Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013
Alderley Park Conference Centre, Cheshire, UK

The 28th annual meeting of the British Society of Toxicological Pathology (BSTP) held jointly with the Safety Pharmacology Society (SPS)
28th ANNUAL SCIENTIFIC MEETING of the BRITISH SOCIETY OF TOXICOLOGICAL PATHOLOGY held jointly with the SAFETY PHARMACOLOGY SOCIETY

I am delighted to welcome you to the 28th annual meeting of the British Society of Toxicological Pathology (BSTP) held jointly with the Safety Pharmacology Society (SPS) and sponsored by the Health and Environmental Sciences Institute (HESI) at The Alderley Park Conference Centre, Cheshire, UK on 14th and 15th November 2013.

The excellent programme on offer at this meeting is a tribute to the work of many people, including the BSTP Council and Education Sub-Committee. However, I would particularly like to thank the Scientific Organisers, Stephanie Klein and Will Redfern, for their ideas and energy in successfully combining morphologic and functional aspects of cardiovascular toxicology. This was the aspiration of the meeting and I think it has been fulfilled.

We know that much scientific progress is made at the intersection of different disciplines, and the BSTP is keen to establish fruitful collaborations with many other societies. This results in meetings of wider interest and allows for hot topics at the edge of our current understanding to be discussed. This meeting, organised with Jean-Pierre Valentin of the SPS, very much exemplifies this approach and I hope it forms the template of many more to come.

The BSTP thanks all the speakers for their participation and the Royal College of Pathologists for awarding the BSTP the Kohn Memorial Lecture for 2013. We are fortunate that this will be delivered by Professor Robert Hamlin of the University of Ohio.

The SPS and BSTP have been able to attract sponsorship in the form of delegate materials and AstraZeneca are kindly covering the cost of the venue hire. In addition we are delighted to have 10 trade exhibitors supporting this event. We thank these companies for their support and encourage delegates to visit their stands and attend the technology showcases. The BSTP hopes to have a long working relationship with all of you.

Last but not least, the BSTP would like to thank you for attending and all those companies who support the BSTP by allowing you to attend.

Enjoy the meeting

Richard Haworth – President, BSTP
Dear Colleagues,

On behalf of the Safety Pharmacology Society (SPS) I would like to welcome you to the "Integrated cardiovascular risk assessment for new candidate drugs from functional and pathological data” meeting jointly held by the BSTP and the SPS on 14th & 15th November 2013, at Alderley Park, Cheshire, UK.

The Scientific Program will feature a range of scientific presentations covering both functional and pathological cardiovascular adverse effects of drugs in drug discovery and development.

An attractive panel of speakers from academia, pharmaceutical companies, contract research organisations, and regulatory authorities has been assembled and the programme has been designed to cover a broad spectrum of issues and technologies.

The programme will include an interactive audience participation session. The meeting will provide opportunities for scientific exchanges around posters and exhibitors booths and for networking with friends, colleagues and leaders in the different disciplines.

There will be a social event in the evening of 14th November to provide further networking opportunities between meeting participants.

Welcome to Alderley Park, and let’s make this 2013 joint BSTP – SPS meeting an event to remember.

Dr Jean-Pierre Valentin  
Director Safety Pharmacology Centre of Expertise, Drug Safety & Metabolism  
AstraZeneca

&

Vice President of the Safety Pharmacology Society
THANK YOU TO OUR SPONSORS
GENERAL INFORMATION

The BSTP and SPS would like to inform you that no part of the presentations/handouts received at this meeting may be reproduced or transmitted in any form, or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the individual speakers/authors.

Registration
All meeting documents will be available at the registration desk. A name badge will be provided and should be worn whilst on site at AstraZeneca.

Speaker Information
A computer and digital projector are available for presentations. Please pass your presentation to the Scientific Organisers when arriving at the registration desk before your session.

Attendance sheet
Separate sheets are required for each day; please ensure that you sign them. This is a requirement for the allocation of Royal College of Pathologists CPD credits.

CPD points
The Royal College of Pathologists have awarded 10 CPD credits for full attendance at this meeting.

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Mobile Phones
It is respectfully asked that for the benefit of everyone, you restrict the use of your mobile phone during the talks; if possible, please can you switch your phone off or change the settings to mute.

Safety and Security
Please remove your name badge when leaving AstraZeneca.

You are also reminded to keep your belongings (including your delegate bag) with you at all times. The BSTP/SPS and AstraZeneca will not accept responsibility for any belongings left in the meeting rooms at any time and particularly overnight.
The Alderley Park Conference Centre at AstraZeneca opened in 2008 and provides a facility for science and business conference style events.

Set amongst the parklands of Alderley, it offers a state of the art auditorium and has a high standard of facilities, including wireless connectivity.
WELCOME RECEPTION AND CONFERENCE DINNER

Mottram Hall
Wilmslow Road
Mottram St Andrew
Cheshire SK10 4QT
UK

The Welcome Reception and Conference Dinner will be held in the St Andrews Suite at Mottram Hall on Thursday 14th November.

Delegates and guests attending the Welcome Reception should arrive at 19.30 hours with the dinner starting at 20.00 hours.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

MEETING ORGANISERS

Scientific Organisers:

Stephanie Klein
AstraZeneca, UK

Will Redfern
AstraZeneca, UK

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Senior Vice President
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Junior Vice President
Adam Hargreaves

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Website
Jayne Harris

Newsletter
Peter Clements

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EPSR Coordinator
Matt Jacobsen

ESTP Representatives
Franck Chanut and Ian Taylor

Outreach Advisor
Ian Taylor

BTS Representative
Jen Barnes

Trainee Representative
Karen Beebe

Acting Trainee Representative
Alison Rowles

Module 13
Tom McKevitt

Module 14
Jon Carter

Experimental Mouse Pathology Liaison
Cheryl Scudamore

BSTP Secretariat:

Sue Newband
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14\textsuperscript{th} & 15\textsuperscript{th} November 2013, Alderley Park Conference Centre, UK

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Michael Engwall
Niels-Christian Ganderup
Robert Hamlin
John Koerner
Martin Sanders
Krystle Correll, Executive Director
Joachim Kohn was born in Poland in 1912. He qualified in medicine in 1936, served in the Polish armed forces, and became a prisoner of war in Russia until 1941, when he was able to leave for the United Kingdom. He served in the British 8th Army, being awarded the Military Cross and the Silver Order of Merit with swords. After the war, he settled in Britain and trained in pathology at Queen Mary’s Hospital Roehampton, London where he became a Consultant Clinical Pathologist in 1955, and later a Senior Lecturer in Chemical Pathology in the University of London, officially retiring in 1977.

He became a part-time consultant to the Royal Marsden Hospital London and to St Anthony’s Hospital in Surrey. Later he was appointed a visiting Professor to the University of Surrey in Guildford, a post that he held until his death in 1987 at the age of 75. He was an experimental technologist of great distinction and made a major contribution to simplifying the techniques of electrophoresis first introduced by Tiselius in the 1930s, in particular by introducing the use of cellulose acetate membranes which allowed the separated proteins to be fixed, stained and further evaluated. He also devised inexpensive methods for detecting amoebae in tropical diseases, burn dressings (adopted by the World Health Organisation), self-sterilising moisturisers for ventilators, and the first simple dip-stick types of laboratory tests (notably the first dip-stick glucose test strips). He was fluent in six languages, travelled extensively, and was a much sought-after lecturer.

The inaugural Kohn memorial lecture was given in 1989 at the Royal College of Pathologists in London, and is held annually under the auspices of the Royal College of Pathologists.
## Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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### PROGRAMME

#### Day 1: Thursday 14th November 2013

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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</table>
| 08.30 - 09.30 | Registration, coffee and exhibits  
Mount posters                                            |
| 09.30 - 09.35 | Welcome address  
Dr Stefan Platz, Vice President Drug Safety & Metabolism, AstraZeneca |
| 09.35 - 09.45 | Welcome & opening remarks  
Dr Richard Haworth, GlaxoSmithKline, UK (President of BSTP)  
Dr Will Redfern, AstraZeneca, UK (Secretary of SPS) |
| 09.45 - 10.15 | Cardiovascular toxicity: Scale of the problem facing the pharmaceutical industry  
Dr Mark Holbrook, Covance, UK |
| 10.15 - 10.35 | Technology on the pitch  
2-minute overviews from each of the exhibitors |
| 10.35 - 11.00 | Coffee, posters and exhibits |
| 11.00 - 11.30 | Predicting drug-induced QT prolongation and torsade de pointes in vitro and in vivo  
Dr Matt Skinner, AstraZeneca, UK |
| 11.30 - 12.00 | Predicting drug-induced torsade de pointes using computer simulations of the heart  
Dr Blanca Rodriguez, University of Oxford, UK |
| 12.30 - 12.50 | Buffet lunch, posters and exhibits  
Technology Showcase (20 min):  
The Application of xCELLigence System for Safety Assessment Using Stem Cell Derived Cardiomyocytes  
ACEA Biosciences, Inc. |
**CARDIOVASCULAR SAFETY RISK ASSESSMENT FOR NEW CANDIDATE DRUGS FROM FUNCTIONAL AND PATHOLOGICAL DATA**

14th & 15th November 2013, Alderley Park Conference Centre, UK

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**PROGRAMME**

**Day 1: Thursday 14th November 2013 (continued)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 13.00 - 13.30 | Preclinical detection of inotropic effects of drugs  
*Dr Chris Pollard, AstraZeneca, UK* |
| 13.30 - 14.00 | Cardiovascular safety considerations for new drugs in atherosclerosis  
*Professor Alan Daugherty, University of Kentucky, USA* |
| 14.00 - 14.30 | Myocardial lesions induced by drugs  
*Dr Peter Greaves, University of Leicester, UK* |
| 14.30 - 15.00 | Relationships between functional and structural adverse effects on the heart  
*Professor Adam Hargreaves, AstraZeneca, UK, standing in for Phillip Milliken, GSK, UK* |
| 15.00 - 15.30 | Coffee, posters and exhibits |
| 15.30 - 16.00 | Drug-induced valvulopathy  
*Dr Annabelle Heier, Novartis, Switzerland* |
| 16.00 - 16.30 | Drug-induced vascular pathology  
*Dr Vasanthi Mowat, Huntingdon Life Sciences UK* |
| 16.30 - 17.00 | Adverse effects on blood clotting  
*Dr Dana Walker, Novartis Institutes for BioMedical Research Inc., USA* |
| 17.15 - 18.30 | BSTP AGM |
| 19.30 | Welcome Reception (Mottram Hall) |
| 20.00 | Conference Dinner (Mottram Hall) |
## PROGRAMME

### Day 2: Friday 15th November 2013

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.30 - 09.00</td>
<td>Coffee, posters and exhibits</td>
</tr>
</tbody>
</table>
| 09.00 - 09.05 | **Introduction to Day 2**<br>
Dr Jean-Pierre Valentin, Director Safety Pharmacology Centre of Expertise, Drug Safety & Metabolism, AstraZeneca (Vice-President of SPS) |
| 09.05 - 10.05 | Royal College of Pathologists Kohn Memorial Lecture<br>
Use of animal models with disease for studies in safety pharmacology: Parameters to interrogate and what difference makes a difference<br>
Professor Robert Hamlin, University of Ohio/QTest Labs, USA |
| 10.05 - 10.35 | **Cardiac in vivo imaging techniques**<br>
Dr Robert Coatney, GlaxoSmithKline, USA |
| 10.35 - 11.00 | Coffee, posters and exhibits                                         |
| 11.00 - 11.30 | **Blood-borne biomarkers of cardiotoxicity**<br>
Dr Peter Clements, GlaxoSmithKline, UK |
| 11.30 - 12.00 | **An integrated approach to investigate cardiotoxicity of oncology drugs**<br>
Dr Laura Cove-Smith, University of Manchester, UK |
| 12.30 - 12.50 | **Buffet lunch, posters and exhibits**<br>
**Technology Showcase (20 min): Presenting Aperio ePathology Peer Review Module**<br>
Leica Microsystems |
## PROGRAMME

### Day 2: Friday 15th November 2013 (continued)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 13.00 - 13.30 | Cardiovascular toxicity: A regulatory perspective<br>
|               | Dr Jimmy McBlane, UK Medicines and Healthcare Products Regulatory Agency (MHRA) |
| 13.30 - 15.00 | Anonymised case studies of preclinical signals of potential cardiotoxicity: What would YOU decide?<br><br>4 presenters, 10 minutes each + 5 min discussion. With audience voting pads, online voting, and an expert panel! Will also be run as a webinar |
| 15.00 - 15.30 | Coffee, posters and exhibits                                             |
| 15.30 - 16.00 | Use of surgically implanted telemetry devices in toxicology studies: Ensuing pathology<br>
|               | Dr Alys Bradley, Charles River Laboratories, UK                          |
| 1600          | Closing remarks<br>
|               | Dr Richard Haworth, GlaxoSmithKline, UK (President of BSTP)              |
| 1615          | Meeting close<br>
|               | Take down posters and exhibits                                           |

### SESSION CHAIRS

*from AstraZeneca, Alderley Park*

- Dr. Jayne Harris (Pathologist)
- Dr. Najah Abi-Gerges (Safety Pharmacologist)
- Dr. Helen Prior (Safety Pharmacologist)
- Dr. Matthew Jacobsen (Pathologist)
- Dr. Will Redfern (Safety Pharmacologist)
- Prof. John Foster (Pathologist)
- Dr. Mike Rolf (Safety Pharmacologist)
- Dr. Karen Philp (Safety Pharmacologist)
BRITISH SOCIETY OF TOXICOLOGICAL PATHOLOGY
ANNUAL GENERAL MEETING

All members of the Society are entitled to attend

The 28th Annual General Meeting of
The British Society of Toxicological Pathology

will be held at

AstraZeneca
The Alderley Park Conference Centre
Macclesfield

Thursday 14th November 2013
at 17.15

AGENDA

1. Minutes of 27th Annual General Meeting of the Society held on Thursday 15th November 2012 at The Alderley Park Conference Centre, Macclesfield - circulated by email on 24th and 30th October 2013

2. Report of Council

3. Treasurer’s Report and Statement of Accounts

4. Report of Education Subcommittee

5. Presentations and Awards

6. Any Other Business
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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EXHIBITION FLOOR PLAN

1. Data Sciences International
2. Notocord
3. Konigsberg Instruments Inc.
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Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

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Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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SPEAKER BIOGRAPHIES AND ABSTRACTS

Mark Holbrook
Covance Laboratories, UK
Email: mark.holbrook@covance.com

BIOGRAPHY

Education:
PhD, Pharmacology
BSc, Applied Biology

Professional Highlights:
More than 23 years experience in the pharmaceutical industry (Celltech UCB, AstraZeneca and Pfizer) with roles in drug discovery and development from target identification to filing. Co-author of over 25 peer-reviewed drug discovery and development publications. Invited speaker on drug discovery and development topics at more than 20 conferences. Active member of the Safety Pharmacology Society, the British Pharmacology Society, the Association of the British Pharmaceutical Industry.

Publication Journals:
Journal of Molecular and Cellular Cardiology; Journal of Pharmacological and Toxicological Methods; British Journal of Pharmacology; Biochemical Pharmacology; Veterinary Immunology and Immunopathology; Preclinical World

ABSTRACT

Drug induced adverse effects on the cardiovascular system account for, or are implicated in, the attrition of more compounds than any other safety issue. These issues have resulted in many compounds failing during development whilst others have been withdrawn or have significant labelling and restricted use. In some cases patients have been at risk whilst in others it has restricted R&D. Overall it has cost the biopharmaceutical industry billions of dollars and hindered the delivery of new medicines to patients. Thus there is a significant issue and one which requires the focus and close collaboration of non-clinical and clinical scientists from biopharma, contract research organisations, academia and regulatory agencies to address. This presentation will attempt to describe and discuss; the scale of the problem, what learning we can take from past failures, some of the advances that have been made and potential opportunities for the future. This will take us beyond the QT interval, something which has arguably been too much of a focus in the past.
**Predicting drug-induced QT prolongation and torsade de pointes in vitro and in vivo**

Several drugs were withdrawn from the market between 1991 and 2003 due to an association with a rare but life-threatening arrhythmia, torsade de pointes (TdP). Drugs associated with TdP generally cause prolongation of the QT interval on the electrocardiogram and this has been adopted as a biomarker - albeit an imperfect one - for TdP. The most common molecular mechanism by which a drug may prolong the QT interval is the inhibition of a repolarising K+ current (IKr) in ventricular myocytes and the alpha subunit of the channel responsible for IKr is encoded by the human ether-a-go-go-related gene (hERG). The core non-clinical testing strategy to assess drug-induced effects on ventricular repolarisation is an in vitro assay measuring the hERG channel current and an in vivo assessment of QT prolongation in a non-rodent (ICH57B). Over the last decade, there has been a large, industry-wide effort to assess the concordance of these non-clinical assays with the human QT outcome via prospective non-clinical studies using positive and negative reference compounds and also via retrospective analyses of corresponding non-clinical and clinical datasets. The concept of the hERG safety margin also emerged whereby the hERG blockade, measured as an IC$_{50}$, was expressed as a ratio of the therapeutic concentration and this was shown by several authors to correlate to the risk of QT prolongation/TdP in humans. The data gathered to date suggests that there is good translation from non-clinical assays to humans for hERG-mediated QT prolongation whilst mechanisms and translation of non-hERG mediated QT prolongation remain less well understood. Since not all drugs that prolong QT are proarrhythmic, there also remains a desire to investigate more specific biomarkers of TdP.
SPEAKER BIOGRAPHIES AND ABSTRACTS

Blanca Rodriguez
University of Oxford, UK
Email: blanca@cs.ox.ac.uk

BIOGRAPHY

Blanca Rodriguez is interested in discovering the causes and modulators of variability in the response of the heart to disease and therapies. She currently holds a Wellcome Trust Senior Research Fellowship in Basic Biomedical Sciences and a University Lecturership in Computational Medicine in the Department of Computer Science at the University of Oxford. Previously, she was a Medical Research Council Fellow at Oxford and a postdoctoral research fellow at Tulane University in New Orleans, USA. She is an Electronics Engineer by training from the Universidad Politecnica de Valencia, where she also conducted her PhD in Bioelectronics.

ABSTRACT

Predicting drug-induced torsade de pointes using computer simulations of the heart

Computational heart models and simulations are increasingly being used to predict and explain the human heart. In this presentation, I will describe our investigations on causes and modulators of inter-subject variability in the response of the human heart to drugs and disease from the ionic to the whole organ level. I will start by describing the state-of-the-art modelling and simulation technology we develop and apply to augment the information extracted from experimental and clinical imaging and electrophysiological recordings obtained from human hearts. I will then illustrate how we use the computational heart models to investigate the complex mechanisms underlying human ventricular and atrial arrhythmias.

Selected references:
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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SPEAKER BIOGRAPHIES AND ABSTRACTS

Chris Pollard
AstraZeneca, UK
Email: Chris.Pollard@astrazeneca.com

BIOGRAPHY

Dr Chris Pollard: After obtaining a BSc and PhD in physiology at Sheffield University, Chris did post-doctoral ion channel research at London and Newcastle University, focusing on thalamic neurones and pancreatic epithelia, respectively. On moving to the pharmaceutical industry, he spent 11 years at what became AstraZeneca R&D Charnwood, working on ion channel drug discovery in the context of respiratory and inflammatory diseases. In 2001, he moved to AstraZeneca R&D Alderley Park to establish and lead a team focussed on the safety implications of ion channel modulation. He now leads AstraZeneca’s cardiovascular safety strategy, working in the Translational Safety group of the newly established, Drug Safety and Metabolism function.

ABSTRACT

Preclinical detection of inotropic effects of drugs

Even for a drug to treat an acute, life-threatening illness, an effect on cardiac contractility during clinical development can lead to discontinuation. Off-target activity that could lead to such an effect would ideally be detected as early as possible in the discovery phase when there is chemical choice. Whilst there is a strong rationale for in vitro screening of some molecular targets (GPCRs, enzymes and ion channels), there is still the need for a cellular, “black box” approach to early screening in order to capture additional potential mechanisms. Ultimately however, an in vivo risk assessment is required to build on in vitro data. Whilst the measurement of left ventricular pressure in small and/or large animal models can be used as an index of effects on drug-induced contractility, for compounds with a significant effect, translatable data, such as ejection fraction in repeat-dose toxicology studies, represent the final step for an integrated risk assessment. These types of data will be illustrated with examples from discovery projects. Whilst in vitro and in vivo data can be collected and used for decision-making, the difficult question of translation to man remains: a comprehensive pre-clinical risk assessment can be constructed, but the paucity of quantitative clinical data limit our knowledge of the predictive value of pre-clinical information.
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SPEAKER BIOGRAPHIES AND ABSTRACTS

Alan Daugherty
University of Kentucky, USA
Email: Alan.Daugherty@uky.edu

BIOGRAPHY

Alan Daugherty, PhD, DSc, FAHA was born in Liverpool, England. He completed his undergraduate studies in Pharmacology at Sunderland Polytechnic, and received both a Ph.D. and a D.Sc. from the University of Bath. He moved to Washington University in St. Louis for fellowship training on lipoprotein metabolism and atherosclerosis. Subsequently, he was appointed to the faculty in the Division of Cardiovascular Medicine. He continued his studies on mechanisms of lipoprotein modification and immune function on the development of atherosclerosis. These studies also including imaging studies using chemical adducts for noninvasively detecting lipoprotein catabolism by a number of modalities. In 1997, he moved to the University of Kentucky in Lexington where he is now the Senior Associate Dean for Research in the College of Medicine and Director of the Saha Cardiovascular Research Center. Through the generosity of Linda and Jack Gill, he was also awarded the Gill Foundation Chair of Preventive Cardiology. Within the strong collaborative environment for cardiovascular research at the University of Kentucky, he has participated in studies on the role of angiotensin peptides in the development of atherosclerosis and aortic aneurysms. He is highly committed to the research, advocacy, and educational missions of the American Heart Association. He is currently a charter member of the Atherosclerosis and Inflammatory Cardiovascular System NIH study section. In July 2012, he had the privilege of becoming Editor-in-Chief of Arteriosclerosis, Thrombosis, and Vascular Biology (AVTB).

ABSTRACT

Cardiovascular safety considerations for new drugs in atherosclerosis

Atherosclerosis is the process responsible for the most common diseases, including myocardial infarction and stroke. Identifying mechanisms of atherosclerotic lesion formation is complicated by: 1. The chronicity of a disease that progresses over many decades. 2. Deficiency of current imaging techniques to detect and characterize lesions. 3. Complexity of the biochemical and cellular changes. While much of the historic research focused on mechanisms modulating the size of atherosclerotic lesions, there is an increasing appreciation that lesion composition may be the primary determinant of the clinical manifestations. Pharmacological targets of atherosclerosis have focused on reduction of hypercholesterolemia due to increased concentrations of low density lipoprotein cholesterol. Approval of these drugs was based on surrogate markers. A common recent pharmacological target is the cholesterol ester transfer protein that regulates the surrogate marker of increasing plasma concentration of high density lipoprotein cholesterol. However, inhibitors of this enzyme have had unacceptable toxicity and lack of clinical efficacy. Numerous other potential targets have been identified, although none have specificity for atherosclerosis. The challenge of developing drugs to reduce atherosclerosis will be to determine efficacy in a complex phenotype when administered to patients who are treated by current standard of care.
SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Peter Greaves, MBChB FRCPath is based at the Department of Cancer Studies and Molecular Medicine in the University of Leicester. He is a medical graduate from Birmingham University, UK who trained in laboratory medicine and human histopathology at Newcastle General Hospital, UK, the Medizinische Hochschule Hannover, Germany and Westminster Hospital, University of London. He started in toxicological pathology at Pfizer where he was Head of Pathology at the Centre de Recherche, Amboise, France. Subsequently, he has been Head of Toxicology at Wellcome Research Laboratories, Beckenham, Kent and Director of the Parke-Davis Research Institute at Mississauga, Canada. He joined ICI Pharmaceuticals (now AstraZeneca) in 1989 where he was Head of Safety of Medicines Alderley Park, UK and Wilmington, Delaware, US, responsible for preclinical safety assessments and clinical drug kinetics and metabolism on all drugs entering clinical trials and reaching the market over a 10 year period. Since leaving AstraZeneca in 2000 he has been engaged in experimental pathology and cancer research at the MRC and the University at Leicester. He consults for a number of major pharmaceutical and chemical companies in Europe and the US as well as UK government and EU advisory bodies on issues in toxicological pathology and risk assessment. His book 'Histopathology of Preclinical Toxicity Studies now in its 4th edition (Elsevier 2012). He is currently a member of the UK government's Committee on Carcinogenicity.

ABSTRACT

Myocardial lesions induced by drugs

Animal studies have shown that the myocardium can be structurally modified by therapeutic agents in a number of ways through different mechanisms. The size of the myocardium can adapt to drug-induced changes in circulatory demand. The myocardium also alters in size and shape as a result of administration of anabolic steroids and other hormones. Agents that induce exaggerated or excessive functional alterations are associated with various patterns of regional myocardial damage. Some therapies such as anthracyclines and other cancer therapies produce another form of myocardial injury through a direct adverse effect on cardiac myocytes.

The overall correlation of drug induced cardiac effects in humans with those in laboratory animal studies where physiological monitoring is performed is quite good. However, the overt pathological changes which are seen in animal studies are not commonly encountered in treated patients. Nevertheless, autopsy and biopsy evidence suggest a similar range of pathological alterations can occur in the myocardium of people if high exposures to such drugs are achieved.

In contrast to the generally good correlation of cardiac effects in laboratory animal studies with adverse myocardial effects in humans, hypersensitivity (allergic) myocarditis associated with drugs such as streptomycin and penicillin or endomyocardial fibrosis typically produced by ergot alkaloids and related drugs in people appear to be not easily reproduced in animal models.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Adam Hargreaves is a Principle Pathologist, currently working within Drug Safety and Metabolism, at AstraZeneca. Adam has special interests and skills in preclinical and translational pharmaceutical efficacy/safety assessment, toxicologic endocrinology, oncology, pharmacodynamic modelling, target identification and validation, early-stage compound selection and regulatory submission/interaction.

Adam is British (FRCPath) and American (Dipl.ACVP) board-certified in veterinary/toxicologic histopathology.

Adam is currently setting up his own company within the Biohub at Alderley Park.

ABSTRACT

Relationships between functional and structural adverse effects on the heart

Functional and structural cardiovascular (CV) liabilities are a leading cause of attrition during preclinical development, clinical development, and post-approval. Prior to first time in human studies, a wealth of CV data is generated through functional single-dose telemetered safety pharmacology studies (haemodynamic and ECG endpoints), and from repeat-dose toxicology studies (CV structural assessment). Relationships between these data sets remain largely undetermined, and there is increasing interest in utilising this data for predictive associations, for earlier detection of compounds with risk for CV pathologies.

Here we describe the preliminary findings of a cross-pharma collaboration between AstraZeneca, Eli Lilly, GlaxoSmithKline, and Pfizer, assessing trends between single-dose functional CV studies and the occurrence of CV structural changes in repeat-dose toxicology studies.
SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Annabelle Heier Dr. med. vet., Dip ECVP, FVH Pathology, Novartis; studied veterinary medicine at the Free University of Berlin (Germany) and at the Veterinary School of Alfort (France). She followed a residency program in veterinary pathology at the University of Berne (Switzerland), where she continued to work in the dermatopathology service. In 2004, she joined Frimorfo, Fribourg (Switzerland), a company specialized in phenotyping mice. In 2007, she moved to work with AstraZeneca, and joined Novartis in 2011, where she currently holds a position in the Discovery & Investigative Pathology Group, providing support to different disease areas.

ABSTRACT

Drug-induced valvulopathy

Several compounds have been withdrawn from the market or stopped during development due to drug-induced valvulopathies. The amphetamine-derived compounds fenfluramine, phentermine and benfluorex were widely prescribed as anorexigens as well as in diabetes patients, when associations with heart valve lesions were reported. Ergot alkaloids such as methysergide and ergotamine used in migraine prophylaxis and ergot-derived drugs such as pergolide and cabergoline for Parkinson’s disease patients represent another class of compound known to produce valvulopathies in humans. The lesions, characterized by thickening of heart valve leaflets, were associated with clinical signs of heart failure. All the before-mentioned compounds could be identified as potent agonists of the 5-HT_{2B} receptor. Activation of this receptor, expressed by valvular interstitial cells, could be demonstrated as the underlying mechanism. While preclinical animal studies failed to predict these drug-induced valvulopathies, recently described heart valve lesions induced by ALK5 inhibitors showed hemorrhage, degeneration and inflammation of heart valves in rats within a few days.

In summary, drug-induced heart valve lesions lack good predictive animal models, are difficult to monitor, serious and of unknown reversibility, thus representing serious liabilities.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Vasanthi Mowat, BVSc MVSc MRCVS FRCPath, Director of Pathology, graduated as a vet in India where she also studied for an MVSc in pathology, writing her thesis on hepatopathies in poultry. She worked in practice for some years in India, treating a wide variety of species. She has worked in both diagnostic and toxicological pathology and has over twenty years’ experience in toxicological pathology, gained at CROs in the UK and Europe.

Her first appointment was at Charles River Scotland, where she gained membership of the Royal College of Veterinary Surgeons in 1992 and membership of the Royal College of Pathologists in 1996. In 2004 Vasanthi became a Fellow of the Royal College of Pathologists.

Since April 2006 Vasanthi has been employed at Huntingdon Life Sciences, initially as Principal pathologist and since February 2008 as Director of Pathology. She is an examiner for the Royal College of Pathologists and is a member of the STP INHAND cardiovascular group for nomenclature of lesions. She has published articles on background pathology of various species and also on lesions induced in infusion studies.

ABSTRACT

Drug-induced vascular pathology

Conventional laboratory animal models are poorly predictive of drug-induced vascular effects in man for several reasons. Although vascular lesions are not infrequently seen in safety assessment studies, their interpretation and relevance to man are confounded by factors including spontaneous vascular pathology and species differences. In-life monitoring is difficult as many biomarkers used for the detection of vascular injury are non-specific or time-dependent. Investigations used to confirm the pathogenesis of vascular changes seen at termination are often inconclusive.

This presentation provides an overview of drug-induced changes in safety studies and their interpretation. Mechanisms of induction of drug -induced vascular lesions in safety assessment studies include deposition of endogenous materials, hemodynamic perturbation, direct cytotoxicity and immune-complex deposition. Examples of vasculopathies induced by a range of test articles and mechanisms in safety assessment studies are presented. Immune complex-mediated vasculitides induced by biologics are of particular importance, given their potential significance to man and the difficulties of interpreting them. Examples of these lesions are presented and correlated with in-life data.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

SPEAKER BIOGRAPHIES AND ABSTRACTS

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 BIOGRAPHY

Dana Walker is currently Director of Translation Safety Biomarkers and Clinical Pathology at Novartis Institute of Biomedical Research. In previous roles she served as Associate Director in Clinical Safety/Pharmacovigilence, and Site Director of the Clinical Pathology Laboratory in preclinical drug safety testing with Bristol-Myers Squibb. Prior to this, she was a Principle Pathologist with Wyeth Research Laboratories. Her career has been focused on toxicologic pathology since 1994, and included faculty positions at veterinary medical colleges and fellowship research at US Environmental Protection Agency. She holds a MS in toxicology and a PhD in immunology.

ABSTRACT

Drug-induced adverse effects on blood clotting

Blood clotting encompasses all three processes of primary, secondary and tertiary hemostasis. These processes - which involve platelet activity, the coagulation cascade, vascular signaling and fibrinolysis - are highly orchestrated and integrated. Drug induced adverse toxicity on components of these processes are of major concern when they put patient populations at risk of hypo- or hyper-coagulable states. Manifestations of such states can be overt or occult, and at their extremes, present as excessive bleeding to unwanted thrombosis. Understanding the role of drug exposure in these effects is complicated by confounding co-morbidity and concomitant drug therapy. Yet, adverse effects on blood clotting contribute to the relatively high proportion of post marketing drug withdrawals and boxed warnings assigned to cardiovascular events, which further attests to the difficulty in detecting them early in drug development. This difficulty is due not only to varied manifestation and patient factors, but also lack of ideal animal or in-vitro models, or established, sensitive biomarkers.

This presentation will focus on pertinent examples, and currently understood mechanisms of adverse drug-induced effects on blood clotting and the role of contributing factors. Exploratory translational approaches towards early detection of drug-induced adverse effects on blood clotting will also be addressed.
Use of animal-models with disease for studies in Safety Pharmacology: Parameters to interrogate and what difference makes a difference.

The FDA has stated, repeatedly and without reference to whether or not studies might be performed on normal or disease surrogates, that preclinical studies should be conducted under conditions “as close to those in the clinic as possible.” This is unambiguous, and is not consistent with conducting studies on normal animals that do not have and/or could never get the disease for which a test article is indicated, or that lack the receptor for which the test article is to become a drug; nor is it consistent with studying soporifics in the morning, or any test article on cold mice or rats! This presentation will discuss the value of conducting preclinical studies on animal models with diseases ubiquitous in the human population, with pathophysiology for which test articles are indicated, and in which adverse drug events are common. Specific examples of how studies performed on diseased subjects provide information opposite to that obtained from normal animals. Methods will be described for quantitation of each of >16 parameters of cardiovascular function that, if affected by test articles, are know to translate to morbidity and/or mortality, and consensus will be sought on which of those parameters you do not want to interrogate, and what the consequences might be. Finally we will commiserate over the apparent “truth” that—except for QTc—nobody will tell us what change in any other parameter of cardiovascular function constitutes a signal for an adverse clinical event.
SPEAKER BIOGRAPHIES AND ABSTRACTS

Robert Coatney
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BIOGRAPHY

Bob Coatney is currently the Director of Comparative Biology and Medicine and Preclinical and Translational Imaging at GlaxoSmithKline. In this role he guides a diverse group of veterinarians and scientists providing collaborative animal model, imaging, and clinical support for drug discovery and safety scientists globally within GSK. As part of the Preclinical and Translational Imaging platform he oversees an ultrasound imaging group that provides echocardiography and ultrasound imaging support for wide range of therapeutic areas and targets. This group also adapts and validates ultrasound imaging techniques and strategies as robust research tools. Currently the group is focused on evaluating and adapting strain echocardiography as a research tool for early, translational assessment of both efficacy and cardiac risk in novel drug candidates.

ABSTRACT

Cardiac in vivo imaging techniques

Echocardiography, Cardiac Magnetic Resonance Imaging, and Radionuclide Imaging are being used more frequently to evaluate cardiac structure and function in nonclinical and clinical efficacy and safety studies. These imaging platforms offer integrated, high content cardiac structure and function information and substantial translational potential. Emerging imaging techniques may offer increased sensitivity for early detection of myocardial functional changes. However, there are still substantial challenges in using nonclinical imaging platforms in safety assessment studies and translating to clinical studies. This presentation will provide a brief overview of these imaging platforms focused on nonclinical and translational evaluation of cardiac structure and function, and use brief case examples to illustrate how imaging can add value to understanding changes in cardiac structure and function. Additionally the challenges of performing nonclinical CV imaging safety evaluation studies and in translating to clinical studies will be discussed.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Peter Clements is a Director of Pathology at GlaxoSmithKline. He qualified in Veterinary Medicine from Edinburgh University, holds a PhD in molecular pathology/genetics and FRCPath in Veterinary Pathology. Current responsibilities include safety assessment interactions with Discovery colleagues, particularly in the neuroscience therapeutic area, from target validation to candidate selection and project-aligned toxicologic pathology supporting drug candidates into and through clinical development. Interests include cardiovascular pathobiology, the generation of integrated ‘functional and structural’ datasets in drug development, to enhance the detection and understanding of cardiovascular toxicology and its clinical implications. He chairs the internal Preclinical Cardiovascular Advisory Team at GSK.

Blood-borne biomarkers of cardiotoxicity

Blood-borne biomarkers are an important part of a safety scientist’s toolkit of modalities, to detect cardiotoxicity, track it in real-time, and to gain insight into its pathogenesis. Translational application of such minimally-invasive, sensitive and specific safety biomarkers may facilitate compound progression and can be used during clinical trials to assess the relevance of preclinical toxicities to humans at therapeutic doses. Qualification of biomarkers includes an understanding of not only the assay performance, but the background variability, kinetics and relationship to pathophysiology of disease and toxicity states in different species. These biomarkers include proteins, which may be structural components of cardiomyocytes (e.g. cardiac troponins (cTns)), or hormones which may be released by the heart (e.g. natriuretic peptides). Recently, cardiac troponins were qualified for nonclinical use in rats and dogs by the FDA: they are considered to report cardiomyocyte injury and particularly with assay sensitivity increasing, may be elevated in the absence of histological findings. Natriuretic peptides can be used to indicate volume loading of the heart and also show translational relevance. Examples illustrating the utility of such markers in safety studies will be reviewed. Nucleic acids (e.g. microRNAs) have also been associated with cardiac disease states and may represent biomarkers with future utility.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Dr Laura Cove-Smith gained her medical degree at the University of Sheffield in 2003. She spent 4 years completing general medical training in South Yorkshire before moving to Manchester in 2008 to start specialist registrar training in Medical Oncology at The Christie NHS Foundation Trust. She has currently taken a break in registrar training to carry out a translational PhD project in a collaboration with Cancer Research UK and Astra Zeneca. The project involves the exploration of circulating and imaging biomarkers of cardiac damage from cancer treatments. She is working at The Christie Hospital and the Cancer Research UK Manchester Institute co-ordinating a clinical study looking at cardiac MRI and blood borne markers of drug induced cardiac damage and helping to develop a pre-clinical model of chronic cardiotoxicity within drug safety at Astra Zeneca, Alderley Park.

ABSTRACT

An integrated approach to investigate cardiotoxicity of oncology drugs

Cardiotoxicity is a significant problem for cancer survivors and drug development. Many successful cancer treatments, both old and new, cause heart damage that restricts their use and causes significant cardiac morbidity. Clinically, there is no unified way of predicting who is at risk or detecting cardiotoxicity at a reversible stage. Pre-clinically, cardiotoxicity compromises the development of many promising agents. Consequently, translational approaches are needed to find biomarkers that help accurately predict the cardiotoxicity profile of cancer drugs and the potential risk to patients. This presentation explores the clinical impact of cardiotoxicity on cancer patients and outlines one of the current joint ventures between Astra-Zeneca, Cancer Research UK Manchester Institute and The Christie NHS Foundation Trust looking at cardiac MRI and circulating biomarkers of cardiotoxicity.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Jimmy McBlane: After degrees in pharmacology at Dundee and Aston Universities, Dr McBlane worked in the pharmacology research laboratories for the British pharmaceutical company, Wellcome, before moving to the UK national drug regulatory body, to work on postmarketing drug safety. After a short period there, he moved to the Japanese biopharmaceutical company, Chugai, where he worked for almost 10 years in several drug development roles, including regulatory affairs, project management and clinical development and also in medical information, latterly specialising in preclinical development, running programmes to develop both small molecule and biotechnology-derived products, with a focus on early clinical testing. He returned to the Licensing Division of the UK’s Medicines & Healthcare products Regulatory Agency in 2005, since when he has specialised in assessing marketing authorisation applications (MAAs) for biological products, including vaccines, monoclonal antibodies and gene therapy applications and in assessing clinical trial applications (CTAs) for all kinds of products. He has assessed over 200 applications for new products and over 2000 applications for clinical trials. He is the UK’s alternate delegate to the European Medicines Agency’s Committee for Advanced Therapies (CAT) and has written articles and book chapters on preclinical development of biological products, including stem cells and on biosimilar products.

ABSTRACT

Cardiovascular toxicity - a regulator’s perspective

More than 20 years ago there was a recognition that sudden unexplained deaths were happening in fairly young patients with non-life-threatening illnesses due to a specific drug-drug interaction, between terfenadine and erythromycin. Despite warnings to doctors and pharmacists, their co-use persisted, leading to withdrawal from the market of terfenadine. The mechanism was blockade of the hERG channel by unmetabolised terfenadine, leading to cardiac toxicity. In this talk, I shall indicate how this experience continues to influence the assessment of applications today and what assessors look for to ensure such events are prevented.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

SPEAKER BIOGRAPHIES AND ABSTRACTS

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BIOGRAPHY

Alys Bradley  BSc BVSc MAnimSc DipRCPath FRIPH MRCVS FRCPath FIATP attained an Honours degree in Zoology from Manchester University, and a Masters Degree in Veterinary Parasitology from Liverpool School of Tropical Medicine. She then held research posts at the Liverpool School of Tropical Medicine and Liverpool University department of Pathology, in the field of monoclonal antibody development and refinement. She gained her Degree in Veterinary Medicine from Liverpool University in 1994 and, following a year working for the Ministry of Agriculture, joined the Pathology Department of Edinburgh University as HBLB lecturer in Neuropathology. She was recruited to the Pathology Department of Charles River Edinburgh in 1998 and appointed Director of Pathology in 2005. Alys is actively involved in training pathologists and is currently Chair of the Veterinary Pathology board of examiners for the Royal College of Pathologists. Her specialist interests are non-human primate pathology, rabbit pathology, mouse pathology, and neuropathology of all species. She is Treasurer of the British Society of Toxicological Pathology (BSTP), a member of the North American Society of Toxicological Pathology (STP) Education Strategy Committee, STP-Special Interest Groups for Neuropathology and Environmental Toxicology. She is the BSTP representative on the International Harmonisation of Nomenclature and Diagnostic Criteria (INHAND) Executive Committee, and a member of the INHAND Working Groups for the Nervous, Haemopoietic, and Integumentary Systems.

ABSTRACT

Use of surgically implanted telemetry devices in toxicology studies: ensuing pathology
Alys Bradleya, Jennifer Chiltonb, Aileen Milnea (a CRL, Edinburgh, Scotland ; b, CRL,Reno, Nevada)

Telemetric blood pressure monitoring (TBP) in repeat-dose toxicology studies satisfies the 3Rs by combining endpoints and minimizing animal use. However, the histopathological impact of long term TBP implantation remains largely uncharacterized. We evaluated the pathology following chronic TBP implantation in 6 monkeys and 6 dogs by examination of selected tissues. TBP devices (TA11PA-C10-TOX-LA, DSI) were surgically implanted with attendant femoral artery catheterization. Tissues were evaluated by gross and light microscopic examination and findings associated with the implantation site (femoral artery, iliac artery, proximal muscle) will be discussed in this presentation.

No TBP-related histopathological changes were noted in any systemic tissues. Localised findings were confined to fibrosis/myositis at the subcutaneous implantation site. The femoral artery exhibited varying degrees of intimal thickening and non-occlusive thrombosis. Two of 6 femoral arteries in the primates and one out of 6 arteries in the dogs had focal minimal to mild chronic mural inflammation. The iliac artery exhibited varying degrees of intimal thickening. These data demonstrate that chronic, subcutaneously implanted TBP devices employing femoral catheterization were well tolerated in both monkeys and dogs. The localised pathology seen in the arteries would be already familiar to many pathologists experienced with the evaluation of femoral veins and distal vena cava for infusion studies, and were due to local irritation effects of having an indwelling catheter. There were no associated histopathological changes in the major target organs which would preclude their use in repeat-dose toxicology studies, facilitating robust toxicological assessments that are not possible in standalone study designs.
ACEA Biosciences, Inc. (ACEA) is a privately owned biotechnology company that is a pioneer in the development and commercialization of high-performance and cutting edge life science research instrumentation. ACEA’s mission is to transform cell-based assays by providing innovative and cutting edge products and solutions to the research and drug discovery community. ACEA launched its first product for real-time, label-free cell-based assays based on a microelectronic readout in 2004.

ABSTRACT

Using Stem Cell Derived Cardiomyocytes for Cardiac Safety Assessment of Pharmaceutical Compounds

The vast majority of the drugs withdrawn from the market due to association with Torsades de Pointes (TdP) arrhythmia appear to interfere with the I_{kr} repolarization current mediated through the hERG potassium channel. Consequently, the ICH S7B guidelines recommend that all new chemical entities should be subjected to hERG repolarization assay, typically using cell lines that recombinantly express hERG protein. However, in the last decade it has become evident that not all hERG channel inhibitors result in TdP and not all compounds that induce QT prolongation and TdP necessarily inhibit hERG.

In order to better understand and assess the different kinds of drug liabilities associated with hERG channel inhibition and modulation we have used a panel of drugs and compounds which (i) directly bind and inhibit hERG channel function (overt inhibitors); (ii) compounds which inhibit hERG as well as other channels and therefore compensate for the I_{kr} block (covert inhibitors) and (iii) compounds which interfere with the trafficking of hERG channel protein to the plasma membrane (trafficking inhibitors).

We have assessed the activity of these compounds using human induced pluripotent stems cell-derived cardiomyocytes (iCells) together with a system that can measure the beating activity of the spontaneously beating cardiomyocytes. Our data clearly shows that overt hERG channel inhibitors disrupts the periodicity of beating of iCell cardiomyocytes leading to plateau oscillations and a signature waveform that is typical of these class of compounds. Covert hERG channel inhibitors at physiologic concentrations do not appear to affect cardiac function and therefore appear to be safe. hERG trafficking inhibitors display a time-dependent effect on the periodicity of beating that manifests several hours after compound dosing.

In summary, the results clearly show that dynamic monitoring of stem cell derived cardiomyocyte beating can be used in a predictive way to assess various types of hERG channel modulators and provide additional information to electrophysiological methods.
Technology Showcase

Friday, 15th November, 12.30 – 12.50

Leica Microsystems UK Ltd

Website:  http://www.leicabiosystems.com
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Leica Biosystems is a global leader in workflow solutions for anatomic pathology providing a comprehensive product range, from sample preparation and staining to imaging. The addition of Aperio ePathology Solutions enables greater access for Pathologists through market-leading scanning, management and image analysis solutions to improve productivity, reproducibility and consistency.

ABSTRACT

Presenting Aperio ePathology Peer Review Module

Less than 6% of New Molecular Entities (NME) progress from Preclinical trials, with failures attributed to findings identified during Pathology review. NME’s which fail during preclinical development are costly primarily due to R&D investment, however the cost of failure during clinical trials has been shown to come at a much greater price, resulting in company downsizing, legal fees, bankruptcy, and at the extreme, the loss of human life.

Digital pathology has revolutionised the practice of pathology with growing adoption throughout pharmaceutical companies and CROs. To date, the benefits of digital pathology have not been capitalized upon for peer review primarily due to speed of review and dedicated workflows that support, rather than change traditional work practices.

The new ePathology Peer Review Module from Leica Biosystems has been developed in collaboration with toxicological pathologists and delivers a tailored workflow solution enabling high throughput peer review of digital slides and associated pathology data in a secure environment. Optimised to support external collaboration via the Cloud, the Peer Review module is designed to significantly reduce travel and shipping costs and improve TAT on studies.

This exciting new product will be available in Q1 2014.
ANONYMISED CASE STUDIES OF PRECLINICAL SIGNALS OF POTENTIAL CARDIOTOXICITY: WHAT WOULD YOU DECIDE?

Cardiovascular finding in a mouse carcinogenicity study
Silvia Guionaud
Shire Pharmaceuticals, UK

Rare Cardiovascular Lesions after Chronic Administration in the Dog: A Mechanistic Perspective
Virgile Richard; Marie-Luce Brodzinski-Rosseels
UCB Pharma, Belgium

What to do with a QT shortener?
Chris Pollard
AstraZeneca, UK

Response to ‘therapy’ of left ventricular and aortic pressure curves
Robert Hamlin
Ohio State University/QTest Labs, USA
Evaluation of ionotropic and chronotropic compounds in vitro using human iPS-derived cardiomyocytes and impedance-based contractility assay

Xiaoyu Zhang, Biao Xi, Xiaobo Wang, Xiao Xu and Yama A. Abassi

Acea Biosciences Inc. 6779 Mesa Ridge Rd, San Diego, CA 92121

The β-adrenergic receptor (βAR) signaling system is one of the most powerful regulators of cardiac ionotropic and chronotropic function. βAR antagonists, commonly known as beta-blockers (β-blockers) have been used for decades to treat hypertension, ischemic heart disease, some arrhythmias, and more recently to treat congestive heart failure. Up to date, 3 types of β-blocker drugs have been developed for therapeutic purpose. In order to better understand the cardiac effects of different types of β-blockers, we have developed an in vitro assay using human iPS-derived cardiomyocytes in conjunction with impedance measurement. We evaluated the activities of six β-blocker drugs and compounds including (1) non-selective β-blockers; (2) cardioselective β-blockers; and (3) nonselective α and β-blockers. The data as measured by impedance readout revealed that the β-blockers from different classes displayed subtle but unique profile of acute impedance changes post compound addition. With the exception of atenolol and metoprolol, pindolol, alprenolol, propanolol and carvedilol significantly decreased the cell beating rate (BR) and even temporally led to beating arrest at the highest tested concentration (3 uM). In addition, the 1 hour pretreatment with all these four compounds at higher doses abolished the isoproterenol-induced positive chronotropic effects on BR. Carvedilol was the only drug that appeared to profoundly reduce cell beating amplitude (CA) in a dose-dependent manner. The in vitro assay used here indicates that human iPS-derived cardiomyocytes respond similarly to the β-blockers from the same group. However, each type of β-blockers generates distinct profiles and do have different chronotropic and ionotropic effects which we will summarize in the current poster.
hERG channel trafficking mutations - their role in the drug triggered arrhythmia - simulation study

Anna Glinka, Barbara Wiśniowska

Unit of Pharmacoepidemiology and Pharmacoeconomics, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

The aim of the study was to assess the effect of hERG gene mutations connected with defective channel protein trafficking on AP curve characteristic in different pacing conditions and after administration of a drug with hERG channel blocking potency.

The hERG trafficking-defective mutants were simulated and their influence on proarrhythmic effect of a drug was assessed. The total current inhibition was considered as sum of current density decrease due to mutation and drug-dependent current inhibition. All AP simulations were run with the use of modified O'Hara-Rudy dynamic model implemented in C++. Observed endpoints were the incidence of EADs or arrhythmia and APD90.

The highest incidence of arrhythmia was observed with the heart rate of 120 bpm. Additionally, with the heart rate of 40 bpm early afterdepolarisations were observed. The minimal APD90 value was obtained for the epicardium cells, with HR=120 bpm, in the absence of both mutation and drug. The highest ADP90 value was obtained for the endocardium cells, with HR=60 bpm, with A561V mutation and after thioridazine administration.

The simulation results suggest that the assessment of proarrhythmic potential of the drug should cover not only the ion channels blocking-property but also physiological parameters (i.e. heart rate, genetics).
Development of a spontaneously beating human cardiac microtissue model for the study of drug-induced cardiotoxicity

Stephanie Ravenscroft\textsuperscript{1,2}, Amy Pointon\textsuperscript{2}, Mike Cross\textsuperscript{1}, James Sidaway\textsuperscript{2}

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\textsuperscript{2} Innovative Medicines, Global Safety Assessment, AstraZeneca, Alderley Park, Cheshire, SK10 4TG, UK

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Cardiotoxicity is a major cause of drug withdrawal from the market and of attrition during drug development. We assessed the effect of 8 drugs with known cardiotoxic liability on human embryonic stem cell-derived cardiomyocytes (hESC-CM’s), human cardiac microvascular endothelial cells (HCMEC’s) and human cardiac fibroblasts (HCF’s). Cells were seeded into 96 well plates and incubated for 6, 24 or 72 h with drugs. Automated live cell microscopy was carried out with the ImageXpress (Molecular Devices) high content screening system using fluorescent dyes for mitochondrial membrane potential, endoplasmic reticulum, calcium mobilization (and membrane permeability). The cells were then lysed for assessment of cytotoxicity. Comparative potency between all 3 cell types revealed increased sensitivity of the non-myocyte cells following 6 h drug exposure. To expand on this study, we have developed spontaneously beating spherical-shaped human cardiac co-culture microtissues composed of hESC-CM’s, HCMECs and HCFs. These microtissues are of uniform shape and size and can be maintained for at least 4 weeks and utilized in structural and functional cardiotoxicity studies. The microtissues may provide a human relevant model to replace dog cardiomyocytes currently used in functional contractility assays.
Are GPR81 agonists associated with cardiovascular effects?

Amanda Benjamin¹, Teresa Collins¹, Ola Fjellström², David Lengel¹, Pia Thalén³, Göran Wahlund³, Kristina Wallenius³ and Annika Westin Eriksson¹

Drug Safety and Metabolism AstraZeneca R&D¹, Chemistry AstraZeneca R&D Mölndal², Bioscience AstraZeneca R&D Mölndal³

GPR81 is a class B G_{i} coupled GPCR expressed mainly in adipocytes for which lactate is a known endogenous ligand. Activation of GPR81 in adipose tissue leads to inhibition of lipolysis and FFA release through a cAMP dependent mechanism.

AZ13415538 and AZ13087136 are two novel GPR81 agonists also active on GPR109A and the ghrelin receptors. In anaesthetized Wistar rats both compounds, at efficacious doses, caused a transient increase in blood pressure and a transient decrease in heart rate when given iv. A tool compound, which is structurally similar to AZ13087136 and active on the ghrelin receptor but inactive on GPR81 and GPR109A, did not show any cardiovascular effects when tested at a dose 10-fold above the AZ13087136 ED₅₀ for fatty acid lowering in the anaesthetized rat model. The GPR109A selective agonists’ nicotinic acid, MK-0354 or SCH900271, were also tested in the same model and did not show CV effects at efficacious doses. In conscious Wistar rats, iv infusion of AZ13415538 resulted in an increase in blood pressure at a plasma concentration corresponding to efficacy on FFA in rat.

These data suggest an association between GPR81 agonism and CV effects which will be further investigated in GRP81 KO mice using telemetry.
Cardiovascular drug toxicities associated with pharmacological activity: data harmonisation makes the “known” visible

Sidaway, James E.; Rolf, Mike G.; Roberts, Stephanie; Huby, Russell D.J.; Nicholson, Andrea; Pemberton, John; South, Marie C.; Noeske, Tobias; Engkvist, Ola; Bradley, Paul; Reed, Jane Z.


Incompatible database formats limit the value of the large amount of publicly available data on adverse events caused by drugs. Instem’s Safety Intelligence Program (SIP) is a harmonised knowledgebase that links compounds to biomedical observations from both clinical and preclinical data sources. We have combined human observations from SIP with target profiles of drugs to identify associations between pharmacological activities and cardiac adverse events.

Compound-pathology associations were grouped by tissue and Medical Dictionary for Regulatory Activities (MedDRA) class. Fisher’s exact test (adjusted for false discovery) was used to identify significant associations between compounds in each tissue or MedDRA group and activity (< 1402 significant target-tissue associations were identified at the MedDRA Preferred Term level within the Cardiac Disorder System Organ Class. These included well known relationships such as hERG/long qt interval and cyclooxygenase 2/congestive heart failure. Less well-known associations were also identified including vasoactive intestinal peptide receptor 1 and heart valve fibrosis and adenosine receptor 1 and unstable angina.

In summary, we have validated an approach to identify significant drug target-AE pairs in the cardiovascular system. This could also be applied to compound characteristics, including physicochemical properties and structural moieties.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

POSTER ABSTRACTS

Quantitative evaluation of drug-induced microvascular constriction using a novel tool for 3D geometrical analysis of ex-vivo organ vasculature

Raul Brauner 1,2, Kongbin Kang 2, Stacia Furtado 3, Abraham Nyska 4, Yuval Ramot 5

1 Corresponding author: Founder, President, CEO, 2 Bio-Tree Systems, Inc., 16 Lantern Road, Framingham, MA 01702. Authors and Vasculomics™ inventors Tel: +1 (508) 380-7329; fax: +1 (508) 620-9807, e-mail: raulb@bio-tree.com, 3 Brown University, Providence RI, 4 Toxicologic pathologist, Timrat 36576, Israel\, 5 Hadassah – Hebrew University Medical Center, Jerusalem 91120, Israel

Blood vessel analysis carries special importance for toxicological sciences, and especially for evaluation of drug-induced vascular toxicity. This field presents a special challenge in non-clinical drug safety assessments since there are currently no reliable vascular toxicity biomarkers.

Therefore, we aimed to systematically investigate the use of microvascular 3D geometrical analysis for evaluation of drug-induced vascular toxicity, utilizing a novel image investigation tool which allows full 3D quantified geometrical analysis of the entire vascular tree structure. Vascular casts of the mouse kidneys featuring very high quality perfusion of capillaries of control and low- and high-dose ephedrine/caffeine-treated mice were scanned by a micro CT, and images were processed and analyzed using the VasculomicsTM platform.

Treatment resulted in a significant and dose-related reduction in overall micro-vessel density throughout the kidney cortex. This effect was most pronounced for vessels with diameters between 25 to 35µm, and affected mostly vessels located in the superficial part of the kidney cortex.

The use of 3D analysis tools in drug-induced vascular toxicity studies allows for very high-resolution and global characterization of drug effects on the microvasculature, and can be used as a valuable tool in drug safety assessments.
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‘RECYCLED’ POSTERS

These posters have been presented elsewhere during 2013, and are therefore listed without an abstract. The presenting authors are in bold.

Translational modelling of preclinical cardiovascular findings to patients

James WT Yates1, Michael G Rolf2, Katie Stamp2, Elizabeth A Martin2, Gary Wilkinson1, Glen Clack3, Paul Howarth4 and Jean-Pierre Valentin2

1 IMED Oncology DMPK, AstraZeneca, Alderley Park, Cheshire SK10 4TG; 2 Drug Safety & Metabolism, AstraZeneca, Alderley Park, Cheshire SK10 4TG; 3 Global Medicines Development, AstraZeneca, Alderley Park, Cheshire SK10 4TG; 4 Translational Patient Safety, AstraZeneca, Alderley Park, Cheshire SK10 4TG

In silico pro-arrhythmic risk assessment: Can the results of the Thorough QT study be predicted?

G. Mirams1, M. Davies2, J. Stott2, B. Rodriguez1, Y. Cui3, D. Noble1, D. Gavaghan1, N. Abi-Gerges2

1 Computational Biology, Department of Computer Science, University of Oxford, Oxford, United Kingdom; 2 Innovative Medicines and Early Development, AstraZeneca R&D, Alderley Park, Macclesfield, United Kingdom; 3 GlaxoSmithKline R&D, Ware, Hertfordshire, United Kingdom.

Enhancement of cardio-respiratory safety assessment in toxicology studies

D. Butler, K. Melliti, K. Meecham

Huntingdon Life Sciences, Woolley Road, Alconbury, Huntingdon, Cambs, PE28 4HS

Predicting cardiac toxicity from data generated via high-throughput screening

Hitesh Mistry, Frances Brightman, Eric Fernandez, David Orrell, Jonathan Swinton, Christophe Chassagnele

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Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

14th & 15th November 2013, Alderley Park Conference Centre, UK

‘RECYCLED’ POSTERS

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How Do Large Pharmaceutical Companies Mitigate Concerns of Drug-Induced QT Prolongation in Drug Discovery?

Jean-Pierre Valentin1, David Baker1, David Gallacher2, Gary Gintant3, Andrea Greiter-Wilke4, Jean-Michel Guillon5, Herbert Himmel6, Chieko Kasai7, Derek Leishman8, Paul Levesque9, James Louttit10, Sian Ratcliffe11, Frederick Sannajust12, Willi Suter13, Hugo Vargas14, Keiji Yamamoto15.

1AstraZeneca, 2Johnson & Johnson, 3AbbVie, 4Hoffman-La Roche, 5Sanofi Aventis, 6Bayer, 7Astellas, 8Eli Lilly & Co., 9Bristol-Myers Squibb, 10GlaxoSmithKline, 11Pfizer, 12Merck & Co., 13Novartis, 14Amgen, 15Takeda

Predictivity of non-clinical repolarization assay data for clinical TQT data in FDA database.

J Koerner1, JP Valentin2, J Willard1, EJ Park1, D Bi1, WT Link1, M Fiszman1, D Kozeli1, M Skinner2, HM Vargas3, L Cantilena4, G Gintant5, T Wisialowski6, S Pettit7.

1FDA, 2AstraZeneca, 3Amgen, 4Uniformed Services University of the Health Sciences, 5Abbott, 6Pfizer, 7HESI on behalf of the Cardiac Safety Pro-Arrhythmia Working Group.

The In Vitro Assessment of L-type Calcium Channel Safety Liability


Safety Pharmacology, Global Safety Assessment, AstraZeneca R&D, Mereside, Macclesfield, SK10 4TG, U.K.
Cardiovascular safety risk assessment for new candidate drugs from functional and pathological data

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ACE: AstraZeneca Cardiovascular Exploration

Xia Wang PhD¹, Jim Weatherall, PhD¹, Magnus Nord, MD, PhD², David Cook, PhD², Glenn Carlson, MD⁴, Joanna Parkinson, PhD³, Chris Pollard, PhD³,⁴ Corina Dota, MD³

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Assessing cardiovascular safety beyond QT

Translational PK/PD modelling of cardiovascular parameters to improve safety and efficiency in drug development

Linnéa Bergenholm¹,⁴, Joanna Parkinson¹, Lars Carlsson¹, Teresa Collins², James Yates², Chris Pollard², Mats Jirstrand³, Neil Evans⁴, Michael Chappell⁵

¹AstraZeneca, Innovative Medicines and Early Development, Drug Safety and Metabolism, Discovery Safety, Mölndal, Sweden; ²AstraZeneca, Innovative Medicines and Early Development, Drug Safety and Metabolism, Translational Safety, Alderley Park, UK; ³Fraunhofer-Chalmers Research Centre Industrial Mathematics, Gothenburg, Sweden; ⁴Biomedical & Biological Systems Laboratory, School of Engineering, Univ. of Warwick, Coventry CV4 7AL, UK
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The BSTP grants a travel bursary of £500 for a member of the society to attend a recognised scientific meeting, and give a platform presentation or present a poster on a toxicological pathology subject of their choice. There is no limitation on the toxicological pathology experience of the applicant or which meeting is chosen.

All applications must be in writing to the Honorary Treasurer of the BSTP either directly or via the BSTP Secretariat – bstpsecretariat@aol.com.

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Criteria for application:

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2. Must contain at least a brief summary of the presentation, preferably a PowerPoint handout of draft 1.

3. All successful alternative funding details must be disclosed.

4. The application must be accompanied by a copy of the applicant’s CV and a letter of recommendation by their Head of Department.

5. The successful applicant must be willing to write up the presentation as a short case report/article for the BSTP Website.

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NOTICE OF FUTURE BSTP MEETINGS

2nd – 6th December 2013
Module 13 – Musculoskeletal system & skin
Cambridge

5th – 7th February 2014
Mouse models of disease
Cambridge

March 2014
Module 14 – Infectious & spontaneous disease of laboratory animals
Cambridge

July 2014
Module 1
Cambridge

November 2014
ASM/AGM

December 2014
Module 2
Cambridge

March/April 2015
Module 3
Cambridge

July 2015
Module 4
Cambridge

November 2015
ASM/AGM

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Announcement next SPS meeting

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