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Abstract

At a symposium convened on March 8, 2007 by the Institute on Aging at the University of Pennsylvania, researchers from the University's Schools of Medicine and Veterinary Medicine explored the convergence of aging research emerging from the two schools. Studies in human patients, animal models, and companion animals have revealed different but complementary aspects of the aging process, ranging from fundamental biologic aspects of aging to the treatment of age-related diseases, both experimentally and in clinical practice. Participants concluded that neither animal nor human research alone will provide answers to most questions about the aging process. Instead, an optimal translational research model supports a bidirectional flow of information from animal models to clinical research.

Keywords

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Disciplines

Disease Modeling | Geriatrics | Veterinary Medicine

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Exploring human/animal intersections: Converging lines of evidence in comparative models of aging

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Abstract

At a symposium convened on March 8, 2007 by the Institute on Aging at the University of Pennsylvania, researchers from the University's Schools of Medicine and Veterinary Medicine explored the convergence of aging research emerging from the two schools. Studies in human patients, animal models, and companion animals have revealed different but complementary aspects of the aging process, ranging from fundamental biologic aspects of aging to the treatment of age-related diseases, both experimentally and in clinical practice. Participants concluded that neither animal nor human research alone will provide answers to most questions about the aging process. Instead, an optimal translational research model supports a bidirectional flow of information from animal models to clinical research.

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The distance between the medical and veterinary schools at the University of Pennsylvania is small, both physically and intellectually. Yet investigators from the two schools bring different perspectives to the research they conduct, even when they are probing similar questions. In the most simplistic terms, veterinarians view animals as patients, whereas medical researchers, even those who trained and work at veterinary schools, often view them strictly in terms of their ability to model human disease.

At a symposium convened on March 8, 2007 explicitly to explore the convergence of aging research emerging from the two schools, participants demonstrated that these two divergent perspectives need not be in conflict. Molecular physiologist H. Lee Sweeney, who studies the basic design and function of the molecular motor, myosin, said that as a result of his collaborations with veterinary cardiologist Meg Sleeper, he began to think of companion animals (dogs and cats) as veterinary patients rather than as dog and cat models. "The paradigm in my mind has shifted to the point where we really are trying to develop veterinary therapies

that will, in many ways, pilot and give us long-term information about safety and efficacy for the same strategies that someday we would like to take to humans.”

Veterinary ophthalmologist and geneticist Gustavo Aguirre, who studies retinal degeneration in dogs, cited four major reasons for studying animal models: (1) gene discovery, (2) characterization of disease mechanisms, (3) development of novel therapies, and (4) translation of potential therapies to humans. Small animal models, particularly mouse and rat, have been particularly valuable because their genomes have been mapped and scientists have generated thousands of inbred strains with which they can characterize and compare different genes.

Yet mouse and rat models have limitations as well. Physiologically, they are far removed from humans. For example, they are poor models for studying cardiovascular disease because their small size results in hearts with very small stroke volumes but high heart rates to modulate cardiac output; thus they use entirely different strategies to adapt to environmentally or genetically induced abnormalities in cardiac function. In contrast, dogs and cats have hearts that respond much more similarly to humans. Moreover, dogs and cats suffer from many, if not all, of the cardiovascular diseases that affect humans. Dogs are also better than mice for studying viral-based gene transfer because of their relatively sophisticated immune systems, which, as in humans, make gene therapy more problematic.

Companion animals not only acquire many diseases that are similar to humans, but the interventions, including surgical interventions, are also similar in many cases. In addition, they offer a degree of genetic homogeneity far greater than that seen in humans. Not only are isolated breeding populations far more homogeneous than the relatively homogeneous human populations that have been studied, such as Amish and Finnish populations, but extensive genomic resources are also available, including detailed information on pedigrees.

Of course, dogs and cats cannot model all human diseases. For example, dogs and cats lack a foveomacular region in the eye, making their use in Dr Aguirre’s research on retinal diseases somewhat problematic. “We have to end a maculocentric view of life to use dogs and cats and instead look at other phenotypes that might provide insight,” he said.

1. What can dogs and cats tell us about human aging?

Because dogs and cats acquire age-related diseases similar to those that humans do and live in similar environments but tend to live shorter lives, they offer a window into human diseases and how to treat them, even though veterinary researchers might intend only to relieve suffering in their animal patients. For example, although most studies of animal nutrition have been conducted in agricultural animals by investigators seeking to optimize feed efficiency and growth, dogs have provided extensive information on how diet influences the aging process, according to veterinarian and nutritionist Kathryn Michel. In one study, funded by Nestlé Purina, Kealy et al [1] studied the effect of diet restriction in Labrador retrievers. Dogs were fed either a normal diet or a restricted diet containing 25% fewer calories. Dogs fed the restricted diet weighed less, developed degenerative joint disease later in life, and had a longer life span in comparison to the full-fed dogs.

Dennis Lawler, a co-investigator in the Kealy study, said that in various species, the effect of diet restriction is robust but not universal. For example, in rodents, some tumors have been shown to respond poorly to diet restriction. Moreover, the same degree of calorie restriction in the mouse or dog might not result in proportional changes in life span, further clouding the implications for human diet restriction.

Other studies have examined the role of diet on cognitive function in aging dogs. On the basis of the theory that cognitive decline in aging animals results from oxidative stress, Milgram et

al [2] gave a diet rich in antioxidants and mitochondrial cofactors to both old and young animals and then tested them by using an oddity discrimination task of increasing difficulty. Although old animals did not perform as well as young animals, this age-associated decline was mitigated in the animals fed the antioxidant-enriched diet.

The influence of diet on aging might be transferable to humans, and many people are already promoting antioxidant-enriched diets as a means of combating the effects of aging. Yet the transferability of animal research to humans and vice versa might not always be so simple. For example, Rebecka S. Hess, a veterinarian who studies canine diabetes mellitus, looked to humans as a model to help her better understand the genetics of diabetes mellitus in dogs. Unfortunately, she said, humans are not good animal models for studying the genetic aspects of canine diabetes mellitus because they are unpredictable breeders, their pedigrees are not always known, they have a long life span, and the environmental factors they encounter vary significantly.

Instead, she chose to study Samoyeds and Australian terriers, two dog breeds that have been shown to have a high risk of developing diabetes mellitus. Both are relatively small breeds and thus have a limited and more homogeneous genetic pool. Hess asked whether canine diabetes more closely resembles human type 1 or type 2 diabetes. She found evidence that it actually resembles both. In untreated Samoyeds with familial diabetes, about 50% have anti-beta cell antibodies and require insulin, suggesting a similarity to type 1 diabetes, yet overweight Samoyeds also develop diabetes in middle age, suggesting more of a similarity to type 2 diabetes. She went on to study genetic factors in diabetic Australian Terriers and found that these dogs were more likely to have certain major histocompatibility complex alleles that suggest, by homology with the human disease, an autoimmune etiology.

Hess's research, while focused on understanding diabetes as it occurs naturally in dogs, is likely to have implications for human disease, particularly because in both humans and dogs the disease is multifactorial, with genetics, immunity, nutrition, and other environmental factors all playing significant roles. Dogs have already proved their value as a model for preclinical testing of human diabetes treatments.

Similarly, dogs and cats are afflicted with many forms of heart disease that are common in humans. According to veterinary cardiologist Meg Sleeper, degenerative valve disease (DVD) is the most common heart disease seen in the veterinary hospital at the University of Pennsylvania, with as many as five or six new cases seen each week. There have been many studies evaluating DVD in dogs, primarily with the aim of finding better ways to treat the animals, said Sleeper, but these dogs also have enormous potential as a model for valve disease in humans. For example, dog models have been used to identify biomarkers of heart diseases, to study genetic and molecular mechanisms of the diseases, and to evaluate potential treatments. Currently, veterinary school investigators are collaborating with investigators at the medical school on studies of therapeutic gene transfer to treat dilated cardiomyopathy in dogs as well as with the pharmaceutical industry and other academic institutions on many other studies examining basic and clinical aspects of heart disease.

2. Examining the fundamental processes of aging in mice

Although dog and cat models might be particularly useful for studying diseases common in aging, such as heart disease, diabetes, and osteoporosis; rodent models have proved valuable for studying the fundamental processes of aging such as cellular senescence, the immunobiology of aging, and neurodegeneration. One of the advantages of using mouse models to study human disease is that even when the fundamental processes being studied are vastly different across the two species, genetic engineering can be used to generate mice with more human-like physiologic processes. For example, Brad Johnson studies telomeres, DNA

sequences that cap the ends of chromosomes and protect them from degradation and from recombination with other chromosomes during mitosis. However, telomeres get shorter with each cell division, and telomere shortening can lead to cellular senescence, an irreversible state of growth arrest. Thus, telomere shortening puts the brakes on unlimited cell proliferation and so inhibits the growth of cancer cells, but at the same time it might limit cell division needed to maintain tissue function and thus contribute to age-related disease. In other words, although telomeres guard against cancer in younger people, they might also accelerate the aging process.

Telomere shortening is counteracted by the action of the enzyme telomerase, although telomerase does not appear sufficient to prevent telomere shortening with age. Unlike humans, mice lacking telomerase do not age more rapidly, and, in fact, a graduate student in Johnson's lab demonstrated an inverse correlation between life span and telomere length in mammals. Mice, for example, have longer telomeres and more telomerase than do humans, and they are less sensitive to the loss of telomerase, observations that all support the notion that telomere biology plays a role in human, but not mouse, aging. As a result, aging related to telomere biology cannot be modeled in mice without significant modifications.

Johnson has been particularly interested in the role of telomeres in Werner's syndrome and Bloom syndrome, two genetic disorders associated with premature aging. These syndromes are associated with loss-of-function mutations in *Wrn* and *Blm*, which encode helicases in the RecQ family of helicases. In mice, however, loss of *Wrn* or *Blm* has no significant effect. Johnson hypothesized that the difference in sensitivity to loss of *Wrn* and *Blm* might be due to a difference in telomeres, with longer telomeres and higher telomerase levels making mice less dependent on these helicases. Therefore, he engineered mice that not only had *Wrn* and *Blm* mutations but also lacked the telomerase RNA template *Terc*. These triple mutant mice displayed pathology similar to what is seen in Werner's syndrome and Bloom syndrome and also had dysfunctional telomeres, suggesting that, indeed, telomere dysfunction contributes to the pathogenesis of these two syndromes [3] and allowing Johnson to further investigate telomere biology in the mouse model.

Mice with *Wrn* and *Terc* mutations are not only used to study fundamental aspects of aging, but they are also being used as models of osteoporosis, said Robert Pignolo, a physician-scientist at the Ralston-Penn Clinic for Osteoporosis and Related Bone Disorders. Pignolo's double-mutant mice have genome instability and premature bone loss that occurs in an age-related fashion. Pignolo's research suggests that the *Wrn* and *Terc* mutations primarily affect osteoblast but not osteoclast differentiation in bone marrow stem cells, recapitulating the mechanism of senile bone loss in humans.

Mouse models have also been used extensively to study the immunobiology of aging. According to immunologist Michael Cancro, aging is associated with an overarching syndrome called immune senescence, which encompasses alterations in immune responsiveness, immune system physiology, and immunoregulation. As a result of immune senescence, overall immune responses decline as a person ages, whereas the incidence of autoimmune syndromes, such as systemic lupus erythematosus and rheumatoid arthritis, increases.

Cancro attributes these changes in the immune system to altered lymphocyte homeostasis and has been using mice to study how the numbers and composition of lymphocyte pools change as individuals age. Cancro focuses his research on B lymphocytes, which are responsible for humoral immunity. B lymphocytes go through a series of developmental stages from their generation and initial maturation in the bone marrow through several transitional stages to finally become mature B cells in the periphery. Cancro and colleagues have shown that the subsets of B cells in the bone marrow change with age, with reduced production of pre-B cells in old mice. However, despite that reduced production, the effect on mature B cells is less than

one would predict, suggesting that homeostatic mechanisms compensate for reduced production. Understanding these and other homeostatic mechanisms might help explain the phenomenon of immune senescence as well as reveal what goes wrong, for example, in autoimmune diseases.

3. Which mouse model?

Developing animal models of human disease is, in itself, a complex science. Virginia Lee, a neuroscientist who specializes in neurodegenerative diseases, described the efforts her lab has taken during the past 7 years to generate a good model of tauopathies, human degenerative diseases such as Alzheimer's disease that result from the neuronal accumulation of filamentous tau protein. Generating animal models of human diseases requires consideration of a number of factors. An optimal animal model should simulate the disease, recapitulate characteristics of the disease, mirror the disease behaviorally, and respond to appropriate therapeutic agents. The most successful uses of animal models thus far, said Lee, have been in recapitulating the pathology of disease.

Lee's lab developed six tau transgenic mouse models, searching for one that displays the pathology seen in humans with tauopathies: neurofibrillary tangles with tau protein in both neurons and glial cells, as well as early pathogenic effects of tau neuropathology, neuron loss similar to that seen in humans, and a shortened life span. In a recent article [4] Lee and colleagues introduced a line of P301S tau transgenic mice. P301S is a tau gene mutation that causes a form of rapidly lethal and early onset presenile dementia called frontotemporal dementia with Parkinsonism-17 (FTDP-17). The P301S mice they created recapitulated almost all of the neuropathologic features of human P301S tauopathies, she said, showing early neurodegenerative changes, motor weakness, and muscular atrophy.

These mice have allowed Lee and colleagues to better understand the mechanisms at work in the tauopathies, in particular that synaptic pathology and microglial activation are the earliest manifestations of the neurodegenerative process and that early microglial activation precedes tau pathology. They further showed that the immunosuppressant FK506 attenuated tau pathology and extended the lives of the mutant mice, demonstrating the feasibility of targeting microglia-mediated neuroinflammation to develop treatments for neurodegenerative disease.

4. Bidirectional animal-human research models

Neither animal nor human research alone will provide answers to most questions about the aging process. Rather, an optimal translational research model supports a bidirectional flow of information from animal models to clinical research, said Karen Teff, a nutrition and obesity researcher who directs translational research at University of Pennsylvania's Institute of Diabetes, Obesity, and Metabolism. Just as obesity in humans has reached epidemic proportions, a similar trend is seen in people's pets, according to Teff. Genetic and environmental factors play a role in both animal and human obesity, and the biologic pathways that influence obesity might be similar. Yet although animal data have provided key information about pathways involved in obesity, human data have forced a reexamination of those data and vice versa.

Teff and others use inbred mouse and rat models to examine the roles of two opposing hormones, leptin and ghrelin. Leptin, secreted by adipocytes in adipose tissue, decreases food intake and adiposity; whereas ghrelin, secreted by the stomach, is thought to increase food intake. When leptin was first identified in obese mice in 1994, it changed the course of obesity research, said Teff, because it stimulated very sophisticated research about how body weight is regulated and because it drew the attention of the pharmaceutical industry. "At the time, people thought leptin was going to be the magic bullet for the cure for obesity," said Teff.

However, a few years later, human studies showed that only a handful of people had leptin deficiency, whereas most obese people were, in fact, hyperleptinemic. This observation forced a reanalysis of the role leptin plays in human obesity, eventually leading to the theory of central leptin resistance, which posits that either leptin is not getting into the brain or that it is not recognized once it reaches the brain.

Meanwhile, administration of ghrelin was shown to stimulate food intake in rodents, with plasma ghrelin levels increased before a meal and then repressed by nutrient ingestion. However, human studies showed that the effect of ghrelin was attenuated in obese people, leading to further animal studies that showed that knocking out ghrelin had no effect on food intake or body weight. These animal data, in other words, argued against what was thought about the role of ghrelin.

Teff argued that one of the problems with studying a complex phenomenon such as weight gain in animals is that the psychological, sociocultural, and socioeconomic factors that influence weight gain might be overriding some of the basic physiologic mechanisms in humans. “And I think this is where the animal models are going to fail us, because it’s very hard to ask these questions in animals,” she said.

5. Companion animals in clinical studies of diseases of aging

As treatment options for age-related diseases in animals become available, veterinary researchers grapple with similar problems as human clinicians do with regard to conducting clinical trials: how to recruit patients and what are the appropriate end points to measure. Add to this the fact that pharmaceutical companies commit far less money to animal than to human clinical studies, and the problem is magnified. However, as became evident at this symposium, animal studies have much knowledge to offer in terms of the pathogenesis and treatment of human disease.

The only impediment to conducting these trials is funding, said Joan Hendricks, Dean of the University of Pennsylvania Veterinary School. The infrastructure is already in place, she said, including a well-trained staff of clinical trial nurses to conduct these trials. Moreover, she said, many pet owners are eager to enroll their pets in clinical studies; they are close observers and are willing to fill out long questionnaires about their pet’s behavior. An additional advantage of using companion animals for some studies is that the animals are in their natural environment and represent a cross-sectional sample. Potential disadvantages include the difficulty of monitoring compliance with dietary regimens, although there might be engineering solutions to the problem of measuring food intake, such as introducing tracers into the food and then monitoring the fate of those tracers. Such technologies might be more acceptable in animal studies than they would be in human trials.

Given the enormous potential benefit that research on companion animals offers and the wealth of genetic information already available, the question of funding becomes paramount. As mentioned previously, the pet food industry has funded some studies of the impact of diet on aging and cognition, yet that industry lacks sufficient resources to support the scope of research needed. The Department of Defense has also funded some dog studies because of the need to extend the lives of highly trained guard dogs. Allan Pack suggested that an international consortium, similar to the one that formed around mouse genetics, is needed to fully exploit the potential of research on companion animals. Moreover, he said that the commitment of all sectors—the pharmaceutical industry and other private companies, academia, and government—will be required to fund the types of studies that will yield benefits for both humans and their pets.

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