

## Prolific Scientist Profiles

### Gairdner Awards 40th Anniversary: A Canadian Tradition

Susan Quesnel, M.Sc. (OT2)

This section will offer a glimpse at the people behind the science of medicine, with a focus on those at the University of Toronto. In this first issue, Prolific Scientist Profiles begins with this year's Gairdner Awards, an event hosted annually in Toronto.

This year marks the 40th Anniversary of the Gairdner Foundation International Awards. The Awards are given annually to leading scientists, whose work promises breakthroughs in medical treatment. The foundation was established in 1959 by James A. Gairdner, a Canadian businessman who wanted to reward and encourage medical scientists who have made contributions in the conquest of disease. Although the Gairdner Foundation is a Canadian institution, it recognizes leading scientists from around the world. It is often referred to as the Canadian version of the Nobel Prize in Medicine, although the Gairdner Foundation selects the recipients earlier. Since their founding, 51 of the 249 recipients have gone on to win a Nobel Prize, which means winning a Gairdner award is the most accurate single predictor of winning the better known Swedish prize.

However, the Gairdner is an award in its own right. To celebrate its 40th Anniversary, the foundation organized a week-long program from Oct 14-22, 1999 entitled "Minds that Matter," in which 50 of the world's leading medical scientists participated in mini-symposia in 14 cities across Canada, ending with a three-day symposium and awards dinner in Toronto. The awards, which come with a cash prize of \$30,000 each and a sculpture, *Le Coeur*, are given for two different categories:

1. The Gairdner Foundation International Awards are given to individuals from diverse fields for outstanding discoveries with contributions to medical science.
2. The Gairdner Foundation Wightman Award is given from time to time to a Canadian individual who has demonstrated outstanding leadership in medicine and medical science.

#### 1999 Gairdner Foundation Award Winners

##### Recipients of the Gairdner Foundation International Award

Drs. Andrew H. Wyllie and H. Robert Horvitz were jointly recognized for their pioneering contributions to our understanding of programmed cell death.

**Andrew H. Wyllie**, M.B., Ch.B., Ph.D., F.R.C.Path., F.R.S.E., F.R.S.  
Cambridge University, Cambridge, United Kingdom



Dr. Wyllie's research has played a pivotal role in bringing attention to the study of programmed cell death, an area that has generated considerable excitement in biology over the past few decades. He was one of the three pathologists in the early 1970's at the University of Aberdeen who noticed the morphological characteristics of a previously described "physiological"

form of cell death that accompanies cell turnover. This work was the first to describe the controlled changes in cellular structure that take place during this form of cell death. For this, they coined the term "apoptosis" (Greek for "falling off" of petals from flowers, or leaves from a tree), the pronuncia-

tion of which has become its own subject of debate. The initial studies also provided a link between apoptosis and other processes, such as controlling the growth of neoplasms and tumour regression. Dr. Wyllie's observations formed the basis for the ongoing elucidation of the molecular mechanisms involved in apoptosis, which has provided enormous insight into our understanding of a vast number of processes, such as cancer, development, autoimmune disorders, systemic viral infection, neurodegenerative diseases, tissue toxicity, and ischemic injury.

Apoptosis is a field of study that will clearly have an impact on treating human disease, and targeting the regulators of this process is the focus for discovering new types of therapy. Although Dr. Wyllie appreciated the importance of apoptosis during his initial research, even he is surprised by how the popularity of the subject has exploded and reached virtually all areas of medical research today.

**H. Robert Horvitz, S.B., Ph.D.**  
Massachusetts Institute of Technology, Boston, U.S.A.



In his initial research, it would have been hard for a young Robert Horvitz to imagine how his work would eventually complement the findings of Dr. Wyllie. He started off by determining the complete cell lineage of the nematode *Caenorhabditis elegans*. In the late 1970's, he demonstrated that of the 1090 cells found in the embryo, only 959 are

found in the adult (he is often chided that this finding was aided by his degree in Mathematics). Therefore, 131 embryonic cells are programmed to die. The precise nature of this genetic program became the subject pursued by his group and others. His group was responsible for identifying important genes, such as *ced-3* and *ced-4*, whose products are proteases crucial for carrying out cell suicide in this organism in a systematic and orderly way. The human equivalent to these genes and others have been found to be involved in numerous pathways leading to programmed cell death and apoptosis and to play a role in development and many other processes, such as tumour suppression.

Dr. Avram Hershko and Dr. Alexander Varshavsky were both recognized for the discovery of the ubiquitin system of intracellular protein degradation and the crucial functions of this system in cellular regulation.



**Avram Hershko,**  
M.D., Ph.D.  
Technion-Israel Institute of  
Technology, Haifa, Israel

What is known about the ubiquitin system of intracellular protein degradation began with Dr. Hershko's biochemical analysis. He initially observed that protein degradation requires ATP dependent conjugation of protein with a specific polypeptide (ubiquitin). This

set the stage in the early 1980's for his group to identify and characterize the multi-component system that degrades proteins and the biochemical steps involved. The 26S complex consists of components of the ubiquitin ligase system, E1, E2, and E3, required for the conjugation of ubiquitin to different types of target protein, and a 20S protease, which forms the catalytic core of the proteolytic pathway. The rapid protein degradation catalyzed by the ubiquitin system is now known to be crucial to progression of the cell cycle, chromosome structure, signal transduction, transcription, development, virology, immunology, and memory. Perturbation of the ubiquitin-dependent degradation pathways is associated with many disease states, including cancer, heart disease and hypertension, cystic fibrosis, muscle wasting, immune invasion by viruses and neurodegenerative diseases.



**Alexander J. Varshavsky,**  
Ph.D.  
California Institute of  
Technology, Pasadena,  
U.S.A.

Dr. Varshavsky's contribution to the study of the ubiquitin system began as a complement to Dr. Hershko's work. By studying a mouse cell line harboring a temperature sensitive E1 mutant, he was able to confirm the importance

of this enzyme in ubiquitin protein conjugation. His research led to further advances in this area by analyzing the nature of the targets of ubiquitination. His "N-end rule" describes the degradation signal that targets a short-lived protein for ubiquitin-dependent proteolysis: a destabilizing amino-terminal residue and a specific internal lysine residue. Dr. Varshavsky has also identified the yeast equivalents of the enzymes involved in this degradation pathway and has highlighted the importance of the ubiquitin system as a component of the stress response system, as well as its importance in mediating progression through the cell cycle.

## Recipients of the Gairdner Foundation Wightman Award

In recognition of his outstanding contributions to Canadian medicine and medical science as a leader of the Canadian academic medical community:

**Charles H. Hollenberg**, O.C., M.D., F.R.C.P.(C), F.R.S.C.  
University of Toronto, Toronto, Canada



For the past thirty years, Dr Hollenberg has provided leadership to academic medicine in Canada through his influence on education and administration. In his positions as Chair of the Department of Medicine of the University of Toronto and Physician-in-Chief of the Toronto General Hospital, which he held throughout the

1970's, he recruited a large number of clinician-scientists to the department, which blossomed into one of increasing scientific investigation. In his position as the Charles H. Best Professor of Medical Research at the University of Toronto, he played a pivotal role in the creation of the Banting and Best Diabetes Centre for interdisciplinary diabetes research. In 1991, he became President of the Ontario Cancer Treatment and Research Foundation, where he was instrumental in the formation of Cancer Care Ontario, which he served as President and Chief Executive Officer from 1997-1999. The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is dedicated to developing the CCOPGI Guidelines, evidence-based clinical practice guidelines (CPGs) on cancer care including treatment, diagnosis, prevention and follow-up. The goal is to ensure that all Ontario residents have timely, equitable access to an integrated system of coordinated and efficient programs in prevention, early detection, care, education and research.

In recognition of his leadership in academic medicine and for outstanding contributions to clinical care and research in respiratory diseases:

**Peter T. Macklem**, O.C., M.D., F.R.C.P.(C), F.R.S.C.  
McGill University, Montreal, Canada



Dr. Macklem has made significant contributions to medicine through both scientific investigation and academic leadership. After obtaining his M.D. from McGill in 1956, he became a Fellow of the Royal College of Medicine in 1963. He has been a leading scientist in respiratory research ever since. He played a crucial

part in influencing pulmonary function testing, which he used to explore mechanisms of airway resistance, the site of airway obstruction and its implications for disease. He identified the deleterious effects of smoking on the function of the small airways. He also demonstrated the role of dyspnea and respiratory muscle fatigue in ventilatory failure.

In his positions as Director of the Meakins-Christie Laboratories and founding Director of Inspiraplex, the Respiratory Health Network of Centres of Excellence, Dr. Macklem has inspired and influenced many physicians who have also gone on to be leaders in respiratory medicine. As Chair of Medicine at McGill University, he recruited many talented physician-scientists to Montreal.

On how they got started...

**Dr. Horvitz**

"I was an undergraduate major in mathematics and economics, without any background in biology whatsoever, and as a senior I was advised by a roommate that biology had become interesting. So I registered for a course in my first term senior year in biology and the question was whether it made sense to consider this for graduate school and a possible career. I went to the Professor that taught my introductory biology course and said 'I am majoring in math and also getting a degree in economics and I'm thinking about going into graduate school in biology. Is that ridiculous?' And he replied 'I have my undergraduate degree in economics and my Ph.D. in Physics and I'm teaching your biology course!'"

**Dr. Hershko**

"I was a medical student and I did one year of research. It was a different project than my present one, but I realized that I liked research. So after I finished my medical studies, I never practiced medicine; I went into Biochemistry. My present project started about thirty years ago, after my post-doctoral training. I became interested in how proteins are degraded in cells because I realized that nobody knew how this was done."

**Dr. Varshavsky**

"There's a common misconception that people come to science to make discoveries. In fact the best way to see it is to want to enter the subject, to become competent, if not excellent at what you do. Discoveries will come; they will be a function of one's abilities and where you land. The territory of science where you land is determined partly by preference, because you avoid certain things, and partly by accident because some of these things suddenly begin to work and you don't want to leave them. So a lot of these seemingly rational choices at the beginning are anything but."

**Dr. Macklem**

"...I came to the lab and there were all of these toys. I said to myself, 'I can get paid to play? Why should I ever want to work?'"

**Gairdner Foundation International Award Winners from the University of Toronto**

1959 - Wilfred G. Bigelow for his contribution to the knowledge of cardiology and especially for his achievement in developing the hypothermia method of open heart surgery.

1964 - Gordon D.W. Murray for his contributions to the knowledge of cardiac physiology and pathology, and the development of several important techniques in cardiac surgery.

1967 - Peter J. Maloney for contributions to immunology and diabetes, including introduction of toxoids for immunization against diphtheria and tetanus, the demonstration of antibodies against insulin, and the development of sulphated insulin, which is effective in patients who have become insulin resistant.

1969 - Ernest A. McCulloch and James E. E. Till for their development of the spleen colony technique for measuring the capacity of primitive normal and neoplastic cells to differentiate in the body.

1969 - Robert B. Salter for his contribution to an understanding of cartilage degeneration, epiphyseal necrosis, torsional deformation of bone and dysplasia of joints in relation to numerous musculoskeletal disorders, especially congenital dislocation of the hip.

1971 - Charles H. Best for his part in the discovery and development of insulin and for many other contributions to medical research.

1972 - Oleh Hornykiewicz for his elucidation of the biochemical lesion in Parkinson's disease and for other contributions to our knowledge of the physiology of the brain.

1973 - Harold E. Johns for his pioneering work in the development of cobalt and high energy radiotherapy, and for his many other contributions to education and research in the field of clinical physics and biophysics.

1975 - William T. Mustard for his contributions in the area of cardiovascular surgery especially for transposition of the great vessels.

1975 - John D. Keith for contributions to our understanding of the natural history of congenital heart disease.

1980 - Irving B. Fritz for his discovery of the role of carnitine in the regulation of fatty acid metabolism.

1986 - Harald Sonnenberg, along with Adolfo J. de Bold and T. Geoffrey Flynn, for the discovery and characterization of atrial natriuretic factor.

1989 - Ronald G. Worton, along with Louis M. Kunkel, for their contributions to the isolation and cloning of the gene for Duchenne/Becker muscular dystrophy.

1989 - Tak W. Mak, along with Mark M. Davis, for contributions to the cloning and sequencing of the gene for the T-cell receptor.

1990 - Lap-Chee Tsui, John R. Riordan, along with Francis S. Collins, for contributions to the identification of the gene for cystic fibrosis.

1990 - Victor Ling for his discovery of the role of P-glycoprotein in the development of multidrug resistance of cancer cells.

1991 - David H. MacLennan for his contributions to our understanding of muscle membranes and ion transport.

1994 - Anthony J. Pawson, along with Tony Hunter, for contributions to our understanding of the role of tyrosine kinases in signal transduction pathways that control cell growth.