Paul Ehrlich Award Lecture Professor D.P.Lane

Ladies and Gentlemen,

it is a great privilege and honour to be here on the Birthday of Paul Ehrlich , the father of modern chemotherapy to receive the Paul Ehrlich and Ludwig Darmstaedter prize. What brings us all together here this year is a remarkable human protein called p53. This protein which we identified almost 20 years ago to the day in our preparations of the viral SV40 T antigen now has a central place in our growing understanding of human cancer and is a key area for study in devising new tests and treatments for cancer.

The progress that has been made in the last twenty years is awe inspiring built upon the work of thousands of dedicated scientists and has resulted in an enticing model for the function of p53 and an elegant understanding of its regulation. The p53 gene encodes a 393 amino acid protein that resides principally in the cell nucleus where it can act as a master switch to control the activity of a set of other genes. The p53 protein seems to be essential to protect our normal cells from turning into cancer cells. We find that at least half of the common human cancers such as lung , breast, colon , bladder, brain and pancreatic cancer have lost all normal p53 function either by virtue of mutations in the gene or due to the action of p53 neutralising proteins produced by viruses. Mice that have been bred to lack the p53 gene entirely will all die of cancer within 9 months of birth and in man individuals who inherit only one normal copy of the gene as opposed to the normal two copies show an extraordinarily high rate of cancer. The p53 gene is thus truly called a tumour suppressor protein.

How does a master switch gene act to prevent the frequent occurrence of cancer? The key lies in the way in which the p53 switch is activated and the consequence of turning on that switch. Normally p53 is a very unstable protein each new molecule we produce lasting on average only 20 minutes before it is broken down. This results in our cells containing only very small amounts of the protein at However the p53 switch is activated when in response to a variety of DNA damaging signals this rapid breakdown of p53 is blocked and the protein starts to accumulate to high levels. The signals that cause this accumulation include radiation and carcinogenic chemicals in our environment such as those found in tobacco smoke. Once the p53 protein switch is turned on in this way it acts to block cell division and to induce cell suicide thus protecting our bodies from the survival and division of cells that have sustained damage. This is a vital pathway not only to protect our bodies from cancer but also paradoxically if a successful outcome to many anti-cancer treatments is to be achieved. Thus when the p53 gene is itself damaged by mutation and unable to exert its function as "Guardian of the Genome" cells survive and divide that are damaged and can progress to malignant cancers. These dangerous cells are not easily killed by radiation or chemotherapeutic drugs as the p53 protein normally mediates these responses.

The restoration of p53 function to tumour cells or the exploitation of the loss of p53 to create tumour specific therapies is the great challenge that now faces us. I am sure I speak for all my colleagues when I say that our real prize would come from bringing this rational

knowledge based approach to cancer therapy into the clinic. Already several clinical trials are underway of p53 gene therapy and we and others are searching hard for drugs that might regulate or mimic p53 function. It is a great challenge , one that Paul Ehrlich himself would I am sure have found deeply engrossing and we can only hope that some of his skill and wisdom will come to our collective efforts. I cannot accept this award without acknowledging the tremendous support from my wife Birgit ,who is here today. I also would like to thank my two mentors who helped me through my early career Prof Avrion

Mitchison , himself a recipient of this award in 1975, and Dr Lionel Crawford who created a superb environment for discovery. Finally I would like to thank all my co-workers and colleagues for their loyalty and trust and the Imperial Cancer Research Fund for their previous support of my team in London and the Cancer Research Campaign for their current support of my research team in Dundee