

## **New Horizons for Neglected Diseases**

**A microsposium to celebrate a College Alumnus Award to  
Professor Patrick Brennan.**

**Joly Lecture Theatre, Hamilton Building, Trinity College Dublin  
4th November 2010**

**1.10** Introduction **Prof. Luke O'Neill**

**1.15** Opening remarks by **Prof. Patrick Brennan**

“Global Leprosy today and the contribution from the Medical Research Council of Ireland at Trinity College Dublin in the 1960’s”.

### **Tuberculosis**

**1.20** TB–how can we change the world? **Prof. Joseph Keane (TCD)**

**1.35** Genomic analysis of the BCG vaccine strain. **Prof. Stephen Gordon (UCD)**

### **Helminths**

**1.50** Helminths and the immunome. **Prof. Padraic Fallon (TCD)**

**2.05** From the field to the laboratory: *Ascaris* in mice and men. **Prof. Celia Holland (TCD)**

### **Protozoan Parasites**

**2.20** Antimalarial lead and target discovery: still a high priority. **Dr. Angus Bell (TCD)**

**2.35** African trypanosomes: elusive enemies casting a shadow on a continent. **Dr. Derek Nolan (TCD)**

### **New partnerships and cooperation with developing countries**

**2.50** New partnerships for tackling diseases of poverty – an Irish perspective  
**Dr. Noel Murphy (NUIM)**

### **Alumnus address**

Professor Patrick Brennan

The cell wall of *Mycobacterium tuberculosis*: structure, biosynthesis, new targets, new drugs, mode of action of old drugs.

**3.50** Concluding remarks Prof. Luke O'Neill

**4.00** Reception (Pavillion Bar, College Park)

## Introduction

Each year Trinity College Dublin recognizes the achievements of graduates who have made a distinguished contribution to their field of study with the Alumnus Awards. This year Trinity honors Professor Patrick Brennan (Distinguished Professor, Colorado State University) who carried out his PhD research in the Department of Biochemistry (1962 – 1965) under the supervision of the late Professor Frank Winder. He is internationally recognized for his work in the area of health and disease in developing countries, but especially for his studies on the twin scourges of tuberculosis and leprosy. Recognition of his work also serves as a reminder of the strong tradition in this area established by Dr. Vincent Barry and his team at the Medical Research Council laboratory at TCD half a century ago. That work culminated in the discovery of Clofazimine which is still used today in the treatment of leprosy. In recognition of his award and to celebrate this tradition at Trinity and other Irish universities the School of Biochemistry and Immunology has invited Prof Brennan to address a small symposium that will also allow Irish investigators to give a brief perspective of their research and its implications for diseases of developing countries.

## CONTRIBUTORS



### **Prof. Patrick Brennan Distinguished Professor at Colorado State University .**

Patrick Brennan was born in County Roscommon in 1938 and completed his secondary education in Blackrock College . He graduated from UCC with the degrees of B.Sc. (1961) and M.Sc. (1962) before coming to TCD to undertake research, leading to the degree of Ph.D. (1965), on the mode of action of the anti-tuberculosis drug Isoniazid : His research work was supervised by Professor Frank Winder and the work was carried out in the Medical Research Council Laboratories (long since demolished and replaced by the O'Reilly Institute) which already had a high reputation for research in the areas of tuberculosis, leprosy and cancer. This was followed by a two year postdoctoral fellowship at the University of California (Berkeley) studying the structures and biosynthesis of the phosphatidylinositol mannosides of *Mycobacterium tuberculosis* (the infectious organism causing tuberculosis). He returned to TCD as a Research Lecturer in November 1967 and the following year was married to Dr. Carol Blair who was a postdoctoral fellow in Biochemistry and subsequently Lecturer in Microbiology (1970-'75). Patrick served as a College Lecturer at UCD (1971-'76) but the left Ireland for the USA to join his wife Carol who had been appointed an Assistant Professor at the University of Colorado. He held senior posts in the National Jewish Centre for Immunology and Respiratory Medicine and the University of Colorado School of Medicine in Denver before being appointed Associate Professor, Professor and ultimately Distinguished Professor ( a very rare honour ) at Colorado State University (Fort Collins). He founded a major research centre to study Mycobacteria and has published more than 300 peer reviewed papers on Tuberculosis and Leprosy. The outstanding quality of his research, together with his personal dedication to the elimination of leprosy and tuberculosis, is recognized throughout the world: He has served as Chairman of the World Health Organisation Program for Tropical Disease Research; research advisor to the Sasagawa Memorial Health Foundation who, through the Nippon Foundation, underwrites most of the Global Leprosy Elimination Campaign; and Chairman of the U.S.-Japan Cooperative Medical Sciences Program.



### **Antimalarial lead and target discovery: still a high priority.**

Dr. Angus Bell. School of Genetics and Microbiology (TCD)

The protozoan parasites responsible for malaria are responsible for 300 million clinical cases each year. Each day at least 3,000 children under the age of five succumb to this illness, the majority in sub-Saharan Africa. Recent improvements in the fight against malaria have been attributed to vigorous application of control measures, particularly insecticide-treated bednets and artemisinin-combination therapies (ACTs). Recent reports of emerging resistance to artemisinins in south-east Asia have cast a cloud over these measures. Moreover, there are few alternatives to ACTs, and barely a trickle from the new drug 'pipeline'. Current research at Trinity on the identification and development of new anti-malarial drugs is therefore especially appropriate and reminds us that basic research on malaria biology, parasite drug targets, and new therapeutic leads is as important as ever. Dr Bell's research is supported by funding from Science Foundation Ireland



### **Helminths and the immunome.**

Prof. Padraic Fallon. School of Medicine (TCD)

Schistosomes are trematode worms that live in the mammalian bloodstream and are the agents responsible for bilharzia in humans. The World Health Organization considers these illnesses to be the second most important parasitic disease, after malaria, with hundreds of millions infected worldwide. Professor Fallon's research focuses on the co-evolution of these helminths with their human host. Much of this is a genetic arms race between the worm and the host's immune system (the immunome). Professor Fallon will present examples of insights into immune functions from the study of helminth immunobiology. Prof Fallon's research is supported by funding from Science Foundation Ireland, the Wellcome Trust and the Health Research Board.



### **Genomic analysis of the BCG vaccine strain**

Prof. Stephen Gordon. School of Agriculture, Food Science & Veterinary Medicine (UCD)

Tuberculosis (TB) is a bacterial infection of man and animals and is widely acknowledged as the single, most serious infectious disease in developing countries. With up to a third of the world's population infected this disease is also resurgent in developed countries. Professor Gordon is seeking to exploit completion of the genome sequence of the human TB pathogen, *Mycobacterium tuberculosis*, and the bovine TB pathogen, *Mycobacterium bovis*, to accelerate vaccine design and the development of diagnostics. Recent highlights include the annotation and interpretation of the *M. bovis* and BCG Pasteur genome sequences, and comparative virulence and evolutionary analyses across the *M. tuberculosis* complex. Prof. Gordon's research is supported by funding from Science Foundation Ireland, the Wellcome Trust, EU FP7 and the BBSRC.



### **From the field to the laboratory: *Ascaris* in mice and men**

Prof. Celia Holland. School of Natural sciences (TCD)

The soil-transmitted helminths (STHs) are some of the most prevalent parasitic infections with *Ascaris lumbricoides*, the human roundworm infecting in the order of a quarter of the world's population. Despite this, the STHs and *Ascaris* in particular, remain neglected tropical diseases. Prof Holland's research has focused upon the key epidemiological patterns that *Ascaris* and other macroparasite infection manifest – aggregation and predisposition. Despite the ubiquity of these patterns, the generative mechanism(s) of these observed phenomena are currently unknown and difficult to elucidate in humans and pigs for ethical and logistical reasons. Prof Holland will highlight the challenges of conducting field-based research and describe the development of a mouse model to explore susceptibility and resistance to early *Ascaris* infection. Prof Holland's research is supported by funding from Science Foundation Ireland, the Health Research Board and the Irish Research Council for Science, Engineering and Technology.



### **TB—how can we change the world?**

Prof. Joseph Keane. School of Medicine (TCD)

TB is one of the oldest diseases known to man but remains a national and global public health issue. Currently there are no good vaccine and rather poor diagnostic tests. Current treatments are also in trouble with the development of drug-resistance. In Trinity College we are addressing basic questions of clinical and scientific importance to generate new vaccines, treatments and tests. Our new data gives a mechanistic link between smoking, vitamin D deficiency and TB reactivation. We also have new data on how macrophages deal with the infection and how the bacillus subverts this process. Finally, we are working with the RCSI to develop microparticle inhalational therapies that might address this killer infection in a more selective way than current treatments. Prof. Keane's research is supported by funding from the Health Research Board, Science Foundation Ireland, Royal City of Dublin Trust, Trinity Trus



### **New partnerships for tackling diseases of poverty – an Irish perspective**

Dr Noel Murphy. Department of Biology (NUIM)

Dr. Noel Murphy has a long-standing interest in tropical diseases of humans and their animals, specifically African trypanosomes. He worked on trypanosome infection of livestock at the international Livestock Research Institute (ILRI) at Nairobi, Kenya for over a period of 14 years focusing on the mechanisms of innate resistance to this disease in African wildlife species and analysis of the molecular mechanisms that the parasites use to communicate with each other to control their population size and differentiation status. Since his return to Ireland has been instrumental in establishing a postgraduate M.Sc. degree in Immunology and Global Health at NUI Maynooth and in leading a major programme entitled the Combat Diseases of Poverty Consortium funded

through the Irish Aid Programme for Strategic Co-operation with third level institutes. This new initiative brings together scientific, academic, NGO and private sector expertise to build educational and research capacities both nationally and in developing countries for combating diseases of poverty. Dr. Murphy's research is supported through funding from Irish Aid and the HEA.



**African trypanosomes: elusive enemies that still cast a shadow on a continent**

Dr Derek Nolan. School of Biochemistry and Immunology (TCD).

Trypanosomes are a significant medical, veterinary and economic burden throughout sub-Saharan Africa. They cause sleeping sickness in humans, which untreated is fatal, and wasting diseases in domestic animals, which are a major constraint to livestock productivity. Current treatments are difficult and largely depend on old, expensive, toxic and increasingly ineffective drugs. Vaccination is not currently an option so there is an urgent need to develop new anti-trypanosomal therapies. The aim of research at Trinity is to identify parasite specific targets for novel intervention strategies. Recent discoveries have revealed novel features of the biochemistry and cell biology of trypanosomes that offer great potential for the development of a new family of specific anti-parasite drugs. Dr Nolan's research is supported by funding from the Wellcome Trust, Science Foundation Ireland and the Health Research Board.