Animal Experimentation: Working Towards a Paradigm Change

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How to Evaluate the Science of Non-human Animal Use in Biomedical Research and Testing: A Proposed Format for Debate

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1 Introduction

Over time, the interpretation of science has occasionally been corrupted by vested interest groups, be they financially motivated or ego driven. Scientific consensus and widespread public beliefs usually catch up with the evidence, but this can take a very long time and often costs lives. The use of non-human animals in biomedical research and testing is a scientific endeavor and, as such, can and should be evaluated in light of the best science currently available. But facts that have been accepted in all areas of science are routinely ignored or called into question by well-funded, vested interest groups, compromising the scientific integrity of biomedical research. History is replete with examples of practices deemed scientifically viable in one era, but later abandoned as more facts about the material universe were discovered. There are also many instances of practices being rejected by the scientific establishment, in spite of the fact that they were valid based on scientific criteria. In this chapter, we discuss why science is important in the context of animal modeling, how scientific positions are currently evaluated through the peer-review process, and how an evaluation of the science of animal modeling should be conducted now. We reach the conclusion that, in order to formally evaluate the scientific viability of animal modeling, a debate is urgently needed with experts in the relevant fields of science reviewing pro and con arguments written in position papers.

2 Context

The use of non-human animals in science, in general, and in biomedical research and testing, in particular, has historically been controversial. Formal objections to the practice emerged as early as the seventeenth century, primarily based on moral objections (Franco, 2013). The peak controversy, perhaps, began with the popularization of the animal rights movement, circa 1975. Welfare concerns aside, there are many stakeholders with vested interests in the continued use of non-human animals in research. First, many scientists and nonscientists worldwide are employed, either directly or indirectly, due to the use of non-human animals in biomedical science, with jobs spanning both private-sector and publicly-funded entities. The volume and variety of entities that conduct and/or fund animal-based research complicates any attempt to quantify the dollar magnitude of associated expenditures; but a conservative estimate indicates that at least US$10 billion is spent annually on animal-based research and testing in the United States, only taking account of funds originating from the National Institutes of Health (Monastersky, 2008). If one considers other grant-funding sources and private-sector sources, both in the US and in the many other countries where non-human animals are used, the amount spent annually is likely many orders of magnitude more than this conservative figure.

Of course, human nature is such that people generally oppose technological changes which may render their own employment obsolete or may otherwise interfere with their personal objectives. Furthermore, people may even be reluctant to embrace technological change that simply alters the specific tasks they undertake in completing their work. For instance, scholarly researchers who have entire laboratories devoted to animal modeling may be reluctant to consider adopting non-animal-based research methods if doing so might require the development of new tools, jeopardizing their publishing prospects or their ability to continue training graduate students to emulate the type of research they have always undertaken. That is, it takes time and effort for people to develop new skills, and people are naturally averse to changes that might require that they do so. Additionally, universities and other research institutions rely on research grant overhead fees as a form of revenue to help cover the administrative costs of running their organizations. When a sizeable portion of that overhead-fee revenue stream originates from grants that fund animal-based research, executives and even employees at those institutions may be reluctant to consider a future free of animal modeling. A researcher at Columbia University wrote that one reason animal modeling continues is due to the "frailties of human nature. Too many eminent laboratories and illustrious researchers have devoted too much of their time to studying malignant

diseases in mouse models, and they're the ones reviewing one another's grants and deciding where the NIH [National Institutes of Health] money gets spent. They're not prepared to concede that mouse models are basically valueless for most cancer therapeutics" (Raza, 2015, p. 232).

In recognition that a wide variety of conflicts of interest can influence scholarly researchers, including non-monetary, *Nature Research* journals, for example, require authors "to declare any competing financial and/or non-financial interests," including "present or anticipated employment by any organization that may gain or lose financially through this publication"; unpaid memberships or advisory positions; writing or consulting for an educational company; and other considerations (see Nature Research, 2011). Because of vested interests—whether monetary, emotional, or philosophical—the outcome of any change in the animal-model paradigm has the potential to affect many people adversely, some of whom are represented by societies, lobbyists, nonprofits, nongovernmental organizations, and other groups that may be keen to attract media attention to promote their agendas. Consequently, vested interests can interfere with the adoption of progressive policies and behaviors.

The social and political atmosphere surrounding animal use is similar to that of other science-based controversies (or in some cases, pseudo-controversies), such as vaccines, global warming, and genetically modified organisms (GMOs). There are typically advocates on both sides of such issues, and it is often the case that one needs an advanced science background to understand the relevant issues. Thus, the general public, and even some scientists, may not be able to determine rightly which side the scientific facts actually support. The more money at stake in any given debate (e.g., the interests of the oil and coal industries in the context of the global warming controversy), the more propaganda will likely emerge, potentially confounding the public's ability to understand and evaluate the facts. Even when there is scientific consensus because of overwhelming evidence—as there is on the overall effectiveness of vaccines, the safety of GMOs in terms of human health, and the existence of global warming—the opposition can be so well funded and prone to promoting unscientific points of view that the general public can almost be forgiven for incorrectly believing there exists real controversy on these points.

Regarding the use of non-human animals to model human responses to drugs and diseases, articles questioning the scientific viability of the practice began appearing in the scientific literature in the 1980s. These critiques have taken various forms and, unfortunately, have included arguments that appear on the surface to be science-based, but are in fact not valid science-based attacks. The first four of the following five points list the most common themes of these attacks, and we provide a brief explanation of why each argument

lacks merit. The fifth point represents a valid objection to animal modeling, by which we mean the objection is logical and is based on scientific facts. In the discussion that follows, we make frequent reference to the concept of *predictive value*. We refer the reader to the *empirical evidence* section of Chapter 17 (in this volume), for a detailed discussion of the mathematical calculation of numerical predictive value. Briefly, predictive value is an important metric by which a test or methodology correctly identifies an outcome or condition in humans. The specific threshold by which a particular modality is deemed to have an acceptably high predictive value varies by context. In medicine, where lives lie in the balance, one could argue that nothing short of 100% is acceptable. In some cases, even drugs tested with modalities that offer predictive value as high as 99.9% have been pulled from the market due to life-threatening consequences. In practice, animal models have predictive value below 50%, making them less informative than a coin flip and rendering them of no practical use in predicting human outcomes. Given the poor predictive value of animal modeling, Kramer and Greek (2019) propose existing drug development and disease research resources ought to be redirected towards personalized medicine, a new field which offers the promise of 100% predictive value due to its basis in each patient's own unique genetic makeup.

We now turn to listing the most common critiques of the use of non-human animals to model human responses to drugs.

1. *The methodology of the experiment was poor, and, therefore, animal modeling should be abolished.* This argument is invalid because implicit within the argument is the false premise that if the methodology had been good then that would have reflected well on the viability of the entire paradigm of animal modeling. Of course, the use of good or bad methodology in a given experiment is not sufficient for making general statements about whether animal modeling should be abolished overall.
2. *The history of medical science has not been as dependent on animal modeling as we have been led to believe, and, therefore, animal modeling should be abolished.* This argument is invalid. Whether or not the current state of modern medical science was dependent on researchers having used animal models in the past has no bearing on whether the continued use of non-human animals is vital. Decisions about any future use of animal models should be based on modern scientific knowledge about whether animal models have predictive value for human outcomes, taking into account information that may not have been available or considered when past decisions were made.
3. *Review articles conclude that specific non-human animal species have not been vital to various medical developments, and, thus, animal modeling should be abolished.* This argument is not valid. Even if it were true that

specific non-human animal species were not essential parts of specific medical advancements, this would not be a sound basis for evaluating whether the overall use of animal models has predictive value for human outcomes.

4. *There are now alternatives to using non-human animals, and, therefore, animal modeling should be abolished.* There exist alternatives to many uses of non-human animals in science but not others. Currently, for example, there are no toxicity tests that have high enough predictive value for humans. Nor can we ethically instrument the human brain the way we do in non-human animals. The position in this point is further weakened by the fact that it does not address whether animal modeling is scientifically viable in the first place, nor does it offer a scientific theory to tie together areas where animal use is successful and areas where it is not.
5. *The paradigm of animal modeling is not scientifically viable for predicting human response to drugs and diseases, and, thus, animal models should not be used to predict human response to drugs and diseases.* In contrast to the previous four points, this particular point is based on critical thinking, logic, and scientific facts; and, hence, it is a valid scientific argument. Scientific knowledge from complexity science and evolutionary biology, supported by empirical evidence, establishes that animal modeling does not have predictive value for human outcomes. Past research in these areas was summarized by authors, including Greek and Rice (2012), LaFollette and Shanks (1996), LaFollette and Shanks (1998), and Shanks and Greek (2009), forming the basis for trans-species modeling theory (TSMT): "While trans-species extrapolation is possible when perturbations concern lower levels of organization or when studying morphology and function on the gross level, one evolved, complex system will not be of predictive value for another when the perturbation affects higher levels of organization" (Greek and Hansen, 2013a, p. 245).

In Chapter 17 in this volume, Greek and Kramer (2019) discuss TSMT in great depth. Briefly, TSMT draws on established knowledge in evolutionary biology and complex systems science to draw the conclusion that animal models cannot be predictive of human response to drugs and disease. We refer the interested reader to Chapter 17 for further details. TSMT is the only scientific argument that invalidates using animal models to predict human response to perturbations that occur at higher levels of organization. TSMT is also the only critique of animal modeling that both explains past apparent successes and failures and why future reliance on animal models will lead to continued significant failures in predicting human responses (Greek, 2014; Greek and Hansen, 2013a,b; Greek and Menache, 2013; Greek and Rice, 2012; Jones and Greek, 2013). Unlike TSMT, points 1–4 above do not offer any definitive resolution to

the animal modeling controversy; indeed, many animal modeling advocates agree with various aspects of these points. Furthermore, points 1–4 offer no scientific evaluation of the problem, nor do they make reference to science to support their assertions. Point 5, in contrast, is based on valid scientific foundations, and, hence, we focus here on TSMT as the only viable opposition to the paradigm of animal modeling.

TSMT is a theory and, like all scientific theories, it is consistent with the following definition from the National Academies of Sciences, Engineering, and Medicine (2017): "In everyday usage, "theory" often refers to a hunch or a speculation. When people say, "I have a theory about why that happened," they are often drawing a conclusion based on fragmentary or inconclusive evidence. The formal scientific definition of theory is quite different from the everyday meaning of the word. It refers to a comprehensive explanation of some aspect of nature that is supported by a vast body of evidence". Stated differently, fact-supported theories should not be guesses but, instead, must be reliable accounts of the real world. To that end, the facts associated with evolution and complex systems have been established beyond doubt by observation and experiments. Furthermore, there is extensive empirical evidence from animal modeling to support TSMT. Additionally, TSMT is characterized by consilience—it agrees with facts from other fields. It is also falsifiable and generalizable, and it offers predictions for future outcomes. TSMT fulfills all of the qualifications for a scientific theory.

In this chapter, we suggest a peer-reviewed debate process by which scientists and society, in general, could formally evaluate the scientific validity of the statement in point 5 and, in so doing, could resolve the deep disagreement about the predictive value of animal modeling. This process could have been applied in the past and lethal errors would consequently have been avoided. It could also be applied to other science-based controversies facing society. The peer-reviewed debate we recommend is not a panacea appropriate for all disagreements. Many disputes in life (and even those relating to the use of non-human animals in certain contexts) do not center on science but rather arise due to fundamental differences in opinion, which are rooted in ideology. However, the process we propose is appropriate for settling controversies related to science, such as those that arise in the context of using animal models as predictors of human outcomes.

3 Why Science Is Important

The use of non-human animals in science and science education is not confined to biomedical research and testing where predictive value is touted as an

TABLE 2.1 Nine categories of animal use in science and research (Greek and Shanks, 2009)

1.	Non-human animals are used as predictive models of humans for research into such diseases as cancer and AIDS.
2.	Non-human animals are used as predictive models of humans for testing drugs or other chemicals.
3.	Non-human animals are used as "spare parts", such as when a person receives an aortic valve from a pig.
4.	Non-human animals are used as bioreactors or factories, such as for the production of insulin or monoclonal antibodies or to maintain the supply of a virus.
5.	Non-human animals and animal tissues are used to study basic physiological principles.
6.	Non-human animals are used in education to educate and train medical students and to teach basic principles of anatomy in high school biology classes.
7.	Non-human animals are used as a modality for ideas or as a heuristic device, which is a component of basic science research.
8.	Non-human animals are used in research designed to benefit other animals of the same species or breed.
9.	Non-human animals are used in research in order to gain knowledge for knowledge sake.

objective. There are, in fact, many categories of animal use, as shown in Table 2.1, some of which do not lean on predictive value as a determining factor for using non-human animals.

In general, it may be possible to justify the use of non-human animals associated with Categories 3–9 based on scientific grounds, without reliance on predictive value for perturbations that occur at higher levels of organization. For instance, one can make a logical argument, with valid reference to science, to support the claim that human lives may be saved by using tissue retrieved from an animal (Category 3) or to make the claim that one can learn about the broad structure of lungs in mammals by examining the lungs of rats (Category 6). (This does not rule out the possibility that, in some cases, there may also be valid scientific objections; for example, the risk of facilitating the cross-species transmission of viruses.) Furthermore, there may exist valid ethical objections to the use of non-human animals in specific instances of Categories 3–9. We leave aside possible objections such as these for the purposes of this discussion and focus, instead, exclusively on scientific arguments

regarding utility. Likewise, using some non-human animals in order to learn more about other animals of the same species is scientifically uncontroversial in veterinary medical research. However, it is not scientifically justifiable to use non-human animals in the context of Categories 1 and 2, for reasons based in complex systems science and evolutionary biology (for more details on complex systems science and evolutionary biology, see Chapter 17, the above-cited papers regarding TSMT, and the references therein).

Nevertheless, the literature is filled with cases where researchers make (baseless) claims that animal models have predictive value for human outcomes in the context of drugs and diseases. For example, the widely-used *Handbook of Laboratory Animal Science* states: "[An] important group of animal models is employed as predictive models. These models are used with the aim of discovering and quantifying the impact of a treatment, whether this is to cure a disease or to assess toxicity of a chemical compound" (Hau, 2003, p. 2). A highly cited article in *Clinical Cancer Research* states: "GEMs [genetically engineered mice] closely recapitulate the human disease and are used to predict human response to a therapy, treatment or radiation schedule [...] GEMs that faithfully recapitulate human brain tumors and will likely result in high-quality clinical trials with satisfactory treatment outcomes and reduced drug toxicities" (Fomchenko and Holland, 2006, p. 5296). The popular textbook, *Animal Models in Toxicology* (Gad, 2007), states: "Biomedical sciences' use of animals as models [is to] help understand and predict responses in humans, in toxicology, and pharmacology [...] [B]y and large animals have worked exceptionally well as predictive models for humans" (Preface). "Animals have been used as models for centuries to predict what chemicals and environmental factors would do to humans [...] The use of animals as predictors of potential ill effects has grown since that time" (p. 2). "If we correctly identify toxic agents (using animals and other predictive model systems) in advance of a product or agent being introduced into the marketplace or environment, generally it will not be introduced" (p. 3). These are but a few of the many instances where researchers make vastly over-reaching claims about the prediction value of animal models. A balanced assessment of the overall evidence shows, instead, that animal models, for all practical purposes, do not have predictive value for human responses to drugs and diseases.

Further to that point, the medical literature contains many papers that show, based on the (standard) statistical concept of predictive value, that there is no basis to continue using non-human animals to predict human response to drugs and diseases (Greek, 2014; Greek and Greek, 2010; Greek and Hansen,

2013a; Greek, Pippus and Hansen, 2012b; Greek and Rice, 2012; Greek, Shanks and Rice, 2011b; Shanks and Greek, 2009; Shanks, Greek and Greek, 2009). Since advocates of animal modeling appeal to the predictive value argument to *justify* their use of non-human animals, the onus is on those advocates to clearly establish predictive value. Yet, such evidence based on predictive value, which may support of the use of animal models, is notably absent from the scientific literature. That evidence is also absent from the legally binding documents that the Institutional Animal Care and Use Committees and funding bodies, such as the National Institutes of Health (NIH) in the US, require animal modelers to sign, testifying that their projects have a reasonable expectation to translate to humans. The lack of evidence is a direct consequence of the fact (shown by the studies cited above, and, in turn, the many studies they cite) that responses to perturbations, such as drugs and diseases, in an animal have effectively no predictive value for responses in humans.

The fact that animal models do not have predictive value for human responses has several important implications, including the following:

1. The extent to which the general public supports the use of non-human animals in research rests on an assumption that the outcome of the research benefits humans directly. For example, writing in *Nature*, Giles states: "public opinion is behind animal research only if it helps develop better drugs." (2006, p. 981) Since animal models do not have predictive value for human outcomes, their use should be abandoned.
2. Continuing to use non-human animals in the absence of predictive value wastes time and money (see Chapter 10) which could instead be devoted to scientifically valid pursuits.
3. Various members of the pharmaceutical industry and various scientists have acknowledged the failure of the animal model for predicting human responses to drugs and diseases (Arrowsmith, 2011a,b; Ennever, Noonan and Rosenkranz, 1987; Fletcher, 1978; Food and Drug Administration, 2004; Johnson et al., 2001; Kola and Landis, 2004; Kummar et al., 2007; Lumley, 1990; Morgan et al., 2012; Seok et al., 2013; van Meer et al., 2012). Nevertheless, there is a widespread belief among lawmakers and members of the public that animal models cannot be abandoned until "alternatives" have been developed. The logic behind this belief is specious. To demonstrate this, we offer the following thought experiment. Imagine if regulators were to choose which drugs to endorse for human use based on a simple coin flip (e.g., heads, we allow humans to use a given drug; tails, we do not). Such an approach would do nothing to ensure the safety or efficacy of drugs reaching the market. This is because

coin flips do not have predictive value for determining human responses to drugs. Consequently, it would make no sense to continue using coin flips to choose drugs until an alternative to coin flips could be identified. Likewise, animal models do not have predictive value in determining human responses to drugs, and their use must be halted independent of whether an alternative exists.

4. Animal-based research lacks predictive value for human responses to drugs and diseases, and, thus, it is reckless to continue to justify the use of animal models with myths about protecting humans in clinical trials or learning about human disease. Abundant theoretical and empirical evidence has established unequivocally that the animal model does not have predictive value for humans and indeed cannot. Thus, the only scientifically valid conclusion is to stop attempting to use animal models to predict outcomes for humans. See Kramer and Greek (2018) for an extensive discussion of the many ways various groups of human stakeholders, including but not limited to patients, are directly harmed by the continued use of animal models.

While the vested interests we described earlier have served as an obstacle to acceptance of the fact that animal models do not have predictive value for human responses, the truth has, nevertheless, been acknowledged in the scientific literature, on occasion. For example, Markou, Chiamulera, Geyer, Tricklebank (of Eli Lilly) and Steckler (of Johnson and Johnson) state: "Despite great advances in basic neuroscience knowledge, the improved understanding of brain functioning has not yet led to the introduction of truly novel pharmacological approaches to the treatment of central nervous system (CNS) disorders. This situation has been partly attributed to the difficulty of predicting efficacy in patients based on results from preclinical studies [mainly animal studies, although *in vitro* would also be included in preclinical studies] [...] Few would dispute the need to move away from the concept of modeling CNS diseases in their entirety using animals" (Markou et al., 2009, p. 74). Additional examples include: Alini et al. (2008); Arrowsmith (2011a, b); Begley (2003a, b); Butler (2008); Contopoulos-Ioannidis, Ntzani and Ioannidis (2003); Crowley (2003); Dragunow (2008); Editorial (2010, 2012); Ferdowsian and Beck (2011); Geerts (2009); Grant, Green and Mason (2003); Hackam and Redelmeier (2006); Hampton (2006); Höerig and Pullman (2004); Holmes, Solari and Holgate (2011); Hurko and Ryan (2005); Ioannidis (2004); Jin and Wang (2003); Johnston (2006); Kaste (2005); Langley (2014); Ledford (2008, 2012); Leslie (2010); Liebman (2005); Lindl, Voelkel and Kolar (2005); Mankoff et al. (2004); Marincola (2003); Markou et al. (2009); Mullane and Williams (2012); Pammolli, Magazzini and Riccaboni (2011); Philips (2004); Pound et al. (2004); Pound and Bracken

(2014); Reynolds (2012); Rosenberg (2003); Rothwell (2006); Sena et al. (2007); Smith (1987); van der Worp et al. (2010); Xiong, Mahmood and Chopp (2013); and Zerhouni (2005).

Further evidence that animal models are extremely limited in what they can inform, regarding druggable targets and future cures, comes from a comment in the *American Journal of Medicine* about Contopoulos-Ioannidis et al.'s (2003) article:

> The article by Contopoulos-Ioannidis et al. in this issue of the *Journal* addresses a much-discussed but rarely quantified issue: the frequency with which basic research findings translate into clinical utility. The authors performed an algorithmic computer search of all articles published in six leading basic science journals (*Nature*, *Cell*, *Science*, the *Journal of Biological Chemistry*, the *Journal of Clinical Investigation*, the *Journal Experimental Medicine*) from 1979 to 1983. Of the 25,000 articles searched, about 500 (2%) contained some potential claim to future applicability in humans, about 100 (0.4%) resulted in a clinical trial, and, according to the authors, only 1 (0.004%) led to the development of a clinically useful class of drugs (angiotensin-converting enzyme inhibitors) in the 30 years following their publication of the basic science finding. They also found that the presence of industrial support increased the likelihood of translating a basic finding into a clinical trial by eightfold.[…] Still, regardless of the study's limitations, and even if the authors were to underestimate the frequency of successful translation into clinical use by 10-fold, their findings strongly suggest that, as most observers suspected, the transfer rate of basic research into clinical use is very low.
>
> CROWLEY, 2003, p. 503

Note that of the 101 articles that formed the primary focus of Crowley's study, about 64% were animal studies. An Editorial (2010, p. 499) in *Nature* supports the above position:

> The readers of *Nature* should be an optimistic bunch. Every week we publish encouraging dispatches from the continuing war against disease and ill health. Genetic pathways are unravelled, promising drug targets are identified and sickly animal models are brought back to rude health. Yet the number of human diseases that can be efficiently treated remains low—a concerning impotency given the looming health burden of the developed world's ageing population. The uncomfortable truth is that scientists and clinicians have been unable to convert basic biology advances

> into therapies or resolve why these conversion attempts so often don't succeed. Together, these failures are hampering clinical research at a time when it should be expanding.

Given the vast amount of money that funds animal-based research and testing, the many hours of human effort that are devoted to these pursuits, and the reliance of all humans whose well-being relies on scientific knowledge for maintaining health and treating disease, there is an urgent need for unbiased, expert scientists to assess the predictive value of animal models. We propose a debate for this purpose, and we now turn to outlining the parameters for ensuring such a debate is sound.

4 How to Evaluate Scientific Arguments

Science is a process of observing the material universe, possibly conducting experiments related to those observations, and ultimately ascertaining facts. According to E.O. Wilson (1999, p. 58): "Science [...] is the *organized, systematic enterprise that gathers knowledge about the world and condenses the knowledge into testable laws and principles*." Often, time will determine whether a given scientist's conclusions are representative of the material universe. But in the interim, the best method for separating fact from fiction involves the peer-review process. The peer-review process uses experts in specific areas of science to evaluate the work of others and to determine whether the research and conclusions of that research are reliable enough to be published in a science journal for dissemination to a broad readership.

The peer-review process of scientific journals works as follows. A number of experts are asked to review a submission to the journal and determine (among other factors):

- whether the submission is in accordance with known facts about our current scientific understanding
- whether the terms and assumptions are consistent with proper usage
- whether the methodology is appropriate
- whether the statistics were correctly calculated
- whether or not there are flaws in the authors' reasoning
- whether the findings are likely to be of interest to the scientific community, policy makers, and/or the general public.

This process is not foolproof, but under the appropriate circumstances, it is usually capable of separating potential facts from sheer nonsense. Depending on the contents of the submission, experts from several different areas of science may be asked to review the submission and judge the part of the

submission that falls under his or her area of expertise. We propose that something akin to this peer-review process should be employed in order to evaluate the scientific viability of using one species to predict response for another in the context of developing drugs and treating diseases.

The peer-review process has been used repeatedly to resolve disputes in many scientific settings, for instance at conferences where select scholars presented evidence for and against a particular position in front of an audience of other experts in the field. A consensus is sought, if not in terms of who is right, at least in terms of which statements can be taken as fact and which must still be taken as conjecture. However, many controversies in science have, instead, been left to simply play out on their own without interference in the form of peer review. Some of these events have had lethal consequences. For example, in 1847, Ignaz Semmelweis introduced the idea that the unwashed hands of medical students and physicians spread the disease known as puerperal fever, an infection related to child bearing. Despite the fact that his patients demonstrated a reduced mortality rate after he and his students began washing their hands, his colleagues ostracized him, and his idea died along with many more patients. Had experts been convened to study and debate the evidence, antiseptic techniques would have been developed much sooner and many mothers' lives would have been saved (Ataman, Vatanoğlu-Lutz, and Yıldırım, 2013). Other prominent examples of scientific breakthroughs being ignored include the following: Barbara McClintock's idea of jumping genes, transposons, was ignored by a mostly male establishment in biology. McClintock could not even find a publisher for her research. Darwin's theory of evolution was almost forgotten in the early twentieth century. Alfred Wegener's idea of continental drift was ignored because he did not propose a mechanism for the notion.

Science has also allowed nonsense to go unchallenged until someone publicly proved the status quo wrong or, occasionally, until disaster occurred. Some cases persisted simply because no one exhibited the courage to disrupt the status quo; unfortunately, history is full of such examples. The *Columbia* disaster of 2003 occurred because the craft was allowed to launch despite engineers knowing there were problems with the tiles (Langewiesche, 2003). Similarly, the space shuttle *Challenger* disaster of 1986 was caused by engineers ignoring a problem with the O-rings. Descartes' unsubstantiated assertions convinced society that non-human animals were not sentient, and some members of society are still clinging to that position. Smoking was defended by some physicians for years because they were employed by the tobacco industry (Jackler, 2015). Scientific consensus can also be wrong. For instance, Earth contraction theory was wrong and was eventually replaced by Wegener's movement of continents and eventually plate tectonics. Newton was shown to be partially wrong by Einstein's theory of relativity. Some of Einstein's objections

to quantum mechanics turned out to be wrong. The notion that ulcers were relieved by decreasing anxiety and drinking milk was abandoned after Marshall proved that ulcers were the result of an infectious disease, and research revealed that milk actually stimulated acid production in the stomach. Peer-review, debate, and the convening of experts at conferences, all played a role in ensuring that obsolete scientific views were replaced by positions rooted in modern knowledge.

Science has historically advanced slowly and by consensus, which is why Planck (1949, pp. 33–34) stated: "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." Reaching consensus slowly and methodically can have its advantages in certain contexts; but when lives are at stake, as was the case with Semmelweis and is the case with using animal models to predict human outcomes, a slow pace is not acceptable. The debate we propose can help expedite the formal evaluation of conflicting views and is especially appropriate for facilitating discussions about complex topics with foundations that span multiple disciplines.

5 Peer-reviewed Debate

We propose to borrow elements of the process used in peer-reviewed science journals and implement them in a debate format to evaluate the scientific issues surrounding the use of animal models, specifically, to resolve whether non-human animals have a high predictive value in terms of modeling human response to drugs and diseases. The scientific literature contains an abundance of articles that ought to convince a scientifically-minded reader that animal models do not have predictive value for human response to drugs and diseases; a small sampling includes, Arrowsmith (2011a, b); Crowley (2003); Greek (2012, 2016); Greek and Greek (2010); Greek and Hansen (2012, 2013a); Greek, Hansen and Menache (2011a); Greek and Menache (2013); Greek, Menache and Rice (2012b); Greek and Rice (2012); Greek, Shanks and Rice (2011b); Hurko and Ryan (2005); Jones and Greek (2013); Marincola (2003); Mullane and Williams (2012); Shanks and Greek (2008, 2009); and Shanks, Greek and Greek (2009). We propose the debate as a supplement to the existing literature, not only to help promote scientific consensus but also to reach a much broader audience of interested parties, including members of the general public.

A formal debate, sponsored by a government or major science organization and with implications for future funding and legislation, would compel the animal model community to participate and address the problems with

animal modeling. Engaging in less formal debates, including traditional oral debates organized by university departments or student groups (as we have done frequently; see Sandgren and Greek, 2007; Skolnick and Greek, 2005), has far less scope for effecting a change in consensus views about animal modeling. The reasons for this are many, including the fact that layperson members of the audience typically do not understand the science (and there are typically no expert judges present to help the audience evaluate the debaters' positions); if there are judges present, their expertise may not span all the areas of science that are pertinent to a full and careful evaluation of animal modeling; and time and format constraints prevent the debaters from going into sufficient detail to substantiate their cases. We propose a formal debate that would address these issues, permitting a fair evaluation of both sides of the debate. We recommend the following rules for the debate:

1. The subject of the debate will be the position that animal models have insufficient predictive value for human response to perturbations that occur at higher levels of organization (e.g., human response to drugs and diseases) and the implication that the vast majority of animal use in science, in general, and research and testing, in particular, should cease.
2. Each side of the debate will be represented by a single individual who is recognized as an expert by the public and the scientific community. That individual may, in turn, consult any number of experts for input and guidance.
3. A single person or a group of not more than three people will be appointed as moderator(s) of the debate.
4. A panel of scientists who are experts in the relevant fields will act as judges and will evaluate the positions put forward by the debaters. These panel members may come from academia or industry and must be recognized as experts by the public and the scientific community. In all, 12–20 scientists will be selected to serve on the expert panel, and their collective expertise will span and encompasses the following fields:
    a. clinical medicine, in general, as well as infectious diseases, cancer, heart diseases, and neurology
    b. statistics
    c. evolutionary biology, including evolutionary and developmental biology
    d. clinical research
    e. drug development
    f. personalized medicine
    g. basic research

h. complexity theory (expert(s) should come from the math or physics department of a university)
i. critical thinking, the history of the science behind medical discoveries, and philosophy of science, in general (expert(s) should have extensive training and credentials in science as well as the stated areas).

5. The judges and moderator(s) must have no vested interests in the outcome of the debate, including any of the following:
   a. a direct financial interest in the outcome of the debate, such as currently receiving money for conducting or facilitating animal-based research
   b. a significant indirect financial interest that arises from animal-based research or testing
   c. an indirect vested interest, such as having, at least in-part, made one's reputation through having conducted research using non-human animals
   d. an indirect financial interest in the form of having a first-degree relative or spouse who currently receives or formerly received funding for animal-based research or testing
   e. a philosophical or emotional interest in the use of non-human animals in research and testing, such as well-known figures from the animal protection movement or pro-vivisection/pro animal-use movement.
6. The debate itself will consist of the following steps:
   a. The debaters, panel members, and moderators will agree on a set of panel members, textbooks, or position papers that specify basic principles of science and critical thinking. Any disagreements will be settled by the expert in the relevant area prior to the proceeding with next steps and will be disclosed by the moderator(s) in the last step of the debate. This will encourage all parties to play fairly, as the communications will be a matter of record.
   b. Each of the debaters will submit a written position paper.
   c. If the judges have questions or comments about the position papers, they will compile them and submit them to the appropriate debater(s).
   d. Each debater will have the option to respond in writing to the set of judges' questions/comments.
   e. The judges will render their judgement after evaluating the position papers and (if appropriate) responses. The judges' evaluations must be based on the validity of each side's position, as stated in the position paper and responses to questions, and each side's adherence to the rules of engagement. In evaluating this set of information, each judge must verify (based on their respective area of expertise) whether

the provided evidence supports the debaters' claims and whether the arguments and reasoning in the position papers are sound and valid.

f. The judges will compile a list of claims made in each side's position paper which were rejected by the judges as false or unsubstantiated, as well as instances in each position paper which were deemed by the judges to be inconsistent with the agreed-upon principles of critical thinking and science. Advance knowledge that these disclosures will occur, will encourage all parties to play fairly, because all of their statements will be a matter of record.

g. The full proceedings, including the names of all participants, the position papers, the judges' questions and comments, the debater's responses, the judges' final decision, and the disclosures described above will all be published in a scholarly outlet, such as an open-access journal.

6 Conclusion

Science has evolved since the time when animal modelers first began using non-human animals in earnest in the nineteenth century. But never have experts convened to formally examine the evidence for and against the continued use of non-human animals. The debate we propose for this purpose, conducted in public and judged by unbiased experts, is long overdue. There is no argument in modern society about whether scientists should receive funding to develop a perpetual motion machine; this is because science has established that such a device cannot exist. Analogously, society's continued investment in animal modeling can and should be evaluated based on its scientific merit. Given the fact that governments and businesses devote scarce resources and vast sums of money to the enterprise of using animal models to predict human responses to drugs and diseases, and the fact that human lives are at stake, there is an urgent need to evaluate whether science supports the continuation of this practice. The debate we propose would serve as a significant step forward to that end.

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