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Ralph L. Brinster, VMD, PhD Earns Prestigious National Medal of Science

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Ralph L. Brinster, VMD, PhD is the first veterinarian to be honored with the National Medal of Science. Photo credit: Scott H. Spitzer.

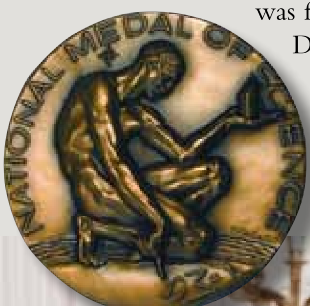
beyond**luck**

Penn Vet's Ralph L. Brinster, VMD, PhD earns National Medal of Science for a lifetime of breakthroughs

BY KELLY STRATTON

If you ask Ralph L. Brinster, VMD, PhD the secret to his success, he will say it is luck. But if you ask anyone else — including colleagues with whom he has worked for more than five decades — they will tell you it is much more than that — it is brilliance and unyielding curiosity.

Dr. Brinster, the Richard King Mellon Professor of Reproductive Physiology at Penn Vet, was one of seven scientists to be honored by President Barack Obama in October 2011 with a 2010 National Medal of Science, the highest accolade bestowed by the United States government on scientists and engineers. Since the award was first established 50 years ago, Dr. Brinster is the first veterinarian and the eighth scientist from Penn to win the National Medal of Science.



President Barack Obama congratulates Dr. Brinster on his National Medal of Science honors in October 2011.

The reason for this highest of honors? Dr. Brinster is often regarded as the father of transgenesis, and it was his research on the manipulation of the mammalian germ line, the cells that give rise to sperm and eggs, for which he was honored. By inserting new genes into the germ line of a developing organism — the process known as transgenesis — researchers can produce animals with selected traits that are indispensible models in understanding life processes and disease.

Penn President Amy Gutmann said, "Ralph Brinster is a trailblazer in the field of reproductive biology and genetics whose work has had inestimable influence in science and medicine. His early findings helped usher in the era of transgenic research and represent foundational aspects of techniques used in genetic engineering, in vitro fertilization and cloning. We are extraordinarily proud that he has received the National Medal of Science in recognition of more than five decades of scientific achievement."

Clearly, it took something more than simple luck.

The Path to Discovery

"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," said Dr. Brinster. "Growing up on a farm was a good environment. You work hard and there are no vacations."

That environment and value system paved the way for Dr. Brinster's long academic career and continued quest for understanding animal development.

After earning a bachelor's degree in animal science from Rutgers University in 1953, Dr. Brinster planned to continue his education, but the Korean War was underway.

Above, Dr. Brinster's childhood had a lasting impression on his future career and goals. Here he's pictured with a Champion Buck, circa 1948. Right, Dr. Brinster served one year in Korea as part of the US Air Force.

Dr. Brinster became a second lieutenant in the United States Air Force and served a year in Korea, after which he finished his military commitment in Texas. Still, he did not lose sight of his intention to attend veterinary school. He started Penn Vet in 1956, putting the GI Bill benefits to good use financing his education.

"I was not a great student as an undergraduate; therefore, I was fortunate to be accepted at Penn Vet," recalled Dr. Brinster. "My intent was to work with large animals, but I became more interested in fertility of animals and germ cell biology; thus, following graduation I began PhD training in physiology at Penn Medicine."

Dr. Brinster earned his PhD in 1964, and made near-immediate and long-lasting impacts in science.

Scientific Breakthroughs and Advances

Dr. Brinster's first major breakthrough came from research leading to his PhD. It was this research in the early 1960s that led to the development of an effective and reliable system in which to observe and experiment on eggs and embryos outside of the body. By using a culture method that consisted of placing mouse embryos in culture medium under an oil layer, Dr. Brinster created a system that would be adopted by the scientific community almost immediately. The system is still used today – virtually unchanged – as the go-to technique for experiments involving mammalian eggs and embryos, including all transgenic work, embryonic stem cell research, in vitro fertilization in humans, cloning and knockout technology.

But creating this system was just a first step for Dr. Brinster. Next he planned to manipulate the germ line and germ cells to further understand their development and regulation.

Thinking back to his childhood on the farm and appreciating the need for producing quality livestock, Dr. Brinster said, "I never lost interest in animal breeding and eventually became more and more interested in fertility, specifically the germ line. I wanted to modify the germ line and germ cells to understand how they function."

Using a mouse model, a standard species in the field of genetics because of their short reproductive time of three weeks and their well-defined genetic background, Dr. Brinster in the early 1970s began his work towards transgenesis. By taking stem cells from mouse teratocarcinomas and injecting them into mouse blastocysts, Dr. Brinster was able to demonstrate, through a series of experiments, that the non-embryo injected cells amazingly became part of the developing mouse tissues and were present in the adult.

Dr. Brinster began his studies at Penn Vet in 1956.

Dr. Brinster working in a lab at Penn Vet, circa 1963.

This series of experiments illustrated that donor cells, which could be cultured in vitro and modified genetically, would become part of the adult mouse. Therefore, such cells could carry genetic change into the mouse and into its germ cells, thus permanently altering the germ line of the animal.

"The germ cells are critical cells," said Dr. Brinster. "They are the only cells in the body that will pass DNA to the next generation."

While he and other scientists continued to develop and perfect this approach with stem cells to alter the germ cells and germ line, Dr. Brinster began to explore and perfect another approach to germ line modification. He initiated these experiments by demonstrating in 1980 that fertilized one-cell mouse eggs could be injected with nucleic acids and survive. He and others then used this approach to introduce new genes into the adult mouse by injecting them into the fertilized egg. He and Richard Palmiter of the University of Washington published a foundation paper in 1981 demonstrating the integration and expression of a transgene in mice. The following year, they published the famous giant mouse experiment, which appeared as the cover story in the journal *Nature* in 1982 and was reported on the front page of newspapers throughout the world. In this transformational experiment, they demonstrated that the growth hormone transgene produced rapid growth and large size in the mouse, and the results catalyzed interest in transgenesis. A picture of the mice appears in most textbooks as representing the beginning of the transgenic revolution.

Long-time collaborators, Richard Palmiter of the University of Washington, and Dr. Brinster were the first to develop transgenic mice.

"When we saw the giant mouse," said Dr. Brinster, "we were surprised and delighted. The giant mouse experiment was a fantastic experiment. That is the experiment that made everybody, including us, stop and say, 'This is incredibly powerful.' That you could enter the germ line and make a change like that. It's the first time man was able to experimentally modify the genetic code that will make the next individual."

The implications of this success are far-reaching and include the possibility of understanding the origin of animal and human diseases, as well as studying the mechanisms by which a single cell, the fertilized egg, develops into a complex animal.

Today in the Brinster Lab

Dr. Brinster has recently turned his attention to spermatogonial stem cells (SSCs), the foundation stem cells of the male germ line and spermatogenesis. SSCs self-renew and generate daughter cells to differentiate into spermatozoa throughout the entire lifespan of the male.

"I started thinking about the male germ line, and I reasoned that if you took cells from a fertile testis and injected them into the seminiferous tubules of an infertile testis, they should be able to restore fertility to the animal," said Dr. Brinster. Of all the testis cells transplanted, only the spermatogonial stem cells would colonize the testis and be able to regenerate complete spermatogenesis. "It was a simple concept; I am surprised no one did it before."

This transplantation system is now used worldwide to study and experiment on male germ line stem cells and spermatogenesis in all species.

Dr. Brinster has used the transplantation system to develop cryopreservation and culture methods for spermatogonial stem cells of rodents and higher species, including primates. These techniques make individual male germ lines and their genetic content biologically immortal for all mammalian species. Clearly, the approaches Dr. Brinster has developed in the male mirror those that he introduced for the female back in the 1960s. They will be useful to preserve and genetically modify the germ lines of farm animals to increase productivity and health. Moreover, the techniques will be valuable in human medicine, particularly for prepubertal boys undergoing treatment for

Where Ralph Brinster may have gotten lucky is in his family life. He and his wife Elaine Brinster, RN (of whom he says, "She is much smarter than me") have raised .four children — two daughters and two sons — all of whom have no doubt been influenced by their father's hard work. All four children earned bachelor's degrees from Penn and all four have achieved higher degrees.

Son Clayton J. Brinster also earned an MD from the Perelman School of Medicine at Penn and has just earned a vascular fellowship at Massachusetts General Hospital.

Kristen A. Brinster Waddington went on to earn her juris doctorate from the University of Baltimore School of Law and is now a partner at Sutherland & Brinster, PA.

Lauren R. Brinster followed in her father's footsteps and earned a VMD from Penn Vet in 1990. Today, she is a pathologist at the National Institutes of Health.

Son Derek R. Brinster went on to earn his MD from the Perelman School of Medicine at the University of Pennsylvania followed by a general surgery residency at Penn Medicine. Today, he is an Associate Professor of Surgery at Virginia Commonwealth University, Medical College of Virginia.

Above, the Brinsters from left to right: Clayton, Kristen, Dr. Brinster, Mrs. Brinster, Lauren, Derek at the National Medal of Science Gala at the White House in October 2011.

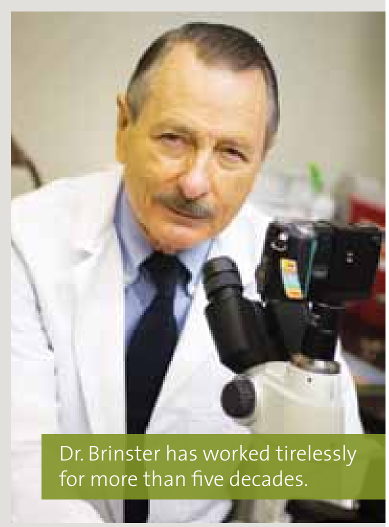
cancer. Approximately 80 percent of these boys recover from the cancer, but one-third are infertile as a result of treatment. Preservation of a testicular tissue biopsy before treatment can preserve the stem cells, and the methods Dr. Brinster has developed can be used to increase the number of SSCs and remove any contaminating cancer cells before reintroduction into the patient to restore fertility.

"There is still much to be learned about male germ cells," said Dr. Brinster. "We and others are particularly interested in the biology of the stem cells as well as the differentiating germ cells. Extremely important are the regulatory mechanisms involved in the self-renewal of the stem cell and the differentiation of the daughter cells as they progress toward spermatozoa. Clearly, the genetic content of the stem cell and germ cell is important, but it is now established that the surrounding cells, the niche cells, play a critical role, perhaps the most critical role, in determining the fate of the stem cell and its differentiating daughter cells."

The importance of the surrounding niche cells of the SSC and germ cells was dramatically demonstrated in a recent experiment in Dr. Brinster's laboratory. When male mice were housed with a female or without a female, it was found that the males residing with females had a reproductive lifespan 20 percent longer than those housed alone. The stimuli clearly came from outside the body through the surrounding somatic niche cells to influence the germ line of the male and its reproductive health and longevity.

The effect of surrounding somatic cells on the function of stem cells has been shown in other systems as well. For example, "In humans, exercise produces more new brain cells. External stimuli dramatically influence the niche cell, which in turn influences the stem cell," said Dr. Brinster. "How can we make these niche cells healthier? An obvious approach is that beneficial external stimuli could be used to increase the function of niche cells to support their associated stem cells."

The Legacy



Dr. Brinster has worked tirelessly for more than five decades.

Among his scientific peers, the work of Dr. Brinster has been influential and has opened exciting new areas of investigation. And many are proud of his achievements.

"Ralph's contributions to the field of reproductive biology, transgenesis and stem cell biology are monumental," said Narayan Avadhani, PhD, chair, Department of Animal Biology, Penn Vet. "Over the past 50 years, he has consistently led the field making many pivotal contributions. In my scientific career I have rarely seen a scientist who is so focused,

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thorough, determined and dedicated to his research as Ralph."

"Of course, my primary interest remains to understand the biology of the mammalian germ line, and secondarily, to determine how the germ line can be manipulated to improve the health and life of animals and man," said Dr. Brinster. Major questions remain and of course always will. "How can we use transgenesis, stem cells, and the germ line to cure human disease? How does an animal develop from a single cell? This is an amazing process. If we can alter the process to cure disease, that would be a powerful and wonderful outcome."

"I am incredibly proud of Ralph," said Joan C. Hendricks, the Gilbert S. Kahn Dean of Veterinary Medicine. "He is undoubtedly the top veterinary scientist in the world, especially if you consider his sustained excellence and demonstrated brilliance over at least five decades, and he is one of the top biomedical scientists anywhere. Penn Vet is thrilled that we are able to count Dr. Brinster as one of our own brilliant scientists."

Still, Dr. Brinster remains humble.

"The actual advance in science is immortal. When I am gone, the information and science will remain and continue to be important to the future of mankind," said Dr. Brinster. "Throughout the years I have worked with many talented students, colleagues and collaborators who have been both brilliant and hard-working. I have just been around and kept the focus on germ cells, the germ line and genes. And of course, luck has been on our side."

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times and less pain to members of the shelter animal medicine community. They would provide spays for those animals still looking for their forever homes, but needed a fund from which to subsidize these procedures.

Having seen what advanced medical technology combined with the best clinical expertise can accomplish, Connie and Alan decided to give a naming gift to complete the construction of the minimally invasive surgery suite, and also to start an endowment that would enable Ryan Hospital clinicians to perform minimally invasive spays on some of the most deserving patients, shelter animals. Seven years in the planning, this dream for what better care would be available for pets became a reality because of Connie and Alan's generosity and love of animals.

Since its opening on October 3, 2011 – a year after Max's first visit to Ryan Hospital – The Buerger Family Foundation Minimally Invasive Surgery Suite has served many routine and some extremely challenging cases. The suite has also become a hub for exchanging knowledge and advancing current veterinary medicine procedures and its teleconferencing capabilities permit remote consultations and broader teaching opportunities as far away as the Veterinary School in Azabu, Japan, among others.

When Connie, Alan, Reid and Krista came to visit The Buerger Family Surgery Suite after its opening, they experienced first-hand the gratitude and excitement of all Ryan Hospital communities. Alan remarked that Penn Vet's Ryan Hospital has always been there to make sure that their dogs, which they deem members of their family, received the best, compassionate care and that they were thrilled to support such a prodigious institution.

Krista and Reid's own philanthropy to support the oncology section at Ryan Hospital, and Krista's leadership on the Penn Vet Board of Overseers, have contributed immensely to Penn Vet. Ryan Hospital is fortunate to have friends like Connie, Alan, Reid and Krista – they help to ensure Penn Vet's leadership position in the field of veterinary medicine.