WILLIAM HARVEY
RESEARCH CONFERENCES

Present a Conference

on

NITRIC OXIDE BASED DRUG THERAPY

Wednesday, 10th - Friday, 12th April 2002

Le Meridien Park Atlantic, Porto, Portugal

Conference Chairmen:

Professor Nigel Benjamin

Professor Sir John Vane FRS

Faculty includes:

N Benjamin	London
N Boughton-Smith	Loughborough
G Butrous	Sandwich
J Cooke	Stanford
S Fiorucci	Perugia
C Frostell	Stockholm
P Gresele	Perugia
T Higgenbottam	Loughborough
D Janero	Bedford
B Jilma	Vienna
R Knowles	Stevenage
T Ormerod	Aberdeen
M Rothblatt	Silver Spring
U Scherrer	Lausanne
P Vallance	London
J Vane	London
A Wallace	Loughborough
J Wallace	Calgary
B Whittle	London

NITRIC OXIDE BASED DRUG THERAPY

10th April - 12th April 2002

INTRODUCTION

Nitric oxide (NO) is now known to be an important biological molecule that is essential for the normal function of a number of diverse biological processes. These include vasodilatation, host defence, neurotransmission and cell proliferation and apoptosis. The discovery of nitric oxide explains the function of currently-used nitrovasodilators as NO donors, and was important in the discovery of sildenafil, designed to enhance nitric oxide action. New approaches to augment or reduce the availability of nitric oxide are now beyond the laboratory stage and are being evaluated as potential new therapies for a wide range of clinical conditions. These compounds include novel NO donors and selective inhibitors of the 3 NOS isoforms (iNOS, eNOS and nNOS) with proposed indications ranging from viral infections to atheromatous vascular disease. This conference will present and evaluate some of the most exciting new nitric oxide-based therapies currently being developed by several different organisations, and consider their potential for improving currently available drug treatment.

WEDNESDAY, 10th APRIL

16.00 to 18.30 *Registration*

19.00 to 20.00 *Welcome Reception & Finger Buffet*

THURSDAY, 11th APRIL

08.00 *Registration*

Chairmen: **John Vane & Ben Benjamin**

09.00 **NO manipulation and clinical disease**

Nitric oxide is a widespread biological mediator that has been implicated in many processes. This talk will outline areas in which nitric oxide has been clearly shown to be of relevance to human disease states and identify opportunities for therapies. In addition, it will cover the importance of endogenous inhibitors of nitric oxide synthesis in regulating nitric oxide in pathophysiology.

Speaker: **Patrick Vallance**
Rayne Institute, University College London, UK

Topical Application of NO

09.45 **Development of topical NO**

NO generation from arginine oxidation is well-known, but this molecule can also be generated in large quantities in humans from nitrate and nitrite reduction. We have developed novel NO-generating therapies based on nitrite reduction to treat a variety of bacterial, fungal and viral infections in humans and animals.

Speaker: **Ben Benjamin**
William Harvey Research Institute, London, UK

10.30 *Coffee and Posters*

11.00 **NO based therapies in skin disease**

NO is a key regulatory molecule in inflammation, in response to infection and in vasculature and healing. Potential roles for NO based therapy will be explored with examples of NO and NO antagonists as therapy for a range of skin diseases.

Speaker: **AD Ormerod**
University of Aberdeen, UK

NO Modified Drugs

Chairmen: **Ben Benjamin & Patrick Vallance**

11.45 **NO-NSAIDs: GI and CV safety plus enhanced anti-inflammatory activity**

Coupling of an NO-releasing moiety to conventional NSAIDs profoundly reduces the toxicity of these agents in the GI tract. These compounds exhibit enhanced anti-thrombotic activity and significant anti-hypertensive activity. The release of NO from these compounds also appears to enhance the anti-inflammatory properties of these drugs.

Speaker: **John L. Wallace**
University of Calgary, Canada

12.30 *Lunch and Posters*

13.45 **Gastrointestinal safety and mechanism of action of nitroaspirin**

Speaker: **Stefano Fiorucci**
University of Perugia, Italy

14.30 **Anti-platelet/anti-thrombotic effects of nitroaspirin**

Nitroaspirin (NCX 4016) combines the pharmacological effects of cyclooxygenase blockade with those of nitric oxide. *In vitro*, it inhibits platelet aggregation by a wider range of agonists than aspirin, prevents shear-stress induced platelet activation, inhibits collagen-induced platelet adhesion and increases intraplatelet cGMP. Simultaneous inhibition of multiple pathways of platelet activation may be advantageous for anti-thrombotic efficacy.

Speaker: **Paolo Gresele**
University of Perugia, Italy

15.15 *Coffee and Posters*

15.45 **Metabolic insulin resistance, hyperlipidaemia and hypertension: a new target for NO delivery drugs?**

Insulin resistance and arterial hypertension are related, but the underlying mechanism is not known. eNOS deficiency may represent a candidate mechanism, since in mice, it causes hypertension, metabolic insulin resistance and hyperlipidemia. NO delivery drugs may represent a novel causal treatment for the metabolic syndrome.

Speaker: **Urs Scherrer**
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

16.30 ***In vivo* clinical pharmacology of nitroaspirin**

Nitroaspirin was compared to aspirin and placebo in a well standardised clinical pharmacological model of systemic inflammation in humans. Endotoxin was injected into healthy volunteers to study the effects of nitroaspirin on a variety of effector systems e.g. cytokines, apoptosis and coagulation.

Speaker: **Bernd Jilma**
Vienna University Hospital, Austria

17.15 **Nitrated cyclooxygenase-2 (COX-2) selective inhibitors**

COX-2 selective inhibitors appear to carry an increased risk of cardiovascular complications compared to conventional NSAIDs, due to lack of anti-thrombotic activity. Addition of NO-donating groups onto selective COX-2 inhibitors is our proprietary approach for reducing the potential of cardiovascular liability associated with this drug class.

Speaker: **David R. Janero**
Nitromed Inc., Massachusetts, USA

FRIDAY, 12th APRIL

Lung Disease and NO Therapy

Chairmen: **Martine Rothblatt & Tim Higgenbottam**

09.00 **Lung disease and NO therapy**

The low vascular resistance at rest and exercise in man is maintained by continuous release of endothelial NO. In disease, reduced release results in pulmonary hypertension and impaired gas exchange. Inhaled supplemental NO is impractical, long-term. Alternatives include oral L-arginine supplements, phosphodiesterase inhibitors and nitric oxide donors.

Speaker: **Tim Higgenbottam**
AstraZeneca R&D Charnwood, Loughborough, UK

09.45 **Inhaled NO in hypoxemic respiratory failure of the newborn**

Inhaled NO is currently approved for clinical use in neonates with severe respiratory failure. Placebo-controlled studies have shown improved oxygenation and a reduced need of extracorporeal gas exchange support. Morbidity is not increased in survivors after exposure to NO.

Speaker: **Claes Frostell**
Karolinska Institutet Danderyd Hospital, Sweden

10.30 *Coffee and Posters*

11.00 **Is arginine an effective adjunctive treatment for coronary artery disease?**

New insights gained from biochemical, molecular, celullar, transgenic animal studies and clinical trials will be presented regarding the role of the arginine analogue ADMA, the endogenous inhibitor of NO synthase.

Speaker: **John Cooke**
Stanford University, USA

11.45 **PDE5 inhibitors in adult and paediatric pulmonary hypertension**

Speaker: **Ghazwan Butrous**
Pfizer Global Research & Development, Sandwich, UK

12.30 *Lunch and Posters*

Selective Inhibition of NOS

Chairmen: **Ben Benjamin & Brendan Whittle**

13.45 **Overview of iNOS inhibitors: from non-selective to selective inhibition**

Inhibition of iNOS has been a therapeutic goal for about a decade. Experience with non-selective NOS inhibitors suggests that a high degree of selectivity may be of crucial importance, and highly-selective iNOS inhibitors have been identified and are being evaluated.

Speaker: **Richard G. Knowles**
GlaxoSmithKline, Stevenage, UK

14.30 **Structural and mechanistic features of NO synthase inhibition**

Inhibition of the various isoforms of NO synthase is expected to have therapeutic benefit in a wide range of diseases. Selective inhibitors of both iNOS and nNOS have been reported and some of the ways in which they interact with the enzyme will be discussed.

Speaker: **Alan Wallace**
AstraZeneca, Loughborough, UK

15.15 *Coffee and Posters*

15.45 **Involvement of iNOS in gut disease**

The role of NO, derived from iNOS, in gut diseases is controversial, with divergent findings reported with different models, iNOS inhibitors and gene-deleted animals. The present work identifies an involvement of both superoxide and NO in gut epithelial and microvascular injury where selective iNOS inhibitors show efficacy, implicating peroxynitrite, rather than NO itself as the injurious mediator.

Speaker: **Brendan J.R. Whittle**
William Harvey Research Institute, London, UK

16.30 **Pharmacological activities of novel iNOS inhibitors in inflammatory models**

There is enormous interest in the role of excessive NO production in inflammatory diseases. The potential of specific inhibitors to modulate and control these processes will be considered.

Speaker: **Nigel Boughton-Smith**
AstraZeneca, Loughborough, UK

17.15 **Chairman's Conclusions**
Ben Benjamin

17.30 *Close of Meeting*

WILLIAM HARVEY RESEARCH CONFERENCES

This meeting is organised by the conference arm of The William Harvey Research Foundation - a registered charity. The objectives of the Foundation are to promote and support fundamental research leading to new treatments for cardiovascular, metabolic, inflammatory and other diseases

The organisers wish to thank

AstraZeneca

NicOx

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United Therapeutics

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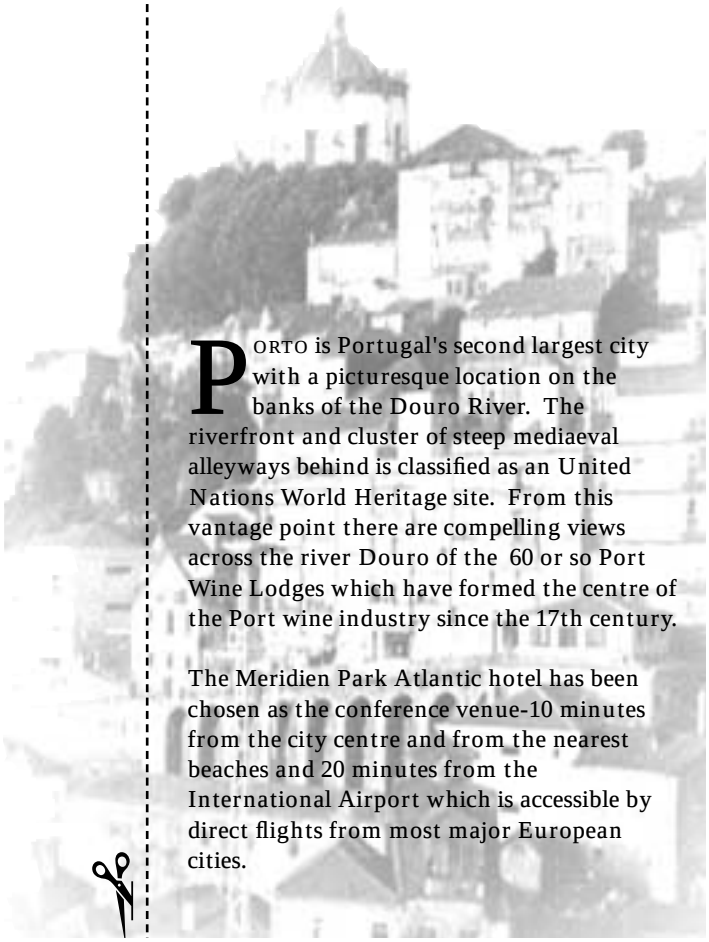

PORTO is Portugal's second largest city with a picturesque location on the banks of the Douro River. The riverfront and cluster of steep mediaeval alleyways behind is classified as an United Nations World Heritage site. From this vantage point there are compelling views across the river Douro of the 60 or so Port Wine Lodges which have formed the centre of the Port wine industry since the 17th century.

The Meridien Park Atlantic hotel has been chosen as the conference venue-10 minutes from the city centre and from the nearest beaches and 20 minutes from the International Airport which is accessible by direct flights from most major European cities.

ADMINISTRATIVE DETAILS

DATE:
Wednesday, 10th - Friday, 12th April 2002

VENUE:
Le Meridien Park Atlantic
Av. da Boavista 1466
Porto, Portugal
Tel: + 351 22 607 2500
Fax: + 351 22 600 3214

FEE:
Euros 1,500 plus tax at 17% (€255) which is payable in advance. The fee includes all scientific sessions, an abstract book, refreshments, lunches and a ticket for the Welcome Reception in the hotel on Wednesday, 10th April. A special fee of Euros 700 plus tax at 17% (€119) is available on request for faculty members, physicians and researchers currently working in University Departments and Hospitals. Payment can be made by a cheque drawn in Euros or by Euro bank draft (all bank charges to be paid by delegate). Alternatively credit card payment can be made in pounds sterling (we will use the exchange rate in operation on the date of processing your payment). Payment can also be made by bank transfer in Euros to HSBC, International Branch, PO Box 181, 27-32 Poultry, London EC2P 2BX, UK. Account No: 57091342. Sort Code: 40-05-15. Swift Code: MIDLGB22. Account Name: William Harvey Research Conferences. All bank charges to be paid by delegate and payment should be referenced to the delegate's name. A copy of the transfer request should be sent with your completed registration form. Please note that under Portuguese Customs and Excise regulations all delegates are required to pay tax on events held in Portugal.

POSTER COMMUNICATIONS:
There will be provision for posters describing the results of recent research, subject to selection by the organisers. Abstracts must be no longer than 250 words including text, references, authors names and addresses. Deadline for submission of abstracts, which must be accompanied by registration and payment, is 14th March 2002.

It may be necessary for reasons beyond the control of the organisers to alter the content and/or timing of the programme or the identity of the speakers.

HOW TO REGISTER:

Facsimile bookings:
Firm bookings may be made by faxing a completed registration form to Dr Jenny Maclagan on +44 (0)20 7882 6084. These must be confirmed in writing within one week, accompanied by payment.

Postal bookings:
Please complete the registration form and send it to: Dr Jenny Maclagan, William Harvey Research Conferences, Medical College, Charterhouse Square, London EC1M 6BQ, UK.

CANCELLATIONS:
Cancellations must be received in writing before 14th March 2002 and will be subject to an administration charge of € 100 plus tax (17%). It is regretted that no refunds can be made for cancellations received after 14th March 2002. However, if you cannot attend, a substitute may attend in your place but please let us know.

ACCOMMODATION
Rooms have been reserved at a special reduced rate at Le Meridien Park Atlantic. A booking form will be sent to you immediately upon receipt of the registration form and payment of the conference registration fee. In order to obtain the special rate reservations must be made via the Conference office. Please do not contact the hotel directly.

ENQUIRIES
All enquiries, telephone bookings and alterations to delegate information to:
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REGISTRATION FORM

Please complete and return to: Dr J. Maclagan, William Harvey Research Conferences, Medical College, Charterhouse Square, London EC1M 6BQ, UK.

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Industry Fee(s) @ €1755.00
Faculty Member(s) €819.00
All above prices include tax

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