

# Expert Opinion

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## Safety Pharmacology Society: 7th Annual Meeting

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Sir James Black, the 1988 recipient of the Nobel Prize for the invention of propranolol and cimetidine, opened the 2007 Safety Pharmacology (SP) Society annual meeting with a lecture on his half-century of professional life entirely dedicated to a quest for novel drugs. The translational power of SP experimental results to humans and emerging SP trends then became the leitmotifs of the meeting. Hence, expertly generated *in vitro* and *in vivo* non-clinical data were shown to satisfactorily predict the outcome of thorough QTc interval studies in volunteers. In keeping with this theme, torcetrapib, a cholesterol esterase transfer protein inhibitor aimed at treating atherosclerosis in a novel way (raising high-density lipoprotein-cholesterol and lowering low-density lipoprotein-cholesterol levels), was shown to produce blood pressure and aldosterone increases in laboratory animals. These off-target effects, occurring also in patients, are probably one of the several mechanisms responsible for the ~ 37% higher, treatment-related, mortality in the very large ILLUMINATE Phase III trial. This disastrous outcome forced the sponsor to suspend the clinical development of this drug, which clearly exerted the desired pharmacological activity in atherosclerotic patients. The translational potential of the core battery strategy recommended by the S7A guideline for determining respiratory liability was shown to be unsatisfactory since it does not consistently capture the airway obstructive activity of clinical candidates. However, this drug's hazardous off-target property is easily captured by performing a pulmonary respiratory resistance assay. Drug-induced QT interval shortening was presented as an emerging cardiovascular safety issue meriting SP scrutiny, as individuals harbouring inherited short QT syndromes can experience syncope and lethal ventricular fibrillation. However, any regulatory intervention on this issue would appear to be untimely, as robust human electrocardiogram data on such drug classes are still lacking. Nevertheless, the pharmaceutical industry cannot presently evade the ethical and regulatory obligations to conscientiously identify and characterise prospective drug-related risks in the framework of benefit, management and minimisation. Future challenges for SP concern the development of unambiguous assays for assessing risks intrinsic to novel therapeutic classes, formulated drug combinations and the use of medicines for specific pathological conditions. In addition, SP should actively and skilfully integrate new promising technologies, such as physiological pharmacokinetic/pharmacodynamic analysis, that can improve the translational power of non-clinical assays, as this will strengthen the prognostic value of SP as discipline striving to ensure the human safety of medicines.

**Keywords:** drug discovery, ethical obligations, non-clinical data, pharmaceutical industry, respiratory system safety, risk management, safety pharmacology, torcetrapib safety issues, translation

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## 1. Introduction

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Non-clinical safety pharmacology (SP) has the explicit mission of determining that new drugs entering clinical investigation programmes and requesting marketing approval are free of unmanageable adverse effects on all vital physiological functions.

This year, the annual Safety Pharmacology Society (SPS) meeting attracted > 500 participants from industry, academia and producers of research equipment. This forum continues to be a dynamic ground for open and constructive exchanges of experimental data, new technologies and strategies for optimising drug safety assessment. A leading theme of the meeting was translation, an issue at the heart of the SP mission as it concerns the human predictive value of data generated in non-clinical assays. A number of established and emerging issues that SP has to expertly address to fulfil its mission were also discussed in depth.

The presentations briefly reviewed herein were selected on the basis of novelty and interest for the prospective readers of this report. Indeed, this author has reviewed in previous reports certain interesting talks given at this meeting by the same or other speakers: mechanism-based pharmacokinetic/pharmacodynamic modelling by Professor Meindert Danhof and Dr Mark Holbrook [1]; safe transition into first-human dose after the cytokine storm produced by TGN-1412 by Drs Lars Wichmann and Jacques Descotes [2]; translation of convulsive risk from preclinical model to clinic arena by Dr Mary-Jeanne Kallman; preclinical physical dependence models by Drs Mary-Jeanne Kallman and Paul Butler [3]; and liability assays in zebrafish by Drs Gareth Waldron and Will Redfern [4]. Although these topics were an important part of this SPS meeting and would have merited updating, space constraints do not allow it. The latter reason also prevented the review of several talks of practical interest such as predicting nausea and vomiting in humans by Dr Paul Andrews; evaluation of auditory function in non-rodents with links to human relevance by Andrea Tipold; animal welfare considerations and SP by Dr David Robb; potential effects of anaesthesia on haemodynamic parameters by Drs Scott Mittelstadt and Richard Briscoe; emerging screening and computational methods by Drs Anthony Bahinski and Scott Boyer; application of translational imaging in drug discovery by Gerard Fox; prediction of proximal tubule kidney toxicity and phospholipidosis by NMR-based urine analysis in rats by Dr Sabine Pestel; and status and perspective of good laboratory practices and SP in China by Dr Li Bo. A number of the > 125 abstracts presented in the poster session also would deserve to be reviewed, but here only the one receiving an award for Young Investigator Best Poster is summarized. All the abstracts will be published next year in the *Journal of Pharmacological and Toxicological Methods*.

## 2. President's keynote addresses

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### 2.1 'Pharmaceutical climate changes: have we anything to learn from dinosaurs?' by Sir James Black, James Black Foundation, London University College, UK

Sir James Black, the 1988 recipient of the Nobel Prize for Medicine, shared his half century of experience on the road to drug invention. This endeavour, he said, requires not only passion, commitment and a deep knowledge of physiology, pharmacology, therapeutics and the clinical sciences, but also the capability to scrutinise and recombine diverse bits and pieces of information derived from apparently unrelated discoveries in order to construct original ideas. Drugs are not the direct outcome of discovery processes, but are the ultimate product of creativity. Indeed, whereas discoverers bring to light unknown, but yet, existing things, inventors give reality to previously nonexistent things. Discovery involves reductionism, but paradoxically, reductionism never simplifies biological reality. What it does is to convert one form of complexity into a different form of complexity. Nevertheless, discoveries are at the heart of inventions, and inventions are the substrates for new discoveries.

Successful drug finders start from concepts of integrative physiology and, more specifically, from the very end of a biological process rather than from one (or more) of the multiple steps preceding integration. This approach allows the exploitation of endogenous signalling molecules, which, even if peptides, are excellent departure points for the synthesis of novel chemical entities. Then, an appropriate array of bioassays needs to be developed to characterise the sought novel drug. A good bioassay replicates physiological processes in the absence of confounding, often with complex regulatory mechanisms operating in fully integrated systems.

Indispensable backgrounds to facilitate the success of any drug research project include a wealth of research experience, pharmacological 'wisdom' and highly motivated colleagues working in concert as a strongly motivated and integrated team, inspired by a common ambition.

That these principles guided Sir James's path to his key inventions is elegantly illustrated in the following text: 'By 1956, based on Ahlquist's hypothesis that two distinct types of adrenoceptors existed,' he reminisced, 'I had clearly formulated the aim of finding a specific antagonist of the cardiac effects of adrenaline. I joined I.C.I. Pharmaceuticals Division at their exciting new laboratories at Alderley Park, Cheshire. All I ever promised was that I could develop a new pharmacological agent which might answer a physiological question. Any commercial utility would be implicit in that answer. My years at I.C.I., were some of the most exciting of my life. Together with many brilliant people, I succeeded in bringing propranolol, the first  $\beta$ -adrenoreceptor antagonist, to the marketplace. There, I learned how to be more than merely curious about a molecule with an interesting biological effect but also how to ask questions about it and how to collaborate across disciplines.'

*By 1963, I was convinced that the histamine antagonists of the day were analogous to the  $\alpha$ -adrenoceptor antagonists and that the equivalent of a  $\beta$ -adrenoceptor antagonist was needed to block histamine-stimulated acid secretion. I carried out this research project at Smith, Kline & French Laboratories. The histamine project was somewhat controversial at the beginning but it succeeded because of the faith of my managers and the scientific skill and devotion of my colleagues. By 1972, the  $H_2$ -receptor antagonist, cimetidine was in development' [5].*

In both these inventions, the route to the goal was hindered and helped by the invention of partial agonists. Partial agonists continue to frustrate discovery as tragically exemplified by the devastating cytokine storm produced in six human volunteers treated with TGN-1412, a super CD28 agonist investigated for cancer treatment [2]. Sir James remarked that this episode was, perhaps, in part, the consequence of safety testing in specific pathogen-free animals, including primates, whose immune systems may have been too naive to appropriately react to CD28 antibody challenges. In this specific case, animal safety tests with a higher translational power might have precluded or minimized the human tragedy.

The professional life of Sir James has been, and still remains, a passionate pursuit for novel drugs. Indeed, in addition to the aforementioned successes that garnered him recognition as a Nobel Laureate, he has participated in the invention of lamotrigine (first new anticonvulsant in 30 years) and gastrin, cholecystokinin (CCK1 and CCK2) and  $H_3$ -histamine receptor antagonists. He always looked for goals, constraints and restrictions, because he thought that was how one can win.

Sir James' concluding thoughts were dedicated to the research climate in today's pharmaceutical organisations *'The inventive process requires passion, creativity and experience. Unfortunately, much of current drug invention is driven by an obsession with technology such that techniques have taken the place of looking for drug ideas rather than the reverse. When technology drives management, passion is the first thing to die. Additionally, the cult of management for hierarchies, growth, and endless committees and reporting destroys creative thinking and the drug-inventing enthusiasm. Where there is no passion to overcome friction due to layers of bureaucracy, drug invention projects flounder. There is no bright future for pharmaceutical organisations, if people with passion are not recruited and given the opportunity and the time to become inventors of new drugs. Indeed, the purpose of drug industry is to supply the society in which is imbedded with new drug, better drugs. It is there to fulfil a need.'*

### 3. Translational track

#### 3.1 'QT-understanding: the complexities of defining the translation of animal data to humans', by Dr Rob Wallis, Pfizer Ltd, UK

Animal data expertly generated and characterised by a high degree of clinical translation are indispensable stepping stones along the path that any drug candidate has to go through to

enter human clinical evaluation. Therefore, translation should become an accurately benchmarked experimental parameter characterising both individual and interrelated groups of SP assays. Whereas the confidence in a preclinical model is grounded in the knowledge of the relevant pathways, associated pathophysiology and available biomarkers, confidence in translation is founded on the correlation between preclinical and clinical data for a number of compounds/pathologies studied, and the free plasma concentrations required for therapeutic activity. For example, a score of 1 – 3 may be used to grade each of the following three features (matching the pathway mechanism, the clinical end point and human pathophysiology) that were selected for determining the degree of confidence to assign to a model. In this scheme, a model receiving a score of 7 – 9 can be highly trusted. High translational power is assumed for a model when four or more compounds/mechanisms have been found to produce the same consistent effects in both animals and humans at clinically efficacious concentrations that are within  $\pm$  threefold (after species scaling) to those exerting the desired activity in the examined experimental model. These concepts were applied to SP assays used for determining QT liability [6,7]. A set of 19 compounds (7 of which were positive comparators) were also clinically characterised in a thorough QT study (TQT) [8]. All studies were designed to exclude a 7- to 10-ms increase in the QTc interval, defined as the threshold for assuming a positive effect. Any compound inhibiting *in vitro* hERG channel function by > 10% was considered hERG liable. Similarly, compounds increasing QTc > 10 ms in dogs (studies planned to detect 10 ms change with 90% power using n = 4 crossover design) were assumed to be *in vivo* QT liable. The hERG and *in vivo* data exhibited, respectively, 78 and 85% concordance with the thorough QT (TQT) study results when a twofold concentration range was taken into consideration for comparing animal to human data. Only 1 of the 19 studied compounds was preclinically negative, but TQT positive. However, this outlier compound was detected as QT liable in a first-in-man clinical trial (FIM) prior to the execution of a TQT study. Interestingly, the cost of hERG, *in vivo* dog, FIM and TQT studies are, respectively, 700, 10,000, 12 million and 2.5 million dollars, whereas their respective risk resolution powers are 80, 90, 100 and 100%. Thus, confidence in translation of non-clinical data signalling potential QT liability as determined in human volunteers by using a TQT study appears to be very satisfactory. However, I wish to remind that what is truly expected from the S7B [6] guideline strategy is a high translational power for the potential of a clinical candidate to trigger life-threatening arrhythmic events in patients, but, unfortunately, we lack such a precious information.

In conclusion, defining translation of SP data to humans requires the knowledge of end points (including magnitude), concentrations, mechanisms of action and clinical data. If SP investigators desire to successfully impact the early drug

discovery process, they must endeavour to characterise, as accurately as possible, the biological mechanisms behind any potential risks and their human impact in order to establish confidence in the translation of their non-clinical results into the clinical environment.

### 3.2 'Off target cardiovascular pharmacology of torcetrapib and human safety implications', by Dr Peter Siegl, Merck & Co., USA

A Phase III clinical trial (ILLUMINATE) was carried out in > 15,000 high-risk patients diagnosed with atherosclerosis to determine whether torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, added to an established efficacious treatment regimen (atorvastatin) offered greater benefit than atorvastatin alone. Regrettably, after 550 days (out of the 4.5 years planned) median follow up on treatment, the number of deaths in the torcetrapib group was ~ 37% larger than in the matched control group (93 versus 59 of which 6 versus 0 were for stroke). The respective major cardiovascular events (cardiac heart disease death, non-fatal myocardial infarction, stroke, hospitalisation for unstable angina) were 464 versus 373. This tragic outcome forced the sponsor (Pfizer) to prematurely terminate this large clinical investigation. An additional troubling observation was a two- to threefold higher number of torcetrapib-treated patients experiencing hypertensive episodes, with blood pressures > 140/90, or with increases > 15 mmHg as compared with the atorvastatin cohort [9,10]. Hence, it is legitimate to question whether the latter adverse blood pressure effects of torcetrapib in humans (that may be responsible for the increased cardiovascular mortality due to stroke and myocardial infarction) were predictable by non-clinical models and, if so, whether they were related to CETP inhibition.

Oral or intravenous administration of torcetrapib elicited dose-related blood pressure increases in anaesthetised and/or conscious mice, rats, dogs and rhesus monkeys. In the dog, the plasma concentration of torcetrapib producing a threshold blood pressure increase of safety concern (+ 10 mmHg) was ~ 5 µM. CETP inhibition, *per se*, is unlikely to mediate this effect as pressor responses to torcetrapib were observed in mice and rats, which are species that do not express the CETP enzyme. In addition, in either wild-type or transgenic (expressing CETP) mice, torcetrapib produced similar blood pressure increases. However, anacetrapib, another CETP inhibitor, did not modify blood pressure in mice, monkeys or dogs.

The pressor response produced by torcetrapib was not affected by endothelin, angiotensin,  $\alpha$ -adrenergic,  $\beta$ -adrenergic or ganglionic nicotinic receptor blockers and could also be replicated in pithed rats (a preparation deprived of CNS control to the cardiovascular system). In addition, in isolated rat aortic and mesenteric rings, torcetrapib changed neither basal vascular tone, nor the vasoconstrictant responses to angiotensin II or endothelin, nor the vasorelaxant effects of acetylcholine. Thus, the *in vivo* blood pressure

effects of torcetrapib are likely elaborated by an endogenous mediator. This hypothesis is expressly supported by the finding that, in acutely adrenalectomised rats, torcetrapib did not significantly modify blood pressure. In addition, in intact rats, torcetrapib increased plasma aldosterone levels, but the intravenous administration of this hormone to rats was not accompanied by blood pressure elevation. Thus, an endogenous substance released by adrenal gland, which is not aldosterone, adrenaline or noradrenaline, is directly or indirectly responsible for the pressor response torcetrapib. Moreover, the latter effect is the haemodynamic resultant of an increase in total peripheral vascular resistance as it was accompanied by a decrease in cardiac output.

These studies indicate that the cardiovascular effects of torcetrapib are not inherently related to CETP inhibition. Indeed, they support the notion that non-clinical, accurately performed SP cardiovascular studies can signal safety concern issues for potential cardiovascular harm with novel clinical candidates. Interestingly, torcetrapib was recently reported to increase aldosterone, serum sodium and bicarbonate and decrease serum potassium in humans. These effects are consistent with an activation of the angiotensin–aldosterone system [10], which is a recognised signal of adverse cardiovascular events. Indeed, aldosterone through activation of the mineralocorticoid receptor not only can elevate blood pressure, but has direct vascular effects, including impaired endothelial function and increased inflammation and vascular smooth muscle migration. The higher death from cardiovascular events in patients of the ILLUMINATE trial with greater changes in serum electrolytes is consistent with the suggestion that this hormonal mechanism played a causal role [10].

### 3.3 'Respiratory safety pharmacology studies: re-evaluation of ICH7A', by Dr Dennis Murphy, GlaxoSmithKline Pharmaceuticals, USA

The basic components of the respiratory system are a pumping apparatus (conveying gases from the environment to airways and vice-versa) and an exchanger (lung) of gases (transferring gases from the airway space to the blood and vice-versa). The function of the pumping apparatus is described by two parameters (tidal volume and respiratory rate), whereas airways resistance and lung compliance are parameters describing lung function. Given the life-sustaining importance of respiratory function, the S7A guideline [7] recommends that any clinical candidate is investigated for its effects on respiratory rate and tidal volume or haemoglobin oxygen saturation before entering human evaluation. If these end points are adversely affected, follow-up studies are warranted for determining specific effects on lung mechanics (airway resistance, lung compliance), pulmonary artery pressure, blood gases and pH.

According to the experimental data presented, the simple determination of changes in ventilatory parameters to assess respiratory safety is a flawed investigational approach as it does not consistently detect drug-induced airway

obstruction (e.g., bronchoconstriction). Indeed, in the animal species generally used for SP studies (rats, dogs and monkeys), intravenous infusions of the bronchoconstrictor agent metacholine increased total pulmonary airway resistance by 100 – 200%, without producing changes of concern in either respiratory rate or tidal and minute volumes.

Drug-induced bronchoconstriction can be as life-threatening as either respiratory depression or stimulation. Based on respiratory SP studies conducted over the past 10 years, significant adverse ventilatory effects and airway resistance increases occurred, respectively, in 34% of 179, and 14% of 111 drug candidates investigated. Thus, drug-induced airway obstruction is not such a rare non-clinical finding. Consequently, the latter parameter should be promoted to a primary, rather than secondary, end point as proposed by the S7A guideline [7]. In addition, whereas this document supports the determination of changes in blood gases (especially haemoglobin oxygen saturation) as an indicator of drug-induced ventilatory changes, numerous published studies provide evidence that in conscious rats, dogs and humans, increases or decreases in ventilation are not consistently accompanied by corresponding modifications in haemoglobin oxygen saturation levels. Arterial PaO<sub>2</sub> and PaCO<sub>2</sub> (partial pressure of blood oxygen and carbon dioxide, respectively) are more sensitive indicators of blood gas changes, although not as sensitive as variations in ventilatory parameters. For instance, in the conscious dog, remifentanyl markedly depressed ventilation (68% decrease in minute volume), moderately increased PaCO<sub>2</sub> (21%) and mildly decreased PaO<sub>2</sub> (14%), without significantly affecting oxyhaemoglobin levels [11].

In conclusion, a future version of the ICH S7A guideline should advocate the study of respiratory rate and tidal volume (pumping apparatus function) and airway resistance (lung airway function) as primary end points to ascertain respiratory safety of clinical candidates. The determination of blood gases would be more appropriate as a follow-up (secondary) end point to better frame the severity of ventilatory changes. Haemoglobin oxygen saturation should no longer be advised as a stand-alone indicator of treatment-provoked changes in blood gas status.

## 4. Emerging trends

### 4.1 'Drug-induced shortening of the QT interval: an emerging safety issue in drug development', by Dr Rashmi Shah, Consultant, UK

QT interval prolongation resulting from genetic disorders (long QT syndrome [LQTS]) and drug treatments may initiate proarrhythmic events, which, at times, are so severe that irreversible ventricular fibrillation (VF) may ensue. These outcomes may be prevented or attenuated by drugs that shorten the QT interval, as hinted by limited clinical observations with primidone, a drug used to control seizure [12], and nicorandil, a K<sub>ATP</sub> channel-opener marketed as an antianginal agent [13].

Compared with the relatively high frequency of occurrence of LQTS, patients with identified inherited short QT syndromes (SQTS) are very few. Electrophysiological abnormalities resulting in inherited short QTc syndromes are either a gain in potassium (I<sub>Kr</sub>, I<sub>Ks</sub>, I<sub>K1</sub>) channel, or a loss of calcium channel (I<sub>CaL</sub>) function. Phenotypic consequences of these ion channel pathologies are (in addition to shortened QTc interval) syncope, ventricular tachycardia and, in the most severe cases, potentially lethal VF [14]. Manifestly, this clinical picture warrants a reflection on whether drug-induced QT shortening should become matter of regulatory concern requiring specific non-clinical and clinical explorations along the drug development trail.

From a non-clinical experimental viewpoint, the general strategy (*hERG* and *in vivo* QT assays) proposed by the S7B guideline [6] for assessing drug-induced QT prolongation has the intrinsic power to reveal QT-shortening potential [15]. In addition, follow-up assays proposed by the latter document can provide evidence of proarrhythmic effects. For example, in the isolated perfused rabbit heart, lemakalim and nicorandil, two K<sub>ATP</sub> potassium channel openers that shorten the QT interval have been found to spontaneously trigger VF, but only at very high concentrations [16]. Furthermore, in the canine arterially perfused left ventricular wedge preparation, pinacidil, another K<sub>ATP</sub> potassium channel opener, shortened QT interval and increased transmural dispersion of repolarisation, which is a recognised substrate favouring the genesis of VT [17]. Therefore, available non-clinical tools allow the recognition and characterisation of agents that shorten cardiac repolarisation. However, for drug developers, the most crucial question is whether the potential human harm of a clinical candidate shortening the QTc interval in animal studies can be accurately quantified in clinical investigations. According to Dr Shah, the evidence of risk for this class of drugs may be difficult to gather in humans as, unlike Torsades de pointes (TdP), VF is uniformly fatal. Nevertheless, in this author's opinion, efforts should be encouraged to develop criteria to accurately determining such a risk, as the availability of reliable biomarkers of such a risk are critical for deciding whether the clinical development of a drug candidate that shortens the QTc interval can, or cannot, be safely pursued. Indeed, for drugs which prolong the QTc interval, the E14 [8] guideline criterion used to signal safety concern is a placebo-corrected increase in QTc interval between 5 and 10 ms. However, corresponding values for QTc shortening remain to be characterised. Similarly, the absolute lower limit QTc threshold values associated with potential proarrhythmic episodes is not known. On the basis of the few available electrocardiogram (ECG)-documented proarrhythmic events suffered by patients with inherited SQTS, it would appear that such a threshold is 300 – 320 ms (in healthy people the value of this parameter is around 360 ms with an oscillation of ± 30 ms) [18,19]. Thus, for the moment, the proarrhythmic harm of drug-induced QT shortening is too speculative to

mandate regulatory intervention. Nevertheless, for drugs that substantially shorten QTc (e.g., in a dose-related manner and by > 50 ms at therapeutic plasma concentrations), it would appear judicious to closely monitor for cardiac adverse events throughout the entire clinical development.

**4.2 'Drug-induced QTc shortening: facts or fears',  
by Prof Marek Malik, St. Paul's Cardiac  
Electrophysiology, UK**

The subject of QTc shortening was presented as a point-counterpoint discussion in which Dr Shah presented the case for the possible human harm of QTc shortening, whereas Dr Malik argued the counterpoint to this position by recalling the contrast between our extensive knowledge concerning the proarrhythmic potential of QTc prolongation and our relative ignorance regarding the proarrhythmic potential of QTc shortening. Indeed, the risks associated with QTc prolongation are rather well categorised, namely, marginal in healthy people, substantial in susceptible patients and clearly life threatening (TdP arrhythmias) in very susceptible patients. However, our understanding of the potential risks associated with QTc shortening is still in the realm of speculation. It might (or might not) increase repolarisation heterogeneity, which might (or might not) progress to VF, which might (or might not) be the consequence of QTc shortening. Indeed, for arrhythmias attributed to QT shortening there are no recognised hallmark patterns, as is the case for QTc prolongation and TdP. The best-known, clinically used drug QTc associated with QTc shortening is digitalis, which despite its long clinical career is not yet a recognised tachyarrhythmic agent. Moreover, Dr Malik reminded us that many physiological mechanisms (increases in sympathetic tone, acceleration in depolarisation, or a change in cardiac axis) can shorten the QTc interval without provoking proarrhythmic events. However, it should be noted that these physiologically mediated QTc-shortening effects are generally of small magnitude.

Proponents of QTc shortening as a cardiac risk factor point out that the current science surrounding this subject is at the same stage as was QTc prolongation in early 1990s. Pending additional data, we nevertheless must be very circumspect of any drug that dramatically (> 50 ms) shortens the QTc interval at therapeutic plasma concentrations, as such an effect would represent a considerable alteration of the normal repolarisation process. In contrast, at the present time, minor drug-induced QTc shortening should not be considered intrinsically dangerous and should not be subject to the same intensely regulated investigational approach applied to drugs that prolong the QTc interval. Indeed, Prof Malik concluded '*in the absence of solid data, we otherwise face a danger that QTc shortening will be perceived important just because it is perceived important*'.

**5. Lecture of recipient of the Prize for  
distinguished service in safety pharmacology**

**5.1 'Successes, threats, and new opportunities  
of safety pharmacology', Dr Tim G Hammond,  
AstraZeneca Pharmaceuticals, UK**

This presentation discussed the evolution of SP during the last 7 years, its impact in the drug development process, the value of adopting an integrated risk assessment approach, the translational power of SP data, and future challenges and opportunities. The last topic is summarised here.

The search for novel drug targets and approaches to treat old and new diseases is a never-ending activity for any vigorous, forward-looking pharmaceutical organisation. In order to keep pace with the incessant quest for innovation demanded, and reasonably expected, by the public health stakeholders, SP should develop and refine strategies for determining the safety of drugs acting at intracellular spaces. In addition, SP should closely track emerging therapeutic approaches such as gene therapy, biopharmaceutical products and drug combinations. For instance, the problem concerning the determination of safety for incessantly appearing pharmaceutical preparations containing two to three established drugs is not easily resolved. Should the integrated risk of such formulations be derived from the known safety margin of each individual component, or should it be determined once again, considering the drug combination as an entirely novel therapeutic entity?

SP cannot ignore any scientific innovation that has the potential of improving our ability to detect, predict and 'eradicate' human safety threats. To this end, SP investigators should accelerate the integration of pharmacokinetic/pharmacodynamic analysis into SP protocols, attempt to understand and predict drug safety issues arising from patients suffering from specific pathophysiological conditions, optimise the translational power of non-clinical assays to humans, and closely follow pertinent technological advances (e.g., human heart cardiomyocytes derived from adult human stem cells) that may help SP investigators to better accomplish their mission.

Regulatory interventions in drug safety have become more and more stringent as evidenced by the continuous promulgation of novel guidelines. Therefore, the SPS should embrace those opportunities where it has the possibility to participate in the official regulation of any given safety issue. Moreover, the SPS should make representatives available to expert working committees in charge of guideline revisions or novel guideline preparation.

SPS should also be actively promoting a dialogue between key opinion leaders and recognised experts from industry, contract research organisations (CRO), academia and regulatory agencies to foster the integration of suggestions from these partners to develop and adopt optimised solutions to recognised safety issues. For instance,

scaling down of animal use according the three Rs (reduction, refinement and replacement) could profit from such collaboration.

Last but not least, SPS should devise means to attract, train, educate and certify investigators in integrative approaches to physiology and pharmacology research through internal and external programs. To be successful and productive, such an initiative will have to be endowed of adequate financial support.

## 6. New President's Keynote Address

### 6.1 'Bridging preclinical to clinical development: a clinical perspective on safety', Dr Konrad Tomaszewski, Pfizer Ltd, UK

Ethical, legal and regulatory obligations compel pharmaceutical organisations to develop and market medicines with robust and reliable safety profiles. A drug is considered to be safe if, under any realistic condition of use, its benefit invariably outweighs a possible risk.

Throughout the entire non-clinical research process, any drug candidate advanced for clinical investigation must be scrutinised for potential, undesirable risks that may affect patient safety. SP investigators should, whenever possible, determine the mechanism of such risks as well as the means to appropriately manage them. Then, clinical investigators should translate this knowledge into an investigational platform for appropriately characterising the human drug safety profile, and effectively managing real and hypothetical risks. Following drug approval, post-marketing vigilance should perform epidemiological studies to further delineate any identified risks, and appropriately address any emerging safety issues.

A risk management plan concerning drug safety issues should comprise *'the comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate, and minimise (mitigate) risks throughout the drug's life cycle so as to establish and maintain a favourable benefit/risk profile in patients.'* The successful application and execution of the risk management plan requires the concurrent cooperation of the marketing company (which should fulfil safety reporting requirements), regulators (who establish safety reporting rules), physicians (who should conform to reporting practices and continuously familiarise themselves with evolving safety information), and patients (who should adhere to physician prescriptions, and faithfully relay any noteworthy adverse event).

Until the tragic outcome of the TGN-1412 human trial [2], serious and life-threatening adverse events have been extremely rare in FIM studies. This excellent safety record is the direct result of the application of strict rules for selecting the initial doses to be administered to humans. These doses should generally not exceed the dose producing 10% of the desired effect in a meaningful preclinical model, approximate

the minimum anticipated biological effect level, or be close to 1/100 of no-observed-adverse-effect level, as determined in the most sensitive toxicological study. Escalation to the maximal tolerated dose should follow conservative principles. The dose of TGN-1412 for FIM did not strictly comply with these basic, established, precautionary measures, as discussed in a previous meeting [2].

Clinical end points used to detect potential risks should be driven by direct toxicological observations (e.g., urinary enzyme measurement in case of renal tubule damage in animals; Synacthen test performance and adrenocorticotrophic hormone measurements if adrenal hypertrophy was observed in animals, etc.).

Due to age, and the absence of disease conditions, the Phase I tolerability study at times does not predict all Phase II and III adverse events. Whereas a mechanism-related AE detected in non-clinical investigations is likely to occur in humans, a non-mechanism-related AE may be missed or underestimated, even at the completion of carefully designed and expertly executed Phase III programme.

In Phase I, the most frequently observed adverse events (10 – 30% occurrence) are headache, nausea, vomiting, loose stools, diarrhoea and dizziness. In general, SP and toxicology data accurately and reliably predict cardiovascular (electrocardiogram), renal and respiratory adverse events, but are less sensitive in the detection of dose-limiting gastrointestinal and CNS (paraesthesias, sensory alterations) adverse events.

A clinical case study on a drug-induced enhanced light perception, blurred vision, photophobia and colour vision alterations was discussed. In order to determine the safety implications of these observations, clinical investigators performed eye electrooculograms, visual evoked potentials, electroretinograms and colour vision measurements in double-blind studies performed in volunteers receiving single and 28-day repeated doses. The resultant data provided evidence that the drug-related adverse events were reversible after dosing discontinuation. The retina was the primary site of action as, in humans and dogs, the electroretinogram showed a decrease in wave amplitude. The absence of retinal or other visual pathway anatomical alterations in the 6- and 12-month canine toxicity studies was an additional reassuring observation. In this example, a well-designed holistic approach provided an adverse event explanation, and a plan to elucidate and successfully manage the potential visual safety outcomes.

In conclusion, the current regulatory environment requires a conscientious clarification of all safety issues in the context of patient benefit, and risk management and minimisation. Preclinical and clinical investigators should consider themselves partners, working hand in hand on the accomplishment of this fundamental endeavour of ethical pharmaceutical organisations.

## 7. Poster presentations

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### 7.1 'Validation of an OptoMotry® system for measurement of visual acuity in Han Wistar rats' by Drs Khine Phu Maung, Sharon Storey, Jenny McKay, Alison Bigley, Dan Heathcote, Katherine Elliott, Jean-Pierre Valentin, Tim G Hammond & Will S Redfern, AstraZeneca, UK

This poster presentation (which won both the SPS Student Travel Award and Young Investigator Best Poster) explored the potential SP value of a new method for detecting visual acuity deficits induced by a variety of drugs associated with human visual acuity loss, retinal toxicity, or visual disturbance. Albino male Han Wistar rats were tested in an OptoMotry® chamber (Cerebral Mechanics, Lethbridge, Canada), which comprises four computer monitors displaying vertical sinusoidal gratings with the animal's viewpoint at the centre of a 'virtual cylinder.' The animal is placed inside the chamber on a platform and a video camera above relays images onto another computer screen monitored by an observer. The grating is rotated to elicit head tracking movements and its rotating frequency is increased progressively until head-tracking ceases. Visual acuity threshold (in cycles per degree) is taken as the highest visible grating frequency [20]. Rats were tested before and 2, 24, 48 and 72 h after dosing with vehicle or sodium iodate, desferrioxamine, ethambutol, quinine, vigabatrin or vardenafil, which are drugs known to adversely affect human vision. Then, they were euthanised at 7 days post dose and their retinæ prepared for both light and electron microscopy analysis in order to compare OptoMotry® measurements with retinal tissue histopathological findings.

All six reference agents studied produced measurable deficits in visual acuity detectable from 2 h after a single administration. The histopathological changes due to these treatments were minimal with the exception of sodium iodate, which produced diffuse moderate degeneration of the retinal pigmented epithelium and outer segment of the photoreceptor layer. Thus, the OptoMotry® system allows detection and quantification of time-related visual acuity deficits caused in rats by a range of retinotoxic agents. Hence, it may be usefully applied preclinically to determine the safety of clinical candidates on visual function.

## 8. Expert opinion

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The principal theme of the 2007 annual meeting of the SPS was the translation of non-clinical SP data to human outcome. Translation should be seen as the keystone of any SP investigation. Indeed, it expresses the power of each SP assay to predict the theoretical risk associated with the use of a drug candidate in volunteers and general and specific patient populations. Perhaps the creation of an SPS committee could be considered, where its mission would be the development of unanimously accepted criteria

to accurately score the various aspects of an SP assay for translation purposes. The knowledge of such a translation power would also allow estimating more accurately the cost of an assay whenever an existing liability is missed for any reason. A seminal presentation of the meeting documented that, for 19 drugs investigated, a strong translation power (close to 90%) existed between the clinical outcome of the TQT study and S7B guideline recommended non-clinical strategy, complemented, if necessary, by appropriate follow-up studies.

SP investigators and development teams should receive robust training on the value and limitations of translation in order to minimise and desirably eradicate the occurrence of disastrous human outcomes such as that of the ILLUMINATE trial (see Section 3.2). Indeed, one wonders why the torcetrapib development team did not adopt, as soon as it became aware, a conservative position on potential harm for atherosclerotic patients of a possible long-term, albeit mild, arterial blood pressure elevation accompanied by a plasma aldosterone elevation, discovered by SP studies in normotensive animals. At the American Heart Association meeting in Orlando (November 2007), Pfizer investigator poster presentation reported that torcetrapib failed to produce changes in blood pressure of concern in an initial haemodynamic study, possibly because the formulation of the compound used was not optimised for elevated exposures. Nevertheless, the accurate assessment of the SP profile of a drug is an ethical and regulatory obligation (see Section 6.1). Moreover, inferring safety from studies with reduced drug bioavailability does not fulfill these requirements. In the case of torcetrapib, an extensive preclinical cardiovascular evaluation required for this class of drugs (including determination of blood pressure effects in atherosclerosis animal models) should have readily detected the significant pressor and hormonal effects produced by torcetrapib. The potential risks of such effects should have been carefully and prospectively considered prior to patient recruitment for the ILLUMINATE trial. This is especially true as the highest doses of torcetrapid (100 and 300 mg; ILLUMINATE trial 60 mg) in the Phase I volunteer study also produced a clear increase (~10 to ~20 mmHg) in systolic blood pressure (above-mentioned poster presentation), which should have raised potential concern for patients with atherosclerosis. Regrettably, in drug development, all too often such poor judgements are not the inevitable outcome of intrinsic hazard or scientific ignorance, but rather, are the consequence of conscious personal or managerial choices [2], which do not always sufficiently weigh the potential of minor adverse non-clinical and Phase I effects for possibly serious consequences in patients. A pertinent comment to these considerations was made by Dr Robert M Califf in his discussion of the outcomes of the ILLUMINATE trial at the November 2007 AHA meeting in Orlando: *'This is a major warning to the biological and medical community that we have an urgent need for reform in two phases of the drug*

*development system: one is the understanding of off-target pharmacology early in the development, and the second is the almost crisis in the need of systems that enable us to look at the results of very large, rapidly done clinical trials.*' In this context, it is of interest to mention that the FDA is now asking sponsors developing CETP inhibitors to assemble and critically evaluate all available specific adverse effect data prior to initiating Phase III trials with agents belonging to this drug class. This *a posteriori* request should become a carefully and competently examined prerequisite for the advancement of any clinical candidate to human evaluation. The torcetrapib sponsor should attempt to satisfy the drug development community desire to better understand the decisional tree that led to the promotion of this drug to an extensive clinical evaluation, without the clear knowledge of, or in spite of, the incorrect evaluation of, potential cardiovascular and hormonal safety concerns. Indeed, from an ethical point of view, the likely reasons of serious, publicly disclosed drug safety outcomes should no longer be considered a proprietary matter providing a competitive advantage, as such knowledge may prevent future human tragedies. A final comment to this issue is that although the mentioned off-target effects of torcetrapib probably contributed substantially to the significant increase of cardiovascular events and death, the higher rate of death (24 to 14 from cancer and 9 to 0 from infection) remains to be explained and SP efforts should be made to unveil possible additional off-target or therapeutic target-related mechanisms contributing to the various adverse effects. Thus, torcetrapib, despite the very favourable lipid profile in humans (increased high-density lipoprotein-cholesterol of 72% and decrease in low-density lipoprotein-cholesterol of 25%) not only failed to reduce, as expected from such a therapeutic mechanism, but increased, major cardiovascular events (25%) and death (40%) [21].

An emerging safety issue covered at this meeting concerned the possible life-threatening risk associated with drugs shortening the QTc interval. Dr Shah concluded his presentation by stating: *'Do we know the cause(s) of sudden unexplained deaths so frequently reported with a number of drugs?'*, implying that the true cause of many sudden unexplained deaths could be the outcome of drug-induced QTc interval shortening. This is a well taken, albeit provocative, hypothesis, as, for the moment, it is not supported by robust electrocardiogram documentation. Without such data, any regulatory intervention pertaining to QTc interval shortening would appear to be premature and unjustified. However, there is unanimous agreement that drugs that substantially shorten the QTc interval (> 50 ms) should be carefully investigated for proarrhythmic potential during the clinical development phases.

Dr Murphy reported that the core battery assays recommended by the S7A guideline [7] to determine pulmonary liability do not routinely detect drug-induced, potentially life-threatening airway obstruction. Thus, SP investigators are encouraged to measure pulmonary

resistance as a primary end point, signalling changes in pulmonary function in order to appropriately address this issue. In this context, the SPS should establish an expert committee to gather and assemble novel scientific findings supporting a revision of the current SP guidelines (S7A and S7B guidelines) [6,7].

The SPS Board of Directors has not yet resolved the problem of making SPS meeting materials rapidly available on its Internet site. This service would be most appreciated, given that many interesting presentations during the annual SPS meeting take place in concurrent scientific sessions. It is regrettable to note, once again, that there are presenters who still decline to share, on request, their presented material, claiming proprietary rights [2]. It is worthwhile to reiterate that the content of presentations made at open meetings becomes part of the public domain. As such, it should be made available in a cooperative manner to those colleagues who request it. The SPS Board of Directors may envisage to require (as many private organisations offering educational meetings do) that the acceptance to deliver a talk at an SPS meeting is conditional on the presentation being publicly available.

Some vendors sponsored interesting satellite scientific sessions, both at lunch and after the close of the regular meeting hours, which were neither noted in the printed programme nor real time announced. In the future, it would be of great benefit to both the SPS members and exhibitors, if the location and time of these satellite meetings were clearly listed in the final SPS program. Finally, it is hoped that future meetings of the SPS will be able to attract and offer a forum for the presentation of cutting-edge science. To accomplish this important goal, the SPS, like other scientific societies, might consider the adoption of a refereed format to ensure the submission, presentation, and publication of the most relevant and novel science.

The last words of this report are dedicated to the important message delivered to us by Sir James Black. He invited us to accomplish our mission as biological investigators with commitment, high competence, and everlasting passion. These are, indeed, indispensable qualities, particularly for those of us who during many years of patient and hard work shepherd ideas and efforts for transforming a mere chemical entity into a medicine that safely and efficaciously treats human disease.

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indispensable in the preparation of this report. The Author assumes responsibility for full content of this report, particularly for any portion that may not accurately reflect the presentation.

## Declaration of interest

The author has declared no conflict of interest and no payment has been received for the preparation of this manuscript.

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•• **Pivotal paper raising concerns on the potential clinical benefit of CEPT inhibitors and discussing the possible off-target mechanisms accounting for the adverse clinical outcome of torcetrapib ILLUMINATE and ILLUSTRATE trials.**

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