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 fulfills 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 Painet
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, and accumulation of PAF which plays a role in subsequent COX-2 transcriptional activation. Evidence will be presented that an intracellular 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

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
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 observations, a new classification is proposed for a new indication for NSAIDs.
Speaker: Helmut Fenner
ETH Zürich, Switzerland

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 diseases.
Speaker: Wolfgang Bolten
Rheumaklinik Wiesbaden II, Germany

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 overexpression 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 extracellular 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
REGISTRATION FORM

If you require further information about the program, please contact the organizers at the above address. Registration fees are non-refundable.

Please complete and return the conference registration to: Dr. Malcolm Stewart, Conference Secretariat, 3 North College, University College, London E8, UK.

April 15th-16th, 1996
NEW Targets in Event Inflammation

INFORMATION

Programme:

- April 15th: Registration opens at 9:00 AM. Welcome reception at 5:00 PM.
- April 16th: Closing dinner at 7:00 PM.
- All events are held at the Conference Venue.

FEES:

- Advance registration fees:
  - Students: £100
  - Members: £300
  - Industry: £700

- On-site registration fees:
  - Students: £120
  - Members: £320
  - Industry: £820

POSTER SESSIONS

Social Program

- Welcome reception on April 15th, 6:00 PM at the Conference Venue.
- Welcome dinner on April 16th, 7:00 PM at the Conference Venue.

ACCOMMODATION

- Accommodation: Contact Conference Secretariat, 3 North College, University College, London E8, UK.
- Room Reservations need to be made no later than March 1, 1996.

CANCELLATIONS

- Cancellations received after April 1, 1996 will incur a £50 fee.
- No cancellations will be accepted after April 10, 1996.

Telephone Registration:

Phone: +44 (0) 20 7936 5000
Fax: +44 (0) 20 7936 5001

Advance registration must be received by March 15, 1996.

ADDITIONAL DETAILS

- Registration fees include meals at the conference venue.
- Conference proceedings will be published.

Date: April 15th-16th, 1996
Location: London E8, UK

Sponsor:

- The conference is sponsored by the British Society for Immunology.

Contact:

- Malcolm Stewart, Conference Secretariat, 3 North College, University College, London E8, UK.
- Tel: +44 (0) 20 7936 5000
- Fax: +44 (0) 20 7936 5001
- Email: secrecyariat@bso.org.uk