Revised Programme

The William Harvey
Medical Research Foundation
a Not-For-Profit Organisation

presents an international symposium on

New targets in inflammation: inhibitors of COX-2 or adhesion molecules

Monday 15th -Tuesday 16th April 1996
to be held at
Sheraton New Orleans Hotel, New Orleans, USA

Conference Chairmen
Nicolas Bazan and Sir John Vane

Faculty includes

- NG Bazan [New Orleans]
- W Bolten [Wiesbaden]
- M Browner [Palo Alto]
- LJ Crofford [Ann Arbor]
- P Cuatrecasas [Ann Arbor]
- D DeWitt [East Lansing]
- R DuBois [Nashville]
- H Fenner [Zurich]
- S Ferreira [Brazil]
- G FitzGerald [Philadelphia]
- AW Ford-Hutchinson [Dorval]
- WM Gallatin [Bothell]
- H Jick [Lexington]
- P Lipsky [Dallas]
- P Loll [Philadelphia]
- SG Morham [Chapel Hill]
- J Oates [Nashville]
- M Pairet [Biberach]
- D Simmons [London]
- JR Vane [London]
- PA Ward [Ann Arbor]

Hosted by

Louisiana State University
Neuroscience Center of Excellence, New Orleans, USA

NEW TARGETS IN INFLAMMATION:

Inhibitors of COX-2 or adhesion molecules

Monday 15th - Tuesday 16th April 1996 at the Sheraton New Orleans Hotel, New Orleans, USA

Non-steroid anti-inflammatory drugs (NSAIDs) act through the inhibition of cyclooxygenase (COX) which synthesizes prostaglandins (PG). This action not only reduces the symptoms of inflammation, but also causes the side effects of NSAIDs, in particular gastric and kidney damage. Of the COX isoenzymes, COX-1 is found constitutively in most cells and fulfils a "housekeeping" function. However, COX-2 is only expressed in response to cytokines, mitogens or hormones. It produces PGs which are associated with the swelling and pain of inflammation. Selective inhibition of COX-2 should, therefore, have an anti-inflammatory effect without harming the stomach or kidneys. Inhibition of COX-2 may also protect in colon cancer by promoting apoptosis. Cytokines induce expression of adhesion molecules and of their receptors on migratory cells. Inhibitors of adhesion molecule expression and receptor antagonists will provide potential new anti-inflammatory drugs.

MONDAY 15TH APRIL

Chairman: **Nicolas Bazan**

09.30 **Overview**

Aspirin-like drugs inhibit COX which makes PGs. This accounts for their anti-inflammatory and side effects on the stomach and kidneys. Selective inhibition of inflammatory PGs produced by inducible COX-2 will reduce inflammation whereas removal of PGs produced by COX-1 results in gastric and renal damage.

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

10.15 **Structure of cyclo-oxygenase and binding sites of NSAIDs**

X-ray crystal structures of complexes of cyclooxygenase with various NSAIDs will be presented. These structures will provide the starting point for a discussion of the molecular mechanisms of NSAID action and of the possible foundations of isoform selectivity.

Speaker: **Patrick Loll**
University of Pennsylvania Medical School, USA

11.00 *Coffee*

11.30 **Dual prostaglandin biosynthetic pathways: biochemical and physiological implications for eicosanoid signalling**

The biochemical rationale for two cyclooxygenases is that they form physically separate biosynthetic pathways, which allows the same prostaglandins to be used for different signalling purposes. The COX-1 pathway signals extracellularly, while the COX-2 pathway can also signal in the nucleus.

Speaker: **David DeWitt**
Michigan State University, USA

12.15 **Differential inhibition of COX-1/COX-2 by NSAIDs**

Pharmacological data supporting the hypothesis that inhibition of inducible COX-2 provides the anti-inflammatory activity of NSAIDs, whereas inhibition of constitutive COX-1 is responsible for their gastric side effects will be presented. A possible role of COX-1 in inflammation will also be discussed.

Speaker: **Michel Pairet**
Dr Karl Thomae GmbH, Biberach, Germany

13.00 *Lunch*

Chairman: **Pedro Cuatrecasas**

14.15 **Blockade of inflammatory hyperalgesia and COX-2**

Inflammatory pain is initiated by a cascade release of interleukins in which IL-1 is responsible for the expression of COX-2 and subsequent liberation of hyperalgesic eicosanoids. Inhibitors of the expression or activity of COX-2 prevent the development of inflammatory hyperalgesia.

Speaker: **Sergio Ferreira**
Faculdade de Medicina de Ribeirao Preto, Brazil

15.00 **Inhibition of COX-2 in the brain; neuroprotection in a brain damage model**

Brain injury triggers rapid activation of PLA_2 and accumulation of PAF which plays a role in subsequent COX-2 transcriptional activation. Evidence will be presented that an inracellular inhibitor of PAF genomic effects blocks brain-injury-induced COX-2 expression and provides neuroprotection in a vasogenic model of cerebral oedema.

Speaker: **Nicolas Bazan**
LSU Neuroscience Centre, Louisiana, USA

15.45 *Refreshment Break*

Chairman: **Daniel Simmons**

16.15 **New highly selective COX-2 inhibitors**

Preclinical data indicates that highly selective inhibitors of COX-2 can be obtained from various structural classes and that such compounds in preclinical models have similar anti-inflammatory, analgesic and anti-pyretic activities to conventional non-steroid anti-inflammatory drugs, but have a much improved side effect profile with respect to gastrointestinal and platelet function. The properties and mechanisms of actions of such compounds will be described.

Speaker: **Tony Ford-Hutchinson**
Merck Frosst, Quebec, Canada

17.00 **Disruption of mouse-genes encoding COX-1 and COX-2**

We have recently developed lines of mice in which *Ptgs-1* and *Ptgs-2* have been disrupted. These mice are thus deficient in the synthesis of COX-1 or COX-2. Our basic characterizations of these mice have important implications for the future directions of NSAID research.

Speaker: **Scott Morham**
University of North Carolina at Chapel Hill, USA

17.45 **X-ray crystal structure of human COX-2**

The three dimensional structure of human COX-2 was determined by X-ray crystallography. The overall structure of the enzyme and the NSAID binding site, in particular, are well conserved. Alternative binding modes at the NSAID site are revealed by the structure of COX-2 with selective inhibitors bound.

Speaker: **Michelle Browner**
Roche Bioscience, California, USA

19.30 *Reception*

TUESDAY 16TH APRIL

Chairman: **John Oates**

09.00 **Risk of GI side effects caused by COX-inhibition (NSAIDs)**

The availability of large, well documented computerized data resources allows for the quantification of risk of upper GI bleeding among different NSAIDs as well as to evaluate the effect of dose on the risk. The results of such a study will be described and discussed.

Speaker: **Hershel Jick**
Boston University Medical Center, Massachusetts, USA

09.45 **Expression and regulation of COX-2 in synovial tissues of arthritic patients**

COX-2 expression in rheumatoid synovial explants and cultured synoviocytes is enhanced by IL-1β, and suppressed by glucocorticoids. Transcriptional regulation of COX-2 by IL-1β is mediated, in part, by nuclear factor κ-B (NF-κB). Glucocorticoid inhibition of NF-κB activity may be one mechanism of COX-2 suppression.

Speaker: **Leslie Crofford**
University of Michigan Medical Center, USA

10.30 *Coffee*

11.00 **Do we need a new classification of NSAIDs based on pharmacokinetics and COX-2 selectivity?**

The pharmacodynamic profile of NSAIDs regarding efficacy and side effects is affected by their COX-2 selectivity and pharmacokinetic properties. Based on these a proposal for a new classification is put forward predicting efficacy and epidemiological data of NSAID safety.

Speaker: **Helmut Fenner**
ETH Zürich, Switzerland

11.45 **Clinical implications of COX-2 inhibition**

COX-2 expression in inflamed synovial tissues and maintenance of renal and gastrointestinal function dependent on COX-1 are the rationale for development of new COX-2 inhibitors. Clinical data with meloxicam promise that selective COX-2 inhibitors are likely to improve the future management of rheumatic patients.

Speaker: **Wolfgang Bolten**
Rheumaklinik Wiesbaden II,Germany

12.30 *Lunch*

Chairman: **John Vane**

13.45 **Cyclooxygenase enzymes in vascular biology**

The cardiovascular benefits of nonselective COX inhibitors (aspirin) have been ascribed to platelet COX-1 inhibition whereas COX-2 inhibitors have more complex effects. The results of targeted COX gene disruption highlight the need for human models of COX dependent inflammation and renal function to define the pharmacology of selective enzyme inhibitors in man.

Speaker: **Garret A FitzGerald**
University of Pennsylvania, USA

14.30 **Cell adhesion and apoptosis after over-expression of COX-2**

COX-2 expression is increased in 85-90% of human colorectal carcinomas. We observed phenotypic changes in intestinal epithelial cells programmed to over-express COX-2 which include increased adhesion to extracellular matrix proteins and inhibition of apoptosis which were reversed by treatment with a COX inhibitor.

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

15.15 **Cytokines and adhesion molecules in the inflammatory response**

Cytokines play a key role in lung inflammation following deposition of IgG immune complexes. Their functions include: upregulation of vascular adhesion molecules (TNFα, IL-1), autocrine stimulation of macrophages (MIP-1α) and regulatory (anti-inflammatory) functions (IL-10).

Speaker: **Peter Ward**
University of Michigan Medical School, USA

16.00 *Refreshment break*

Chairman: **Nicolas Bazan**

16.30 **Adhesion molecules as targets of therapy in rheumatoid arthritis**

Adhesion molecules play a central role in the entry of cells into inflammatory sites. Preliminary results with treatment of rheumatoid arthritis patients with a monoclonal antibody to ICAM-1 indicate that this adhesion molecule plays a critical role in rheumatoid inflammation and, therefore, is a potential target for new therapeutic interventions in this disease.

Speaker: **Peter Lipsky**
University of Texas Southwestern Medical Center, USA

17.15 **Leukointegrins and their ICAM ligands: implications in drug discovery**

The leukocyte integrins and ligands, ICAM-1, ICAM-3, VCAM-1, etc., play important roles in a variety of inflammatory processes. Efforts to identify both extraceullular and intracellular targeted drug candidates for these families of adhesion molecules will be discussed.

Speaker: **W Michael Gallatin**
ICOS Corporation, Washington, USA

18.00 **Closing Remarks**
Nicolas Bazan and John Vane

WILLIAM HARVEY
RESEARCH CONFERENCES

This is the first Conference organized for The William Harvey Medical Research Foundation, a not-for-profit organisation.

Future events

☐ **2nd International Conference on Diabetic Complications as Drug Targets**
Thursday 30th-Friday 31st May 1996
Cavendish Conference Centre,
London, UK

☐ **Tachykinins and their Antagonists**
Thursday 10th-Friday 11th
October 1996
Cavendish Conference Centre,
London, UK

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

The organisers wish to thank
Boehringer Ingelheim
for an educational grant to support this conference

ADMINISTRATIVE DETAILS

DATE:
April 15th-16th, 1996

LOCATION:
Sheraton New Orleans Hotel
500 Canal Street
New Orleans
LA 70130, USA
Telephone: 504 592 5629
Facsimile: 504 592 5615

FEE:
$700 which is payable in advance. The fee includes all scientific sessions, program and abstract booklet, refreshments, lunches and a ticket for a Reception on Monday April 15th. Payment can be made by dollar check drawn on a US bank or by dollar bank draft. Please make check payable to 'William Harvey Research Conferences'. Alternatively credit card payment can be made in pounds sterling with an exchange rate of $1.45=£1. A special fee of $300 is available on request for faculty members, physicians and researchers currently working in University Departments and Hospitals and a fee of $100 for post doctoral fellows, residents and graduate students. No portion of this fee constitutes a tax deductible charitable contribution under the United States Internal Revenue Code.

SOCIAL PROGRAM
There will be a Reception on Monday April 15th in the Sheraton New Orleans Hotel.

POSTER COMMUNICATIONS
Abstracts for poster communications announcing the results of recent research are invited. Deadline March 1st, 1996. Apply for details to the organizers.

HOW TO REGISTER:
Telephone registration:
Advance registration may be made by contacting the conference organizer Dr Jenny Maclagan on +44-(171)-982 6181 followed by confirmation in writing within one week.

Advance registration by mail:
Please complete the registration form and send it to the conference organizer:
Dr Jenny Maclagan,
William Harvey Research Conferences,
St Bartholomew's Medical College,
Charterhouse Square, London EC1M 6BQ, United Kingdom

CANCELLATIONS:
Cancellations must be received in writing before 15th March 1996 and will be subject to an administration charge of $72.50 (£50). No refunds can be made for cancellations received after 15th March 1996. However, if you cannot attend, a substitute may attend in your place, but please inform the organizers.

ACCOMMODATION:
A number of rooms have been reserved at a special rate at the Sheraton New Orleans Hotel. A room reservation form will be sent to you immediately upon receipt of the registration form and payment. Please mention the name of the conference in all correspondence with the hotel in order to obtain the special rate.

INQUIRIES:
All inquiries, telephone or FAX registrations and alterations to delegate information to the conference organizer:- Dr Jenny Maclagan
William Harvey Research Conferences,
St Bartholomew's Medical College,
Charterhouse Square, London EC1M 6BQ, United Kingdom
Telephone: +44-(171)-982 6181 FAX: +44-(171)-982 6084

It may be necessary for reasons beyond the control of the organizers to alter the content and/or timing of the program or to change the speakers.

REGISTRATION FORM

Please complete and return to the conference organizer: Dr J Maclagan, William Harvey Research Conferences, St. Bartholomew's Medical College, Charterhouse Square, London EC1M 6BQ, UK

Title	Initials	Last Name	Position
Name of Company/Institution			
Address			County
City			Zip Code
Country			Telephone:
Reservation made by			Facsimile:

NEW TARGETS IN INFLAMMATION
April 15th-16th 1996

Industry Fee(s) @ $700	$
Faculty member(s) @ $300	$
Student fee(s) @ $100	$
TOTAL	$

☐ *Check enclosed (made payable to William Harvey Research Conferences)*
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