WILLIAM HARVEY
RESEARCH CONFERENCES

**Present a Conference**

**on**

# PROGRESS IN THE FIELD OF SELECTIVE COX-2 INHIBITORS

**Sunday, 30th September - Tuesday, 2nd October 2001**
**Hotel Plaza, Nice, France**

Conference Chairmen:

**Professor Sir John Vane FRS and**
**Professor Tim Warner**

Speakers include:

| | |
|---|---|
| **L Ballou** | Tennessee |
| **R DuBois** | Tennessee |
| **S Curtis** | New Jersey |
| **S Fiorucci** | Perugia |
| **D Fitzgerald** | Dublin |
| **RM Garavito** | Michigan |
| **S Hernández-Díaz** | Massachusetts |
| **P Isakson** | New Jersey |
| **GM Pasinetti** | New York |
| **A Ristimäki** | Helsinki |
| **D Simmons** | Utah |
| **G Triadafilopoulos** | California |
| **J Vane** | London |
| **J Wallace** | Calgary |
| **T Warner** | London |
| **H Zeidler** | Hannover |

# PROGRESS IN THE FIELD OF SELECTIVE COX-2 INHIBITORS

**30th September - 2nd October 2001**

**Nice, France**

## INTRODUCTION

The identification of the second cyclooxygenase (COX) gene in 1991 explained many puzzling questions relating to the actions of the non-steroid anti-inflammatory drugs (NSAIDs). This gene is activated in inflamed tissues by bacterial lipopolysaccharide, mitogens or cytokines and encodes for an enzyme (COX-2) with 60% homology to the previously characterised, constitutive COX-1. Prostaglandins (PGs) produced continuously by COX-1 support physiological functions such as platelet aggregation and cytoprotection of the stomach mucosa, whereas PGs, mainly $PGE_2$, formed by COX-2 mediate the pain, vasodilatation and oedema typical of inflammation. Thus, NSAIDs which are highly selective for COX-2 will suppress the symptoms of inflammation without removing cytoprotective PGs from the stomach lining or preventing platelet aggregation. Since COX-2 is also induced in many tumour cells, such as those of colon cancer, the selective COX-2 inhibitors may provide an effective treatment for various types of cancer. Epidemiological evidence suggests that inhibition of COX may also slow down the progress of Alzheimer's disease and raised levels of COX-2 have recently been shown in the frontal cortex of brains of Alzheimer patients at post mortem. Selective COX-2 inhibitors will also be useful to delay premature labour, since they prevent uterine contractions without inhibiting COX-1 in the foetus.

## SUNDAY 30th SEPTEMBER

*16.00 to 18.30* *Registration*

*19.00 to 20.00* *Welcome Reception & Finger Buffet*

## MONDAY 1st OCTOBER

*08.30* *Registration*

*Chairmen:* **John Vane & Dan Simmons**

*09.30* **An historical overview of COX inhibitors**

An overview of the development of anti-inflammatory drugs will be presented, from willow bark, through salicylates, aspirin, the NSAIDs and on to the selective COX-2 inhibitors. Several are on the market and more are on the way.

*Speaker:* **John Vane**
*William Harvey Research Institute, London, UK*

*10.15* **3 dimensional structure of cyclooxygenases**

The structures of COX-1 and COX-2 have led to important insights into how COX-2 inhibitors work, but they have raised questions about how these enzymes interact with natural ligands. These topics, and the impact on drug design, will be discussed

*Speaker:* **Michael Garavito**
*Michigan State University, East Lansing, USA*

*11.00* *Coffee and Posters*

*11.30* **Unravelling the functional roles of COX-1 and COX-2 in transgenic mice**

The advent of the COX knockout mouse has necessitated an ongoing re-evaluation of the precise biological roles of COX-2 (and COX-1) *in vivo*. Recent information obtained from the study of COX transgenic mice will be discussed in this context.

*Speaker:* **Leslie Ballou**
*University of Tennessee Health Science Center, Memphis, USA*

*12.15* **COX-2 inhibitors and the cardiovascular system**

Concern has been raised over the cardiovascular effects of COX-2 inhibitors, largely on the basis that they may enhance platelet activity. COX-2 is expressed in the normal cardiovascular system, in atherosclerotic plaque and in ischaemic myocardium. COX-2 has also been implicated in angiogenesis around tumours. Conceivably therefore COX-2 inhibitors may influence cardiovascular function at several levels.

*Speaker:* **Desmond Fitzgerald**
*Royal College of Surgeons in Ireland*

*13.00* *Lunch and Posters*

*Chairmen:* **Les Ballou & Tim Warner**

*14.15* **Differential tests for COX-1 and COX-2**

Intelligent assays of NSAID selectivity for COX-1 vs. COX-2 in human systems are central to our understanding of the targets and effects of traditional NSAIDs and newer COX-2-selective compounds. The relationships between these assays and clinical experiences will be discussed.

*Speaker:* **Timothy Warner**
*William Harvey Research Institute, London, UK*

*15.00* **Apoptosis induced with NSAIDs**

Induction of apoptosis in neoplastic cells is evoked following *in vitro* or *in vivo* treatment with NSAIDs, and this induction of programmed cell death has been postulated to underlie the anti-neoplastic activity of aspirin-like drugs. Potential mechanisms by which NSAIDs induce apoptosis in cancer cells will be discussed.

*Speaker:* **Daniel Simmons**
*Brigham Young University, Provo, USA*

*15.45* *Coffee and Posters*

*16.15* **Gastrointestinal effects of NSAIDs**

The mechanisms underlying NSAID induced gastrointestinal injury will be reviewed. The contributions of COX-1 and COX-2 to mucosal defence will be discussed, along with the potential for COX-2 inhibitors to interface with ulcer healing and to exacerbated GI inflammation and injury.

*Speaker:* **John Wallace**
*Mucosal Inflammation Research Group, University of Calgary, Canada*

## TUESDAY 2nd OCTOBER

*Chairmen:* **Michael Garavito & Giulio Maria Pasinetti**

*09.00* **Epidemiology of upper gastrointestinal side effects of NSAIDs**

Epidemiologic studies have described the incidence of serious upper gastrointestinal complications (UGIC) in the general population, the relative risk of UGIC associated with NSAIDs and other risk factors, the effect of patterns of NSAID use, and the modifiers of the association between NSAIDs and UGIC.

*Speaker:* **Sonia Hernández-Díaz**
*Harvard School of Public Health, Boston, USA*

*09.45* **Cyclooxygenase-2 and colorectal cancer**

Numerous reports suggest that use of NSAIDs decreases mortality from colorectal cancer. To better understand all of the mechanisms underlying this effect, the global pattern of gene expression in colon carcinoma cells following treatments with NS-398, a selective COX-2 inhibitor, was evaluated. Our results provide evidence that some of the effects of NS-398 on carcinoma cells may be due to modulation of genes which regulate programmed cell death, cell proliferation and cell-cell communication. The biological function of these novel genes are being studied.

*Speaker:* **Raymond DuBois**
*Vanderbilt University Medical Center, Nashville, USA*

*10.30* *Coffee and Posters*

*11.00* **COX-2 in human carcinomas and preneoplastic lesions**

Use of NSAIDs is associated with reduced risk of several human adenocarcinomas. The best-known target of NSAIDs is the COX enzyme, and expression of the COX-2 isoform is elevated in a variety of human malignancies and preneoplastic lesions. Whether COX-2 targeted therapy is effective against human malignancies is under investigation.

*Speaker:* **Ari Ristimäki**
*Helsinki University Central Hospital, Finland*

*11.45* **Inflammation, cyclooxygenase and Alzheimer's disease**

COX-2 expression in the brain of Alzheimer's disease may be an indicator of progression of early clinical dementia. Moreover, recent evidence in our lab indicates that COX-2 may influence dementia via the altered activation of signal transduction pathways involved in tumour genesis. The elucidation of these mechanisms will provide an impetus to the development of anti-inflammatory therapy for Alzheimer's disease.

*Speaker:* **Giulio Maria Pasinetti**
*Mount Sinai Medical School, New York, USA*

*12.30* *Lunch and Posters*

*Chairmen:* **Raymond DuBois & John Vane**

*13.45* **Prospects for new selective COX-2 inhibitors**

Drugs that target COX-2 have demonstrated robust anti-inflammatory and analgesic activity with reduced gastrointestinal side effects; recent research has defined mechanism based side effects and potential new therapeutic uses for COX-2 selective inhibitors. Newer agents with distinct pharmacological properties will be discussed.

*Speaker:* **Peter Isakson**
*Pharmacia Corporation, Peapack, USA*

*14.30* **Etoricoxib**

Etoricoxib is a selective COX-2 inhibitor in development by Merck and Co. Inc. This lecture will provide a summary review of currently available data on etoricoxib, focusing on clinical safety and efficacy data.

*Speaker:* **Sean Curtis**
*Merck Research Laboratories, Rahway, USA*

*15.15* **NO-releasing NSAIDs modulate COX-2 gene expression**

Nitric oxide (NO) synthase (NOS) and COX isoenzymes expression/activity is tightly regulated showing a high degree of interrelation. NO releasing NSAIDs exert COX-dependent and -independent anti-inflammatory activities. There is evidence that NO-NSAIDs modulate COX-2 activity by interfering with the transduction pathway that regulates COX-2 gene expression in inflamed tissues.

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

*16.00* *Coffee and Posters*

*16.30* **Clinical efficacy data of COX-2 inhibitors - do we know what we need?**

Numerous placebo and active comparator controlled randomised studies have shown that COX-2 inhibitors such as meloxicam, celecoxib and rofecoxib are efficacious analgesic and anti-inflammatory drugs equivalent to traditional NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and pain. Additional information on effectiveness e.g. dose response in individual patients, analgesic versus anti-inflammatory potency, and dosing in special conditions (gouty arthritis) is needed to guide rational therapy.

*Speaker:* **Henning Zeidler**
*Medical School Hannover, Germany*

*17.15* **Gastrointestinal safety and tolerability data - worldwide**

Large scale, randomised, prospective trials with celecoxib, rofecoxib and pooled analysis with meloxicam have shown excellent safety and tolerability profiles for these agents and significant reduction in clinically significant gastrointestinal events, such as bleeding, perforation and gastric outlet obstruction as compared to conventional NSAIDs.

*Speaker:* **George Triadafilopoulos**
*Palo Alto VA Healthcare System, USA*

*18.00* **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

Boehringer Ingelheim

and

NicOx

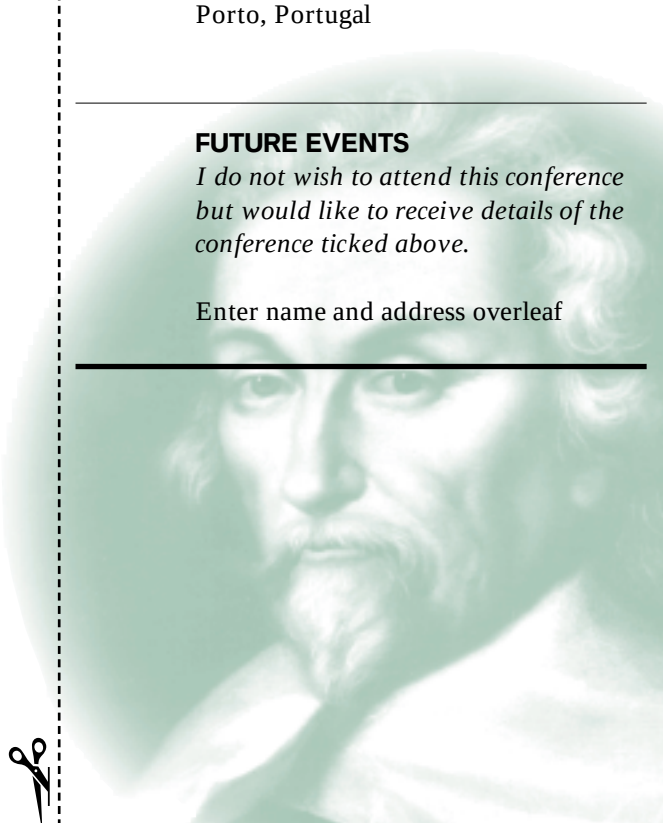
for educational grants to support this conference

FUTURE EVENTS

❑ **Phosphodiesterase in Health and Diseases**
5th-7th December 2001
Le Meridien Park Atlantic
Porto, Portugal

**FUTURE EVENTS**
*I do not wish to attend this conference but would like to receive details of the conference ticked above.*

Enter name and address overleaf



# ADMINISTRATIVE DETAILS

DATE:
*Sunday, 30th September -*
*Tuesday, 2nd October 2001*

VENUE:
*Boscolo Hotel Plaza*
*12 Ave de Verdun, BP 206*
*06004 Nice Cedex, France*

FEE:
*French Francs 9,000 plus TVA at 19.6% (FF 1,764) which is payable in advance. The fee includes all scientific sessions, an abstract book, refreshments, lunches and a ticket for the Reception in the hotel on Sunday, 30th September. A special fee of FF 4,000 plus TVA at 19.6% (FF 784), payable in advance, is available for faculty members, physicians and researchers currently working in University Departments and Hospitals. Please indicate on the registration form. Payment can be made by French Franc cheque drawn on a French bank or by French Franc 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 French Francs to HSBC, International Branch, PO Box 181, 27-32 Poultry, London EC2P 2BX, UK. Account No: 38651750. 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.*

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 6th September 2001.*

*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, St Bartholomew's & the Royal London School of Medicine & Dentistry, Charterhouse Square, London EC1M 6BQ, UK.*

CANCELLATIONS:
*Cancellations must be received in writing before 6th September and will be subject to an administration charge of FF800 plus TVA (19.6%). It is regretted that no refunds can be made for cancellations received after 6th September 2001. However, if you cannot attend, a substitute may attend in your place but please let us know.*

ACCOMMODATION
*A number of rooms have been reserved at a special reduced rate at the Boscolo Hotel Plaza. 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 William Harvey Research Conferences. Please do not contact the hotel directly.*

ENQUIRIES
*All enquiries, telephone bookings and alterations to delegate information to:*
*Dr Jenny Maclagan,William Harvey Research Conferences, St Bartholomew's & the Royal London School of Medicine & Dentistry, Charterhouse Square, London EC1M 6BQ, UK*
*Tel: +44 (0)20 7882 6181 Fax: +44 (0)20 7882 6084*
*E-Mail: whconferences@mds.qmw.ac.uk*
*WebSite: www.whconferences.demon.co.uk*

# REGISTRATION FORM

Please complete and return to: Dr J. Maclagan, William Harvey Research Conferences, St Bartholomew's & the Royal London School of Medicine & Dentistry, Charterhouse Square, London EC1M 6BQ, UK.

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**30TH SEPTEMBER - 2ND OCTOBER 2001**

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| Industry Fee(s) @ FF 10,764 |
| Faculty Member(s) @ FF 4,784 |
| Above prices include tax |

❑ *French Franc cheque/draft enclosed (made payable to William Harvey Research Conferences)*

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