

# Eighth John Vane Memorial Symposium on Prostacyclin Science and Pulmonary Vascular Disease



**22-23 March 2013**  
**Royal Society, London, UK**

**Faculty Chair**

**Professor Chris Thiemermann**, William Harvey Research Institute, Queen Mary, University of London, London, UK

**Faculty**

**Professor Andrew Peacock**, Golden Jubilee National Hospital, Glasgow, Scotland

**Professor Dame Julia Polak**, Imperial College London, London, UK

**Professor Stephan Rosenkranz**, University of Cologne, Cologne, Germany

**Professor Lewis Rubin**, University of California San Diego, San Diego, USA

**Professor Jim White**, University of Rochester, New York, USA

**Professor Brendan Whittle**, William Harvey Research Institute, Queen Mary, University of London, London, UK

**Allocated 8 CPD credits by the Royal College of Physicians**

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# Foreword

## by Professor Chris Thiernermann



On behalf of William Harvey Research Limited it is my great pleasure to welcome you to the Eighth John Vane Memorial Symposium which has been made possible by an unrestricted educational grant from United Therapeutics.

This symposia series, now in its eighth year, continues to make an important contribution to increasing our understanding of the pathophysiology and treatment of pulmonary arterial hypertension (PAH) by discussing the latest advances in both basic and clinical research.

As a result of the phenomenal feedback received on last year's stem cells symposium, we are delighted to confirm that this year's programme will once again showcase the role of regenerative medicine and stem cells in PAH via a symposium chaired by Professor Dame Julia Polak. The symposium explores novel approaches to lung regeneration, a discussion on the hope and hype of lung stem cell research and the role of pluripotent stem cells in PAH. Other highly topical areas to be presented at the meeting include the latest thinking relating to both pharmacology and clinical efficacy of prostacyclins, prognostic factors in PAH and end-points of clinical trials in PAH to name but a few.

As ever, we welcome highly interactive discussion and look forward to providing you with the valuable opportunity to hear from leading international scientific and clinical experts working in this field.

I very much hope that you will find this year's symposium both informative as well as enjoyable and I look forward to meeting you in the coming days.

**Professor Chris Thiernermann, MD PhD FRCP FMedSci**  
**Chief Executive, William Harvey Research Limited**



# Sir John Vane, FRS, Nobel Laureate

## by Rod Flower, FRS

Sir John Vane was one of the pre-eminent pharmacologists of the twentieth century and, during a career spanning over 50 years, made enormous contributions to the pharmacotherapy of hypertension and inflammation.

John was born in Worcestershire and educated at King Edward VI School, Birmingham. His first degree (1946) was a B.Sc. in Chemistry at the University of Birmingham but, as he later explained to his tutor, he did not want to pursue chemistry as a career because the subject did not excite him. By chance, he was offered training as a pharmacologist under the tutelage of Professor J. Harold Burn in Oxford where he really found his *métier*. After obtaining his Ph.D. in 1953 John spent two years in the Department of Pharmacology at Yale University with the (then) chairman Dr. Arnold Welch.

In 1955 John returned to the UK to work with Professor W. D. M. Paton at the Institute of Basic Medical Sciences of the University of London in the Royal College of Surgeons of England. He progressed from Senior Lecturer in 1955, to Reader in 1961, and then Professor of Experimental Pharmacology in 1966. It was during his time at the 'College' that he did some of his finest work. John left the department in 1973 when he was invited to take up the post of R & D Director at the Wellcome Foundation.

In the early 1970s John and his group published research that led directly to the discovery of captopril – the first member of the angiotensin-converting enzyme (ACE) inhibitor family of medicines. ACE inhibitors are now widely used to treat high blood pressure, heart failure and kidney disease. Another strand of John's work was his research on prostaglandins for which he eventually shared the Nobel Prize for Physiology or Medicine (1982). In part this was in recognition of his discovery of how aspirin worked. He showed that this ancient drug blocked the synthesis of prostaglandins through inhibition of the enzyme now widely known as the cyclooxygenase. His work led to a clear understanding of how aspirin and similar drugs produce pain-relief and anti-inflammatory effects. It also provided an explanation for how aspirin helps prevent blood clots, heart attacks and strokes and is one reason why aspirin remains one of the most commonly used medicines for treating people with heart disease. At Wellcome, John and his colleagues also discovered prostacyclin, a key protective factor that helps keep blood vessels healthy. Prostacyclin is a vasodilator prostaglandin that helps prevent blood clots by reducing the stickiness of platelets.

John left the Wellcome Foundation in 1986, aged 59. An invitation from St Bartholomew's Hospital Medical School, brokered by an old friend, Derek Willoughby, and an offer of start-up funding from Glaxo Group Research, gave John the opportunity to begin another venture. He was joined by Erik Änggård, Nigel Benjamin, Iain MacIntyre, David Tomlinson, Brendan Whittle, Willoughby and old colleagues Gustav Born

and Rod Flower. From this confluence of research groups arose the William Harvey Research Institute.

Major funding from Ono Pharmaceuticals in Japan enabled the Institute to expand rapidly and it soon became a veritable pharmacological powerhouse, with a staff of over 120 people, specialising in research into inflammation and cardiovascular disease and focusing especially on inhibitors of COX-2, and the interplay between nitric oxide and endothelin in the regulation of vascular function. John continued to influence the scientific direction of his group and even found time to start up (with Änggård) a new company, Vanguard Medica Ltd. (now Vernalis). He retired as full-time director of the Institute in 1995 but remained Honorary Chairman of the charitable William Harvey Research Foundation until his death in 2004.

During his lifetime John attracted many awards and honours in addition to the Nobel Prize; in 1974 he was made a Fellow of the Royal Society, in 1977 he won the Albert Lasker Basic Medical Research Award and in 1984 he was knighted for services to pharmaceutical science. Over fifty other honorary degrees and fellowships followed over the years.

John had a unique style of working. In 1978 he wrote 'I have always believed in using simple methods, which give results so quickly that the design of the experiment can be modified as it progresses'. It is a style of working that all of us at the William Harvey seek to emulate.



*Photograph of Sir John Robert Vane. Vane was Director of Group Research and Development at the Wellcome Foundation 1973-1985. Image by kind permission of Wellcome Library, London*

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# 22 March 2013

**8.45-9.40am** Registration, tea and coffee

**9.40am** Welcome

**Chris Thiernemann, William Harvey Research Institute, London, UK**

## The Prostacyclins: Basic Science and Clinical Aspects

**Chairs: Chris Thiernemann, William Harvey Research Institute, Queen Mary, University of London, London, UK**  
**Brendan Whittle, William Harvey Research Institute, Queen Mary, University of London, London, UK**

**9.50am** Life and Work of Sir John Vane

**Rod Flower FRS, William Harvey Research Institute, Queen Mary, University of London, London, UK**

**10.20am** Diversity in the Prostacyclins

**Lucie Clapp, University College London, London, UK**

**10.50am** Refreshments

**11.10am** Prostacyclin and Phosphodiesterase Inhibitors: A Novel Rationale for Co-administration in PAH

**Randy Sprague, Saint Louis University, Saint Louis, USA**

**11.40pm** Development of the Oral Prostacyclin Analogue Treprostinil for PAH

**Jim White, University of Rochester, New York, USA**

**12.10pm** How to Make a Rat Inhale Prostacyclin

**Ralph Schermuly, University of Giessen, Giessen, Germany**

**12.40pm** Lunch

## Clinical Aspects of PAH

**Chairs: Lewis Rubin, University of California San Diego, San Diego, USA**  
**Andrew Peacock, Golden Jubilee National Hospital, Glasgow, Scotland**

**2.10pm** Evolution of End-Points of Clinical Trials in PAH

**Lewis Rubin, University of California San Diego, San Diego, USA**

**2.40pm** Long-term Survival with Prostacyclins

**Irene Lang, University of Vienna, Vienna, Austria**

**3.10pm** Refreshments

**3.40pm** Exercise and Outcome in Severe Chronic Pulmonary Hypertension

**Ekkehard Gruenig, Thoraxklinik, University Hospital Heidelberg, Heidelberg, Germany**

**4.10pm** Prognostic Factors in Severe PAH

**Dario Vizza, Università La Sapienza, Rome, Italy**

**4.40pm** Effects of Capsaicin 8% Patches on SC Treprostinil Infusion Site Pain: Experience from a Randomised, Double-Blinded Phase IIa Clinical Trial

**Vincenzo Libri, Imperial College London, London, UK**

**5.00pm** Adjournment

**7.30pm** Conference Dinner

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# 23 March 2013

## Pathophysiology and Treatment of PAH

**Chairs: Jim White, University of Rochester, New York, USA**  
**Stephan Rosenkranz, University of Cologne, Cologne, Germany**

- 10.00am** Pulmonary Hypertension and Air Travel  
**Thomas Smith, University of Oxford, Oxford, UK**
- 10.30am** Role of Micro-RNA miR-145 and miR-21 in Pulmonary Hypertension  
**Andrew Baker, University of Glasgow, Glasgow, Scotland**
- 11.00am** Refreshments
- 11.30am** Natural Killer Cells and PAH  
**Mark Ormiston, Cambridge University, Cambridge, UK**
- 12.00pm** Left Heart – Pulmonary Circulation - Right Heart: Hemodynamic Evaluation and its Consequences  
**Stephan Rosenkranz, University of Cologne, Cologne, Germany**
- 12.30pm** Lunch

## Regenerative Medicine, Stem Cells and PAH

**Chairs: Dame Julia Polak, Imperial College London, London, UK**  
**Edward Morrisey, Penn Institute for Regenerative Medicine, Philadelphia, USA**

- 2.00pm** Ways and Means to Lung Regeneration  
**Dame Julia Polak, Imperial College London, London, UK**
- 2.30pm** Development and Regeneration of the Cardiopulmonary System  
**Edward Morrisey, Penn Institute for Regenerative Medicine, Philadelphia, USA**
- 3.00pm** Next-Generation Regeneration: The Hope and Hype of Lung Stem Cell Research  
**Darrell Kotton, Boston University School of Medicine, Boston, USA**
- 3.30pm** Pluripotent Stem Cells and Differentiation in Cardiovascular Cells  
**Christine Mummery, Leiden University Medical Center, Leiden, The Netherlands**
- 4.00pm** Close of meeting



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*Left to right: Professor Chris Thiernemann, CEO, WHRL and Centre Lead, Translational Medicine and Therapeutics, WHRI and Professor Mark Caulfield, Director, WHRI at the 7th John Vane Memorial Symposium.*



*Speakers of the 7th John Vane Memorial Symposium at the Royal Society, London*



*Dr Jean-Luc Vachieri, Universite Libre de Bruxelles, Speaker at the 7th John Vane Memorial Symposium*

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[www.williamharvey.co.uk/whPress/whPress.htm](http://www.williamharvey.co.uk/whPress/whPress.htm)



# William Harvey Research Institute

The William Harvey Research Institute (WHRI), founded by Sir John Vane, has enjoyed a tremendous decade of expansion as the largest Pharmacological Institute in the UK from 180 to 350 Clinicians and Scientists. Our pulmonary hypertension research programme, led by Adrian Hobbs and Richard Trembath, has highlighted the role of dietary nitrate in pulmonary vasodilatation, prevention of pulmonary vascular remodelling, and reduction of the right ventricular hypertrophy. His group's findings, published in *Circulation*, indicate this depends on endothelial NO synthase and xanthine oxidoreductase conversion of nitrite to NO which may offer new avenues for therapy and Richard is co-leading a large-scale genomewide study of pulmonary hypertension families.

Our microvascular researcher Sussan Nourshargh has won a highly prestigious Wellcome Trust Senior Investigatorship and our new cardiovascular immunology group appointed to the William Harvey Heart Centre have won a Bill and Melinda Gates Programme Award of \$1m awarded to Federica Marelli-Berg. Our critical care team (Rupert Pearse) led the European Surgical Outcomes Study including 46,539 surgical patients demonstrating important variations in mortality between countries when compared with the UK. An element of our inflammation research programme led by Costantino Pitzalis

has won an MRC Stratified Medicine Award and a National Institutes for Health Research Award of £5.9m to explore the potential of ultrasound directed synovial biopsy pathotypes in the stratification of biologic therapy for early rheumatoid arthritis.

In December 2012 we published a number of new genes influencing urate and gout (*Nature Genetics*) and functional characterisation of genes for coronary artery disease (*Circulation Research*). Collectively, within the last five years William Harvey Research Institute faculty have now published over 40 papers in top journals and spent over £60m on research.

On behalf of all of us at the William Harvey I hope you have a great time at this year's John Vane Memorial Symposium on Prostacyclin Science and Pulmonary Vascular Disease.

Professor Mark Caulfield, MD FRCP FMedSci  
Director of the William Harvey Research Institute.  
Barts and The London School of Medicine and Dentistry  
Queen Mary, University of London

[www.whri.qmul.ac.uk](http://www.whri.qmul.ac.uk)



Stain glass display at the William Harvey Heart Centre, depicting the work of William Harvey.



[www.williamharvey.co.uk](http://www.williamharvey.co.uk)



*William Harvey explains the effect of ligatures on blood flow*

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