. It was a pleasure once again to award poster prizes at all of these meetings, reflecting the high quality of the science.

Looking ahead to 2008, we are delighted to report that as an affiliated society of the BTS, we will once again jointly host a symposium at the BTS Annual Congress to be held at the University of Surrey from 6-9 April on *Current Perspectives in Drug and Xenobiotic Metabolism*.

Our membership continues to flourish and it is always a pleasure to welcome new members to the Society, so please continue to spread the word amongst your friends and colleagues. Enthusiastic support from the membership is the lifeblood of any scientific society, and it is very gratifying to see that enthusiasm exemplified by the strong attendance at this meeting. Also, we are pleased to report that the Society continues to be in a healthy financial state, and the revamped newsletter and website continue to be useful resources to members.

On to committee news, where there are a number of changes to report. Earlier this year Mari Johnson stepped down from the committee after four years and I would like to thank Mari for her involvement on the committee. In addition, Anita Naidoo (Secretary) and myself have completed our maximum six year tenure on the committee and will therefore be retiring. On a personal note I would like to thank Anita for her tremendous hard work, dedication and commitment to the committee and Society during the last six years. These changes have meant that we are delighted to welcome three new members onto the committee this year. Camilla Pease from Unilever joined us earlier in the year and during this years winter meeting, Kelly BéruBé from Cardiff University and Jeff Penny from the University of Manchester joined the troops. A very warm welcome to you all!

I would like to finish by expressing my sincere thanks and gratitude to all my friends and colleagues on the committee for their energy, enthusiasm and hard work in ensuring the successful running of the Society and to you, the members, for continuing to support and participate in our activities. It has been an honour to be your Chairman and I wish the Society a long and prosperous future.

Val Baker

Spotlight on 'AltTox' - Have you seen it yet?

AltTox.org was recently launched as a dedicated website for the area of non-animal alternative methods in toxicity testing. It is being developed and supported through a collaboration of the Procter & Gamble Company (P&G) and The Humane Society of the United States (HSUS). All content is overseen and edited objectively by an editorial board of experts and discussion forums on the site are also moderated by this board. It is also intended that this website could host online workshops and virtual meetings.

Three interconnected resources form the basis of AltTox:

- **Online discussion forums - [AltTox.org Forums](http://www.alttox.org/forums)**
- **An informational section on toxicity testing - [Toxicity Testing Resource Center \(TTRC\)](http://www.alttox.org/ttrc)**
- **Invited commentaries - [Way Forward](http://www.alttox.org/wayforward) articles**

The vision for AltTox is to act as a driving force for innovation and change, by providing an interactive platform for users to get involved in posting commentaries, participating in discussion forums, providing feedback etc. There are currently 15 discussion forums under 4 categories: toxicity endpoints and tests, emerging technologies, programs and policies, overarching challenges and opportunities. For anyone interested in developing *in vitro* alternatives it is worth taking a look.



www.alttox.org

i-SUP 2008 Congress (innovation for sustainable production)

Organised by VITO, the Flemish Institute for Technological Research and MIP, the Environmental and Energy Technology Innovation Platform Flanders, the i-SUP 2008 international congress was held in the beautiful 'chocolate' city of Bruges, Belgium from 22nd to 25th April 2008. The event consisted of a total of five separate conferences under one roof at the site of Old St John's and was attended by around 500 delegates. Conference 5 addressed Environment, Health and Safety, Alternative Testing: the future for safety testing which was attended by approximately 80 delegates. Thirty-two speakers covered four themes, Targeted toxicity testing, Implemented test strategies in pharmaceutical, cosmetic and chemical product safety assessment, The Regulatory Arena: challenges in method acceptance and Industrial Centers of Excellence in *in vitro* services. Who does what?

The full and varied programme was well received and provided an excellent overview of new developments in *in vitro* toxicological testing, current research programmes, activities of industry and *in vitro* platform organisations, together with opinions of scientific experts.

It is anticipated that Speaker's presentations will soon be accessible from the i-SUP 2008 website <http://www.i-sup2008.org>. It is planned that the next i-SUP Congress will be held in Belgium in 2010.

Rob Guest

Meeting Report : NC3Rs/BBSRC meeting

'Engineering tissue alternatives to animals' (30th April 2008, London, UK)

This one day meeting was held to review progress with tissue engineering research projects funded by NC3Rs and BBSRC. Twelve presentations were given to over 100 delegates. **Professor Kevin Shakesheff** (University of Nottingham) opened and chaired the meeting, kicking off the proceedings with a brief overview of the key themes of the meeting, namely the increased regulations for industry driving motivation to seek alternatives to animal models, the desire to integrate human *in vitro* approaches earlier during drug discovery and the height of the bar for replacing established *in vivo* approaches with *in vitro* alternatives driving the need for very high quality research and models. **Dr Anthony Holmes** then introduced NC3Rs mission and described the various funding schemes available for research supporting the 3Rs.

Dr Carl Westmoreland (Unilever) then opened the scientific presentations by describing the requirements of the '7th Amendment to the EU Cosmetics Directive' and the reasons for the need to establish and validate alternative models for safety assessment of products, prototypes and ingredients. The 3 validated, accepted alternative models; for skin corrosion, phototoxicity and skin penetration were described. Other models are in development for skin irritation (already validated by ECVAM and accepted in the EU), eye irritation and skin sensitisation. There was discussion about keeping the models simple but using >1:1 *in vitro:in vivo* to facilitate modelling of complex biology. However, if assessment of risk cannot easily be interpreted from these approaches, then more complex models may be required, hence the ongoing need for tissue engineering approaches. The need for these standardised models to be reliably available and compliant with GLP was discussed. Ongoing challenges remain in how to develop alternative approaches to model more complex areas e.g. repeat dose toxicity, toxicokinetics and reproductive toxicity. The industry is working on how to use and integrate data generated from combinations of alternative models to best assess risk and allow decision making.

Dr Christophe Giese (ProBioGen AG) presented a human artificial lymph node model for the assessment of immunogenicity and immunotoxicity. There is a move towards the development of biological therapies to treat human disease and risk assessment for such molecules requires specific, human based *in vitro* test systems. The human artificial lymph node model is based on a hollow fibre bioreactor system and comprises 3D co-culture of human monocyte-derived dendritic cells (immobilized within a transparent matrix) with naïve human lymphocytes (mobile). The model also allows the introduction of B lymphocytes to provide a complex model of lymphatic organoids. Antigens are introduced into the model and supernatants profiled for cytokine and chemokines to investigate Th1/Th2 shifts or secretion of IgG and IgM to profile humoral immune responses.

Dr Nigel Fullwood (Lancaster University) presented a model of the anterior chamber of the eye that has been developed to study wound healing. The cornea is clamped around the sclera into a chamber device, which allows the underside of the cornea to be perfused at a pressure equating IOP. The corneal surface is exposed to air, with a device to irrigate with a tear substitute. Viable limbal stem cells create new corneal epithelia in response to wounding, achieved by peeling off the epithelial layer from the cornea. Currently the model remains viable for just over 2 weeks, when integrity of the clamped sclera is lost, breaking the seal on the perfused unit. The model has also been used to investigate treatment of alkali induced opacification and for investigating the best approaches for gene transfection into limbal stem cells. Both these are currently studied using *in vivo* models. Finally, the model has also been used to evaluate potential materials for artificial corneas prior to evaluation in expensive *in vivo* models.

The morning session closed with a fascinating presentation from **Dr Louise Jones** (University of London), describing a 3D *in vitro* model for studying progression of DCIS (ductal carcinoma *in situ*) to invasive carcinoma. Not all DCIS cases develop into invasive carcinoma, but all patients are treated. Understanding whether DCIS will progress or not will help rationalise patient treatment approaches. The model comprises luminal, myoepithelial and fibroblast populations and was developed initially with human primary cells from both normal and malignant breast. Recently, successful immortalisation of the luminal epithelial cells has enabled the model to develop using a combination of primary cells and cell lines (including the commercially available MCF7 cell line). Inclusion of tumour-derived fibroblasts in this model leads to disruption of the luminal/myoepithelial dual cell co-unit. There was discussion around the importance of thorough validation of cell line approaches to develop such models, the need for multicellular 3D *in vitro* models to ensure cellular interactions are maintained and also the validation *in vitro* models by comparing data, in this case, to both clinical events and the 'gold standard' animal models for breast cancer – a means of convincing and converting researchers to validated alternative approaches ?



The afternoon started with three shorter presentations of selected NC3Rs/BBSRC funded projects. **Dr Keith Barr** (University of Dundee) described an *in vitro* model of skeletal muscle physiology, in which myocytes from either cell lines or primary cells are allowed to grow and differentiate in a fibrinogen matrix under tension between two structures. In this 3D model the muscle can be physically stimulated and the force contraction measured. With similar characteristics to intact muscle, this model is a promising alternative to the 500,000 animals that currently used in skeletal muscle disease research. **Professor Donna Davies** (University of Southampton) highlighted the inadequacies of current animal models of asthma. Her group has just begun an NC3Rs funded project to develop a tissue-engineered model of the human asthmatic airway. This will be used to study the interaction between bronchial epithelial cells, dendritic cells and other immune cell types using sensor technology to monitor the barrier function of the lung epithelium. Another area of high animal usage is in the production of pancreatic islets cell for diabetes research. **Professor Peter Jones** (King's College London) described how the transformed MIN6 beta-cell cell line aggregates to form pseudoislets when grown on a collagen substrate. In contrast to monolayer beta-cell cultures the MIN6-derived pseudoislets secrete comparable levels of insulin to islets derived from animals, and NC3Rs is funding a project to make this model more accessible to the diabetes research community.

In the final part of the programme **Professor Sheila MacNeil** (University of Sheffield) emphasised the importance of 3D models in the development of tissue-engineered skin, which has now been in clinical use for 25 years. This same approach is currently being utilised to create *in vitro* models of psoriasis, melanoma biology, angiogenesis and infection. **Dr Mark Lewis** (UCL Eastman Dental Institute) spoke of pioneering research in tissue engineering models of the neuromuscular junction. Sensory neurons are notoriously difficult to maintain in culture, but he has recently found that they will propagate on engineered skeletal muscle derived from primary human myocytes. It is hoped that this research may eventually lead to the replacement of current animal derived nerve-muscle models. Renal disease is area where tissue engineered models could have a great impact, in the short term to reduce animal usage in research and ultimately for kidney replacement. **Professor Jamie Davies** (University of Edinburgh) described the value of organ culture of embryonic kidney rudiments as models for understanding the developmental biology of the kidney. At present this relies on embryonic tissue from freshly killed animals, but efforts are now focusing on the generation of immortalised cell lines.

Ms Elizabeth Davidson (MHRA) outlined the regulatory considerations and requirements for the safety testing of tissue engineered products. As of December 2008, a new committee for Advanced Therapies at the European Medicine Agency will be responsible for the European approval of tissue-engineered medicines. Many of the same principles that are used for pharmaceuticals apply, but special consideration will be given to the production quality of cells and any accompanying engineering matrix. In the final talk of the meeting **Dr Chris Denning** (University of Nottingham) described impressive progress in standardisation of culture conditions of human embryonic stem cells, such that these can now be cultured on an industrial scale whilst still maintaining a complete cardiac phenotype. Techniques for optimally transfecting and knocking out genes have also been achieved and the model is now being used to study Duchenne Muscular Dystrophy.

The meeting closed with a lively debate, which included a question about why there are so many obstacles to the rapid adoption of new *in vitro* models as alternatives to animal use? There was then a final opportunity to view the posters abetted by plenty of wine and some very tasty canapés. In all, this was an excellent meeting; the listener was certainly left with the view that in the UK significant progress is being made in engineering of tissues and in many areas these will be viable alternatives to animal use in the future.

Amanda Woodrooffe & James Sidaway

Useful websites



DATABASES

Altbib

<http://toxnet.nlm.nih.gov/altbib.html>

ALTBIB is a new bibliographic database for alternatives to animal testing. It features citations concerning methods, tests and procedures that refine, reduce and replace animal testing.

Altweb

<http://altweb.jhsph.edu>

A web site on alternatives developed by CAAT (Centre for Alternatives to Animal Testing) at the Johns Hopkins University. It contains full text articles of many journals, as well as the complete set of ECVAM workshop reports.

AnimAlt-ZEBET

<http://www.dimdi.de/en/db/recherche.htm>

An internet database on alternatives to animal experiments.

ECVAM Scientific Information Service (SIS)

<http://ecvam-sis.jrc.it>

Database contains details of validation studies, methods, protocols, ECVAM reports, bibliography etc.

INVITTOX

<http://www.invittox.com>

In vitro toxicology protocols, also now available on ECVAM database.

EURCA – European Resource for Alternatives in higher education

<http://www.eurca.org>

Website includes a searchable database on alternatives in education.

Visit **ICCVAM** on their
website

[http://
iccvam.niehs.nih.gov](http://iccvam.niehs.nih.gov)

ORGANISATIONS

BITE CIC

<http://www.bitecic.com>

Biomaterials and Tissue Engineering Centre of Industrial Collaboration

FRAME

<http://www.frame.org.uk>

Fund for the Replacement of Animals in Medical Experiments.

ECVAM

<http://ecvam.jrc.it/>

European Centre for the Validation of Alternative Methods

ICCVAM

<http://iccvam.niehs.nih.gov/>

Interagency Coordinating Committee on the Validation of Alternative Methods.

Netherlands Centre for Alternatives to Animal Use

<http://www.nca-nl.org/>

A gateway site with numerous links to *in vitro* testing organizations and animal welfare groups.



Continued.....

ECOPA (European Consensus Platform for Alternatives)

<http://ecopa.vub.ac.be/>

Organisation at EU level promoting the 3Rs at European level.

Institute for In Vitro Sciences

<http://www.iivs.org/>

The Institute for In Vitro Sciences is a non-profit, technology driven, foundation dedicated to the advancement of alternative test methods.

World Health Organization (WHO)

<http://www.who.org>

Organisation for Economic Development (OECD)

<http://www.oecd.org>

EAPB

www.eapb.org

www.new-drugs.com

CORDIS (European Union)

<http://www.cordis.lu>

Cordis - the general database of the EU

European Institutions

<http://Europa.eu.int/idea/ideaen.html>

Directory of European Institutions

CELL/TISSUE COLLECTIONS

UK Human Tissue Bank

<http://www.ukhtb.org/>

A not for profit organisation based at De Montfort University, Leicester.

UK Stem Cell Bank

<http://www.nibsc.ac.uk/divisions/cbi/stemcell.html>

European Association of Tissue Banks

<http://www.eatb.de>

EATB is a scientific, non-profit organisation that promotes cooperation, research and developments in the area of tissue banking in Europe.

American Type Culture Collection (ATCC)

<http://www.atcc.org/>

ATCC-LGC Promochem Partnership

<http://www.lgcpromochem.com/ATCC/>

LGC Promochem's partnership with ATCC facilitates the distribution of ATCC cultures and bioproducts to life science researchers throughout Europe.

German Collection of Micro-Organisms and Cell Cultures

<http://www.dsmz.de/>

European Collection of Cell Cultures (ECACC)

<http://www.ecacc.org/>



The
**UK Human Tissue
Bank**
can be found at
www.ukhtb.org

Continued....

National Cell Culture Centre (NCCC)

<http://www.nccc.com/>

Cell culture services for basic research laboratories.

Aging Cell Repository

<http://locus.umdj.edu/nia>

A collection of human and animal cells for research into aging and associated degenerative diseases such as Alzheimer's and Parkinsonism.

Cell lines from specialised collections and cell banks

<http://www.biotech.ist.unige.it/cldb/indexes.html>

12 collections, including ECACC

SOCIETIES / NETWORKS

British Toxicology Society

<http://www.thebts.org>

Society of Toxicology

<http://www.toxicology.org>

EUROTOX

<http://www.eurotox.com>

European Society of Toxicology In Vitro

<http://www.estiv.org>

European Tissue Culture Society

<http://www.uni-stuttgart.de/etcs/etcsmain.html>

Sens-it-iv project

EU FP6 project

<http://www.sens-it-iv.eu>

European Society for Animal Cell Technology (ESACT)

<http://www.esact.org>

Hepatocyte Users Group (HUG)

<http://www.abdn.ac.uk/~bch196/HUG.htm>

International Conference on Harmonization (ICH)

<http://www.ifpma.org>

Society for In Vitro Biology

<http://www.sivb.org/>

IVTIP (In Vitro Testing Industrial Platform)

<http://www.ivtip.org/>

IVTIP is an informal forum of European companies with an active interest in in vitro testing

ACTIP (Animal Cell Technology Industrial Platform)

<http://www.actip.org>

ACTIP is an informal forum of European companies with activities in animal cell technology.



The Society for In
Vitro Biology

www.sivb.org



BRITE Net (British Interdisciplinary Tissue Engineering Network).

<http://www.briten.org>

The key objectives of BRITE Net are to promote communication & collaboration between key tissue engineering disciplines (academic & industrial).

TCES

<http://www.TCES.org>

Tissue and Cell Engineering Society

Tissue Engineering Society International (TESI)

<http://www.tesinternational.org>

Society brings together the international community of persons engaged or interested in the field of tissue engineering and promotes education and research within the field of tissue engineering through regular meetings, publications and other forms of communication.

European Cell Death Organisation (ECDO)

<http://www.imm.ki.se/ECDO>

The main aim of the ECDO is to share information on current developments in the field cell death research

EUFEPS

www.eufeps.org

The European Federation for Pharmaceutical Sciences (EUFEPS) is the only pan-European body to represent the interests of scientists in industry, academia, government and other institutions engaged in drug research, development, regulation and policymaking through Europe.



Membership information

The annual subscription for membership of the IVTS is £10, payable in January each year. The fee provides a regular income for the Society, enabling us to keep costs of meetings down, and more importantly, continue to invite high calibre speakers. The IVTS currently holds 2 symposia per year, one jointly with the British Toxicology Society (BTS) in the Spring at the BTS Annual Congress, and another in the Autumn/Winter. The committee encourages IVTS members to extend an invitation to all colleagues and associates with a professional scientific interest in *in vitro* toxicology to attend our meetings and to apply for membership. Members receive preferential registration rates for meetings, meeting reports and the IVTS Newsletter (twice yearly).

Most of our members pay by standing order. If you would like to do this please contact a Member of the Committee. Cheques should be made payable to "The In vitro Toxicology Society" and sent to the Treasurer, Amanda Woodroffe.

The IVTS is keen to encourage the participation of postgraduate students in its affairs and meetings and is offering **free membership to the Society for students** with the aim of supporting research and education in *in vitro* toxicology. Membership is free for the duration of postgraduate study and entitles the student to preferential registration rates at IVTS meetings, to apply for bursaries to attend other relevant *in vitro* meetings (see below) and to receive the IVTS newsletter and that of ESTIV (European Society of In vitro Toxicology). These newsletters contain reports of recent meetings, a conference diary, and other items of relevance to *in vitro* toxicology.

Membership is free
for students!!

Please keep us up to
date with any change
in details



Student Bursaries

The IVTS offers student members bursaries to contribute to the registration fees, accommodation and travel costs of forthcoming *in vitro* meetings. Criteria for bursary applications (which should be made to a member of the committee) are:

- student membership of the IVTS
- submission of an abstract (where applicable) and letter of confirmation of full time student status
- provision of a meeting report which will be included in the IVTS newsletter

We regret that there are limits to the number of student bursaries we can give and only one bursary can be awarded per laboratory/organisation per year.

Student Prizes

Student prizes of up to £200 are available for the best student presentations at certain appropriate meetings, including the BTS Annual Congress. All abstracts submitted by students will be eligible for the award and will be judged by the committee.

Student prizes are awarded at a number of meetings each year

A poster prize was awarded at the winter meeting on **In Vitro Models: New alternatives, current status and regulatory requirements/expectations** at AstraZeneca, November 2007. The prize of £100 for the best poster was presented to Eric Hill from Aston University for his poster entitled *Differentiating human NT2/D1 neurospheres as a versatile in vitro 3D model system for developing neurotoxicity testing*. Our congratulations to Eric!!

Financial Support to Academic Groups



With the aim of supporting research in *in vitro* toxicology, the IVTS is offering financial support to academic groups in the U.K. Funds are available to contribute towards the cost of consumables, extensions to research contracts, visits to other laboratories to learn new techniques etc. Applications should be made in writing to a member of the committee. Each application will be reviewed by the committee and funds allocated on merit. It is envisaged that the maximum award will be £500.

Don't forget that **student members** can apply to the IVTS for travel bursaries to help them attend relevant meetings.
So if you have some travel planned please get in touch

Training

Toxicology training courses are available at a number of institutions in the UK including:

- the University of Surrey in Guildford (www.surrey.ac.uk),
- the University of Birmingham (www.bham.ac.uk)

Also visit the BTS website for further information on training.

If you have experience of a good training course and would like to share your experience with others please let us know.



[in Vitro-in Vivo Correlation \(IVIVC\) Training Course](#) [22ND JULY 2008, BSG CONFERENCE CENTRE,](#) [LONDON, UK](#)

Places at this course are by invitation upon application only.

Over the last 20 years, big pharma has been under great pressure to reduce development costs and the time to market. The urgency to maximize a return on investment increases constantly while maintaining successful patient treatments. Because of this, scientists working throughout pharmacy, pharmaceuticals, and pharmacokinetics are collaborating to address physicochemical and biological issues in the early stages of development to avoid problems in later stages. In Vitro-In Vivo Correlation (IVIVC) has been successfully applied in testing the effectiveness of drug substances. This in-depth interactive analysis of IVIVC, instructs you further in the importance of IVIVC in the drug development process. It will inform you fully of the most recent advances and regulatory perspectives on the role of IVIVC in your area. Training workshop led by:

Professor Jean-Michel Cardot

Dept of Biopharmaceutics and Pharmaceutical Technology, Universite d'Auvergne, France

- *1 day training and interactive workshop ticket* - available for only **GBP £599**

If you would like to send more than 1 person then take advantage of the 3 for 2 offer. Send 3 people but only pay for 2. Excellent networking opportunities.

contact **Andres Arias**. TEL: **+44 (0)207 549 2019** or email mailto:

pharma.reports3@conferencesandreports.com Please feel free to contact me should you have any questions, or wish to purchase a copy of the report.

Andres Arias, Visiongain Ltd, BSG House, 226-236 City Road, London, EC1V 2QY
United Kingdom www.visiongain.com

The newsletter can
also be
downloaded from
our website

www.ivts.org.uk

—————
If you have any suggestions or information for the next
newsletter please contact camilla.pease@unilever.com
—————

The IVTS Committee (contact details)



Chairman
Dr James Sidaway
AstraZeneca,
Alderley Park,
Macclesfield,
Cheshire, SK10 4TG
Tel: 01625 510221
Fax: 01625 513779
Email: james.sidaway@astrazeneca.com

Secretary
Dr Pauline Lee
BioApproaches SouthWest
Regus House
1 Friary,
Temple Quay
Bristol, BS1 6EA
Tel: 0113 394 9874
Email: pauline@bioapproaches.co.uk

Treasurer
Dr Amanda Woodroffe
Asterand UK Ltd
2 Orchard Road, Royston
Herts, SG8 5HD
Tel: 01763 211600
Fax: 01763 211555
Email: amanda.woodroffe@asterand.com

Newsletter Editor
Dr Camilla Pease
Safety & Environmental Assurance Centre
Unilever Colworth
Sharnbrook
Bedfordshire, MK44 1LQ
Tel: 01234 264786
Fax: 01234 264744
Email: camilla.pease@unilever.com

If you have a question
about IVTS
membership or our
activity please contact
any of our committee
members

Membership Secretary
Dr Jeff Penny
School of Pharmacy and Pharmaceutical Sci-
ences, University of Manchester
Stopford Building,
Oxford Road
Manchester, M13 9PT.
Tel: 0161 275 8344
Fax: 0161 275 8349
Email: Jeff.Penny@manchester.ac.uk

BTS Liasion
Dr George Kass
School of Biomedical & Molecular Sci-
ence
University of Surrey
Guildford
Surrey, GU2 7XH
Tel: 01483 686449
Fax: 01483 300374
Email: g.kass@surrey.ac.uk

Dr Kelly BéruBé
Cardiff School of Biosciences
Cardiff University
Biomedical Building
Museum Avenue
Cardiff, CF10 3US
Tel: 0292 087 6012
Email: Berube@cardiff.ac.uk

Robert Guest
SafePharm Laboratories Ltd
Shardlow Business Park
London Road, Shardlow
Derbyshire
DE72 2GD
Tel +44 (0)1332 792896
Fax +44 (0)1332 799018
Email: rguest@safepharm.co.uk



Pratibha Mistry
Product Safety
Syngenta Ltd
Jealott's Hill Int. Research Centre
Bracknell, Berkshire, RG42 6EY.
Tel: 01344 413731
Fax: 01344 413638
Email: pratibha.mistry@syngenta.com