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An open letter concerning the scientific underpinnings of the proposed new beagle facility at Grimston.

Animals such as dogs have historically been used in science, research, and testing for many diverse reasons, for example in order to gain more knowledge about living organisms *per se*. However, the use of dogs in medication testing is clearly predicated on the notion that dogs will respond to medicines as humans respond and thus can *predict* whether a medicine will be efficacious and or dangerous to humans. This assumed ability to predict human response is often cited as justification for using animals like dogs in such testing, as society clearly would not be comfortable with the process were it not guaranteed to be scientifically viable. This is illustrated by Giles writing in *Nature*:

> In the contentious world of animal research, one question surfaces time and again: how useful are animal experiments as a way to prepare for trials of medical treatments in humans? *The issue is crucial, as public opinion is behind animal research only if it helps develop better drugs*. Consequently, scientists defending animal experiments insist they are essential for safe clinical trials, whereas animal-rights activists vehemently maintain that they are useless. (Giles 2006) (Emphasis added.)

The Institute for Laboratory Animal Research (ILAR 2004) and other proponents of using animals in research (Frey 1983) have views similar to Giles. An editorial in *Nature* in 2009 reinforced the above stating: "Animal-research policies need to be guided by a moral compass—a consensus of what people find acceptable and unacceptable." (Editorial 2009)

The scientific literature is *unambiguous* on the fact that animal models, such as dogs, **cannot** predict human response to medicines and disease. Furthermore, the notion that animal models can predict human response to medicines and disease has been disproven both empirically and on theoretical grounds. Moreover, we are now entering the age of personalized medicine, which involves the ability of physicians to treat patients based on their own unique genetic makeup. (See *FAQs About the Use of Animals in Science: A*

handbook for the scientifically perplexed and or *Animal Models in Light of Evolution* for more.)

Considering the role dogs play in society, using them in meaningless efforts such as toxicity testing would clearly not be acceptable to society. Yet the practice persists. Why? The vested interest groups frequently use the scare tactic of *your dog or your child* in order to convince society that testing on dogs is necessary in order to ensure that medications are safe for them and their children.

Not only is the scientific literature unambiguous on the fact that animal models, such as dogs, cannot predict how humans will respond to drugs and disease, the pharmaceutical industry has also been outspoken on this. Paul et al.:

> Compounds fail for many reasons, but some are more avoidable than others. Poor oral bioavailability, pharmacokinetic properties or toxicity issues that are not predicted by animal pharmacology models or by preclinical ADMET (absorption, distribution, metabolism, excretion and toxicity) studies, resulting in overlap of efficacious and toxic doses (and thus lower than desired margins of safety) are often reasons for Phase I and Phase II attrition . . . As highlighted by Kola and Landis, clinical attrition rates during the 1990s were higher for central nervous system (CNS) disorders and oncology, with more than 70% of compounds in oncology failing in Phase II and 59% failing in Phase III. The higher failure rates in these areas are in part due to the relatively unprecedented nature of the drug targets being pursued and to the lack of animal models with a strong capacity to predict human efficacy. (Paul et al. 2010)

On January 12, 2006, then U.S. Secretary of Health and Human Services Mike Leavitt stated:

> Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies. (FDA 2006)

Sankar writing in *The Scientist* 2005:

> The typical compound entering a Phase I clinical trial has been through roughly a decade of rigorous pre-clinical testing, but still only has an 8% chance of reaching the market. Some of this high attrition rate is due to toxicity that shows up only in late-stage clinical trials, or worse, after a drug is approved. Part of the problem is that the toxicity is assessed in the later stages of drug development, after large numbers of compounds have been screened for activity and solubility, and the best produced in sufficient quantities for animal studies. Traditionally, compounds are tested in two animal species – typically, the rat and the dog. But the process is far from ideal. Animal studies can be time-consuming, require large quantities of product, and still fail to predict a safety problem that can ultimately halt

> development . . . Rats and humans are 90% identical at the genetic level, notes Howard Jacob, cofounder of Wauwatosa, Wisconsin-based PhysioGenix. However, the majority of the drugs shown to be safe in animals end up failing in clinical trials. "There is only 10% predictive power, since 90% of drugs fail in the human trials" in the traditional toxicology tests involving rats, says Jacob. (Sankar 2005)

Kola and Landis writing in *Nature Reviews Drug Discovery*:

> The major causes of attrition in the clinic in 2000 were lack of efficacy (accounting for approximately 30% of failures) and safety (toxicology and clinical safety accounting for a further approximately 30%). The lack of efficacy might be contributing more significantly to therapeutic areas in which animal models of efficacy are notoriously unpredictive (Kola and Landis 2004)

Seligmann writing in *Drug Discovery World* Winter 2004/5:

> It is well known that the rat, dog and sometimes non-human primate models used for toxicological testing often do not predict human response, and thus drug failures occur during clinical development or even later due to unanticipated adverse effects in humans. (Seligmann 2004/5)

I have praised the pharmaceutical industry for admitting that animal models are not predictive and working to developing methods that will allow a human to know what a drug is going to do to her before she takes it. But there is another industry closely associated with Pharma that is not so honest. Breeders of animals destined for laboratories where drugs are tested make billions from sales and their claims about the importance of their enterprise are not subtle. They, and their representatives, present the false dichotomy of your dog or your child whenever their livelihoods are threatened. David Pruce, pharmacist and Interim (current as of June 11, 2011) Chief Executive of Understanding Animal Research, in an interview on the BBC about the proposed beagle facility stated:

> . . . at the end of the day you have to get to a stage where you need to see what the medicine does in a whole animal or in a whole person and what we want as patients is to know that a medicine when it comes on the market is absolutely safe. So at the moment yes we still do need to use animals.

This was echoed by Barbara Davies, also from Understanding Animal Research, who was quoted in the *Yorkshire Post* as saying: “All mainstream medical and scientific organisations around the world agree that animals are essential in scientific research, medicines development and safety testing.” In both these statements, Understanding Animal Research is clearly stating that animal models can predict human response to drugs and disease.

Make no mistake; prediction is part and parcel of what science does. Albert Hofstadter stated in 1951: “Prediction and explanation are the two main functions of scientific knowledge.” [(Hofstadter 1951) p339] In terms of assessing medication safety and efficacy, prediction is what counts! The notion that animal models can predict human response to drugs and disease has been disproved both empirically and on theoretical grounds. Yet vested interest groups continue to claim children will die if society stops testing on animals.

Building a facility to breed and sell more dogs that will be used in a process that is known to be a failure will not help prevent adverse drug reactions or find cures for diseases like Alzheimer’s, cancer, heart disease, and AIDS.

Sincerely,
Ray Greek MD

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