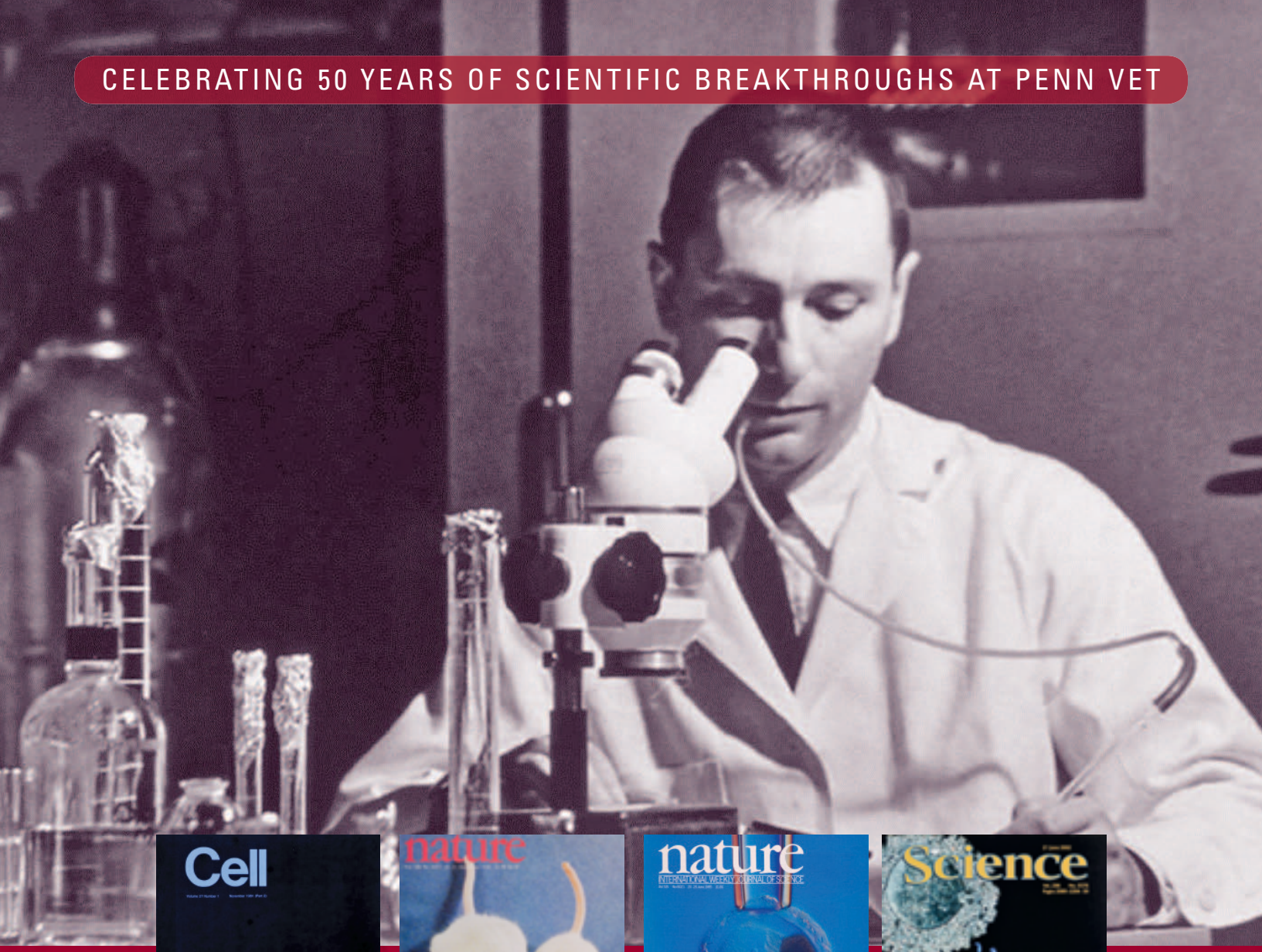
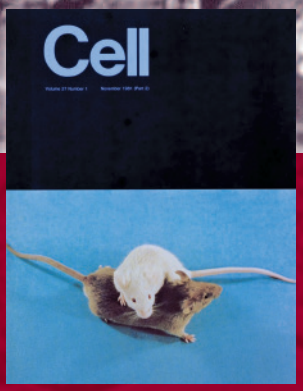
CELEBRATING 50 YEARS OF SCIENTIFIC BREAKTHROUGHS AT PENN VET





August 24 – 25, 2012

PENN SYMPOSIUM

In honor of

Ralph L. Brinster, VMD, PhD

Penn
Veterinary Medicine

Ralph Brinster's accomplishments as a teacher, trainer of young scientists and the development of academic programs at Penn Vet have been truly phenomenal.

Message

FROM PROVOST VINCENT PRICE

It is a pleasure to congratulate Ralph Brinster on his extraordinary fifty years at Penn. He embodies the highest values of our university, in his commitments to teaching, mentoring, and the power of fundamental research to address the most profound and far-reaching questions. His innovations have defined whole fields of inquiry, spurred critical new technologies, and transformed the study of human biology and disease. At the same time, his work vividly demonstrates what we most seek to instill in our students - the dynamism and creativity of the intellectual enterprise, and the combination of curiosity, creativity, and tireless investigation that makes academic research vital and exciting. On behalf of the Penn community, we are honored by his presence, his legacy, and his ongoing influence on our university and on the scientific community around the world.

Message

FROM DEAN HENDRICKS

I am honored to write this letter for the Symposium to Honor Dr. Ralph L. Brinster. Dr. Brinster has been involved with my career here at the School of Veterinary Medicine since the very beginning. He interviewed me when I applied to the Veterinary Medicine Scientist Training Program (VMSTP) in 1974 and I have admired him throughout my own 38 years with Penn Vet.

This year marks 50 years of Dr. Ralph Brinster's association with the University of Pennsylvania, starting as an instructor in 1960, and as faculty member since 1965. Ralph's contributions to the field of reproductive biology, transgenesis and stem cell biology are monumental and unique. Over the past 50 years he has consistently led the field making many pivotal contributions. Ralph has won many National and International awards including the March of Dimes Prize in Developmental Biology, The Bower Award and Prize of Achievement, Pioneer in Reproduction Research Award from NICHD, Ernst W. Bertner Award from the University of Texas, the Wolfe Prize in Medicine, the Gairdner Foundation International Award, and recently, the National Medal of Science. He is the first Veterinarian to win this highly coveted award.

Ralph's contributions have enormously impacted both human and veterinary medicine. In this respect he ranks among the handful of scientists who have revolutionized the field of reproductive biology, and both human and animal health. He has been a great source of inspiration to young scientists at the Penn Campus. He was also instrumental in establishing the combined VMD/Ph.D. program at Penn Vet which is the only NIH funded program in any Vet School in the US. The combined degree program in turn has trained several outstanding scientists who are current leaders in different fields of veterinary medicine. His accomplishments as a teacher, trainer of young scientists and the development of academic programs at Penn Vet have been truly phenomenal.

Message

FROM STEVEN FLUHARTY
Senior Vice Provost for Research

Ralph L. Brinster is one of Penn's preeminent scholars, a world renowned investigator and the recipient of numerous prestigious awards and accolades. Attendees to the Symposium are of course well familiar with Ralph's unsurpassed work ethic, his boundless intellectual curiosity, his collaborative approach to scientific pursuits, and his visionary leadership.

His dedication is the stuff of legends. My first glimpse of Ralph was one Christmas Eve when I had come into the lab with my young son to work on a grant due soon after the first of the year. Ralph was roaming the halls and stopped in to say hello and offer some advice on the grant. He was impressed I was in work with the holiday just hours away. While his advice, as expected, was greatly appreciated, I never volunteered that my wife insisted I leave as soon as possible so as to not disrupt her holiday preparations.

His approach to laboratory science has served as a model of how to conduct large scale collaborative research projects. One of my most memorable interactions with Ralph occurred when his lab created a new transgenic mouse that lacked a key enzyme in the synthesis of catecholamines, a class of neurotransmitters. Ralph was aware that I had worked in this area as a post-doctoral fellow and he invited me to a lab meeting. We discussed the range of physiological and behavioral consequences that might develop in this mouse model. I was thrilled to be consulted and really impressed with Ralph's inclusive approach to laboratory science not to mention his intellectual prowess.

His willingness to take on critical leadership roles has helped shape our University into a world class research enterprise. I relied heavily on Ralph in chairing the search committee that ultimately recruited Hans Schöler to Penn to direct the Germ Cell Center. He offered much needed guidance and was generous with his time during recruitment visits. As Senior Vice Provost for Research, I was again able to call upon Ralph to advance an important University initiative, in this case the founding of Penn's multi-disciplinary, cross-School, Institute for Regenerative Medicine. He played a pivotal role in the founding of IRM, agreeing to serve as co-Director of the Institute. I cannot thank him enough for being an exemplary University citizen.

As both a colleague in the department and as a university administrator, I have had the good fortune to personally interact with Ralph and see his remarkable qualities firsthand. I am sure many of you feel likewise.

A Tribute to Ralph Brinster

FROM ALAN KELLY
The Gilbert S. Kahn Dean Emeritus

At the time I came into the Dean's office in 1994 the School was in the midst of a difficult period, threatened with closure because of problems with State funding. Anxiety in the School was high and moral low. It seemed to me that one of the most immediate things I had to do was to restore the faculty's self confidence and belief in the School's excellence. At the time I read Nature and Science regularly and was aware that papers with Ralph's name on them appeared with remarkable frequency in both journals. Occasionally other faculty also published in these two preeminent journals and I was fairly certain that no other veterinary school in the world could compete at this level. We set about counting all the publications in Nature and Science from 1980 to 1994 that included the names of veterinary school faculty from anywhere in the world. This was tedious as there was no database and the journals are published weekly, however the results made it worth the effort.

In those 15 years we found a total of 119 publications from veterinary schools across the globe, of these 47, or 40% came from PennVet ! That's a remarkable figure but what is even more extraordinary is that of the School's total, 62% or 29 papers came from Ralph. This means that in addition to his contributions to other journals, over the course of 15 years, Ralph published an average of 2 papers a year in Nature or Science, two of the most prestigious international science journals in the world. There can be very few scientists who can begin to compare with this unflagging level of intellectual vigor and creative brilliance. Thomas Edison wasn't kidding when he said that genius was one percent inspiration and ninety nine percent perspiration.

It is Ralph's scintillating quality as a scientist that has played such a leading role in elevating the Department of Animal Biology to be the most accomplished basic science department of any veterinary school in the world and one that is superior in excellence to most basic science departments in medical schools across the U.S. Ralph anchored this grand achievement of which the School can be immensely proud.

In more subtle ways Ralph has also inspired the entire School. As an example, I shared the figures on Nature and Science at our first faculty research retreat in June, 1994 and compared them with contributions from other veterinary schools across the globe. Our nearest rival was Glasgow with just 5 publications. When compared to medical schools in the area, Penn had 97, Jefferson 18, and Temple 16. The results had an immediate effect as many faculty came to me afterwards to say how good the figure made them feel. For me it was a cherished moment, for the faculty it restored belief in our preeminence and renewed a well-spring of confidence in our future. For all of this we shall forever be indebted to Ralph.

A Tribute to Ralph Brinster

FROM ROBERT MARSHAK
Dean Emeritus

With characteristic humility, minimizing his brilliant intellect and phenomenal capacity for work, Ralph Brinster likes to say that his lifetime of monumental contributions to science is attributable in large measure to Lady Luck. He mentioned luck again when he phoned to tell me that someone in Washington had just invited him to the White House to receive the 2012 National Medal of Science from President Obama. To absorb the enormity of this news, I opened a bottle of champagne and, after toasting Ralph, my wife and I talked for hours about the importance and impact of Ralph's science, his many honors, what his presence has meant to the Veterinary School, and how the School had evolved since 1956, the year we both came to Penn, Ralph as an entering student and I as professor and chairman of medicine.

We speculated that owing to Ralph's agricultural, military, and undergraduate animal science background, the Admissions Committee, to our School's ultimate good fortune, viewed him as a high priority applicant. We wondered, as a third and fourth veterinary student, if Ralph sensed that the School was leading the nation and the world in transforming the nature and quality of veterinary medical education, and whether this awareness influenced his decision to choose an academic and research career. I wondered too if during his junior year he shared his classmates' view that my medicine lectures placed too much emphasis on mechanisms of disease and on the reading of original papers in the medical and veterinary literature.

I believe our first significant personal interaction, the beginning of a long friendship, occurred in 1959-1960, when Ralph and I discussed his interest in pursuing a PhD in physiology and I encouraged him to seek financial support from a newly-minted Penn Plan Fellowship Program. I remember telling John Brobeck, Chair of Physiology in the School of Medicine, that there would be a place for Ralph on the faculty of the Veterinary School when he finished his doctoral program. He got the fellowship and, thus, during the course of his graduate studies, began his long and extraordinarily productive scientific career.

I hope that in time Ralph will come to appreciate that the luck he so often mentions applies mainly to his colleagues, his School, and his University. For nearly six decades, and counting, we have been the lucky ones.

Symposium Sponsors

We would like thank all the sponsors that helped make the Penn Symposium possible:

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Schedule

FRIDAY, AUGUST 24TH

7:30AM – 8:30AM	**BREAKFAST** HILL LOBBY	
8:30AM – 8:50AM	**OPENING COMMENTS**	
	Vincent E. Price, Ph.D., Provost, Office of the Provost; Professor and Steven H. Chaffee Term Chair in Communication and Political Science	
	Joan Hendricks, V.M.D., Ph.D., The Gilbert S. Kahn Dean of Veterinary Medicine	
	Narayan Avadhani, Ph.D., Harriet Ellison Woodward Professor of Biochemistry & Chairman, Department of Animal Biology	
	Michael Atchison, Ph.D., Professor of Biochemistry, V.M.D./Ph.D. Program Director	
8:50AM – 9:40AM	**Richard Palmiter, Ph.D.,** Plenary Speaker Investigator Howard Hughes Medical Institute; Professor of Biochemistry; University of Washington School of Medicine *"An incredible journey from metallothionein to neurobiology of feeding behavior"*	**MODERATOR** **John Gearhart, Ph.D.,** James W. Effron University Professor; Director, Institute for Regenerative Medicine
9:40AM – 10:10AM	**Richard Behringer, Ph.D.,** Professor of Genetics, The University of Texas, M.D. Anderson Cancer Center *"Reproductive organ formation, homeostasis, and regeneration"*	
10:10AM – 10:30AM	**John Gearhart, Ph.D.,** James W. Effron University Professor; Director, Institute for Regenerative Medicine; Perelman School of Medicine and School of Veterinary Medicine; University of Pennsylvania *"Remembrance, Gratitude and Cell Conversions"*	
10:30AM – 10:50AM	**COFFEE BREAK**	
10:50AM – 11:30AM	**Rudolf Jaenisch, M.D.,** Plenary Speaker Professor of Biology, Member, Whitehead Institute for Biomedical Research, and Massachusetts Institute of Technology *"Stem cells, pluripotency and nuclear reprogramming"*	**MODERATOR** **Marisa Bartolomei, Ph.D.,** Professor of Cell and Developmental Biology, and HHMI Investigator
11:30AM – 12:00PM	**Hans Schöler, Ph.D.,** Professor and Director; Department Cell and Developmental Biology; Max Planck Institute for Molecular Biomedicine, Münster, Germany *"Induction of stem cell multi- and pluripotency"*	

Schedule

FRIDAY, AUGUST 24TH *(continued)*

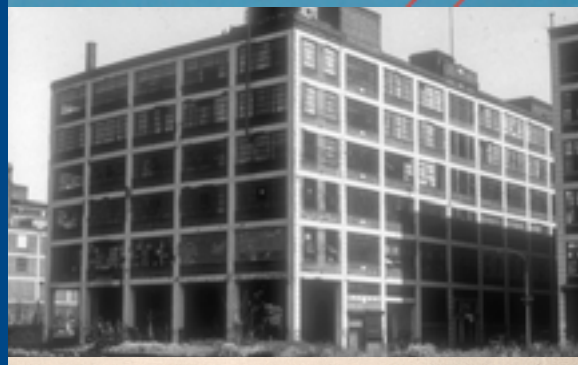
12:00PM – 1:00PM	**LUNCH**	
1:00PM – 1:45PM	**John Gurdon, Kt, DPhil, DSc, FRS,** Plenary Speaker, Emeritus Professor; University of Cambridge *"Nuclear transfer to eggs and oocytes: the stabilization and reversal of cell differentiation"*	**MODERATOR** **Phil Scott, Ph.D.,** Associate Dean for Research; Professor of Microbiology and Immunology, Department of Pathobiology
1:45PM – 2:15PM	**Allan Bradley, Ph.D., FRS,** Director Emeritus and Senior Group Leader; Wellcome Trust Sanger Institute *"Genetic screens in embryonic stem cells"*	
2:15PM – 2:45PM	**Robert Hammer, Ph.D.,** Graydon Heartsill Professorship in Medical Science; Professor in Biochemistry; University of Texas Southwestern Medical Center *"Ribosomopathies, altered tissue homeostasis and cancer-Insights from mice"*	
2:30PM – 2:50PM	**COFFEE BREAK**	
2:50PM – 3:30PM	**Katherine A. High, M.D.,** William H. Bennett Professor of Pediatrics; Investigator, Howard Hughes Medical Institute; and Director of the Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia *"Genome editing as an approach to treating genetic disease"*	**MODERATOR** **Christopher Hunter, Ph.D.,** Chairman and Professor, Department of Pathobiology
3:30PM – 4:00PM	**Kenneth Zaret, M.D., Ph.D.,** Joseph Leidy Professor of Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania *"Programming and reprogramming mammalian cell fates"*	
4:00PM – 5:00PM	**KEYNOTE ADDRESS** **Michael S. Brown, M.D.,** W.A. (Monty) Moncrief Distinguished Chair in Cholesterol and Arteriosclerosis Research; Regental Professor, Paul J. Thomas Chair in Medicine; University of Texas Southwestern Medical School *"Genetically Engineered Mouse Strains (GEMS): Models for Human Disease"*	**INTRODUCTION** **Michael Atchison, Ph.D.**
5:00PM	**Steven Fluharty, Ph.D.,** Senior Vice Provost for Research; Professor of Pharmacology, Psychology, and Neuroscience; School of Veterinary Medicine: Presentation to Dr. Ralph Brinster	
5:30PM – 7:30PM	**RECEPTION** HILL LOBBY	

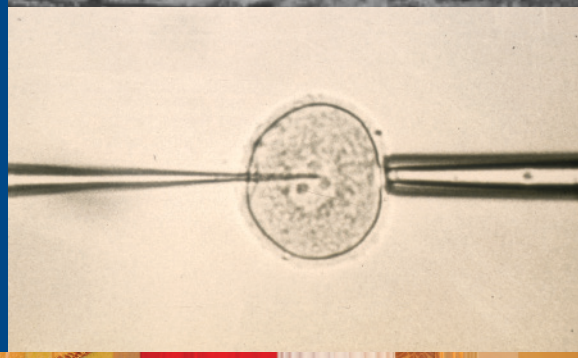
Schedule

SATURDAY, AUGUST 25TH

8:00AM – 9:00AM	**BREAKFAST** HILL LOBBY	
9:00AM – 9:50AM	**James A Thomson, V.M.D., Ph.D.,** Plenary Speaker, John D. MacArther Professorship, Jim Kress Endowed Chair, Director of Regenerative Biology at the Morgridge Institute for Research and Professor of Cell and Regenerative Biology at the University of Wisconsin *"Human pluripotent stem cells"*	**MODERATOR** **Olena Jacenko, Ph.D.,** Professor of Biochemistry/Animal Biology & Director, Diversity Program at the Vet School
9:50AM – 10:30AM	**Ina Dobrinski, Dr.med.vet., M.V.Sc., Ph.D., DACT.,** Professor; Department Head, Comparative Biology & Experimental Medicine; University of Calgary Veterinary Medicine *"Of mice, pigs and monkeys: Using transplantation to study germline stem cells and spermatogenesis"*	
10:30AM – 10:50AM	**COFFEE BREAK**	
10:50AM – 11:30AM	**Richard Schultz, Ph.D.,** Charles and William I. Day Distinguished Professor of Biology; University of Pennsylvania *"From egg to embryo: a peripatetic journey"*	**MODERATOR** **Narayan Avadhani, Ph.D.**
11:30AM – 12:00PM	**Marisa Bartolomei, Ph.D.**, Professor of Cell and Developmental Biology; Perelman School of Medicine; University of Pennsylvania, and HHMI Investigator *"Epigenetic regulation of genomic imprinting"*	
12:00PM – 1:00PM	**LUNCH**	
1:00PM – 1:45PM	**Janet Rossant, Ph.D., FRS, FRSC,** Plenary Speaker, Senior Scientist; Developmental & Stem Cell Biology; Chief of Research, Research Insititute; The Hospital of Sick Children, Toronto "Stem cells & blastocyst development"	**MODERATOR** **Christopher Lengner, Ph.D.,** Assistant Professor of Animal Biology/ Cell and Developmental Biology
1:45PM – 2:15PM	**Takashi Shinohara, M.D., Ph.D.,** Professor; Department of Molecular Genetics; Kyoto University "Reconstruction of germline niche in vitro"	
2:15PM – 2:45PM	**CLOSING COMMENTS** **Ralph Brinster, VMD, PhD ,** Richard King Mellon Professor of Reproductive Physiology *"A 25 Minute Summary of 50 Years - Past and Present"*	

Celebrating 50 Years of Scientific Breakthroughs at Penn Vet





An Autobiography of

RALPH BRINSTER

Prepared Under Extreme Duress From The Organizing Committee

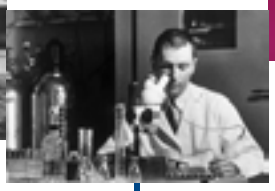
I grew up on a small farm in northern New Jersey, and from my experiences there, I became interested in animal development and breeding, including fertility and transmission of genetic characteristics to progeny. I enrolled in Rutgers University Agricultural School and majored in animal science. Near the end of my studies I decided to continue my education, but the Korean conflict was underway, and I went into military service at the end of college. I served one year in Korea and one year in Texas, following which I began training at the University of Pennsylvania's School of Veterinary Medicine using the G.I. Bill to help finance my education. While a veterinary student, I became more interested in fertility of animals and germ cell biology; therefore, following graduation I began Ph.D. training in physiology at Penn.

Since the early 1900s, scientists had been trying without success to develop a reliable system to culture mammalian eggs. For my Ph.D. thesis, I undertook this problem and was successful in developing a system for culture and manipulation of fertilized mouse eggs, which is still widely used today with little change (J. Exp. Zool., 1965). Using this system, I worked out many aspects of the metabolism and development of eggs and early embryos, but more important became interested in modifying development of the animal and its germline. I began exploring the possibility of introducing new cells into the mouse blastocyst as a way to influence subsequent development and perhaps the germline. One of the cells I tried was the teratocarcinoma cell, because it is capable of developing into all three germ layers of the animal. After many experiments, resulting in the production of more than 100 offspring, I was successful in demonstrating that teratocarcinoma cells injected into the blastocyst were incorporated into the embryo and adult mouse (J. Exp. Med., 1974). This report resulted in great excitement in the field, because teratocarcinoma cells could be cultured and genetic changes introduced into the cells. Within a few years, genetic changes were introduced into mice with teratocarcinoma cells generating prototype transgenic mice. However, the genetic changes were rarely transmitted to progeny, which limited the long-term usefulness of transgenic mice produced in this way. Nonetheless, these experiments demonstrated the potential to change the mouse germline and were the impetus for subsequent development of embryonic stem cells.

While I pursued potential solutions to this problem, I began developing methods by which to introduce nucleic acids directly into the egg as a way to change genes in the germline, because recombinant DNA techniques were making pure populations of genes available. In my pilot experiments, I showed that mouse eggs would survive microinjection of nucleic acids (RNA), which was published in Nature as a letter in January 1980. The following year, I began my collaboration with Richard Palmiter, and we generated transgenic mice containing a fusion gene (Cell, 1981). During 1981, five other groups published success in introducing DNA into mice. In all these experiments, the culture and manipulation techniques from the 1960s and the egg injection techniques reported in the January 1980 Nature paper were used to produce the transgenic mice. In 1982, Richard and I published in Nature the famous giant

DR. RALPH BRINSTER: *A Legacy of Discovery*

1958



1964

Single embryonal carcinoma cells were injected into the blastocytes of homologous mice and transferred the injected blastocytes into the uteri of pseudopregnant mice. Chimeric mice occurred in the resultant litters, as evidenced by coat color mosaicism. Cancer cells were thus regulated to behave like normal embryonic cells, which took part in the normal development of the skin.

Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes.

1982

Production of transgenic rabbits, sheep and pigs by microinjection.

1985

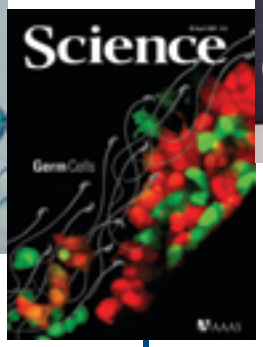
mouse experiment, in which the rat growth hormone gene was expressed in the liver of mice. This report resulted in great interest in the transgenic approach, and many scientists entered the field. During the 1980s Richard and I, with collaborators, generated an enormous number of transgenic mice, as well as transgenic farm animal species (Nature, 1985). These studies demonstrated the first proof of tissue-specific expression of transgenes (Nature, 1984), the first example of cancer from a transgene (Cell, 1984), targeted integration of DNA by egg injection (PNAS, 1989), and many examples of how promoter/enhancers and genes function. It was an exciting time in science for me, and the field developed rapidly. No one anticipated in the beginning how dramatic the impact would be of modifying, selectively and experimentally, genes and individual DNA sequences in an animal. It has truly revolutionized biology, medicine and agriculture. Since 1981, many have contributed to this transformation in our understanding of gene function and in our ability to modify the genetics of a living organism.

My true interest has always been in germ cells and the continuity of the DNA within these cells, which is the basic foundation of biology. Therefore, as the transgenic field matured, I returned to the germ cell field at the end of the 1980s and directed my efforts to the male germline. To study the germline of the male, I needed a system of analysis similar to the one I had developed for eggs in the 1960s that would enable me to assess any experimental affect on the male germline stem cell, the spermatogonial stem cell. I hypothesized that if one were to take cells from a fertile testis and put them into the testis of an infertile mouse, only the stem cells would be able to develop in the seminiferous tubules and generate donor-derived spermatogenesis. Following this line of reasoning, I designed several types of experiments to test my hypothesis. The experiments were successful, and the results were published in PNAS, 1994. As in many situations, the initial development of an analysis or assay procedure, particularly if it is simple and unequivocal, results in a dramatic expansion of the field.

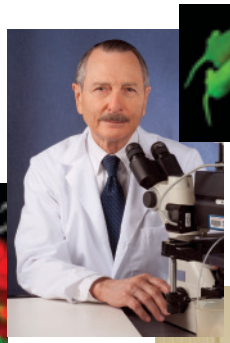
Reconstitution of spermatogenesis from frozen speramtogonial stem cells.

Germline stem cell transplantation and transgenesis.

Phenotypic and functional characteristics of spermatogonial stem cells rats.



Male Germline Stem Cells: From Mice to Men.



Receives National Medal of Science from President Obama.

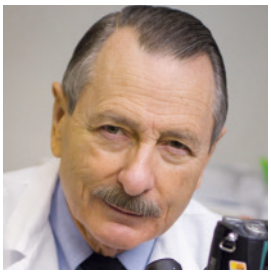
1996 | 2002 | 2004 | 2007 | 2011

Thus, over the next few years, we were able to establish many characteristics of spermatogonial stem cells, including their ability to be readily cryopreserved, which makes individual males biologically immortal. We also demonstrated that these stem cells could survive for months in vitro, which eventually led to culture techniques and the ability to modify the germline using spermatogonial stem cells. Recently, we have extended the culture methods to higher species, including primates. Currently, one of our lines of investigation is the development of an approach to cryopreserve testicular biopsies from prepubertal boys receiving treatment for cancer that will make them infertile. After the cancer is eradicated, the cryopreserved cells can be grown in culture to increase their number and to remove any malignant cells, and then transplanted back into the patient's testes to restore fertility. Of course, my primary interest remains to understand the biology of the mammalian germline, and secondarily, to determine how the germline can be manipulated to improve the health and life of animals and man.

None of these accomplishments would have been possible without the extraordinary contributions of my students, colleagues and collaborators who deserve the credit, but I am fortunate and honored to have worked with them and to be their standard bearer.

[Modified from the 2011 International Society of Technology Transfer Prize presentation]

Speakers



Ralph Brinster, V.M.D., Ph.D. received his VMD degree in 1960 from the School of Veterinary Medicine and a PhD degree in 1964 from the Graduate School both at the University of Pennsylvania. He then became a member of the Department of Animal Biology at the School of Veterinary Medicine, University of Pennsylvania where he is currently the Richard King Mellon Professor of Reproductive Physiology. His research has focused on mammalian germ cells, specifically on their biology, regulation and genetic modification. In his initial studies, he developed culture and manipulation strategies for mammalian eggs, which are still in use today. Subsequently, his studies focused on genetic manipulation of the germline. He demonstrated that the mouse blastocyst could be colonized by foreign stem cells, and that mouse eggs will survive and function following injection of nucleic acids, techniques that served as a foundation for the development of transgenic animals. He then went on to contribute further to the development and use of transgenic animals, and in these studies collaborated closely with Richard Palmiter. Currently, his research is on spermatogonial stem cells and their regulation. For his contributions, he has received several distinguished awards, including the Gairdner Foundation International Award, the Wolf Prize in Medicine and the National Medal of Science.

Marisa S. Bartolomei, Ph.D., received her B.S. in Biochemistry at the University of Maryland in 1982, and her Ph.D. in Biochemistry, Cell & Molecular Biology at the Johns Hopkins University School of Medicine in 1987. She trained as a postdoctoral fellow with Dr. Shirley Tilghman at Princeton University. In 1993, Dr. Bartolomei was appointed as an Assistant Professor of Cell and Developmental Biology at the University of Pennsylvania School of Medicine and was promoted to Associate Professor with tenure in 1999 and Professor in 2006. In 2006, Dr. Bartolomei received the Society for Women's Health Research Medtronics Prize for Contributions to Women's Health. She is on the editorial board of multiple journals and serves on many advisory boards. Dr. Bartolomei's research addresses the epigenetic mechanisms of genomic imprinting and X inactivation in mice.

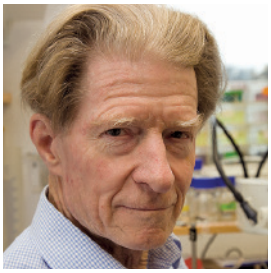
Richard Behringer, Ph.D., obtained his B.A. and M.S. at California State University in 1979 and 1981, respectively, and completed his Ph.D. studies in Biology in 1986 at the University of South Carolina under the mentorship of Dr. Michael Dewey, studying erythroleukemia using mouse chimeras. He pursued postdoctoral studies at the University of Pennsylvania with Dr. Ralph Brinster between 1986 and 1989 using transgenic mice applied to developmental biology, and subsequently performed a postdoc at the University of Washington. Currently, he is the Ben F. Love Chair for Cancer Research in the Department of Genetics at the University of Texas MD Anderson Cancer Center. The primary focus of the Behringer laboratory is to understand, at the molecular level, the events leading to the establishment of the mammalian body plan and how growth and differentiation of various tissues and organs are regulated during embryogenesis.

Allan Bradley, Ph.D., completed his B.A. and M.A. at the University of Cambridge. He stayed at Cambridge to pursue a Ph.D. in Genetics in Martin Evans' laboratory establishing the foundation for making knockout mice. In 1987 Professor Bradley started his own group at Baylor College of Medicine, Houston Texas where his laboratory played a seminal role in developing the techniques, technology and tools for genetic manipulation in the mouse. In 2000 Professor Bradley returned to the United Kingdom as Director of the Wellcome Trust Sanger Institute, a position he held until 2010. Professor Bradley currently directs an active research team who continue to develop tools and technologies for mouse genetics. In 2002 Professor Bradley was honored by election to the Royal Society.

Michael S. Brown, M.D., earned his undergraduate degree in Chemistry in 1962, and his M.D. degree in 1966, both from the University of Pennsylvania. He spent time as an intern and a resident at the Massachusetts General Hospital, then performed post doctoral studies with Earl Stadtman at the National Institutes of Health. He is currently Director of the Jonsson Center for Molecular Genetics at the University of Texas Southwestern Medical School in Dallas. Dr. Brown and his colleague, Dr. Joseph L. Goldstein, discovered the low density lipoprotein (LDL) receptor, which controls cholesterol in blood. They showed that mutations in this receptor cause Familial Hypercholesterolemia, a disorder that leads to premature heart attacks. Their work laid the groundwork for drugs called statins that lower blood cholesterol and prevent heart attacks. Statins are taken daily by more than 20 million people worldwide. Brown and Goldstein shared many awards for this work, including the U.S. National Medal of Science and the Nobel Prize for Medicine or Physiology.

Ina Dobrinski, Dr.med.vet., M.V.Sc., Ph.D., DACT., Dr. Dobrinski became a Graduate Veterinarian in 1987 of the Hannover College of Veterinary Medicine in Hannover, Germany. In 1989 she received her Doctor of Veterinary Medicine, magna cum laude from the same university and went on to receive her Master of Veterinary Science from Western College of Veterinary Medicine, University of Saskatchewan, Canada in 1993. That same year she became a Diplomate in the American College of Theriogenologists. In 1997 she earned her Ph.D. from New York Sate College of Veterinary Medicine at Cornell University. After postdoctoral work with Dr. Ralph Brinster at the University of Pennsylvania, Dr. Dobrinski was appointed Assistant Professor at the University of Pennsylvania and later became Director of the Center for Animal Transgenesis and Germ Cell Research, and the Marion Dilley and Robert George Jones Professor in Reproduction. She joined University of Calgary in 2008 where she is Professor and Head, Department of Comparative Biology & Experimental Medicine. In 2008 she was selected Theriogenologist of the Year by the American College of Theriogenologist. Dr. Dobrinski's group studies the biology of male germ line stem cells in non-rodent models, using germ line modification to generate transgenic non-rodent animal models for biomedical research, and harnessing the plasticity of germ line stem cells for fertility preservation and tissue regeneration.

John Gearhart, Ph.D., obtained his B.Sc. from Penn State University in 1964, M.Sc in Plant Genetics from the University of New Hampshire in 1966, and his Ph.D. in Genetics and Development from Cornell University in 1970. Subsequently he performed postdoctoral training at the Fox Chase Cancer Center. He joined the faculty at Johns Hopkins School of Medicine in 1979 developing and directing programs in gene control of mammalian development, assisted reproductive technologies, trangenesis and the genetic bases of mental retardation. Following his groups derivation of human pluripotential stem cells from primordial germ cells and the acceleration of stem cell biology, he was appointed the Director of the Stem Cell Program at Johns Hopkins School of Medicine. In 2008 he moved to the University of Pennsylvania as the James W. Effron University Professor (Penn Integrates Knowledge Professor) appointed in the Perelman School of Medicine and the School of Veterinary Medicine and as the Director of the Penn Institute for Regenerative Medicine.



John Gurdon, Ph.D., attended Eton College and studied classics and zoology at Oxford. He performed his Ph.D. studies at Oxford under the mentorship of Michael Fischberg. In 1971 he joined the MRC Molecular Biology Lab in Cambridge. In 1989, he was a founding member of the Wellcome/CRC Institute for Cell Biology and Cancer (later Wellcome/CR UK) in Cambridge, and was its Chair until 2001. Dr. Gurdon was made a Fellow of the Royal Society in 1971, and was knighted in 1995. In 2004, the Wellcome Trust/Cancer Research UK Institute for Cell Biology and Cancer was renamed the Gurdon Institute in his honor. He has received numerous awards, medals and honorary degrees and was awarded the 2009 Albert Lasker Basic Medical Research Award. His career has concentrated on nuclear transplantation in the frog, mRNA microinjection, mechanisms of response to morphogen gradients, and recently, mechanisms of nuclear reprogramming in Xenopus oocytes and eggs.

Robert Hammer, Ph.D., obtained his B.A. in Reproductive Biology in 1975 from Kalamazoo College, and his Ph.D. in Cell Biology and Anatomy in 1981 from Wayne State University. He pursued postdoctoral training with Dr. Brinster at Penn School of Veterinary Medicine from 1983 to 1986 and in 1986 joined the faculty at the University of Texas Southwestern Medical Center. He is currently Professor in the Department of Biochemistry and is a Senior Associate of the Howard Hughes Medical Institute. His laboratory studies in vivo models of cancer, oncogene and growth factor collaboration in cancer, regulation of growth and proliferation, and regulation of liver growth

Katherine High, M.D., graduated from Harvard with an A.B. in Chemistry in 1972, and in 1978 from the University of North Carolina (UNC) School of Medicine, where she received her M.D. degree. After completing her training in internal medicine, she trained as a Fellow in the Hematology Section at Yale University School of Medicine. In 1985 Dr. High was appointed Assistant Professor at the University of North Carolina and moved to the University of Pennsylvania in 1992 as an Associate Professor. Presently, Dr. High is the William H. Bennett Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, Investigator, of the Howard Hughes Medical Institute, and Director, Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia. Dr. High has won many awards and was elected to the Institute of Medicine (IOM) and the American Academy of Arts & Sciences (AAAS). Dr. High's research interests focused initially on the molecular basis of blood coagulation, and the use of novel genetic therapies to treat hemophilia. More recently she has pioneered safe and effective clinical translation of genetic therapies for inherited disorders. These clinical trials have led to correction of disease in hemophilia B and in Leber's congenital amaurosis, a hereditary cause of blindness.

Rudolf Jaenisch, M.D., received his doctorate in medicine from the University of Munich in 1967. After performing experimental work at the Max Planck Institute of Biochemistry for several years, and clinical training at the University of Munich, Dr. Jaenisch pursued postdoctoral training at Princeton University with Arnold Levine. He started his independent career at the Salk Institute, later moving to the Heinrich Pette Institute in Hamburg, Germany where he was head of the Department of Tumor Virology. Dr. Jaenisch subsequently became a founding member of the Whitehead Institute at MIT. He has coauthored more than 375 research papers and has received numerous prizes and recognitions, including the Wolf Prize in Medicine, the President's National Medical of Science, and an appointment to the National Academy of Sciences in 2003. Dr. Jaenisch's work focuses on understanding epigenetic regulation of gene expression. Most recently, this work has led to major advances in our understanding of embryonic stem cells and "induced pluripotent stem" (IPS) cells, which appear identical to embryonic stem cells but can be created from adult cells without using an egg. Dr. Jaenisch's work has direct applications to the treatment of diseases such as sickle-cell anemia and Parkinson's disease. IPS cells offer promise for use in regenerative medicine, potentially supporting the growth of healthy cells and tissues derived from a patient's own cells.

Richard Palmiter, Ph.D., received his A.B. degree from Duke University in 1964 and Ph.D. degree from Stanford University in 1968. He was a postdoctoral fellow at Stanford University with Robert Schimke, at G.D. Searle Research Laboratories in England with Norman Carey, and at Harvard University with Fotis Kafatos. He started his academic career at the University of Washington in 1974. Dr. Palmiter has been an investigator of the Howard Hughes Medical Institute since 1976 and a member of the National Academy of Sciences since 1988. The Palmiter laboratory uses molecular biology tools to study animal physiology, behavior and disease. Early work was aimed at dissecting the mechanisms of steroid hormone action in control of egg white protein synthesis. Later his team studied the regulation and function of metal-binding proteins in the mouse. He is well known for the long-standing collaboration with Ralph Brinster during which they developed transgenic mouse technology and applied it to studying animal growth, immunology, spermatogenesis and cancer. Currently, his group uses mouse genetics to explore the role of neurotransmitter signaling in mouse physiology and behavior with emphasis on the role of catecholamines in motivation and learning. They also study signaling pathways that control appetite.

Janet Rossant, Ph.D., FRS, FRSC, trained at the Universities of Oxford and Cambridge, and has been in Canada since 1977, first at Brock University and then at the Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, from 1985 to 2005. She is a Senior Scientist in the Developmental & Stem Cell Biology Program and Chief of Research at The Hospital for Sick Children, Toronto. She is also a University Professor, University of Toronto, and Professor in the Departments of Molecular Genetics, Obstetrics/Gynaecology and Pediatrics, University of Toronto. She is Deputy Scientific Director of the Canadian Stem Cell Network and directs the Center for Modeling Human Disease in Toronto, which is undertaking genome-wide mutagenesis in mice to develop new mouse models of human disease. Her research interests center on understanding the genetic control of normal and abnormal development in the early mouse embryo using both cellular and genetic manipulation techniques. She is a Fellow of both the Royal Societies of London and Canada and a Foreign Associate to the National Academy of Science. In 2007, Dr. Rossant was awarded the March of Dimes Prize in Developmental Biology and the Conklin Medal from the Society for Developmental Biology. She was also awarded the Michael Smith Prize of the Canadian Institutes of Health Research (2005).

Hans Schöler, Ph.D., studied Biology at the University of Heidelberg, and earned his doctoral degree from the University of Heidelberg in 1985 at the Centre for Molecular Biology (ZMBH). After heading a research group for Boehringer Mannheim at the Research Center Tutzing and having worked as a staff scientist at the Max Planck Institute for Biophysical Chemistry in Göttingen, Dr. Schöler started as head of a research group at the European Molecular Biology Laboratory (EMBL) in Heidelberg in 1991. In 1994, he obtained his habilitation at the Biological Faculty of the Heidelberg University. He was appointed Professor of Reproductive Physiology at the University of Pennsylvania in 1999 and returned to Germany in 2004 when he was offered the position of Director at the Max Planck Institute for Molecular Biomedicine, Department for Cell and Developmental Biology. Dr. Scholer's research interests are the molecular biology of germline cells and transcriptional regulation of genes in the mammalian germline.

Richard M. Schultz, Ph.D., received his B.A. in Biology from Brandeis University in 1971 and his Ph.D. in Biochemistry from Harvard University in 1975. He then conducted post-doctoral studies on mammalian oocyte maturation at Harvard Medical School. In 1978 he joined the faculty of the Department of Biology at the University of Pennsylvania, where he is currently the Charles and William L. Day Distinguished Professor of Biology and Associate Dean for the Natural Sciences, having previously served as Chair, Department of Biology. He is an Associate Editor of Biology of Reproduction and serves on the editorial board of Developmental Biology. He has served on the NSF panel for Developmental Biology and the NIH Reproductive Biology Study Section. He has also served as the Program Chair for the Society for the Study of Reproduction and as a Director of the SSR. He is the recipient of the Jan Purkinje Medal from the Czech Academy of Science, an NIH MERIT award, the Society of Reproduction and Fertility's Distinguished Scientist Award, and the Society for the Study of Reproduction Research Award. He is also a Fellow of the AAAS. His research program encompasses the cell and molecular biology of oogenesis, fertilization, and preimplantation development. He and his colleagues have published over 270 papers.

Takashi Shinohara, M.D., Ph.D., earned his M.D. degree at Kyoto University in 1993 and PhD degree at the same University in 1996. Dr. Shinohara performed postdoctoral studies with Dr. Ralph Brinster at Penn from 1996 to 2000. He was appointed Assistant Professor of Medical Chemistry at Kyoto University Medical School in 2002, promoted to Associate Professor in 2003, and Full Professor in 2004. Dr. Shinohara's research focuses on the use of spermatogonial stem cells for genetic modification. The Shinohara laboratory recently succeeded in long-term culture of mouse spermatogonial stem cells, and named them germline stem (GS) cells. GS cells have several advantages over ES cells. First, although ES cells are only available during the embryonic period, GS cells can be derived from postnatal animals. Second, they are not tumorigenic and committed to the germline lineage. Given that ES cells with germline potential have been obtained only from mice, the Shinohara GS cell technology may resolve current challenges with ES cells and greatly contribute to the development of new transgenic technologies.

Jamie Thomson, VMD, Ph.D., earned his B.S. in 1981 from the University of Illinois-Champaign, and subsequently entered the VMD-PhD program at the University of Pennsylvania where he received his VMD-PhD in 1988. He performed postdoctoral studies at Oregon Regional Primate Research Center and Residency training in Pathology at the University of Wisconsin. In 1999 he was appointed Assistant Professor at the University of Wisconsin and is currently Director of Regenerative Biology at the Morgridge Institute for Research in Madison, Wisconsin, is a Professor in the Department of Cell and Regenerative Biology at the University of Wisconsin's School of Medicine and Public Health, and a Professor in the Molecular, Cellular, and Developmental Biology Department at the University of California, Santa Barbara. He holds the John D. MacArther Professorship and is the Jim Kress Endowed Chair. He is also a founder and Chief Scientific Officer for Cellular Dynamics International, a Madison-based company producing derivatives of human induced pluripotent stem cells for drug discovery and toxicity testing. He derived the first human embryonic stem (ES) cell line in 1998 and derived human induced pluripotent stem (iPS) cells in 2007. Dr. Thomson has won many awards and prizes, and in 2008 was elected into the National Academy of Sciences. His research focuses on understanding how a cell can maintain or change identity, how a cell chooses between self-renewal and the initial decision to differentiate, and how a differentiated cell with limited developmental potential can be reprogrammed to a pluripotent cell.

Kenneth S. Zaret, Ph.D., received his B.A. in Biology from the University of Rochester in 1977 and his Ph.D. in Biophysics and Genetics from the University of Rochester Medical School in 1982. In 1991 he was appointed Assistant Professor at Brown University, Associate Professor in 1986, and Full Professor in 1995. From 1999 to 2009 he was a Senior Member at Fox Chase Cancer Center. Currently he is the Joseph Leidy Professor in the Department of Cell and Developmental Biology at the University of Pennsylvania School of Medicine. He is also the Associate Director of the University of Pennsylvania's Institute for Regenerative Medicine and the Co-Director of UPenn's Program in Epigenetics. His laboratory discovered pioneer transcription factors, which bind to silent genes in development, loosen the local chromatin structure, and endow competence for gene activity. His laboratory identified a dynamic signaling network that coordinately induces genes for liver and pancreas cell fates in the embryo, and has unveiled how such signaling leads to selective chromatin modifications that affect cell fate choices. Dr. Zaret is currently on the editorial boards of Science, Genes and Development, and Current Opinion in Genetics and Development, the Board of Directors for the International Society for Differentiation, a Fellow of the AAAS, and a MERIT awardee from the National Institutes of Health.

Acknowledgment

I would like to thank Michael Atchison and Narayan Avadhani, as well as Samantha Halter and other members of the committee for their enormous effort in organizing this Symposium. Of course, the enthusiastic support of the School of Veterinary Medicine and the University of Pennsylvania has been critically important. Additionally, we are all indebted to the sponsors whose contributions made everything possible. I am particularly grateful to all the eminent scientists who came to speak and the attendees who make any symposium educational and enjoyable. It is always a pleasure to emphasize that my research accomplishments over the past 50 years are largely a result of the great talent and hard work of my students, collaborators and colleagues to whom I am greatly in debt and fortunate to have had as friends and fellow research scientists.

Ralph Brinster

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Thank you to James Hayden, Scott Spitzer, John Donges,
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