The Use of Nonhuman Animals in Biomedical Research

Dario L. Ringach, PhD

Abstract: Opposition to the use of animals in biomedical research rests on diverse scientific and ethical arguments. Here I offer a response to key objections and argue that the responsible use of animals in biomedical research with the goal of advancing medical knowledge, science and human health, is scientifically and morally justified. My views are unlikely to be shared uniformly across the scientific community. Thus, I hope this personal perspective persuades other scientists, public health officials, scientific organizations and our academic leadership to join the debate and invites opponents of animal research to create an atmosphere where civil discourse can take place, free of threats and intimidation. The public deserves an open and honest debate on this important topic.

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Scientists have a duty to talk to the public.[1] Why? Because social policies need to be decided on the basis of rational grounds and facts. These include important issues ranging from climate change, to the goals of the space program, to the protection of endangered species, to the use of embryonic stem cells or animals in biomedical research. Both the public and policy makers need to understand not only the scientific justification for our work but also, in some cases, why we deem our studies to be morally justifiable.

The time is ripe for a more open, public and honest debate about the role of scientific experimentation in animals. What follows are some of my thoughts on this topic. I hope this perspective encourages other scientists to join the discussion and prompts opponents of animal research to create an atmosphere where civil discourse can take place, free of the threats, harassment and intimidation that are increasingly directed at biomedical scientists and their families.[2,3]

Criticism to the use of animals in biomedical research rests on varied scientific and ethical arguments. The discussion below is necessarily incomplete but represents an initial effort to answer some key objections. We start by addressing the opposition's claims regarding the validity of the scientific work to human health and then turn our attention to ethical issues.

ARGUMENTS AGAINST THE USE OF ANIMALS IN SCIENTIFIC RESEARCH

Let us first consider some common criticisms directed at the scientific basis for animal research.

From the Departments of Neurobiology and Psychology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California.

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Correspondence: Dario L. Ringach, PhD, Departments of Neurobiology and Psychology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095 (E-mail: dario@ucla.edu).

CLAIM: HUMANS DO NOT BENEFIT FROM ANIMAL RESEARCH

One extreme view holds that information gathered from animal research cannot, even in principle, be used to improve human health. It is often accompanied by catchy slogans such as "If society funds mouse models of cancer, we will find more cures for cancer in mice."[4] It is argued that the physiology of animals and humans are too different to allow results from animal research to be extrapolated to humans.[5]

Such a blanket statement is falsified by numerous cases where experimentation on animals has demonstrably contributed to medical breakthroughs. The experiments on cardiovascular and pulmonary function in animals that began with Harvey and continued with the Oxford physiologists[6] established the understanding of what the heart and lungs do and how they do it, on which the modern practice of internal medicine rests. Modern medical practice is inconceivable in the absence of the insights gained from these experiments. Anticoagulants were first isolated in dogs; insulin was discovered in dogs and purified in rabbits; lung surfactants were first extracted and studied in dogs; rabbits were used in the development of *in vitro* fertilization; mice in the development of efficient breast cancer drugs and so on.

For the sake of completeness, it must be noted that the other extreme—the notion that all medical advances are a result of animal research—is false as well. Important medical advances, such as sanitation and the discovery of aspirin, were conducted without the use of animals.

CLAIM: ANIMAL RESEARCH HAS A VERY LOW SUCCESS RATE

Here the claim is not that animal research has never produced benefits, but it has done so with a very low success rate, which in the minds of our opponents is enough to deem the work unacceptable.[5,7] But what does very low mean exactly? Is the term meant to be interpreted in absolute or relative terms? If the comparison is relative, then very low relative to what?

Absolute Interpretation

If one is to interpret the success rate as an absolute figure, then the assertion does little more than restate what is an inherent property of the scientific method.[8] Scientific research involves a continuous cycle of 3 phases: postulating a theory that can account for the existing data, generating novel predictions from the theory and testing them experimentally. While searching for answers to difficult problems (such as developing a cure for cancer), it is expected for many paths to lead to dead ends. This is a feature of science, not a bug. The scientific method allows us to rule out hypotheses proven wrong by data and systematically narrow down the list of possible explanations until we converge on an answer. History has shown, time and again, that such a strategy works, producing advances in everything from mathematics and physics, to life sciences and medicine. Incorrect hypotheses and negative findings are integral, fundamental and inseparable components of the scientific method.

Grasping the principles of the scientific method is not difficult. Accepting its consequences in the field of animal is hard. The implication is one we would naturally resist: animals, if used in scientific studies, will sometimes be used in experiments that do not yield immediate, tangible benefits.

We must understand and accept the fact that science does not provide recipes. There is no recipe that can ensure a particular type of work that will lead to a unified theory of physics. There is no line of research guaranteed to yield a proof or a rejection of a mathematical conjecture. There is no recipe that can ensure a particular type of work, whether using humans or animals, will lead to cures for cancer, paralysis or autism. Anyone claiming to know with certainty where the answers are to be found, or where they are not to be found, is simply not credible.

Relative Interpretation

An alternative interpretation is that the success rate of animal research should be interpreted as relative to a baseline. The critics are vague about what this baseline is, but the implication seems to be the success rate one would achieve solely by human-based medical research.[7]

This claim can be verified because there is plenty of scientific research performed with human subjects alone, from cancer to Alzheimer's and Parkinson's disease. If there was an obvious advantage for such work in yielding new cures and therapies, we would certainly know by now. To the best of my knowledge, there are no data to support this view.

One may also interpret the baseline success rate as the one we all wish it could be. Patients and families that anxiously await new developments to treat their loved ones surely must feel the rate at which new therapies are generated is low. So does everyone else, including the physicians who care for the patients and the scientists who do their best to develop new cures and therapies as fast as they possibly can. We all wish that effective treatments could be developed faster. In the absence of a viable alternative, this lament is hardly an argument against the use of animals in medical research.

Finally, and perhaps most surprising, it has been stated that the success rate of animal research is comparable to that of astrology.[9] Our discoveries, we are told, are mere chance events that are not causally related to our investigations. The origin of the claim rests on anecdotes describing serendipitous discoveries in science. Yet, as Louis Pasteur commented, "Chance favors the prepared mind." What he meant, of course, is that an accidental observation will generate a finding only in the mind of someone who has been thinking about the problems for some time, and who is a keen observer.

CLAIM: RESEARCHERS MUST PROVE ANIMALS ARE NECESSARY FOR THEIR WORK

Faced with irrefutable causal links between animal studies and medical breakthroughs, opponents of animal research typically respond with a claim and a demand of their own.

The claim is that such research represents work performed decades ago.[5,7] On one hand, they accept that we have learned much about the respiratory, circulatory and digestive systems from animals that has been relevant for human health. On the other, they contend that the problems we face today are more complex and subtle. There is little or nothing left to be understood about basic biological function from animals that is relevant to human conditions. In other words, the entire field of animal research is declared to be exhausted of fundamental results.

Any scientist will be perplexed and baffled by such statements. Surely, the claims must come from those with a poor appreciation of the time scales involved in bringing basic research results to the clinic. Indeed, it can take many years, even decades. For example, consider the development of electrocardiography, which relied on classic studies on bioelectricity in the 18th century by Galvani and Volta, with the first measurements of electrocardiograms in humans near the beginning of the 20th century.[10]

Second, only someone lacking in scientific humility can declare an entire field to be depleted of fundamental results. Can we imagine a similar claim made about mathematics or physics? After all, one may argue, these are areas of research that are more than 2000 years old! What else could be left to discover? But our critics do not claim these fields to be depleted of results. Oddly enough, their claims are restricted just to those areas of scientific inquiry that involve the use of animals.

One can simply point to some recent examples to prove the claim false. Consider the development of Herceptin to fight breast cancer,[11–13] antivascular endothelial growth factor (VEGF) therapy for retinal vascular disorders[14–16] or RNAi drug delivery.[17–21] All these represent recent breakthroughs that were obtained by the scientific use of animals (including worms, mice and monkeys) in just the last 2 decades.

What about their demand? Our critics insist that if scientists are to claim that animals are necessary for their research, that a proof be provided showing there was no other way of obtaining the results that circumvented animal use.

What do scientists mean when they say animals are necessary in their work? In most cases, I submit the meaning is that animals are necessary in the sense that the data they seek requires the use of invasive methods, which we would not apply in humans because of the high risks involved and the resulting ethical concerns. Furthermore, it means that a reasonable effort was made to identify potential alternatives in which the data could have been collected without the use of animals. Thus, the necessity is partly an ethical one, not a scientific one. There is nothing in the science per se that would invalidate the use of invasive methods in human subjects. For example, cancerous tumors can certainly be grown in humans as they are in mice, but we do not consider the practice morally acceptable. In other cases, there are clear practical reasons for the selection of animal species. In many genetic studies, one needs to work with organisms that have short generational times, like fruit flies. In studying development, the ability to observe deep tissue *in vivo*, such as in transparent zebrafish eggs, offers a tremendous practical advantage. Finally, animals allow scientists to control many external factors that might otherwise affect the outcome of experiments, such as diet, temperature, humidity and genetic composition, in ways that are not possible in humans.

In contrast, our critics often adopt a stricter interpretation of necessity, arguing that scientists are claiming that animal research is the only possible way to obtain the data they need, and they demand proof to this effect. In the words of Greek[22]:

> "[. . .] the claimant must essentially prove a negative; that the discovery could not have been made any other way. Although difficult, this can be done and indeed must be done for the claimant to say the discovery was dependent on animal use."

This is an unreasonable demand based on a straw-man argument. First, as noted above, this is not what scientists mean. Second, there are infinite possibilities that must be considered for one to prove that no other method could have