

# Plenary Lectures

## The EPHAR 2008 Lecture

### Monday 14 July

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#### Plenary 1

#### **Understanding molecular mechanisms of cell injury and death: a way to improve drug safety and design**

*P. Nicotera MRC Toxicology Unit, University of Leicester, UK*

Identification of drug targets relevant to disease has become of less importance in designing new therapeutic strategies. High throughput screening and chemical modelling have become a priority in lead identification and development. While this strategy has obvious advantages, it has often resulted in drugs with high specificity but low efficacy. In neurodegenerative disorders the lack of good animal models and clinical biomarkers has made the process of drug selection and design even more complicated. It is now becoming clear that neurodegenerative disease may initiate from dysfunction in selected sub-cellular processes including mitochondrial alterations and disruption of the control of synaptic maintenance. The latter

interestingly involves mechanisms that neurons recruit to execute cell death. It has also become apparent that neurons can execute not only one, but several biochemical death programs, especially under pathological conditions. The predominance of one or another death executing mechanism may be dictated by factors as different as energy requirement, signalling molecules and the intensity of a given insult. In addition, differentiation patterns may direct tissue-specific death routines. Spatial selectivity of death signals and promiscuity of execution systems can result in the complex and relatively slow demise, which occurs in neurodegenerative disease. This may pose serious problems in the design of selected drugs. In this presentation I will focus on the cross-talk between different cell death programmes, synaptic dysfunction and potential effects of drugs on these processes.

# The Merck, Sharp & Dohme Lecture

## Tuesday 15 July

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### Plenary 2

#### **New therapeutic targets for asthma and COPD**

*EP Nijkamp Section Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands*

Asthma and chronic obstructive pulmonary disease (COPD) are characterized by chronic airway inflammation, mediated by increased expression of inflammatory mediators such as cytokines, chemokines, adhesion molecules and inflammatory enzymes. Several novel therapeutic approaches for treating inflammation in these diseases have been initiated, such as inhibition of the effects of individual mediators or inhibition of central mechanisms, found in the higher cascade of events. Examples of the latter involve targeting specific transcription factors, such as inhibition of NF- $\kappa$ B or more specific for asthma inhibition of GATA3 function. Recently, in an animal model for lung emphysema, we have identified a collagen

breakdown product (acetyl-proline-glycine-proline; PGP) that can activate and attract neutrophils to the lung and causes lung emphysema via the CXCR1 and CXCR2 receptor (Nature Med 2006; 12: 317.). PGP levels are increased in COPD patients. A PGP antagonist was able to inhibit all disease symptoms. In another study we showed, that beside IgE mediated mast cell activation, antigen specific immunoglobulin free light chains (FLC), play a role in the pathogenesis of inflammatory diseases by activating the mast cell (Nature Med. 2002; 8: 694.). In a preclinical model for non-atopic asthma, FLC were found to be of essential importance for the development of clinical symptoms of disease such as airway hyperreactivity, mucosal exudation and local inflammation (PNAS 2005; 102: 1578–1583.). FLC concentrations are increased in serum of both allergic and non-allergic asthma patients. F991, an FLC antagonist inhibits the clinical symptoms of non-atopic asthma and might be a new agent for the treatment of asthma.

# EPHAR President's Lecture

## Wednesday 16 July

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### Plenary 3

#### Calcium signalling in health and disease

M Berridge Babraham Institute, UK

Calcium ( $\text{Ca}^{2+}$ ) is a highly versatile intracellular signal capable of regulating many different processes. To achieve this versatility, cells have access to a very extensive  $\text{Ca}^{2+}$  signalling toolkit from which each cell type expresses a unique set of components to create  $\text{Ca}^{2+}$  signalling systems with widely different spatial and temporal properties. Spatial properties are particularly relevant for fast responses where components of the ON reactions and their downstream effectors are closely associated. This spatial contiguity is less apparent for the slower responses such as

gene transcription, fertilization and cell proliferation where  $\text{Ca}^{2+}$  signals tend to operate more globally and where temporal properties of signalling become increasingly important with signalling represented as repetitive  $\text{Ca}^{2+}$  transients and waves. Such  $\text{Ca}^{2+}$  signalling systems are not fixed in stone, but are constantly being remodelled to adapt to changing circumstances.  $\text{Ca}^{2+}$  plays a critical role in an internal assessment mechanism that remodels its own signalling pathway. Abnormal remodelling of  $\text{Ca}^{2+}$  signalling systems is responsible for a number of important disease states such as congestive heart failure, a major cause of human morbidity and mortality.

# The AstraZeneca Lecture

## Thursday 17 July

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### Plenary 4

#### **The Health Impact Fund: boosting innovation without obstructing free access**

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Pharmaceutical patents as globalised through TRIPS cannot be defended by appeal to natural rights. Nor can they be justified in terms of mutual benefit or usefulness, because the global poor lose their freedom to buy medicines at competitive prices yet often cannot benefit from the enhanced arsenal of advanced medicines. One way of mitigating the injustice involves creation of a Health Impact Fund (HIF) that would afford a standing option to forgo monopoly pricing on any new medicine worldwide in exchange for a reward based on this medicine's global health impact. By

registering a drug with the HIF, a firm agrees to sell its product globally at cost. In exchange, it receives for a fixed time payments based on the product's assessed global health impact. The firm may patent a HIF-registered product anywhere it likes, but must not charge more for it than the designated price. Complementary to patents, the HIF would correct seven of its shortfalls. HIF-rewarded medicines avoid the high mark-ups of patented medicines which cause (i) exclusion of the poor, (ii) waste through litigation and deadweight losses, (iii) excessive marketing to doctors and patients, and (iv) criminal counterfeiting. In addition, the HIF would (v) end the neglect of diseases concentrated among the poor, (vi) avoid the bias toward symptom-relieving medications in preference to cures and vaccines and (vii) incentivise efforts to eradicate a target disease rather than let it proliferate among non-customers.