Business and Society Review
Journal of the Center for Business Ethics
Bentley University

Business and Society Review **123:1** 3–58

Human Stakeholders and the Use of Animals in Drug Development

LISA A. KRAMER AND RAY GREEK

ABSTRACT

Pharmaceutical firms seek to fulfill their responsibilities to stakeholders by developing drugs that treat diseases. We evaluate the social and financial costs of developing new drugs relative to the realized benefits and find the industry falls short of its potential. This is primarily due to legislation-mandated reliance on animal test results in early stages of the drug development process, leading to a mere 10 percent success rate for new drugs entering human clinical trials. We cite hundreds of biomedical studies from journals including *Nature*, *Science*, and the *Journal of the American Medical Association* to show animal modeling is ineffective, misleading to scientists, unable to prevent the development of dangerous drugs, and prone to prevent the development of useful drugs. Legislation still requires animal testing prior to human testing even though the pharmaceutical sector has better options that were unavailable when animal modeling was first mandated. We propose that the U.S. Food and Drug Administration (FDA) and Congress should work together

Lisa A. Kramer is a Professor of Finance, at the University of Toronto, Toronto, ON, Canada. E-mail: Lkramer@rotman.utoronto.ca. Ray Greek is President at the Americans for Medical Advancement, Goleta, CA. E-mail: DrRayGreek@gmail.com.

> to abolish regulations and policies that require animal use. Doing so will benefit pharmaceutical industry stakeholders, including patients whose health depends on drugs and the many people who rely on the financial well-being of pharmaceutical firms.

There exists a significant business ethics problem related to human well-being in the context of the drug development industry.[1] The origin of this problem rests in false assumptions about science in the execution of drug research. An article in *Nature* highlights the problem:

> 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, p. 981).

We provide detailed evidence that the use of animals in the drug development process is harmful to key stakeholders. There is a rich literature which examines ethical issues—from the perspective of animals[2]—arising from the use of animals in biomedical research, testing, and science in general. See LaFollette (2011) and Ferdowsian and Beauchamp (2013) for recent discussions of those ethical issues. We purposely sidestep the ethical question of animal well-being to focus instead on other stakeholders harmed as a consequence of current drug development practices.

Who are these other stakeholders?[3] Investors represent one group, since the managers of publicly traded firms are expected to maximize shareholder value vis-à-vis the theory of the firm and agency theory; see Friedman (1970) and Jensen and Meckling (1976); also see Martin (2011) for a critique of the modern value-maximization proposition. Pharmaceutical firms additionally have responsibilities to employees, suppliers, the general public, and of course perhaps most importantly the patients for whom their drugs are intended to treat. We posit that the vast majority of

public firms in the drug development business are falling short of their ethical responsibilities to all of these stakeholders, and we contend this is due to a constraint imposed by regulators, specifically to require animal tests. This constraint was put in place many decades ago and drastically and adversely affected the way the pharmaceutical companies serve their stakeholders. Absent this regulatory constraint, we argue drug development firms would be naturally inclined to better serve their stakeholders. But with the constraint, they fall woefully short of their potential to do so.

We propose a remedy—the abandonment of standards that require the use of animal models in the drug discovery process—that would allow firms like GlaxoSmithKline, Merck, and Pfizer to vastly improve the way they meet their responsibilities to all of these stakeholders, especially the patients themselves through improved health outcomes, but also the other groups through the improved profits that would arise from the development of safer and more effective drugs.

We document the fact that animal-based research for drug development is grounded on a scientific paradigm that is flawed. We present voluminous evidence that this blind spot regarding animal modeling is depriving humans of promising treatments and costing shareholders in the drug development business at least scores of billions of dollars of foregone revenue annually.[4] Specifically, in many cases, results from animal-based research lead to the labeling of drugs as safe that are ultimately found to be harmful to humans, and animal-based research deems as harmful many drugs that are in fact beneficial to humans (these are occasionally discovered by accident later, but there are likely many cases where beneficial drugs are discarded and never rediscovered). If such instances were rarities, they might be considered unavoidable perils along the pathway toward medical progress. Unfortunately, we show these failures are commonplace. Overall, the use of animal models in medical research has poor predictive value in terms of its ability to distinguish between treatments that will be helpful versus harmful to humans, a point we make by citing extensive evidence from biomedical research. Reliance on animal-based research causes much more harm to humans than the accidental good that arises from using animals in the context of drug development.

While the public (mis)perception of the use of animals in biomedical research might be succinctly characterized as an unfortunate but still necessary evil, we show that many experts in biomedical research across academia, industry, and government have come to recognize that use of the animal model in drug development is unreliable and ill-advised. The main reason for continued use of animals is legislative—existing policies simply require, without exception, that new drug compounds be tested on animals before they can be explored in human clinical trials, in spite of the fact that these tests do not help identify compounds that are safe or effective for humans.

Fortunately, a more promising option exists. A new field called personalized medicine is built on the recognition that in order to determine which drugs will or will not work in any given individual, one needs to consider that individual's unique genetic makeup. Not only is the animal model a poor predictor of humans' responses to a given drug, it is also the case that different people can have grossly different reactions to the same treatment. As we explain, many existing treatments are tailored to an individual's genetic makeup in a manner that maximizes benefit while minimizing harm. By redirecting more resources to personalized medicine, the pharmaceutical industry will better serve its direct stakeholders as well as society at large.

The remainder of this article is structured as follows. First, we discuss the scientific basis for the view that use of the animal model in drug development has effectively no predictive value for humans. Next, we detail the ways in which reliance on animal models in this context harms patients through lack of safety, lack of efficacy, and the opportunity cost of drugs that are discovered belatedly if at all. Then we consider the ways in which use of animals in the drug development process is harmful to stakeholders other than patients. This includes a discussion of the economic side of the pharmaceutical industry. Next, we consider why the animal model continues to be employed in spite of its role in preventing firms from meeting their social and ethical responsibilities, and how those hurdles can be overcome. And finally, we discuss personalized medicine, which offers a means of safely and effectively treating and curing illness without reliance on the animal model.

CURRENT SCIENCE REGARDING ANIMAL-BASED RESEARCH

We contend that there is an urgent need for a sea change in the way innovation occurs in the drug development process. As we will show in this section, the regulatory requirement to test new compounds on animals is built on invalid assumptions. Consequently, the industry spends more than a hundred billion dollars each year (see Mullane and Williams 2012) building upon misleading results from animal tests to develop drugs that have little chance of being safe and effective for humans and, in fact, have a high chance of being harmful. The end result of this undertaking is disappointing. Researchers have identified cures for various forms of cancer in mice, for example, yet cures for cancer in humans remain elusive. Nevertheless, the National Institutes of Health (NIH) funding model currently devotes about 50 percent of its grant money to fund animal models (see Committee on Models for Biomedical Research Board on Basic Biology 1985; Greek and Greek 2010; Monastersky 2008).

It is worthwhile to examine, briefly, the science undergirding the fact that animal models are ineffective. Advances in the fields of evolutionary biology and complex systems have called into question the value of animal modeling. The issue rests on the fact that humans and animals are evolved, complex systems.

Complex systems are characterized by being composed of many parts that themselves have hierarchal levels of organization. They have feedback loops, exhibit self-organization, and respond to perturbations in a nonlinear fashion. Because small changes in a complex system can result in outcomes that are not proportional to the input, one biological complex system can die because of what at first appears to be a minor change or difference between it and another almost identical complex system. Importantly, complex systems are very dependent on initial conditions such as the genetic make-up of individuals or species. This means that a very small change in the initial conditions of two otherwise identical complex systems might result in death for one while the other thrives; see Pearson (2002) and Belmaker et al. (2012) for example.

The whole of a complex system is greater than the sum of its parts, and hence complex systems have properties that cannot be determined even with total knowledge of the components of the

system. Examples of complex systems include cells, animals and humans, ecosystems, economies, ant colonies, social interaction, and the U.S. electrical grid. In contrast, simple systems, like an analog watch, are nothing more than the sum of their parts. For more on biological complex systems see Ahn et al. (2006), Gell-Mann (1994), Goodwin (2001), Greek (2013), Greek and Rice (2012), Kitano (2002), Morowitz (2002), Sole and Goodwin (2002), and van Regenmortel (2004).

Informally, evolution can be thought of as small changes in genes (i.e., initial conditions) that occur over long periods of time, resulting in new species with traits different from those of the ancestor organism. In other words, chimpanzees and humans are both different from the primate that we descended from, and we are different from each other. But the notion that differences among genes can result in new species is separate from the fact that very small differences in genes can also lead to members of the same species reacting quite differently to drugs and diseases. Humans and animals are examples of complex systems that have evolved over time—their initial conditions changed in the form of genetic make-up, and these changes affected the organism in a nonlinear fashion over time.

Even for two individuals within the same species, small differences in DNA can mean the difference between life and death. A tiny difference of one amino acid within the human chromosome is all that separates a patient with life-threatening sickle cell anemia from those of us who do not suffer from that condition. Dramatic differences can exist across species even without changes in amino acid sequences. Genes are regulated—turned on and off—by other genes. For example, mice and humans share the gene that allows mice to grow a tail. The reasons humans do not normally grow a tail during development is that the gene is never turned on (i.e., expressed). Differences in gene regulation and expression vary within and between species and account for differences in response to drugs and disease (see Kasowski et al. 2010; Marchetto et al. 2013; Morley et al. 2004; Pritchard et al. 2006; Rifkin et al. 2003; Rosenberg et al. 2002; Sandberg et al. 2000; Storey et al. 2007; Warren et al. 2014; Zhang et al. 2008). So while it is a fact that humans share a large percentage of their genes with other mammals, the commonality is largely immaterial in terms of predicting how humans will respond to perturbations like drugs and disease.

Our intent in this section has been to briefly summarize the theoretical underpinnings of the observation that animal models are not predictive for humans. We direct readers interested in more details to other sources and the references contained therein.[5] In the next section we turn to extensive supportive evidence that the use of animal models in drug discovery has very dire implications for patients.

COSTS BORNE BY PATIENTS

If firms in the drug development industry are to meet their responsibilities to patients seeking treatments and cures for disease, they ought to employ research methods that lead to good outcomes. Specifically, the methods should accurately identify drugs that are safe for human consumption, and they should accurately identify drugs that are effective in achieving cures and/or alleviation of symptoms in humans. There is extensive empirical evidence that the use of animal models fails on both counts, as we show. We also provide evidence that patients bear a substantial indirect cost, namely the opportunity cost of drugs that are identified decades later than they were ultimately found to be safe and effective for humans (if they are ever identified), due to poor predictions arising from animal research. An unknowably enormous number of patients have suffered longer or died prematurely due to this opportunity cost alone. We also discuss undue financial costs patients bear as a result of animal modeling.

In the remainder of this section, we detail many striking examples relating to the safety, efficacy, opportunity cost, and financial cost categories. Space constraints naturally limit the number of quotations and citations that we include; hundreds of additional examples are available.

Lack of Safety

A particularly catastrophic failure of the animal model that captured the collective attention of the public is the case of fen-phen, a combination of two diet drugs that were recalled from the market after causing serious heart valve damage in as many as 30 percent of people who took the drugs. The New York Times, in announcing the recalls, wrote that Dr. Michael A. Friedman, the acting commissioner of the U.S. Food and Drug Administration (FDA), speculated

that heart damage hadn't been expected in humans because animal studies had not revealed any adverse effects on the heart (see Kolata 1997).

Another well-known failure arose with thalidomide, a drug which was prescribed in in the 1950s and 1960s for pregnant women suffering from nausea. Unfortunately, it soon became apparent that thalidomide caused infants to be born with severe abnormalities including abbreviated or complete lack of limbs. Researchers had tested thalidomide in animals prior to its use in humans, and research performed after the birth-defect side effect was identified has since shown that thalidomide does not cause birth defects in several species, including rodents.[6] See Greek et al. (2011) for more background on the thalidomide case and the question of drug toxicity for embryonic development in general.

Vioxx (rofecoxib) is a non-steroidal anti-inflammatory drug that was famously taken by more than 80 million people before it was shown to cause heart attacks and strokes in humans; see Topol (2004) for details. Graham et al. (2005) estimate that "88,000–140,000 excess cases of serious coronary heart disease probably occurred in the US over the market-life of rofecoxib" (Graham et al. 2005, p. 480). In the subset of several thousand cases the authors evaluated directly, more than a quarter were fatal. Not only did studies based on animal models fail to alert researchers to these serious adverse effects, some studies actually showed the use of rofecoxib was beneficial to cardiac function in animals; see LaPointe et al. (2004) for instance.

Other drugs that made their way to the marketplace on the basis of deceptive evidence from animal models and then caused significant harm in humans include Rezulin (troglitazone) and Propulsid (cisapride). Rezulin caused liver failure and Propulsid caused life-threatening heart rhythm abnormalities. Many people died from taking these drugs. Between 2001 and 2010, about one third of drugs approved by the FDA were later withdrawn or had black box or other safety warnings issued (Downing et al. 2017).

Many other drugs caused harm to humans enrolled in clinical trials; that is, patients were harmed even in cases where drugs were never marketed. For instance, the drug TGN1412 was developed to treat some forms of cancer, rheumatoid arthritis, and multiple sclerosis.

Unfortunately, it caused life-threatening multi-organ failure and intensive-care stays for study participants, even at doses 500 times

lower than had proven safe in animal models. Similarly, the anti-viral drug Fialuridine caused the death of study participants after the drug was shown to be safe in animal models at much higher doses. Details on the failure of both drugs are discussed by Attarwala (2010).

Smoking was anecdotally linked to cancer in the first half of the twentieth century, but animal studies failed to link the two, thus tobacco companies continued to promote cigarettes as safe, if not healthy, for decades (see Janofsky 1993; Lindsay 2005; Northrup 1957; Utidjian 1988). And Smith et al. (1965) reported that tests on several animal species failed to replicate the lung cancer that arises in humans from exposure to asbestos.

van Meer et al. (2012) retrospectively studied whether serious adverse drug reactions in humans could have been identified using animal models prior to the release of various drugs. They evaluated drugs currently on the market and discovered that only 19 percent of 93 serious adverse drug reactions were seen in animals.

Animal modelers were aware of the poor predictive value of the animal model well before van Meer et al.'s article was published. Salén (1994), writing in the *Handbook of Laboratory Animal Science, Volume II, Animal Models* stated:

> It is impossible to give reliable general rules for the validity of extrapolation from one species to another. This has to be assessed individually for each experiment and can often only be verified after first trials in the target species [humans] . . .
>
> Extrapolation from animal models, like medical art itself, will always remain a matter of hindsight . . . (Salén 1994, p. 6; parenthetic text added).

The van Meer et al. results are consistent with other studies. Arrowsmith (2011a,b), DiMasi et al. (2010), Morgan et al. (2012), and Paul et al. (2010) each examine the high failure rate of drug tests at various phases of human clinical trials, in large part due to safety (and efficacy) problems that did not emerge during animal tests.

Lack of Efficacy

Approximately 37 percent of drugs that make it to human trials fail in Phase I human clinical trials, 55 percent fail in Phase II, and 12.6 percent fail in Phase III. The failure rates are increasing over

time; see Hurko (2006). Most of these drug failures are due to lack of efficacy (66 percent), followed in frequency by safety issues (21 percent); see Arrowsmith (2011a,b). Here we consider a few specific examples of lack of efficacy.

The failure of the animal model for predicting efficacy in humans is perhaps most evident in cancer research. A former director of the National Cancer Institute, Dr. Richard Klausner, remarked "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades—and it simply didn't work in humans" (Cimons et al. 1998). And an associate director at the U.S. National Cancer Institute, Dr. Edward Sausville, said that the use of xenograft models has led to the discovery of "compounds that were good mouse drugs rather than good human drugs" (Gura 1997, p. 1041).

Efficacy failures are rampant across a broad spectrum of drugs intended to treat other diseases as well. A drug developed by Eli Lilly to treat Alzheimer's disease, semagacestat, showed great promise in animal models. According to the NIH, clinical trials in humans had to be halted because the drug not only failed to help humans (see Salloway et al. 2014) but also led to "worsening of clinical measures of cognition and the ability to perform activities of daily living."[7] That is, patients taking the drug experienced the opposite of its intended outcome.

Approximately 100 vaccines have been proven effective against HIV-like viruses in animal models to date. None have been effective in humans; see Bailey (2008), *Nature Medicine* Editorial (2007), Gamble and Matthews (2010), and Greek (2012). This likely relates to the fact that the progression of HIV to AIDS, which is common in humans, has been very rarely observed in great apes. To that end, Varki and Altheide (2005) write, "it is a striking paradox that chimpanzees are in fact not good models for many major human diseases/conditions" (p. 1746).

Around 1,000 drugs have been seen to protect against nervous system damage in animal models of stroke, performed across hundreds of experiments. None of these drugs ended up being protective in humans; see Dirnagl (2006), Dirnagl and Macleod (2009), Macleod (2004), O'Collins et al. (2011), O'Collins et al. (2006), Sena et al. (2007), and Sena et al. (2010). Over 20 drugs have been shown to be protective in animal models of spinal cord injury, with none being effective in humans (American Paraplegia Society

1988). And of the hundred-plus drugs to treat amyotrophic lateral sclerosis, commonly known as Lou Gehrig's disease, none have worked in the thousands of humans who have taken these drugs in clinical trials (Perrin 2014). The drug saridegib tested successfully in mice for treating a particular form of cancer, showing a five time increase in survival rates. It showed no effect in humans (See Mak et al. 2014).

These are a handful of examples from the vast population of drugs that seemed effective in animal models but proved to be ineffective for treating human diseases.

Opportunity Cost: Failure to Identify New Drugs

An indirect cost to patients comes in the form of an opportunity cost. The drug development industry's reliance upon animal models prevents as-yet-undiscovered safe and effective drugs from coming to market (see Gura 1997; Lazzarini et al. 2006). Many drugs that would have been safe and effective in humans are being eliminated in the development process because of poor outcomes in animal tests, and other drugs known today to be efficacious would have been eliminated during the animal testing phase if not for the determination of investigators. See Sankar (2005) for a general overview of this point. Clif Barry, a researcher who specializes in tuberculosis at the U.S. National Institute of Allergy and Infectious Disease observed that the tendency to conduct tests in animals before humans "has cost us a new generation of medicines" (Engber 2011a).

For specific examples of the opportunity cost that arises from animal testing, consider the following. The development of penicillin was delayed because the researcher Dr. Alexander Fleming thought it was ineffective in a rabbit model of systemic infection (see Greek and Hansen 2013a). In fact, Fleming later stated "How fortunate we didn't have these animal tests in the 1940s, for penicillin would probably never have been granted a license, and possibly the whole field of antibiotics might never have been realised." (See Parke 1994, p. 208.) A vaccine against polio was developed in the 1950s, but only after the animal model first misled scientists and delayed the vaccine for decades (see Horstmann 1985; Oshinsky 2005; Paul 1971; Sabin 1984). The antituberculosis drug

pyrazinamide demonstrated only a weak effect in mice (see Engber 2011b). Furosemide, commonly called Lasix, could have been discarded because it causes liver damage in mice, rats, and hamsters, but not humans (see Walker and McElligott 1981; Weatherall 1982). Isoniazid, another anti-tuberculosis drug, causes cancer in many lab animals but not humans (see Clayson 1980; Shubick 1980). The heart medication digoxin caused high blood pressure in animals (see Jover et al. 1992; Okita 1967). Fluoride was withheld because of its cancer-causing properties in rats (see American Cancer Society 2013; Bucher et al. 1991). The pain reliever acetaminophen and the antibiotics chloramphenicol and metronidazole were seen to cause cancer in rodents (see Anisimov et al. 2005). Statins cause liver damage in animals (see Navarro and Senior 2006; Tolman 2002). Tacrolimus (also known as FK506), a drug used to reduce the risk of rejection of transplanted organs, was toxic in animals (see Calne et al. 1989; Neuberger 1991). The drug nabilone, a synthetic version of cannabis used as a pain reliever in humans, produced toxic reaction in dogs but not rhesus monkeys or rats (see Morton 1990, p. 7). Phenobarbital causes cancer in mice and rats but not humans (see Clemmensen and Hjalgrim-Jensen 1980). The breast cancer treatment and prevention drug tamoxifen demonstrated carcinogenesis in rats, and COX-2 inhibitors were thought ineffective based on animal studies (see *Nature Reviews Drug Discovery* Editorial 2003b). Many of these drugs would not have been discovered as being safe and effective in humans in absence of attempts by doctors of near-death patients to try them in a "last-ditch" attempt.

Dr. Susanta Sarkar of GlaxoSmithKline stated: "High attrition rates, particularly at the late stage of drug development, is a major challenge faced by the entire pharmaceutical community. The average success rate ... for all therapeutic areas combined is 11%. For oncology, this is even lower at 5%. Approximately 59% of all oncology compounds that enter in Phase III of development [human clinical trials] undergo attrition [failure]" (Sarkar 2009, p. 33, parenthetic text added).

The number of truly new drugs—new chemical entities—is dropping, and the remaining other drugs being developed and marketed are "me-too" drugs—variations on a known theme (see *Modern Drug Discovery* Editorial 2002; *Nature Biotechnology* Editorial 2008; *Nature Reviews Drug Discovery* Editorial 2003a,). The new

chemical entities are the ones most valuable to industry and most needed by patients.

Mullane and Williams (2012) discuss why pharmaceutical companies and society are facing a crisis in terms of developing new drugs that are safe, effective, and inexpensive. They cite the decrease in number of new chemical entities entering the market and the late failure of many drugs in development, for example, with a success rate of only 5 percent for oncology drugs that enter clinical trials (see Munos and Chin 2011) and an 82 percent failure rate for drugs in Phase II proof of concept trials (see Arrowsmith 2011a). (The success rate for drugs entering clinical trials varies slightly on a year-to-year basis but the average is around 10 percent. See Munos 2009, for more on failure rates and costs.) Mullane and Williams (2012) juxtapose the stagnation of the development of new drug introductions over the past decade with the fact that total government investment in biomedical research in the United States reached $150 billion in 2010. They state: "The difficulties in predicting drug efficacy from preclinical models have been of concern for more than two decades" (Mullane and Williams 2012, p. 461).

A statement in *Nature Reviews Drug Discovery* puts the current situation in stark reality: "the number of new drugs that are approved annually is no greater now than it was 50 years ago" (Munos 2009, p. 959). Donald Prater, then-Deputy Director in the European Office of the FDA, said the following during an October 10, 2012 lecture at the conference "Advancing Safety Science and Health Research Under Horizon 2020 with Innovative, Non-Animal Tools," which was hosted by the European Parliament at Brussels: "Product development is increasingly costly, success rates remain low, many uncertainties exist, including, as a major component, failures in predicting toxicity despite extensive animal testing" (Prater 2012).

A recent Reuters article profiled a computer-based method for predicting drug toxicity. The computer chip would test for activation of genes and proteins in various human tissues:

> "If things are going to fail, you want them to fail early," Dr. Francis Collins, the director of the NIH, told Reuters on Friday. "Now you'll be able to find out much quicker if something isn't going to work." Collins said a drug's toxicity is one of the most common reasons why promising compounds fail. But

> animal tests – the usual method of checking a drug before trying it on humans – can be misleading. He said about half of drugs that work in animals may turn out to be toxic for people. And some drugs may in fact work in people even if they fail in animals, meaning *potentially important medicines could be rejected* (Yukhananov 2011, emphasis added).

Furthermore, Gura (1997) observed in a *Science* article that use of xenograft models (where human tissue is implanted in an animal for drug testing purposes) routinely causes researchers to miss effective drugs. In the same article, she quoted an executive at Merck Research Laboratories, Alan Oliff, who said "The fundamental problem in drug discovery for cancer is that the [xenograft] model systems are not predictive at all" (p. 1041, parenthetic text added).

Financial Costs Borne by Patients

While monetary matters may seem less significant in comparison to the mortality risk patients face as a result of animal testing, it is worth noting that patients are also bearing costs in the form of elevated health-care expenditures. Consider the case of sepsis, which was studied extensively in mice before it became evident that sepsis in the mouse model very poorly mimicked the human condition. Drugs emerging from that research have been useless in treating sepsis in humans, and so sepsis continues to cost U.S. hospital inpatients at least $14 billion per year; see Mayr et al. (2014). It is impossible to estimate with any precision the total financial cost to patients that can be attributed to the failure to identify safe and effective treatments arising from reliance on animal models. It is safe to say, however, that several of the most-costly-to-treat conditions, including sepsis, cancer, coronary artery disease, congestive heart failure, stroke, and lung disease, have been extensively explored using animal models, with dismal results relative to the volume of resources invested, and at great cost to patients in terms of continued high cost of treatment.

Discussion

We have considered examples of costs borne by patients, including lack of safety, lack of efficacy, opportunity costs, and financial

costs. Despite the widely held faith among members of the public that animal modeling must take place in order to identify drugs that are safe and effective for humans, neither theory nor the empirical evidence supports the position. Moreover, many experts in the drug development process cite the failure of animal modeling as the main reason for high attrition rates and costly medications. Additionally, directing resources to animal models stands in the way of viable research that might have identified more promising treatments.

The shockingly dismal state of the status quo with respect to the use of animal models to determine human outcomes is perhaps well demonstrated with a hypothetical analogy from the world of marketing. Imagine a marketing firm that used octogenarians as focus group participants to evaluate audience reaction to new movies intended for teen audiences. Such a firm would not survive in the free market. Now imagine a world where the Motion Picture Association of America mandated the use of octogenarians for such market research. This is the world we live in for drug development.

If society wants to see advances in diseases like cancer and Alzheimer's then researchers must use human data and perform human-based research. Each of us has different genes and different networks of genes. Scientists are now matching gene response to disease, and great variation is being observed across species. For instance, Seok et al. (2013) studied inflammatory processes such as sepsis, burns, and trauma in mice and humans and found no correlation between what the genes and responses did in mice versus what they did in humans, describing the match between gene changes in humans and mice as "close to random" (Seok et al. 2013, p. 3507). Based on their findings, they recommend "research to focus on the more complex human conditions rather than relying on mouse models" (Seok et al. 2013, p. 3507). There is urgent need to do so. The following statement by a science journalist puts the Seok et al. findings in context:

> Yet, despite the fact that some compounds have repeatedly reversed the symptoms of sepsis in animal tests, not a single drug has proven effective in human clinical trials, even though more than 30,000 people have been included in randomized control studies involving candidate antisepsis agents over the past 25 years (Dolgin 2013, p. 118).

That is, tens of thousands of people were exposed to the risks of a new drug to treat sepsis and billions of dollars were spent on the basis of results from animal studies that proved invalid for predicting human response. Even more patients were deprived of treatments that might have been identified through other means. The failure of animal models in these cases appears to be due to differences in gene response between humans and mice; see Warren et al. (2014) for further information. Based on the track record of drugs that have been tested on animals to date and the fact that animals and humans are evolved complex systems, yet-to-be-developed drugs will similarly exhibit profoundly different responses in animals versus humans.

Many medical researchers are acknowledging that animal models are inadequate for their needs. For example, Dr. Azra Raza, an oncologist and Professor of Medicine at Columbia University recently wrote the following regarding mouse models of cancer, in response to the question "What Scientific Idea Is Ready For Retirement?"

> An obvious truth, which is either being ignored or going unaddressed in cancer research, is that mouse models don't mimic human disease well and are essentially worthless for drug development. We cured acute leukemia in mice in 1977 with drugs that we are still using in exactly the same dose and duration today in humans—with dreadful results . . . there are no appropriate mouse models that can "mirror the human situation" (Raza 2015, pp. 231–232).

Hugo Geerts, then-Chief Scientific Officer at In Silico Biosciences, stated:

> The successful development of new innovative drugs for chronic CNS [central nervous system] diseases is in jeopardy and new paradigms need to be explored. The current drug-discovery paradigm is based upon detection of activity and toxicity in animal models; however, these models show a rather limited predictability for the clinical situation (Geerts 2009, p. 924, parenthetic text added).

Eugene C. Butcher of the Department of Pathology, Stanford University stated in *Nature Reviews Drug Discovery*: "Current mouse-genetics-focused methods of target validation cannot

reliably predict human biology; and even if a model is predictive of human target biology, target biology cannot reliably predict drug biology" (Butcher 2005, p. 461).

Authors of a meta-analysis which considered 2,000 articles that had been published in the seven most highly cited scientific journals and that had individually been cited at least 500 times reached the following conclusions about applying animal-based research to humans: "patients and physicians should remain cautious about extrapolating the findings of prominent animal research to the care of human disease" and "poor replication of even high-quality animal studies should be expected by those who conduct clinical research" (Hackam and Redelmeier 2006, p. 1731).

We have catalogued some noteworthy excerpts from journal articles and quotes from scientists regarding the lack of predictive value animal models have for human outcomes in the context of drug development. These are a small sample of the many such instances that have been recorded in the medical literature and popular press showing the animal model's overall lack of predictive value. Numerous other studies as well as scientists both in and outside of the drug development industry have made similar statements.[8]

COSTS BORNE BY OTHER STAKEHOLDERS

So far, this discussion has focused only on the dire implications for patients which arise from continued reliance on animal models. We turn now to examining more closely the way other interested parties suffer.

Financial Costs Borne by Investors, Employees, and Suppliers

The notion that firms in the drug development industry are inadequately meeting their responsibilities to their investors, employees, and suppliers requires a discussion of the industry's costs relative to revenues. A hint about the scale of the problem comes from a statement by Clif Barry, then-chief of the Tuberculosis Research Section at the National Institute of Allergy and Infectious Diseases:

"The vast majority of the money that we spend in clinical trials based on mouse data is completely wasted" (Engber 2011a); also see Engber (2011b,c).

To get a sense of the financial costs associated with the continued use of the animal model in the drug development enterprise overall, it is useful to consider the rates of attrition for drugs in the development process. The majority of the cost to industry in developing a new drug is associated with human clinical trials, and the top reasons drugs fail in human clinical trials are safety/toxicity and efficacy, the very properties animal studies are purported to assess. (See Arrowsmith 2011a, 2011b; Khanna 2012; Kola and Landis 2004; Koppal 2002; Paul et al. 2010.) To put in perspective the costs associated with the scientific invalidity of animal models, consider the fact that the pharmaceutical industry spends more money on research and development as a percentage of revenues than any other industrial sector.[9] This includes the entire drug development process except for what occurs in academia. Khanna states: "From a global perspective, the total R&D investment for top 20 pharmaceutical companies amounted to 96 billion dollars [during 2010]. This is fairly high investment considering that only 20 percent of approved drugs make more money than the associated R&D cost" (Khanna 2012, pp. 1088–1089, parenthetic text added). The drugs that make the most money are the new chemical entities and they are the ones that are hardest to discover and develop and the ones where animal models are most likely to fail as predictive models.

Roy (2012) writes: "The true amount that companies spend per drug approved is almost certainly even larger today. Matthew Herper of *Forbes* recently totaled R&D spending from the 12 leading pharmaceutical companies from 1997 to 2011 and found that they had spent $802 billion to gain approval for just 139 drugs: a staggering $5.8 billion per drug" (Roy 2012, p. 1). Catherine Shaffer, Contributing Editor of *Drug Discovery & Development* agrees, having stated: "Much of [the cost of drug development] ... is attributable to drug failures late in development, after huge investments have been made. Drugs are equally likely to fail at that stage for *safety* reasons, as for a *lack of efficacy*, which is often well established by the time large trials are launched" (Shaffer 2012, parenthetic text and emphasis added). Pharmaceutical companies want unsafe and ineffective drugs to fail early in the development

process, before the costly clinical trials. But because the animal data are so unreliable, pharmaceutical companies do not know whether any given new drug is safe or effective until they try it in humans. This can be remedied using a technique called microdosing, which we describe later.

A senior editor at the journal *Drug Discovery & Development*, wrote: "The major costs incurred by a drug company are for clinical trials and marketing. The amount of money spent on initial discovery and development is only about 2–5 percent of the total cost of getting the drug to market" (Koppal 2002, p. 35). This means the animal tests performed by a pharmaceutical company are not extremely expensive relative to other elements of the full drug discovery process. (Note that the 2–5 percent figure does not include the money spent on basic science research conducted at universities, which supplements that paid for by industry. Later we discuss the portion of that cost borne by taxpayers, estimated to be at least $10–12 billion per year.) Ignoring for the moment the massive cost of human clinical trials that are often built on misleading results from animal tests, one might be tempted to conclude that if animal testing is itself relatively inexpensive for pharmaceutical companies, it may still make sense to continue employing the method. This would be an erroneous conclusion, in light of the evidence described above that the animal model leads to poor human outcomes in terms of safety and efficacy, and considering the fact that resources currently devoted to animal models might be better directed to human-based methods with better predictive value, some of which are currently available as we discuss below.

Overall, pharmaceutical companies devote vast resources to likely-to-fail drugs in their extremely costly human clinical trials (and other institutions such as universities expend significant funds on the animal-based studies that underlie the clinical trials). These undertakings represent a massive collective investment on the part of society. Individuals who rely directly on the returns to these entities' investments, including employees, suppliers, and investors, are being consistently and predictably short-changed. They would be better served if the drug discovery industry had the freedom to direct their resources to drug development methods that do not seem doomed to fail from the outset, such as the personalized medicine methods we describe later.

Additional harms to employees arise as a consequence of the bonds formed between laboratory workers and the animals under their charge. (These bonds are fostered in part by regulations that call for the "humane" care of animals used for research and policies that encourage the use of procedures that "avoid or minimize, discomfort, distress, and pain"; see Walshaw 1994). According to Halpern-Lewis (1996), lab workers may experience guilt, uneasiness, and frustration during a study involving live-animal research, as well as grief and mourning when animals are harmed during a study or killed at the end of a study. Specific medical consequences of these experiences can include depression, headaches, sleeplessness, and gastric disturbances. Halpern-Lewis further reports that these problems can spill over to the rest of the workplace through lost days of work, low morale, diminished productivity, and high employee turnover. The American Association for Laboratory Animal Science (2001) provides additional information about the ill-effects suffered by workers who oversee animals used in laboratory research.

Implications for Other Stakeholders

Independent of consumers who use drugs and individuals directly associated with pharmaceutical firms, other stakeholders are also suffering adverse consequences due to the use of the animal model in drug research.

Among these stakeholders are, importantly, the human research subjects who take part in clinical trials. (Chang 2016, discusses the notion that these individuals should be considered stakeholders even after clinical trials have ended.) These individuals are among the first humans to be exposed to compounds that perhaps appeared safe in animal models. Since we know compounds that appear safe in animal models can be extremely toxic to humans, these individuals face significant physical risks when they take part in clinical trials. And they are likely unaware of the magnitude of the risks; in their clinical trial recruiting materials, research scientists do not typically highlight the methodological problems we identify above.

Turning to another set of stakeholders, new generations of scientists are learning how to use flawed animal models instead of

learning new, effective techniques like microdosing and gene-based medicine, which we explain more fully below. This represents a dead-weight loss to society, as their valuable skills are being wastefully devoted to a field of research that offers no predictive value for human health when instead they could be experiencing the satisfaction of advancing scientific progress through use of better methods.

Importantly, taxpayers are stakeholders of pharmaceutical companies by virtue of supporting the legal infrastructure and economic environment in which the firms operate. Like other stakeholders, taxpayers are also bearing large and unnecessary costs as a direct result of animal testing. A lower bound on government expenditures on animal-based research is $10–12 billion per year simply to fund the fraction of the NIH budget that directly funds animal-based research conducted at universities.[10] There are additional costs associated with animal testing conducted by researchers at universities beyond that being funded by NIH grants. These costs are often covered by funds that can be traced back to the pocketbook of the general public, whether through taxes that support university operations, tuition fees, or charitable donations.

Further, while not a primary focus of this analysis, the animals we are discussing are actually sentient and sapient organisms.[11] When society allows such beings to suffer for no reason, another societal loss is experienced.

IF THE ANIMAL MODEL IS MISLEADING, WHY IS IT USED?

In previous sections we detailed the abysmal failure of the animal model in drug development. A reasonable question in light of the evidence is why the drug development industry began using and continues to rely so heavily on the results of animal-based research. The reasons originate with international and U.S. domestic events that date back as far as World War II.

We consider first the international events. With the end of World War II and the Doctors' trial at Nuremburg highlighting the horrors of Nazi experiments on humans, animal modeling became institutionalized in the moral codes of research: Principle 3 of the

Nuremburg Code and Principle 12 of the Declaration of Helsinki both state firmly that medical research on humans must be based on findings that arise from animal tests. Being ethical guidelines, these codes are not necessarily legally binding themselves. However, the principles codified in the Nuremburg Code and Declaration of Helsinki have been adopted into various countries' laws, including those of the United States, as we explain below. Current laws continue to enshrine these principles in spite of the fact that medical science and medical research methods were in their infancy at the time the codes were developed and paradigm-shifting advances have occurred since (see Greek et al. 2012b).

Regarding domestic laws in the United States, two key medical disasters led to Congress formalizing the way drug safety and efficacy would be regulated. First, in the 1930s, more than a hundred people were killed in the United States when ethylene glycol (a main component of antifreeze) was used as an additive in a sulfa drug used to treat infections. In response to that tragedy, Congress passed the 1938 Federal Food, Drug, and Cosmetic Act. Section 505 of the act required, for the first time, that anyone applying to introduce a new drug provide "full reports of investigations which have been made to show whether or not such drug is safe for use," which in practice typically involved animal tests, but as Wax (1995, p. 459), the specific nature of the animal tests was not standardized by the 1938 act.

The second medical disaster that helped to enshrine the use of animal tests in the drug development process in the United States was the occurrence of birth defects in the offspring of pregnant women who had been prescribed thalidomide in the early 1960s. Largely in response to that calamity, Senator Estes Kefauver led the initiative to revise the regulations governing the drug development process, and the result was the 1962 Drug Efficacy Amendment to the Federal Food, Drug, and Cosmetic Act, also known as the Kefauver Harris Amendment. This revision formalized the notion that both safety and efficacy must be demonstrated in new drug applications (NDAs). While the 1962 amendment did not explicitly stipulate that animal tests must be used to demonstrate safety and efficacy, the interpretation of the law was and continues to be such that animal tests are the primary means of supporting NDAs.

This is evident from various government sources. For instance, a 1968 government document reports that prior to conducting

human clinical trials, "The sponsor of clinical investigations must submit to FDA the animal data from which he has concluded that they can be conducted with reasonable safety" (Goldenthal 1968, p. 13). Further, an article in the FDA Consumer magazine states "Drug sponsors must show the FDA results of preclinical testing they've done in laboratory animals and what they propose to do for human testing before they can begin" (Meadows 2006).

Consistent with these sorts of government communications, the understanding among experts in the field was and is consistent with the belief that the FDA requires as a matter of policy that animal testing is a precursor to conducting human clinical trials. In a book about the pharmaceutical industry, Schnee (1978, pp. 10–11, parenthetic text added) states that the following was widely understood after the 1962 amendment:

> With respect to drug testing, the amendments and implementing regulations empowered the FDA to specify the testing procedure a manufacturer must use to produce acceptable information for evaluating the new drug application (NDA). The sponsor of a new drug was required to submit a "Notice of Claimed Investigational Exemption for a New Drug" to the FDA prior to human testing. The investigational new drug (IND) form is actually required to permit the interstate shipment of new drugs for clinical studies. The major impact of the IND was to require comprehensive data on animal tests before the FDA would allow human trials. Subsequently, animal toxicologists at the FDA formulated minimum standards for a satisfactory animal testing program.

Of course, the FDA employs some scientists who realize, or historically employed some scientists who realized, the use of the animal model is futile, and some have been quoted in previous sections. Therefore, it may seem obvious that the FDA should be willing to consider changing the regulations and policies that shape the drug development initiative. In general, the FDA has been unwilling to change policies without action from Congress; certainly the biggest changes in the way the FDA oversees drug development were brought about by the 1938 Federal Food, Drug, and Cosmetic Act and the 1962 Drug Efficacy Amendment. It is reasonable to assume that the abolishment of policies and regulations that currently mandate the use of animals will likewise require

some action from Congress even if the FDA may technically have the power to decide what evidence it accepts to support safety and efficacy. There are a few obstacles.

First, humans are generally prone to exhibit "status quo bias," which causes people to favor doing nothing or maintaining their previous habits when facing a decision. This bias has been robustly documented to be a pervasive influence on human decisions across a wide range of contexts; see Samuelson and Zeckhauser (1988) for instance. Status quo bias has likely been a strong factor interfering with regulators' willingness to deviate from the standard practice of requiring animal tests, even in the face of extensive and compelling evidence that such tests fail to ensure safety or efficacy for humans.

Second, members of Congress who are interested in being re-elected (and officials at the FDA interested in continued employment) are unlikely to be keen on taking responsibility for having mistakenly told their constituents that animal testing made their medications safe. To pursue the abolishment of animal testing requirements, they would need to be able to recommend replacing animal tests with methods that are able to ensure safety and efficacy. In other words, lawmakers and regulators have an incentive to keep the animal test requirements in place until science can replace them with something that is about 100 percent predictive. Fortunately, 100 percent predictability is feasible through personalized medicine, as we discuss in the next section.

Third, the pharmaceutical industry appears internally divided regarding whether to recognize the futility of animal models. On one hand, many scientists with ties to industry have made statements acknowledging that animal testing is an impediment to the drug development process; some are quoted above. On the other hand, firms in the pharmaceutical industry enjoy a period of patent protections on their drug discoveries, and during that period they have been able to implement pricing that allows them to cover their costs and earn a favorable return on investment. In light of these protections, pharmaceutical companies have had little incentive to change the system. In cases where drugs that that tested as safe on animals ended up harming humans in sufficient numbers that class-action lawsuits were successfully litigated by consumers, the magnitude of the fine has often been a small fraction of the revenues the firm accrued from selling the drug to unsuspecting

patients. (See Philippidis 2014, for relevant figures associated with some of the larger recent class-action lawsuits in the United States.)

A related reason the regulators have not yet fixed the problem is because the drug industry has enormous influence in Washington. The pharmaceutical industry has more registered lobbyists than the number of senators and congressmen combined (ABC News 2002). The relationship between that industry and the US Congress is illustrated by the 21st Century Cures Act (US Congress 2015–2016). Introduced in January 2015 and signed into law by President Obama in December 2016, this law does several things. It provides more money to the NIH, much of which will go to animal modeling. Writing in the *New England Journal of Medicine*, and quoting from the 21st Century Cures Act itself, Avorn and Kesselheim (2015, p. 2472) report that the bill also includes

> the use of "shorter or smaller clinical trials" for devices and the request that the FDA develop criteria for relying on "evidence from clinical experience," including "observational studies, registries, and therapeutic use" instead of randomized, controlled trials for approving new uses for existing drugs. Although such data can provide important information about drug utilization and safety once a medication is in use, there is considerable evidence that these approaches are not as rigorous or valid as randomized trials in assessing efficacy.

The bill essentially takes science out of drug development in terms of human clinical trials. The use of "observational studies" would allow the pharmaceutical industry to sell more medications even in absence of evidence that the drugs are safe and effective. The bill also allows drugs to be marketed based on the response of surrogate markers—chemical reactions that we think mimic what we actually want the drug to do. But there are problems with this approach, as suggested by the following example:

> In 2013, patients began to receive a new drug for tuberculosis approved on the basis of a randomized trial relying on a surrogate measure of bacterial counts in the sputum—even though patients given the drug in that trial had a death rate four times that in the comparison group, mostly from tuberculosis (Avorn and Kesselheim 2015, p. 2472).

Further, the bill allows some medications to be administered after animal studies without any human clinical trials being mandated. This does not bode well for safety and efficacy in humans. These are not the only problems with the bill, according to Avorn and Kesselheim (2015).

Beyond the legislative constraint, other possible reasons that help fortify the continued reliance upon animal modeling may include tradition, ego, conflict of interest, and money.

Columbia University's Dr. Azra Raza, explains:

> [Another reason for the continuation of animal modeling is] related 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 money gets spent. They're not prepared to concede that mouse models are basically valueless for most cancer therapeutics (Raza 2015, p. 232, parenthetic text added).

The drug development process begins in academia with basic science grants to researchers. 40–50 percent of grant money from the NIH funds animal models (see, for instance, Committee on Models for Biomedical Research Board on Basic Biology 1985; Greek and Greek 2010; Monastersky 2008). This process results in the successful development of a new drug only a very small fraction of a percent of the time (see Contopoulos-Ioannidis et al. 2003; Crowley 2003). The status quo still may appear to be a good deal for those who conduct basic research, but many of the eventual failures of drugs due to poor efficacy in human trials can be traced back to the druggable targets found by academia. (Druggable targets are typically proteins that are involved in a disease process and that can be potentially affected by a new medication for the benefit of the patient.) Even though the pharmaceutical industry does not necessarily fund academia directly—though sometimes it does—firms in the industry are still failing to serve the interests of their stakeholders because they take the results from academia, specifically the results from animal models used in academia, and a vast majority of the time those results do not result in a new drug. Nine out of ten times the drugs that make it to costly clinical trials do not make it to the market (see Sarkar 2009). This failure is not typically confirmed until after expensive human clinical trials have taken place.

Overall, researchers, institutions, and regulators have had little incentive to publicize the shortcomings of the animal model, though some have spoken out. As consumers and other stakeholders become more broadly aware of these shortcomings, and the significant costs associated with them, they may opt to mount grassroots efforts to pressure the FDA and their congressional representatives to eradicate policies and regulations that mandate the pointless use of animals in the drug development industry. In lobbying to eliminate the requirement that drugs be tested on animals, ideally one would like to promote a better option. Fortunately, scientists currently have options that were unavailable when the FDA regulations requiring animal testing were originally written, and they offer a very clear path forward. We now turn to discussing those options.

A BETTER OPTION: PERSONALIZED MEDICINE

We contend that by using animal models to predict human outcomes, the drug development industry is behaving like the proverbial drunk looking for his lost keys under a streetlamp rather than where he dropped them, in the dark. This is especially tragic given more promising methods are readily available. Personalized medicine is a more modern approach to delivering healthcare that is customized to an individual patient, taking account of her unique biological makeup.[12] To this end, instead of seeking druggable targets from animal tissues, scientists are using human tissue. Scientists are also linking genes to diseases and designing drugs around the proteins produced by the genes. Instead of testing drugs on animals to determine safety and efficacy, humans are being treated with drug using a technique called microdosing (see Garner and Lappin 2006; Lappin and Garner 2003, 2008; Lappin et al. 2006, 2013). With microdosing, nanogram quantities of a drug (measured in billionths of a gram), which are safe, are administered to patients, and both safety and efficacy can be evaluated.[13] This line of inquiry speaks to the promise of personalized medicine, whereby doctors are already identifying the genes that are involved in the effects and side effects of new drugs, and in turn are optimizing the outcome for patients. The future of medicine must continue to follow along this newly forged path, matching a patient's genes to her disease and drug response, accounting for the fundamentals of molecular biological and

TABLE 1 Response Rates of Patients to a Major Drug for a Selected Class of Therapeutic Areas (Spear et al. 2001)

Therapeutic Area	Efficacy Rate (percent)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac arrhythmias	60
Depression (SSRI)	62
Diabetes	57
HCV*	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

*Hepatitis C virus.

differences in genetic make-up across individuals; see Greek et al. (2012a) for further background on personalized medicine.

Nineteenth century animal modelers thought that all species were physiologically the same when scaled for size; see Bernard (1957) for instance. Likewise, physicians had long believed that all humans were more or less the same in terms of response to drugs and disease. In the twentieth century, physicians noted differences in responses to drugs and disease between the sexes, among races, and even between identical twins.[14]

Clinical observations showed that individual patients responded differently to medications, with each patient requiring individualized dosages of drugs. (A few examples include the muscle relaxant succinylcholine, the antituberculosis agent isoniazid, the antihypertensive agent hydralazine, and the antiarrhythmic drug procainamide.) It was discovered that some of the enzymes that metabolized these drugs were inherited in different amounts: some patients had more than one or two copies of the gene that coded for the enzyme and thus had higher concentrations of the enzyme and therefore lower concentrations of the drug.

The pharmaceutical industry is currently aware that individual patients respond differently to drugs. (See Table 1, which shows there

is remarkable heterogeneity in the way different patients respond to drug treatments for various conditions.) Allen Roses, then-worldwide vice-president of genetics at GlaxoSmithKline, said fewer than half of the patients prescribed some of the most expensive drugs derived any benefit from them: "The vast majority of drugs—more than 90 percent—only work in 30 or 50 percent of the people" (Connor 2003). See also Roses (2000) and Spear et al. (2001).

In contrast, personalized medicine is "coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements" (Mirnezami et al. 2012, p. 489). In other words, personalized medicine matches a specific drug to a specific patient in order to maximize efficacy and minimize side effects. By understanding which genes perform what functions in the human body and which genes are affected by specific medications, physicians can match a drug to a particular patient in terms of efficacy and safety. Patients who do have the gene and thus protein necessary for a drug to be effective will not be prescribed that drug; nor will patients who have genes known to result in severe adverse reaction for a drug. Note that even humans do not have a high enough predictive value to be used as a model for predicting what a drug will do for other humans. Physicians must determine each patient's genetic make-up and base treatment on that unique set of information.

Craig Venter, formerly of the Human Genome Project, stated:

> If you have lung cancer, as you know, the most important thing is to sequence the cancer gene, which determines whether Pfizer's crizotinib [a personalized drug for non-small cell lung cancer] will work on your type of tumor . . . . It really depends on the pharmaceuticals. The Pfizer drug was discovered almost by accident in that the clinical trial failed. Then they found that if you had a certain point mutation you had a 60% chance of tumor regression with crizotinib (Topol and Venter 2013).

In its 2014 report, *The Case for Personalized Medicine*, the Personalized Medicine Coalition documented the growth of commercially available personalized medicine products from 13 in 2006 to over 100 at the time the report was written. The report outlined various scenarios in which personalized medicine products are currently used:

> Patients with melanoma, leukemia, or metastatic lung, breast, or brain cancers are now routinely offered a "molecular diagnosis" in some clinical centers; this allows their physicians to select tailored treatments that can greatly improve the chances of survival. Melanoma can now be sub-classified by its genetics . . . .
>
> Treatments targeting . . . gene mutations represent a remarkable improvement over trial-and-error medicine, and we are not far from a time at which most cancer cases will be given a targeted course of treatment (Personalized Medicine Coalition 2014, p. 4).

In each of the years 2014 through 2016, more than 20 percent of all new molecular entities approved by the FDA were based on personalized medicine (Personalized Medicine Coalition 2016). Some of the new drugs approved in 2016 include the following. Epclusa is a drug used for the treatment of chronic hepatitis C infection which can be prescribed only after genetic testing. The same is true for Venclexta for the treatment of chronic lymphocytic leukemia and Zepatier which is used for the treatment of chronic hepatitis C infection.

Cancer treatment is the area of medicine being most transformed by personalized medicine. As reported by the Personalized Medicine Coalition 2014, pp. 9–13), several types of cancer treatment are well informed by genetic testing. For instance, patients with particular genetic mutations can take Zelborat as a treatment for melanoma that is surgically inoperable, and patients who exhibit a particular genetic expression are the only ones who can be treated effectively with Xalkori for non-small cell lung cancer. Likewise, genetic testing is used to identify the 30 percent of breast cancer patients who can reduce the likelihood of a tumor recurrence by 52 percent by taking Cerceptin. Additional genetic testing can determine which patients are best treated with hormone therapy alone or in combination with more aggressive modalities.

Personalized medicine can also help prevent adverse reactions to drugs. Koren et al. (2006) report that genotyping can prevent infant mortality in cases where analgesics are given to women during childbirth (which is common practice): between 1 and 29 percent of the population in different regions of the world exhibits a genetic characteristic that can lead to the death of newborns who are

breastfed by mothers taking particular pain relievers. Genetic testing prior to prescribing such drugs can save the lives of babies.

But personalized medicine does not just apply to prescribing drugs. By studying tissues from human cancer patients, researchers at Duke-National University of Singapore Graduate Medical School discovered that stomach cancer is actually two different diseases, and a patient's response to therapy depends on the genome of the cancer (see Tan et al. 2011). The effect of HIV and other diseases on different people is also known to vary with genetics; see Li et al. (2014), Lu et al. (2014), Serao et al. (2011), Trivedi (2010), Xu et al. (2012), and Xu et al. (2013).

The mutation that causes sickle cell anemia is called single nucleotide polymorphism, and, as described above, it arises from a small variation in DNA. Single nucleotide polymorphisms may be the reason not all children can be protected by the same vaccine (see King 2009; Yucesoy et al. 2009). In the future, children with a common genotype will be given a vaccine based on that genotype. It is estimated that "between 5 and 20 per cent of people vaccinated against hepatitis B, and between 2 and 10 per cent of those vaccinated against measles, will not be protected if they ever encounter these viruses" (King 2009, p. 11). Human variation is also caused by copy number variation—where a person has a different number of copies of the same gene (see Greek et al. 2012a). This can also lead to variation in response to drugs and disease.

Even if a more promising option were not currently available, it still would not suffice to continue with the current practice in drug development. That is, lack of personalized medicine as a viable option would not be sufficient grounds to continue to waste billions of dollars every year on animal-based practices that are proven not to work. Furthermore, the fact that scientists occasionally discover by accident safe or effective treatments using ineffective animal-based research methods is itself not a logical justification to continue with the status quo. Given the billions of dollars and countless number of researchers engaged in use of the animal model, it is inevitable that successful treatments would occasionally emerge simply due to random chance.

Flipping coins does not make for well-reasoned science, and that is unfortunately analogous to the practice the drug development industry engages in today. Fortunately, a better option is available by way of personalized medicine.

Personalized medicine is not some futuristic fantasy; it is currently happening for many diseases and medications. In fact, approximately 200 drugs currently require genetic information to be considered before prescribing (see FDA 2017). For a sample of recent discussions about the current practice of personalized medicine from the popular press and peer-reviewed journals including *Nature Medicine*, the *New England Journal of Medicine* and the *Lancet*, see Aldous (2013), Bates (2010), Belmaker et al. (2012), Bhathena and Spear (2008), Blair (2009), Dolgin (2013), Flaherty et al. (2010), Froehlich et al. (2011), Hudson (2011), Hughes et al. (2008), Lu et al. (2014), Powell et al. (2012), Serrano et al. (2011), Spear et al. (2001), Tan et al. (2011), and Wang et al. (2011).

CONCLUSIONS

In spite of decades of research that demonstrates the lack of predictive value of animal testing for determining the safety and efficacy of drugs, the pharmaceutical industry continues to rely on data from outmoded animal-based research and animal-based tests that are still routinely employed by scientists. This is costly to society in many ways: patients who suffer adverse reactions to drugs that appeared safe in animals; patients who fail to experience benefits from drugs that appeared to be effective in animals; patients facing an opportunity cost by missing out on drugs that might otherwise have been found to be safe and effective; harm to investors, employees, and suppliers due to the billions of dollars wastefully expended not only on animal tests but also on the much-more-costly human clinical trials that build on the misleading results of animal tests; and harm to various other parties. In contrast, the abandonment of animal modeling is in the best interest of those to whom pharmaceutical companies bear responsibility, even irrespective of the interests of animals.

National drug regulatory agencies like the U.S. FDA and conventions like the Nuremburg Code and the Declaration of Helsinki require animal modeling prior to administering a drug to humans. These regulations and codes are outdated and must be changed. The pharmaceutical industry has one of the most powerful lobbies on Capitol Hill and would have little trouble in updating Congress and asking them to mandate that the FDA eliminate the animal

testing requirements. The pharmaceutical industry should also educate Congress regarding the misleading and wasteful nature of basic science research that relies on animal modeling. This is necessary because universities, as entities that profit from animal modeling, are a strong lobby promoting the continuation of animal modeling. There is currently no lobbyist for human-based research. Unless the pharmaceutical industry takes these issues seriously, patients will continue to suffer and die prematurely, and the rest of society will continue to bear sizable, avoidable costs.

NOTES

1. We use phrases such as *drug development industry* and *drug development process* to include all research leading to a new drug. This includes research performed by those in academia, by pharmaceutical companies, and by companies that, while not pharmaceutical companies *per se*, are closely associated with that sector: for example, biotechnology companies.

2. Humans are, of course, animals, but we adhere to the convention of using the word animal to mean non-human animal.

3. We identify this set of stakeholders based on concepts discussed by Freeman (1994, 2004), Phillips (1997), Mitchell et al. (1997), and Phillips et al. (2003).

4. Precise estimates vary. We quote sources below that put the amount in a range between 53 billion dollars per year to over a 100 billion dollars per year.

5. See Greek (2012), Greek (2014a,b,c), Greek and Greek (2010), Greek and Hansen (2012, 2013a, 2013b), Greek et al. (2011, 2012a, 2012b), Greek and Menache (2013), Greek and Pound (2002), Greek and Rice (2012), Greek and Shanks (2009), Jones and Greek (2013), Shanks and Greek (2008), and Shanks et al. (2009).

6. The reader might wonder, if the animal model is so poor at predicting birth defects in humans, then why have we not seen another thalidomide-like disaster? The answer is both simple and disheartening: physicians simply avoid prescribing pregnant women most drugs, adopting a "better safe than sorry" policy. While this is an appropriate adjustment in physician behavior in light of their current information set, it highlights one of the hidden costs of a regime that relies so heavily on the animal model, namely a virtual freeze on progress in some areas of medical science.

7. See the clinical trial study record detail maintained by the U.S. National Institutes of Health: https://clinicaltrials.gov/ct2/show/NCT00594568.

8. Additional sources that discuss evidence on the poor predictability associated with the animal model include the following (among many others): Abbott 2005; Akhtar 2015; Alini et al. 2008; Alving 2002; Bendtsen and Møller 2008; Björquist et al. 2007; Brennan et al. 2010; Butcher 2005; Calabrese 1984, 1991; Chabner and Roberts 2005; Chapman 2011; Collins 2011; Connors 1996; Cook et al. 2012; Dennis 2006; Dixit and Boelsterli 2007; Dixon 1972; Dragunow 2008; Drake et al. 2012; Duyk 2003; Eason et al. 1990, Elferink et al. 2011, Engber 2011b; Enna and Williams 2009; FDA 2004, 2006; Fedorov et al. 2011; Ferdowsian and Beck 2011; Fletcher 1978; Force and Kolaja 2011; Garattini 1985; Geerts 2009; Giri and Bader 2011; Grass and Sinko 2002; Greek and Greek 2010; Greek et al. 2011a, 2012a; Greek and Shanks 2009; Gura 1997; Hait 2010; Hampel et al. 2010; Herper 2012; Heywood 1990; Hörig and Pullman 2004; Holmes et al. 2011; Horrobin 2003; Hurko 2006; Kamb 2005; Kay 2011; Khanna 2012; Kola and Landis 2004; Ledford 2012; Lin 1995; Littman and Williams 2005; Loisel et al. 2007; Lumley 1990; Lutz 2011; Mahmood 2000; Markou et al. 2009; Marusina 2012; Matthews 2008; McArthur 2011; McGee 2006; Meijers et al. 1997; Millan et al. 2012; Mullane and Williams 2012; Mullard 2011; *Nature Reviews Drug Discovery* Editorial 2005; *Nature Reviews Drug Discovery* News & Analysis 2011; Neuzil et al. 2012; Noble 2000; O'Collins et al. 2006; Opar 2012; Oser 1981; Palfreyman et al. 2002; Pammolli et al. 2011; Paul et al. 2010; Prater 2012; Raven 2012; Regenberg et al. 2009; Reynolds 2012; Rice 2012; Royal Society of Medicine 1980; Seligmann 2004; Seok et al. 2013; Shaffer 2012; Shanks and Greek 2009; Shanks et al. 2009; Sharp and Langer 2011; Shepard and Lemire 2004; Sietsema 1989; Sitaram and Gershon 1983; Smith and Caldwell 1977; Smith et al. 1965; Suter 1990; Taneja et al. 2012; Taylor 2009; Uhl et al. 2012; van Meer et al. 2012; van Zutphen 2000; Wall and Shani 2008; Weaver et al. 2003; Young 2008; Yukhananov 2011; Zbinden 1993; Zhang et al. 2010; Zielinska 2010.

9. The U.S. pharmaceutical industry's spending on R&D as a percentage of revenues is 15.8 percent compared to 3.2 percent across all industries according to Pham (2010, table 6). Total U.S. pharmaceutical industry spending on R&D is now in the range of $50 billion per year, up from $2 billion in 1990; see PhRMA (2015). For additional industry statistics, see Khanna (2012) and Vernon et al. (2010).

10. According to an article by Monastersky (2008) in *The Chronicle of Higher Education*, the NIH has devoted a relatively constant 42 percent of its awards since 1990 to grants and contracts involving animal-based research. Its program-level budget was over 30 billion dollars in 2015 and 2016, and it is forecasted to be over 33 billion dollars in 2017 (see National

Institutes of Health 2016). Another approximation of how much of the government's research dollars in general went to animal-based studies is provided by a government-produced table from 1985 showing that about 50 percent of such research dollars went to animal models; see Committee on Models for Biomedical Research Board on Basic Biology (1985) and Greek and Greek (2010). This reinforces the point that animal modeling in basic research is very expensive for society directly and industry indirectly, since all parties rely on the data that emerge from basic research. Despite appeals for an update on the 1985 estimate, the NIH has not provided these data.

11. Studies such as those by Brosnan and de Waal (2003) and Bekoff (2004) demonstrate that nonhuman animals exhibit precursors to morality, such as empathy, sympathy, fairness, and cooperation. More recent work has begun to show evidence not only of precursors to morality, but a capacity for moral reasoning itself. For instance, Lin et al. (2008) find evidence that apes are capable of right versus wrong value judgements. Additionally, studies have shown that a wide range of animals are capable of feeling pain, including even fish (see Duncan 2006). Further, animals across a broad range of species evidently experience human-like emotions, for example, grieving the death of their peers; see King (2013).

12. In his 2015 State of the Union speech, President Obama voiced his desire for Congress to provide additional funding for a new "Precision Medicine Initiative," or personalized medicine.

13. One nanogram of the most toxic substances on earth can be safely ingested; see Gill (1982) and National Institute of Occupational Safety and Health (1996). This dose can be incrementally increased until efficacy is either established or the beginning signs of toxicity are seen. See Greek (2013) for more information on microdosing.

14. See, for instance, Alexanderson and Borgå (1972), Bell and Spector (2011), Bruder et al. (2008), Canto et al. (2012), Chapman and Hill (2012), Cheung et al. (1997), Couzin (2007a,b), Czyz et al. (2012), Dempster et al. (2011), Dewland et al. (2013), Edelstein et al. (2013), Favoni and Alama (2013), Fraga et al. (2005), Gordon et al. (2011), Gregor and Joffe (1978), Haiman et al. (2006), Halder et al. (2012), Herndon and Jennings (1951), Holden (2005), Javierre et al. (2010), Kaiser (2005), Kalow (1991), Klein and Huber (2010), Kopp et al. (2011), Lin et al. (1989), Lyons et al. (2013), Macdonald (2002), Maiti et al. (2011), Misch et al. (2010), Muqit et al. (2008), Ollikainen and Craig (2011), Pinto et al. (2013), Sarkar et al. (2012), Simon (2005), Sloan et al. (2002), Spielman et al. (2007), Stamer and Stuber (2007), Stankiewicz and

Lupski (2010), Wald and Wu (2010), Wilke and Dolan (2011), Willyard (2009), Wong et al. (2005), Xu et al. (2012), and Zhao et al. (2012).

ACKNOWLEDGMENT

We are grateful to Joel Amernic, Len Brooks, Mark Kamstra, Chi Liao, and Roger Martin for comments on earlier versions. We also thank participants of the Jackman Humanities Institute's Animals in the Law and Humanities Working Group at the University of Toronto.

REFERENCES

Abbott, A. 2005. "Animal testing: More than a cosmetic change," *Nature* 438: 144–146.

ABC News. 2002. *Transcript of Bitter Medicine – Pills, Profit and the Public Health*. (On 29 May 2002, ABC News aired Bitter Medicine – Pills, Profit and the Public Health', a special expose narrated by Peter Jennings.).

Ahn, A. C., Tewari, M., Poon, C. S., and Phillips, R. S. 2006. "The limits of reductionism in medicine: Could systems biology offer an alternative?," *PLoS Medicine* 3: e208.

Akhtar, A. 2015. "The flaws and human harms of animal experimentation," *Cambridge Quarterly of Healthcare Ethics* 24: 407–419. https://doi.org/10.1017/S0963180115000079419, accessed February 2, 2018.

Aldous, P. 2013. "Your genomic future: Personalised medicine is here," *New Scientist* 2933. https://www.newscientist.com/article/mg21929333-100-your-genomic-future-personalised-medicine-is-here/, accessed February 2, 2018.

Alexanderson, B., and Borgå, O. 1972. "Interindividual differences in plasma protein binding of nortriptyline in man – A twin study," *European Journal of Clinical Pharmacology* 4: 196–200.

Alini, M., Eisenstein, S. M., Ito, K., Little, C., Kettler, A. A., Masuda, K., Melrose, J., Ralphs, J., Stokes, I., and Wilke, H. J. 2008. "Are animal models useful for studying human disc disorders/degeneration?," *European Spine Journal* 17: 2–19.

Alving, C.R. 2002. "Design and selection of vaccine adjuvants: Animal models and human trials," *Vaccine* 20: S56–S64

American Association for Laboratory Animal Science. 2001. "The cost of caring: Recognizing human emotions in the care of laboratory animals." https://aalaslearninglibrary.org/pdf/course2593/cost_of_caring.pdf, accessed February 2, 2018.

American Cancer Society. 2013. "Water fluoridation and cancer risk." June 24, http://www.cancer.org/cancer/cancercauses/othercarcino

gens/athome/water-fluoridation-and-cancer-risk, accessed February 2, 2018.
American Paraplegia Society. 1988. "Symposium on spinal cord injury models. Presented at the 33rd annual meeting of the American Paraplegia Society. September 1987," *Journal of the American Paraplegia Society* 11: 23–58.
Anisimov, V. N., Ukraintseva, S. V., and Yashin, A. I. 2005. "Cancer in rodents: Does it tell us about cancer in humans?," *Nature Reviews Cancer* 5: 807–819.
Arrowsmith, J. 2011a. "Trial watch: Phase II failures: 2008–2010," *Nature Reviews Drug Discovery* 10: 328–329.
Arrowsmith, J. 2011b. "Trial watch: Phase III and submission failures: 2007–2010," *Nature Reviews Drug Discovery* 10: 87.
Attarwala, H. 2010. "TGN1412: From discovery to disaster," *Journal of Young Pharmacists* 2: 332–336.
Avorn, J., and Kesselheim, A. S. 2015. "The 21st century cures act — Will it take us back in time?," *New England Journal of Medicine* 372: 2473–2475.
Bailey, J. 2008. "An assessment of the role of chimpanzees in AIDS vaccine research," *Alternatives to Laboratory Animals* 36: 381–428.
Bates, S. 2010. "Progress towards personalized medicine," *Drug Discovery Today* 15: 115–120.
Bekoff, M. 2004. "Wild justice and fair play: Cooperation, forgiveness, and morality in animals," *Biology and Philosophy* 19: 489–520.
Bell, J.T., and Spector, T. D. 2011. "A twin approach to unraveling epigenetics," *Trends in Genetics: TIG* 27: 116–125.
Belmaker, R., Bersudsky, Y., and Agam, G. 2012. "Individual differences and evidence-based psychopharmacology," *BMC Medicine* 10: 110.
Bendtsen, F., and Møller, S. 2008. "Pharmacological effects are model specific in animal models of portal hypertension," *Hepatology International* 2: 397–398.
Bernard, C. 1957. *An Introduction to the Study of Experimental Medicine*. New York, NY: Dover.
Bhathena, A., and Spear, B. B. 2008. "Pharmacogenetics: Improving drug and dose selection," *Current Opinion in Pharmacology* 8: 639–646
Björquist, P., Sartipy, P., Strehl, R., and Hyllner, J. 2007. "Human ES cell derived functional cells as tools in drug discovery," *Drug Discovery World Winter* 17–24.
Blair, E. 2009. "Predictive tests and personalised medicine," *Drug Discovery World Fall* 27–31.
Brennan, R., Federico, S., and Dyer, M. A. 2010. "The war on cancer: Have we won the battle but lost the war?," *Oncotarget* 1: 77–83.
Brosnan, S. F., and de Waal, F. M. B. 2003. "Monkeys reject unequal pay," *Nature* 425: 297–299.
Bruder, C. E., Piotrowski, A., Gijsbers, A. A., Andersson, R., Erickson, S., de Stahl, T. D., Menzel, U., et al. 2008. "Phenotypically concordant and

discordant monozygotic twins display different DNA copy-number-variation profiles," *American Journal of Human Genetics* 82: 763–771.

Bucher, J. R., Hejtmancik, M. R., Toft, J. D. II, Persing, R. L., Eustis, S. L., and Haseman, J. K. 1991. "Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride," *International Journal of Cancer* 48: 733–737.

Butcher, E. C. 2005. "Can cell systems biology rescue drug discovery?," *Nature Reviews Drug Discovery* 4: 461–467.

Calabrese, E. J. 1984. "Suitability of animal models for predictive toxicology: theoretical and practical considerations," *Drug Metabolism Reviews* 15(3): 505–23.

Calabrese, E. J. 1991. *Principles of Animal Extrapolation*. Boca Raton, FL: CRC Press.

Calne, R. Y., Collier, D. S., Lim, S., Pollard, S. G., Samaan, A., White, D. J., and Thiru, S. 1989. "Rapamycin for immunosuppression in organ allografting," *Lancet* 2(8656): 227.

Canto, J. G., Rogers, W. J., Goldberg, R. J., Peterson, E. D., Wenger, N. K., Vaccarino, V., Kiefe, C. I., Frederick, P. D., Sopko, G., and Zheng, Z.-J. 2012. "Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality," *Journal of the American Medical Association* 307(8): 813–822.

Centers for Disease Control and Prevention. 1998. "Fatal cercopithecine herpesvirus 1 (B virus) infection following a mucocutaneous exposure and interim recommendations for worker protection," *Morbidity and Mortality Weekly Report* 47(49): 1073–1076.

Chabner, B. A., and Roberts, T. G., Jr. 2005. "Timeline: Chemotherapy and the war on cancer," *Nature Reviews Cancer* 5(1): 65–72.

Chang, P. L. 2016. "The abandoned stakeholders: Pharmaceutical companies and research participants," *Journal of Business Ethics* 1–11.

Chapman, A. R. 2011. "Addressing the ethical challenges of first-in-human trials," *Journal of Clinical Research and Bioethics* 2(4): 113.

Chapman, S. J., and Hill, A. V. S. 2012. "Human genetic susceptibility to infectious disease," *Nature Reviews Genetics* 13(3): 175–188.

Cheung, D. S., Warman, M. L., and Mulliken, J. B. 1997. "Hemangioma in twins," *Annals of Plastic Surgery* 38(3): 269–274.

Cimons, M., Getlin, J., and Maugh, T. H. 1998. "Cancer-cure story raises new questions – New York times reporter backs out of book deal on new therapy," *The Seattle Times*, May 6, http://community.seattletimes.nwsource.com/archive/?date=19980506&slug=2749152, accessed February 2, 2018.

Clayson, D. 1980. "The carcinogenic action of drugs in man and animals," in F. Coulston and P. Shubick, eds., *Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis*. New York, NY: Ablex Publishing, pp. 185–195.

Clemmensen, J., and Hjalgrim-Jensen, S. 1980. "On the absence of carcinogenicity to man of phenobarbital," in F. Coulston and S. Shubick,

eds., *Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis*. New York, NY: Ablex Publishing, pp. 251–265.
Collins, F. S. 2011. "Reengineering translational science: The time is right," *Science Translational Medicine* 3(90): 90cm17.
Committee on Models for Biomedical Research Board on Basic Biology. 1985. *Committee on Models for Biomedical Research. Board on Basic Biology. Commission on Life Science. National Research Council. Models for Biomedical Research: A New Perspective*. Washington, DC: National Academy Press.
Connor, S. 2003. "Glaxo chief: Our drugs do not work on most patients," *The Independent*, December 8, http://www.independent.co.uk/news/science/glaxo-chief-our-drugs-do-not-work-on-most-patients-5508670.html, accessed February 2, 2018.
Connors, T. 1996. "Anticancer drug development: The way forward," *Oncologist* 1(3): 180–181.
Contopoulos-Ioannidis, D. G., Ntzani, E. E., and Ioannidis, J. P. 2003. "Translation of highly promising basic science research into clinical applications," *The American Journal of Medicine* 114(6): 477–484.
Cook, N., Jodrell, D. I., and Tuveson, D. A. 2012. "Predictive in vivo animal models and translation to clinical trials," *Drug Discovery Today* 17(5/6): 253–260.
Couzin, J. 2007a. "Cancer research. Probing the roots of race and cancer," *Science* 315(5812): 592–594.
Couzin, J. 2007b. "Human genetics. In Asians and whites, gene expression varies by race," *Science* 315(5809): 173–174.
Crowley, W. F. 2003. "Translation of basic research into useful treatments: How often does it occur?" *The American Journal of Medicine* 114(6): 503–505.
Czyz, W., Morahan, J., Ebers, G., and Ramagopalan, S. 2012. "Genetic, environmental and stochastic factors in monozygotic twin discordance with a focus on epigenetic differences," *BMC Medicine* 10(1): 93.
Dempster, E. L., Pidsley, R., Schalkwyk, L. C., Owens, S., Georgiades, A., Kane, F., Kalidindi, S., et al. 2011. "Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder," *Human Molecular Genetics* 20(24): 4786–4796.
Dennis, C. 2006. "Cancer: Off by a whisker," *Nature* 442(7104): 739–741.
Dewland, T. A., Olgin, J. E., Vittinghoff, E., and Marcus, G. M. 2013. "Incident atrial fibrillation among Asians, Hispanics, Blacks, and Whites," *Circulation* 128(23): 2470–2477.
DiMasi, J. A., Feldman, L., Seckler, A., and Wilson, A. 2010. "Trends in risks associated with new drug development: Success rates for investigational drugs," *Clinical Pharmacology and Therapeutics* 87(3): 272–277.
Dirnagl, U. 2006. "Bench to bedside: The quest for quality in experimental stroke research," *Journal of Cerebral Blood Flow and Metabolism* 26(12): 1465–1478.
Dirnagl, U., and Macleod, M. R. 2009. "Stroke research at a road block: The streets from adversity should be paved with meta-analysis and good laboratory practice," *British Journal of Pharmacology* 157(7): 1154–1156.

Dixit, R., and Boelsterli, U. 2007. "Healthy animals and animal models of human disease(s) in safety assessment of human pharmaceuticals, including therapeutic antibodies," *Drug Discovery Today* 12(7–8): 336–342.

Dixon, R. L. 1972. "Toxicology of environmental agents: A blend of applied and basic research," *Environmental Health Perspectives* 2, 103–116.

Dolgin, E. 2013. "Animal rule for drug approval creates a jungle of confusion," *Nature Medicine* 19(2): 118–119.

Downing, N. S., Nilay, D. S., Aminawung, J. A., Pease, A. M., Zeitoun, J.-D., Krumholz, H. M., and Ross, J. S. 2017. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA* 317(18): 1854–1863.

Dragunow, M. 2008. "The adult human brain in preclinical drug development," *Nature Reviews Drug Discovery* 7(8): 659–666.

Drake, D. R. III., Singh, I., Nguyen, M. N., Kachurin, A., Wittman, V., Parkhill, R., Kachurina, O., et al. 2012. "In vitro biomimetic model of the human immune system for predictive vaccine assessments," *Disruptive Science and Technology* 1(1): 28–40.

Duncan, I. J. H. 2006. "The changing concept of animal sentience," *Applied Animal Behaviour Science* 100(1–2): 11–19.

Duyk, G. 2003. "Attrition and translation," *Science* 302(5645): 603–605.

Eason, C. T., Bonner, F. W., and Parke, D. V. 1990. "The importance of pharmacokinetic and receptor studies in drug safety evaluation," *Regulatory Toxicology and Pharmacology* 11(3): 288–307.

Edelstein, L. C., Simon, L. M., Montoya, R. T., Holinstat, M., Chen, E. S., Bergeron, A., Kong, X., et al. 2013. "Racial differences in human platelet PAR4 reactivity reflect expression of PCTP and miR-376c," *Nature Medicine* 19(12): 1609–1616.

Elferink, M. G., Olinga, P., van Leeuwen, E. M., Bauerschmidt, S., Polman, J., Schoonen, W. G., Heisterkamp, S. H., and Groothuis, G. M. 2011. "Gene expression analysis of precision-cut human liver slices indicates stable expression of ADME-Tox related genes," *Toxicology and Applied Pharmacology* 253(1): 57–69.

Engber, D. 2011a. "Black-6 lab mice and the history of biomedical research," *Slate*, November 17, http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/black_6_lab_mice_and_the_history_of_biomedical_research.html, accessed February 02, 2018.

Engber, D. 2011b. "Lab mice: Are they limiting our understanding of human disease?," *Slate*, November 16, http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/lab_mice_are_they_limiting_our_understanding_of_human_disease_.single.html, accessed February 02, 2018.

Engber, D. 2011c. "Naked mole rats: Can they help us cure cancer?," *Slate*. November 16, http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/naked_mole_rats_can_they_help_us_cure_cancer_.html, accessed February 02, 2018.

Enna, S. J., and Williams, M. 2009. "Defining the role of pharmacology in the emerging world of translational research," *Advances in Pharmacology* 57, 1–30.

Favoni, R. E., and Alama, A. 2013. "Preclinical strategies targeted at non-small-cell lung cancer signalling pathways with striking translational fallout," *Drug Discovery Today* 18(1–2): 11–24.

FDA. 2004. "Innovation or stagnation? Challenge and opportunity on the critical path to new medical products," *FDA*, http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPAthOpportunitiesReports/ucm113411.pdf, accessed February 02, 2018.

FDA. 2006. "FDA issues advice to make earliest stages of clinical drug development more efficient," *FDA*, June 18, http://web.archive.org/web/20141011121434/ http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108576.htm, accessed February 02, 2018.

FDA. 2017. "Table of pharmacogenomic biomarkers in drug labeling," https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm, accessed February 02, 2018.

Fedorov, V. V., Glukhov, A. V., Ambrosi, C. M., Kostecki, G., Chang, R., Janks, D., Schuessler, R. B., Moazami, N., Nichols, C. G., and Efimov, I. R. 2011. "Effects of KATP channel openers diazoxide and pinacidil in coronary-perfused atria and ventricles from failing and non-failing human hearts," *Journal of Molecular and Cellular Cardiology* 51(2): 215–225.

Ferdowsian, H. R., and T. L. Beauchamp. 2013. "Animal experimentation," *The International Encyclopedia of Ethics* 271–285.

Ferdowsian, H. R., and Beck, N. 2011. "Ethical and scientific considerations regarding animal testing and research," *PLoS ONE* 6(9): e24059.

Flaherty, K. T., Puzanov, I., Kim, K. B., Ribas, A., McArthur, G. A., Sosman, J. A., O'Dwyer, P. J., et al. 2010. "Inhibition of mutated, activated BRAF in metastatic melanoma," *New England Journal of Medicine* 363(9): 809–819.

Fletcher, A. P. 1978. "Drug safety tests and subsequent clinical experience," *Journal of the Royal Society of Medicine* 71(9): 693–696.

Force, T., and Kolaja, K. L. 2011. "Cardiotoxicity of kinase inhibitors: The prediction and translation of preclinical models to clinical outcomes," *Nature Reviews Drug Discovery* 10(2): 111–126.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., Heine-Suner, D., et al. 2005. "Epigenetic differences arise during the lifetime of monozygotic tins," *Proceedings of the National Academy of Sciences* 102(30): 10604–10609.

Freeman, R. E. 1994. "The politics of stakeholder theory: Some future directions," *Business Ethics Quarterly* 4(4): 409–421.

Freeman, R. E. 2004. "A stakeholder theory of the modern corporation," in T. L. Beauchamp and N. E. Bowie, eds., *Ethical Theory and Business*. Upper Saddle River, NJ: Pearson Prentice Hall, pp. 55–64.

Friedman, M. 1970. "The social responsibility of business is to increase its profits," *New York Times Magazine* 32–33: 123–126.

Froehlich, T. E., Epstein, J. N., Nick, T. G., Melguizo Castro, M. S., Stein, M. A., Brinkman, W. B., Graham, A. J., Langberg, J. M., and Kahn, R. S. 2011. "Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder," *Journal of the American Academy of Child and Adolescent Psychiatry* 50(11): 1129–1139.e2.

Gamble, L. J., and Matthews, Q. L. 2010. "Current progress in the development of a prophylactic vaccine for HIV-1," *Drug Design, Development and Therapy* 5, 9–26.

Garattini, S. 1985. "Toxic effects of chemicals: Difficulties in extrapolating data from animals to man," *Critical Reviews in Toxicology* 16(1): 1–29.

Garner, R. C., and Lappin, G. 2006. "The phase 0 microdosing concept," *British Journal Clinical Pharmacology* 61(4): 367–370.

Geerts, H. 2009. "Of mice and men: Bridging the translational disconnect in CNS drug discovery," *CNS Drugs* 23(11): 915–926.

Gell-Mann, M. 1994. *The Quark and the Jaguar: Adventures in the Simple and Complex*. Boston, MA: Little, Brown and Company.

Giles, J. 2006. "Animal experiments under fire for poor design," *Nature* 444(7122): 981.

Gill, D. M. 1982. "Bacterial toxins: A table of lethal amounts," *Microbiological Reviews* 46(1): 86–94.

Giri, S., and Bader, A. 2011. "Foundation review: Improved preclinical safety assessment using micro-BAL devices: The potential impact on human discovery and drug attrition," *Drug Discovery Today* 16(9/10): 382–397.

Goldenthal, E. 1968. "Current views on safety evaluation of drugs," *FDA Papers* 2: 13–18.

Goodwin, B. 2001. *How the Leopard Changed Its Spots: The Evolution of Complexity*. Princeton, NJ: Princeton University Press.

Gordon, L., Joo, J. H., Andronikos, R., Ollikainen, M., Wallace, E. M., Umstad, M. P., Permezel, M., et al. 2011. "Expression discordance of monozygotic twins at birth: Effect of intrauterine environment and a possible mechanism for fetal programming," *Epigenetics* 6(5): 579–592.

Graham, D.J., Campen, D., Hui, R., Spence, M., Cheetham, C., Levy, G., Shoor, S., and Ray, W.A. 2005. "Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: Nested case-control study," *Lancet* 365(9458): 475–481.

Grass, G. M., and Sinko, P. J. 2002. "Physiologically-based pharmacokinetic simulation modelling," *Advanced Drug Delivery Reviews* 54(3): 433–451.

Greek, R. 2012. "Animal models and the development of an HIV vaccine," *Journal of AIDS and Clinical Research* 1(S8): 1–11.

Greek, R. 2013. "Evolved complex systems," *Biological Systems: Open Access* 2(4): e107.

Greek, R. 2014a. "A discussion of the role of complex evolved systems in the development of invasive cardiovascular interventions as illustrated

by the blalock-taussig shunt and intra-arterial stents," *Biological Systems – Open Access* 3: 124.
Greek, R. 2014b. "The ethical implications for humans in light of the poor predictive value of animal models," *International Journal of Clinical Medicine* 5(16): 966–1005.
Greek, R. 2014c. "Your dog or your child," in J. Sorenson, ed., *Critical Animal Studies: Thinking the Unthinkable*. Toronto, ON: Canadian Scholars Press Inc, pp. 117–133.
Greek, R., and Greek, J. 2010. "Is the use of sentient animals in basic research justifiable?" *Philosophy, Ethics, and Humanities in Medicine* 5(14): 1–16.
Greek, R., and Hansen, L. 2012. "The development of deep brain stimulation for movement disorders," *Journal of Clinical Research & Bioethics* 3: 338–345.
Greek, R., and Hansen, L. A. 2013a. "The strengths and limits of animal models as illustrated by the discovery and development of antibacterials," *Biological Systems: Open Access* 2(2): 109.
Greek, R., and Hansen, L. A. 2013b. "Questions regarding the predictive value of one evolved complex adaptive system for a second: Exemplified by the SOD1 mouse," *Progress in Biophysics and Molecular Biology* 113(2): 231–253.
Greek, R., and Menache, A. 2013. "Systematic reviews of animal models: Methodology versus epistemology," *International Journal of Medical Sciences* 10(3): 206–221.
Greek, R., Menache, A., and Rice, M. J. 2012a. "Animal models in an age of personalized medicine," *Personalized Medicine* 9(1): 47–64.
Greek, R., Pippus, A., and Hansen, L. A. 2012b. "The Nuremberg code subverts human health and safety by requiring animal modeling," *BMC Medical Ethics* 13(1): 16.
Greek, R., and Pound, P. 2002. "Animal studies and HIV research," *British Medical Journal* 324(7331): 236–237.
Greek, R., and Rice, M. J. 2012. "Animal models and conserved processes," *Theoretical Biology and Medical Modelling* 9(1): 40.
Greek, R., and Shanks, N. 2009. *FAQs About the Use of Animals in Science: A Handbook for the Scientifically Perplexed*. Lanham, MD: University Press of America.
Greek, R., Shanks, N., and Rice, M. J. 2011. "The history and implications of testing thalidomide on animals," *The Journal of Philosophy, Science & Law* 11(3): 1–32.
Gregor, Z., and Joffe, L. 1978. "Senile macular changes in the black African," *British Journal of Ophthalmology* 62(8): 547–550.
Gura, T. 1997. "Cancer models: Systems for identifying new drugs are often faulty," *Science* 278(5340): 1041–1042.
Hackam, D. G., and Redelmeier, D. A. 2006. "Translation of research evidence from animals to humans," *Journal of the American Medical Association* 296(14): 1727–1732.

Haiman, C. A., Stram, D. O., Wilkens, L. R., Pike, M. C., Kolonel, L. N., Henderson, B. E., and Le Marchand, L. 2006. "Ethnic and racial differences in the smoking-related risk of lung cancer," *New England Journal of Medicine* 354(4): 333–342.

Hait, W. N. 2010. "Anticancer drug development: The grand challenges," *Nature Reviews Drug Discovery* 9(4): 253–254.

Halder, A., Jain, M., Chaudhary, I., and Varma, B. 2012. "Chromosome 22q11.2 microdeletion in monozygotic twins with discordant phenotype and deletion size," *Molecular cytogenetics* 5(1): 13.

Halpern-Lewis, J. C. 1996. "Understanding the emotional experiences of animal research personnel," *Contemporary Topics in Laboratory Animal Science* 35(6): 58–60.

Hampel, H., Frank, R., Broich, K., Teipel, S. J., Katz, R. G., Hardy, J., Herholz, K., et al. 2010. "Biomarkers for Alzheimer's disease: Academic, industry and regulatory perspectives," *Nature Reviews Drug Discovery* 9(7): 560–574.

Herndon, C. N., and Jennings, R. G. 1951. "A twin-family study of susceptibility to poliomyelitis," *American Journal of Human Genetics* 3(1): 17–46.

Herper, M. 2012. "Can bush's NIH chief fix the drug industry?," *Forbes*, May 6, http://www.forbes.com/sites/matthewherper/2012/06/06/can-bushs-nih-chief-fix-the-drug-industry/, accessed February 2, 2018.

Heywood, R. 1990. "Clinical toxicity–Could it have been predicted? Post-marketing experience," in C. E. Lumley and S. Walker, eds., *Animal Toxicity Studies: Their Relevance for Man*. Lancaster: Quay Publishing, pp. 57–67.

Holden, C. 2005. "Sex and the suffering brain," *Science* 308(5728): 1574.

Hörig, H., and Pullman, W. 2004. "From bench to clinic and back: Perspective on the 1st IQPC translational research conference," *Journal of Translational Medicine* 2(1): 44.

Horstmann, D. 1985. "The poliomyelitis story: A scientific hegira," *Yale Journal of Biology and Medicine* 58(2): 79–90.

Holmes, A. M., Solari, R., and Holgate, S. T. 2011. "Animal models of asthma: Value, limitations and opportunities for alternative approaches," *Drug Discovery Today* 16(15/16): 659–670.

Horrobin, D. F. 2003. "Modern biomedical research: An internally self-consistent universe with little contact with medical reality?," *Nature Reviews Drug Discovery* 2(2): 151–154.

Hudson, K. L. 2011. "Genomics, health care, and society," *New England Journal of Medicine* 365(11): 1033–1041.

Hughes, A. R., Spreen, W. R., Mosteller, M., Warren, L. L., Lai, E. H., Brothers, C. H., Cox, C., et al. 2008. "Pharmacogenetics of hypersensitivity to abacavir: From PGx hypothesis to confirmation to clinical utility," *Pharmacogenomics Journal* 8(6): 365–374.

Hurko, O. 2006. "Understanding the strategic importance of biomarkers for the discovery and early development phases," *Drug Discovery World* 7(2): 63–74.

Janofsky, M. 1993. "*On cigarettes, health and lawyers*," *New York Times*, http://www.nytimes.com/1993/12/06/business/on-cigarettes-health-and-lawyers.html, accessed February 2, 2018.

Javierre, B. M., Fernandez, A. F., Richter, J., Al-Shahrour, F., Martin-Subero, J. I., Rodriguez-Ubreva, J., Berdasco, M., et al. 2010. "Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus," *Genome Research* 20(2): 170–179.

Jensen, M. C., and Meckling, W. 1976. "Theory of the firm: Managerial behavior, agency cost, and capital structure," *Journal of Financial Economics* 3(4): 305–360.

Jones, R. C., and Greek, R. 2013. "A review of the institute of medicine's analysis of using chimpanzees in biomedical research," *Science and Engineering Ethics* 20(2): 481–504.

Jover, R., Ponsoda, X., Castell, J. V., and Gomez-Lechon, M. J. 1992. "Evaluation of the cytotoxicity of ten chemicals on human cultured hepatocytes: Predictability of human toxicity and comparison with rodent cell culture systems," *Toxicology in Vitro* 6(1): 47–52.

Kaiser, J. 2005. "Gender in the pharmacy: Does it matter?," *Science* 308(5728): 1572.

Kalow, W. 1991. "Interethnic variation of drug metabolism," *Trends in Pharmacological Sciences* 12(3): 102–107.

Kamb, A. 2005. "What's wrong with our cancer models?," *Nature Reviews Drug Discovery* 4(2): 161–165.

Kasowski, M., Grubert, F., Heffelfinger, C., Hariharan, M., Asabere, A., Waszak, S. M., Habegger, L., et al. 2010. "Variation in transcription factor binding among humans," *Science* 328(5975): 232–235.

Kay, M. A. 2011. "State-of-the-art gene-based therapies: The road ahead," *Nature Reviews Genetics* 12(5): 316–28.

Khanna, I. 2012. "Drug discovery in pharmaceutical industry: Productivity challenges and trends," *Drug Discovery Today* 17(19–20): 1088–1102.

King, B. J. 2013. *How Animals Grieve*. Chicago, IL: University of Chicago Press.

King, C. 2009. "Personalised vaccines could protect all children," *New Scientist* 17(2737): 11.

Kitano, H. 2002. "Systems biology: A brief overview," *Science* 295(5560): 1662–1664.

Klein, S., and Huber, S. 2010. "Sex differences in susceptibility to viral infection," in S. Klein and C. Roberts eds., *Sex Hormones and Immunity to Infection*. Berlin: Springer-Verlag, pp. 93–122.

Kola, I., and Landis, J. 2004. "Can the pharmaceutical industry reduce attrition rates?," *Nature Reviews Drug Discovery* 3(8): 711–715.

Kolata, G. 1997. "2 top diet drugs are recalled amid reports of heart defects," *New York Times*, September 16, http://www.nytimes.com/1997/09/16/us/2-top-diet-drugs-are-recalled-amid-reports-of-heart-defects.html, accessed February 2, 2018.

Kopp, J. B., Nelson, G. W., Sampath, K., Johnson, R. C., Genovese, G., An, P., Friedman, D., et al. 2011. "APOL1 genetic variants in focal

segmental glomerulosclerosis and HIV- associated nephropathy," *Journal of the American Society of Nephrology* 22(11): 2129–2137.

Koppal, T. 2002. "Inside the FDA," *Drug Discovery & Development* 5(10): 32–38.

Koren, G., Cairns, J., Chitayat, D., Gaedigk, Al., and Leeder, S.J. 2006. "Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother," *Lancet* 368(9536): 19–25.

LaFollette H. 2011. "Animal experimentation in biomedical research," in T. L. Beauchamp and R. G. Frey eds., *The Oxford Handbook of Animal Ethics*. Oxford: Oxford University Press, pp. 812–818.

LaPointe, M. C., Mendez, M., Leung, A., Tao, Z., and Yang, X. P. 2004. "Inhibition of cyclooxygenase-2 improves cardiac function after myocardial infarction in the mouse," *American Journal of Physiology – Heart and Circulatory Physiology* 286(4): H1416–H1424.

Lappin, G., and Garner, R. C. 2003. "Big physics, small doses: The use of AMS and PET in human microdosing of development drugs," *Nature Reviews Drug Discovery* 2(3): 233–240.

Lappin, G., and Garner, R. C. 2008. "The utility of microdosing over the past 5 years," *Expert Opinion on Drug Metabolism & Toxicology* 4(12): 1499–1506.

Lappin, G., Kuhnz, W., Jochemsen, R., Kneer, J., Chaudhary, A., Oosterhuis, B., Drijfhout, W. J., Rowland, M., and Garner, R. C. 2006. "Use of microdosing to predict pharmacokinetics at the therapeutic dose: Experience with 5 drugs," *Clinical Pharmacology and Therapeutics* 80(3): 203–215.

Lappin, G., Noveck, R., and Burt, T. 2013. "Microdosing and drug development: Past, present and future," *Expert Opinion on Drug and Metabolism Toxicology* 9(7): 817–834.

Lazzarini, L., Overgaard, K. A., Conti, E., and Shirtliff, M. E. 2006. "Experimental osteomyelitis: What have we learned from animal studies about the systemic treatment of osteomyelitis?," *Journal of Chemotherapy* 18(5): 451–460.

Ledford, H. 2012. "Success through cooperation," *Nature News: Q&A*, February 1, http://www.nature.com/news/success-through-cooperation-1.9924, accessed February 2, 2018.

Li, S. S., Gilbert, P. B., Tomaras, G. D., Kijak, G., Ferrari, G., Thomas, R., Pyo, C.-W., et al. 2014. "FCGR2C polymorphisms associate with HIV-1 vaccine protection in RV144 trial," *Journal of Clinical Investigation* 124(9): 3879–3890.

Lin, H., Franks, B., and Savage-Rumbaugh, S. E. 2008. "Precursors of morality in the use of the symbols "good" and "bad" in two bonobos (*Pan paniscus*) and a chimpanzee (*Pan troglodytes*)," *Language and Communication* 28, 213–224.

Lin, J. H. 1995. "Species similarities and differences in pharmacokinetics," *Drug Metabolism and Disposition* 23(10): 1008–1021.

Lin, T. M., Chen, C. J., Wu, M. M., Yang, C. S., Chen, J. S., Lin, C. C., Kwang, T. Y., Hsu, S. T., Lin, S. Y., and Hsu, L. C. 1989. "Hepatitis B virus markers in Chinese twins," *Anticancer Research* 9(3): 737–741.

Lindsay, M. A. 2005. "Finding new drug targets in the 21st century," *Drug Discovery Today* 10(23–24): 1683–1687.

Littman, B. H., and Williams, S. A. 2005. "The ultimate model organism: Progress in experimental medicine," *Nature Reviews Drug Discovery* 4(8): 631–638.

Loisel, S., Ohresser, M., Pallardy, M., Dayde, D., Berthou, C., Cartron, G., and Watier, H. 2007. "Relevance, advantages and limitations of animal models used in the development of monoclonal antibodies for cancer treatment," *Critical Reviews in Oncology/Hematology* 62(1): 34–42.

Lu, Y., Fuchs, E. J., Hendrix, C. W., and Bumpus, N. N. 2014. "Cytochrome P450 3A5 genotype impacts maraviroc concentrations in healthy volunteers," *Drug Metabolism and Disposition* 42(11): 1796–1802.

Lumley, C. 1990. "Clinical toxicity: Could it have been predicted? Premarketing experience," in C. Lumley and S. Walker, eds., *Animal Toxicity Studies: Their Relevance for Man*. London: Quay Publishing, pp. 49–56.

Lutz, D. 2011. *New study calls into question reliance on animal models in cardiovascular research. Washington University*, August 3, 2013. http://news.wustl.edu/news/Pages/22540.aspx, accessed February 2, 2018.

Lyons, M. R., Peterson, L. R., McGill, J. B., Herrero, P., Coggan, A. R., Saeed, I. M., Recklein, C., Schechtman, K. B., and Gropler, R. J. 2013. "Impact of sex on the heart's metabolic and functional responses to diabetic therapies," *American Journal of Physiology – Heart and Circulatory Physiology* 305(11): H1584–H1591.

Macdonald, J. S. 2002. "Vive la difference: Sex and fluorouracil toxicity," *Journal of Clinical Oncology* 20(6): 1439–1441.

Macleod, M. 2004. "Systematic review and meta-analysis of experimental stroke," *International Journal of Neuroprotection and Neuroregeneration* 1: 9–12.

Mahmood, I. 2000. "Can absolute oral bioavailability in humans be predicted from animals? A comparison of allometry and different indirect methods," *Drug Metabolism and Drug Interactions* 16(2): 143–155.

Maiti, S., Kumar, K. H. B. G., Castellani, C. A., O'Reilly, R, and Singh, S. M. 2011. "Ontogenetic De Novo copy number variations (CNVs) as a source of genetic individuality: Studies on two families with MZD twins for schizophrenia," *PLoS ONE* 6(3): e17125.

Mak, I. W., Evaniew, N., and Ghert, M. (2014). "Lost in translation: Animal models and clinical trials in cancer treatment," *American Journal of Translational Research* 6(2): 114–118.

Marchetto, M. C., Narvaiza, I., Denli, A. M., Benner, C., Lazzarini, T. A., Nathanson, J. L., Paquola, A. C., Desai, K. N., Herai, R. H., Weitzman, M. D., Yeo, G. W., Muotri, A. R., and Gage, F. H. 2013. "Differential L1 regulation in pluripotent stem cells of humans and apes," *Nature* 503(7477): 525–529.

Markou, A., Chiamulera, C., Geyer, M. A., Tricklebank, M., and Steckler, T. 2009. "Removing obstacles in neuroscience drug discovery: The future path for animal models," *Neuropsychopharmacology* 34(1): 74–89.

Martin, R. L. 2011. *Fixing the game: Bubbles, crashes, and what capitalism can learn from the NFL*. Boston, MA: Harvard Business Review Press.

Marusina, K. 2012. "Animal models get closer to mimicking humans," *Genetic Engineering & Biotechnology News* 32(17): 52–55. October 1, http://www.genengnews.com/gen-articles/animal-models-get-closer-to-mimicking-humans/4529/?page=1=1, accessed February 2, 2018.

Matthews, R. A. 2008. "Medical progress depends on animal models – Doesn't it?," *Journal of the Royal Society of Medicine* 101(2): 95–98.

Mayr, F. B., and Yende, S. 2014. "Epidemiology of severe sepsis," *Virulence* 5 (1): 4–11.

McArthur, R. 2011. "Editorial: Many are called yet few are chosen. Are neuropsychiatric clinical trials letting us down?" *Drug Discovery Today* 16(5/6): 173–175.

McGee, P. 2006. "Breeding better animal models," *Drug Discovery & Development* 18–23.

Meadows, M. 2006. "Promoting Safe & Effective Drugs for 100 Years." FDA, Last Modified February 1, 2018. https://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/ucm2017809.htm, accessed February 2, 2018.

Meijers, J. M., Swaen, G. M., and Bloemen, L. J. 1997. "The predictive value of animal data in human cancer risk assessment," *Regulatory Toxicology and Pharmacology* 25(2): 94–102.

Millan, M. J., Agid, Y., Brune, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., Connor, R., et al. 2012. "Cognitive dysfunction in psychiatric disorders: Characteristics, causes and the quest for improved therapy," *Nature Reviews Drug Discovery* 11(2): 141–168.

Mirnezami, R., Nicholson, J., and Darzi, A. 2012. "Preparing for precision medicine," *New England Journal of Medicine* 366(6): 489–491.

Misch, E. A., Berrington, W. R., Vary, J. C., Jr., and Hawn, T. R. 2010. "Leprosy and the human genome," *Microbiology and molecular biology reviews: MMBR* 74(4): 589–620.

Mitchell, R. K., B. R. Agle & D. J. Wood. 1997. "Toward a theory of stakeholder identification and salience: Defining the principle of who and what really counts," *Academy of Management Review* 22(4): 853–886.

Modern Drug Discovery Editorial. 2002. "Rush to judgement," *Modern Drug Discovery*, July 7, http://pubs.acs.org/subscribe/archive/mdd/v05/i07/pdf/702editorial.pdf, accessed February 2, 2018.

Monastersky, R. 2008. *Protesters fail to slow animal research. The Chronicles of Higher Education*, April 18, http://chronicle.com/weekly/v54/i32/32a00102.htm, accessed February 2, 2018.

Morgan, P., Graaf, P. H. V. D., Arrowsmith, J., Feltner, D. E., Drummond, K. S., Wegner, C. D., and Street, S. D. A. 2012. "Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving phase II survival," *Drug Discovery Today* 17(9/10): 419–424.

Morley, M., Molony, C. M., Weber, T. M., Devlin, J. L., Ewens, K. G., Spielman, R. S., and Cheung, V. G. 2004. "Genetic analysis of genome-wide variation in human gene expression," *Nature* 430(7001): 743–747.

Morowitz, H. J. 2002. *The Emergence of Everything: How the World Became Complex*. Oxford: Oxford University Press.

Morton, D. 1990. "Expectations from animal studies," in C. Lumley and S. Walker eds., *Animal Toxicity Studies: Their Relevance for Ma. CMR Workshop Series*. Lancaster: Quay Publishing, pp. 3–14.

Mullane, K., and Williams, M. 2012. "Translational semantics and infrastructure: Another search for the emperor's new clothes?," *Drug Discovery Today* 17(9/10): 459–468.

Mullard, A. 2011. "Marc Kirschner," *Nature Reviews Drug Discovery* 10(12): 894–894.

Munos, B. 2009. "Lessons from 60 years of pharmaceutical innovation," *Nature Reviews Drug Discovery* 8(12): 959–968.

Munos, B. H., and Chin, W. W. 2011. "How to revive breakthrough innovation in the pharmaceutical industry," *Science Translational Medicine* 3(89): 89cm16.

Muqit, M. M., Larner, A. J., Sweeney, M. G., Sewry, C., Stinton, V. J., Davis, M. B., Healy, D. G., et al. 2008. "Multiple mitochondrial DNA deletions in monozygotic twins with OPMD," *Journal of Neurology, Neurosurgery, and Psychiatry* 79(1): 68–71.

National Institutes of Health. 2016. *Congressional Justification of the NIH, Fiscal Year 2017 Budget Request*, https://officeofbudget.od.nih.gov/pdfs/FY17/31-Overview.pdf, accessed February 2, 2018.

National Institute of Occupational Safety and Health. 1996. *Registry of Toxic Effects of Chemical Substances (R-TECS)*. Cincinnati, OH: National Institute of Occupational Safety and Health.

Nature Biotechnology Editorial. 2008. "Raising the game," *Nature Biotechnology* 26(2): 137.

Nature Medicine Editorial. 2007. "Cold shower for AIDS vaccines," *Nature Medicine* 13(12): 1389–90.

Nature Reviews Drug Discovery Editorial. 2003a. "Facing our demons," *Nature Reviews Drug Discovery* 2(2): 87.

Nature Reviews Drug Discovery Editorial. 2003b. "Follow the yellow brick road," *Nature Reviews Drug Discovery* 2(3): 167.

Nature Reviews Drug Discovery Editorial. 2005. "The time is now," *Nature Reviews Drug Discovery* 4(8): 613.

Nature Reviews Drug Discovery Editorial. 2007. "Same old story?," *Nature Reviews Drug Discovery* 6(2): 97.

Nature Reviews Drug Discovery News & Analysis. 2011. "Moving towards quantitative and systems pharmacology," *Nature Reviews Drug Discovery* 10(12): 889.

Navarro, V. J., and Senior, J. R. 2006. "Drug-related hepatotoxicity," *New England Journal of Medicine* 354(7): 731–739.

Neuberger, J. 1991. "FK 506 – A promise of good things to come?," *Hepatology* 13(6): 1259–1260.

Neuzil, P., Giselbrecht, S., Lange, K., Huang, T. J., and Manz, A. 2012. "Revisiting lab-on-a-chip technology for drug discovery," *Nature Reviews Drug Discovery* 11(8): 620–632.

Noble, M. 2000. "Can neural stem cells be used as therapeutic vehicles in the treatment of brain tumors?," *Nature Medicine* 6(4): 369–370.

Northrup, E. 1957. *Science Looks at Smoking: A New Inquiry into the Effects of Smoking on Your Health*. New York, NY: Coward-McCann.

O'Collins, V. E., Macleod, M. R., Cox, S. F., Van Raay, L., Aleksoska, E., Donnan, G. A., and Howells, D. W. 2011. "Preclinical drug evaluation for combination therapy in acute stroke using systematic review, meta-analysis, and subsequent experimental testing," *Journal of Cerebral Blood Flow and Metabolism* 31(3): 962–975.

O'Collins, V. E., Macleod, M. R., Donnan, G. A., Horky, L. L., van der Worp, B. H., and Howells, D. W. 2006. "1,026 experimental treatments in acute stroke," *Annals of Neurology* 59(3): 467–477.

Okita, G. T. 1967. "Species difference in duration of action of cardiac glycosides," *Federation Proceedings* 26(4): 1125–1130.

Ollikainen, M., and Craig, J. M. 2011. "Epigenetic discordance at imprinting control regions in twins," *Epigenomics* 3(3): 295–306.

Opar, A. 2012. "Overtaking the DILI model-T," *Nature Reviews Drug Discovery* 11(8): 585–586.

Oser, B. L. 1981. "The rat as a model for human toxicological evaluation," *Journal of Toxicology and Environmental Health* 8(4): 521–542.

Oshinsky, D. M. 2005. *Polio: An American Story*. Oxford: Oxford University Press.

Palfreyman, M. G., Charles, V., and Blander, J. 2002. "The importance of using human-based models in gene and drug discovery," *Drug Discovery World Fall* 33–40.

Pammolli, F., Magazzini, L., and Riccaboni, M. 2011. "The productivity crisis in pharmaceutical R&D," *Nature Reviews Drug Discovery* 10(6): 428–438.

Parke, D. V. 1994. "Comment: Clinical pharmacokinetics in drug safety evaluation," *Alternatives to Laboratory Animals: ATLA* 22, 207–209.

Paul, J. R. 1971. *A History of Poliomyelitis*. New Haven, CT: Yale University Press.

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., and Schacht, A. L. 2010. "How to improve R&D productivity: The pharmaceutical industry's grand challenge," *Nature Reviews Drug Discovery* 9(3): 203–214.

Pearson, H. 2002. "Surviving a knockout blow," *Nature* 415(6867): 8–9.

Perrin, S. 2014. "Preclinical research: Make mouse studies work," *Nature* 507: 423–425.

Personalized Medicine Coalition. 2014. *The Case for Personalized Medicine*, 4th ed. Washington, DC: Author. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_case_for_personalized_medicine.pdf, accessed February 2, 2018.

Personalized Medicine Coalition. 2016. *Personalized Medicine at FDA*. Washington, DC: Author. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM-at-FDA.pdf, accessed February 2, 2018.

Pham, N. D. 2010. *The Impact of Innovation and the Role of Intellectual Property Rights on U.S. Productivity, Competitiveness, Jobs, Wages, and Exports*. Washington, DC: NDP Consulting.

Philippidis, A. 2014. "Top 10 biggest biopharma marketing fines: 2014 edition," *Genetic Engineering & Biotechnology News*, January 27, http://www.genengnews.com/insight-and-intelligence/top-10-biggest-biopharma-marketing-fines-2014-edition/77900021/?page=2, accessed February 2, 2018.

Phillips, R. A. 1997. "Stakeholder theory and a principle of fairness," *Business Ethics Quarterly* 7(1): 51–66.

Phillips, R., Freeman, R. E., and Wicks, A. C. 2003. "What stakeholder theory is not," *Business Ethics Quarterly* 13(4): 479–502.

PhRMA 2015. "2015 profile," *Pharmaceutical Research and Manufacturers of America*, http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf, accessed February 2, 2018.

Pinto, J. M., Schumm, L. P., Wroblewski, K. E., Kern, D. W., and McClintock, M. K. 2013. "Racial disparities in olfactory loss among older adults in the United States," *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 69: 323–329.

Powell, A. A., Talasaz, A. H., Zhang, H., Coram, M. A., Reddy, A., Deng, G., Telli, M. L., et al. 2012. "Single cell profiling of circulating tumor cells: Transcriptional heterogeneity and diversity from breast cancer cell lines," *PLoS ONE* 7(5): e33788.

Prater, D. A. 2012. "Development and use of advanced testing approaches by the U.S. FDA," http://www.hsi.org/issues/advancing_science/facts/ep-workshop-oct-2012/prater.pdf, accessed February 2, 2018.

Pritchard, C., Coil, D., Hawley, S., Hsu, L., and Nelson, P. S. 2006. "The contributions of normal variation and genetic background to mammalian gene expression," *Genome Biology* 7(3): R26.

Raven, K. 2012. "Rodent models of sepsis found shockingly lacking," *Nature Medicine* 18(7): 998–998.

Raza, A. 2015. "Mouse models," in J. Brockman ed. *This Idea Must Die: Scientific Theories That Are Blocking Progress*. New York: Edge Foundation, pp. 231–333.

Regenberg, A., Mathews, D. J., Blass, D. M., Bok, H., Coyle, J. T., Duggan, P., Faden, R., et al. 2009. "The role of animal models in evaluating reasonable safety and efficacy for human trials of cell-based interventions for neurologic conditions," *Journal of Cerebral Blood Flow and Metabolism* 29(1): 1–9.

Reynolds, P. S. 2012. "Twenty years after: do animal trials inform clinical resus citation research?," *Resuscitation* 83(1): 16–17.

Rice, J. 2012. "Animal models: Not close enough," *Nature* 484(7393): S9–S9.

Rifkin, S. A., Kim, J., and White, K. P. 2003. "Evolution of gene expression in the Drosophila melanogaster subgroup," *Nature Genetics* 33(2): 138–144.

Rosenberg, N. A., Pritchard, J. K., Weber, J. L., Cann, H. M., Kidd, K. K., Zhivotovsky, L. A., and Feldman, M. W. 2002. "Genetic structure of human populations," *Science* 298(5602): 2381–2385.

Roses, A. D. 2000. "Pharmacogenetics and the practice of medicine," *Nature* 405(6788): 857–865.

Roy, A. S. A. 2012. "Project FDA report No. 5. Stifling new cures: The true cost of lengthy clinical drug trials," *Manhattan Institute for Policy Research*, http://www.manhattan-institute.org/html/fda_05.htm, accessed February 2, 2018.

Royal Society of Medicine. 1980. "Successes, failures and hopes in cancer chemotherapy." *Proceedings of an International Symposium by the Royal Society of Medicine*. London: Medico-Pharmaceutical Forum.

Sabin, A. 1984. *Testimony Before the Subcommittee on Hospitals and Health Care, Committee on Veterans Affairs, House of Representatives*. April 26, 1984 serial no. 98–48. Washington, DC: US Government.

Salén, J. C. W. 1994. "Animal models—Principles and problems," in P. Svendsen and J. Hau eds., *Handbook of Laboratory Science Volume II. Animal Models*, 1st ed. Boca Raton, FL: CRC Press, pp. 1–6.

Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., Raskind, M., Sabbagh, M., et al. 2014. "Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease," *New England Journal of Medicine* 370(4): 322–333.

Samuelson, W., and Zeckhauser, R. 1988. "Status quo bias in decision making," *Journal of Risk and Uncertainty* 1(1): 7–59.

Sandberg, R., Yasuda, R., Pankratz, D. G., Carter, T. A., Del Rio, J. A., Wodicka, L., Mayford, M., Lockhart, D. J., and Barlow, C. 2000. "Regional and strain-specific gene expression mapping in the adult mouse brain," *Proceedings of the National Academy of Sciences* 97(20): 11038–11043.

Sankar, U. 2005. "The delicate toxicity balance in drug discovery: Can pricey late-stage failures – or dangerous drugs – be prevented with better products for predicting drug toxicity?," *The Scientist* 19(15): 32–35. http://www.the-scientist.com/?articles.view/articleNo/16636/title/The-Delicate-Toxicity-Balance-in-Drug-Discovery/, accessed February 2, 2018.

Sarkar, S. K. 2009. "Molecular imaging approaches," *Drug Discovery World Fall* 33–38.

Sarkar, M., Bacchetti, P., French, A. L., Tien, P., Glesby, M. J., Nowicki, M., Plankey, M., Gange, S., Sharp, G., Minkoff, H., and Peters, M. G. 2012. "Lower liver-related death in African-American women with human immunodeficiency virus/hepatitis C virus coinfection, compared to Caucasian and Hispanic women," *Hepatology* 56(5): 1699–705.

Schnee J. E. 1978. "Governmental control of therapeutic drugs: Intent, impact and issues," in C. M. Lindsay and E. Caglarcan eds. *The Pharmaceutical Industry: Economics, Performance, and Government Regulation*. New York: Wiley, pp. 9–14.

Seligmann, B. 2004. "Gene expression as a toxicological screening tool. The use of microarray data in drug development and requirements for FDA audit and approval," *Drug Discovery World* 77–83.

Sena, E. S., van der Worp, H. B., Bath, P. M. W., Howells, D. W., and Macleod, M. R. 2010. "Publication bias in reports of animal stroke studies leads to major overstatement of efficacy," *PLoS Biology* 8(3): e1000344.

Sena, E., van der Worp, H. B., Howells, D., and Macleod, M. 2007. "How can we improve the pre-clinical development of drugs for stroke?," *Trends in Neurosciences* 30(9): 433–439.

Seok, J., Warren, H. S., Cuenca, A. G., Mindrinos, M. N., Baker, H. V., Xu, W., Richards, D. R., et al. 2013. "Genomic responses in mouse models poorly mimic human inflammatory diseases," *Proceedings of the National Academy of Sciences of the United States of America* 119(9): 3507–3512.

Serao, N., Delfino, K., Southey, B., Beever, J., and Rodriguez-Zas, S. 2011. "Cell cycle and aging, morphogenesis, and response to stimuli genes are individualized biomarkers of glioblastoma progression and survival," *BMC Medical Genomics* 4(1): 49.

Serrano, D., Lazzeroni, M., Zambon, C. F., Macis, D., Maisonneuve, P., Johansson, H., Guerrieri- Gonzaga, A., et al. 2011. "Efficacy of tamoxifen based on cytochrome P450 2D6, CYP2C19 and SULT1A1 genotype in the Italian tamoxifen prevention trial," *Pharmacogenomics J* 11(2): 100–107.

Shaffer, C. 2012. "Safety through sequencing," *Drug Discovery & Development*, January 1, http://www.dddmag.com/articles/2012/01/safety-through-sequencing, accessed February 2, 2018.

Shanks, N., and Greek, R. 2008. "Experimental use of nonhuman primates is not a simple problem," *Nature Medicine* 14(10): 807–808.

Shanks, N., and Greek, R. 2009. *Animal Models in Light of Evolution*. Boca Raton, FL: Brown Walker.

Shanks, N., Greek, R., and Greek, J. 2009. "Are animal models predictive for humans?," *Philosophy, Ethics, and Humanities in Medicine* 4(1): 2.

Sharp, P. A., and Langer, R. 2011. "Promoting convergence in biomedical science," *Science* 333(6042): 527.

Shepard, T., and Lemire, R. 2004. *Catalog of Teratogenic Agents*, 11th ed. Baltimore, MD: Johns Hopkins.

Shubick, P. 1980. "Statement of the problem," in F. Coulston and P. Shubick, eds., *Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis*. New York, NY: Ablex Publishing, pp. 5–17.

Sietsema, W. K. 1989. "The absolute oral bioavailability of selected drugs," *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 27(4): 179–211.

Simon, V. 2005. "Wanted: Women in clinical trials," *Science* 308(5728): 1517.

Sitaram, N., and Gershon, S. 1983. "From animal models to clinical testing–promises and pitfalls," *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 7(2–3): 227–228.

Sloan, J. A., Goldberg, R. M., Sargent, D. J., Vargas-Chanes, D., Nair, S., Cha, S. S., Novotny, P. J., Poon, M. A., O'Connell, M. J., and Loprinzi, C. L. 2002. "Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer," *Journal of Clinical Oncology* 20(6): 1491–1498.

Smith, R. L., and Caldwell, J. 1977. "Drug metabolism in non-human primates," in D. V. Parke and R. L. Smith, eds., *Drug Metabolism – From Microbe to Man*. London: Taylor & Francis, pp. 331–356.

Smith, W. E., Miller, L., Elsasser, R. E., and Hubert, D. D. 1965. "Tests for carcinogenicity of asbestos," *Annals of the New York Academy of Sciences* 132(1): 456–488.

Sole, R., and Goodwin, B. 2002. *Signs of Life: How Complexity Pervades Biology*. New York, NY: Basic Books.

Spear, B. B., Heath-Chiozzi, M., and Huff, J. 2001. "Clinical application of pharmacogenetics," *Trends in Molecular Medicine* 7(5): 201–204.

Spielman, R. S., Bastone, L. A., Burdick, J. T., Morley, M., Ewens, W. J., and Cheung, V. G. 2007. "Common genetic variants account for differences in gene expression among ethnic groups," *Nature Genetics* 39(2): 226–231.

Stamer, U. M., and Stuber, F. 2007. "The pharmacogenetics of analgesia," *Expert Opinion on Pharmacotherapy* 8(14): 2235–2245.

Stankiewicz, P., and Lupski, J. R. 2010. "Structural variation in the human genome and its role in disease," *Annual Review of Medicine* 61, 437–455.

Storey, J. D., Madeoy, J., Strout, J. L., Wurfel, M., Ronald, J., and Akey, J. M. 2007. "Gene-expression variation within and among human populations," *American Journal of Human Genetics* 80(3): 502–509.

Suter, K. 1990. "What can be learned from case studies? The company approach," in C. Lumley and S. Walker, eds., *Animal Toxicity Studies: Their Relevance for Man*. Lancaster: Quay Publishing, pp. 71–78.

Tan, I. B., Ivanova, T., Lim, K. H., Ong, C. W., Deng, N., Lee, J., Tan, S. H., et al. 2011. "Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy," *Gastroenterology* 141(2): 476–485.e11.

Taneja, A., Di Iorio, V. L., Danhof, M., and Della Pasqua, O. 2012. "Translation of drug effects from experimental models of neuropathic pain and analgesia to humans," *Drug Discovery Today* 17(15–16): 837–849.

Taylor, D. L. 2009. "Human vs rodent," *Drug Discovery & Development* 12(3): 16–18.

Tolman, K. G. 2002. "The liver and lovastatin," *American Journal of Cardiology* 89(12): 1374–1380.

Topol, E. J. 2004. "Failing the public health—Rofecoxib, merck, and the FDA," *New England Journal of Medicine* 351(17): 1707–1709.

Topol, E. J., and Venter, J. C. 2013. "*Venter and topol on the true revolution in medicine*," *Medscape*, March 10, http://www.medscape.com/viewarticle/780324, accessed February 2, 2018

Trivedi, B. 2010. "Learning from the elite," *Nature* 466(7304): S4–S4.

Uhl, E. W., Whitley, E., Galbreath, E., McArthur, M., and Oglesbee, M. J. 2012. "Evolutionary aspects of animal models," *Veterinary pathology* 49(5): 876–878.

US Congress 2015–2016. "The 21st century cures act," *US Congress*, January 4, https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf, accessed February 2, 2018.

Utidjian, M. 1988. "The interaction between epidemiology and animal studies in industrial toxicology," in B. Ballantyne, ed. *Perspectives in Basic and Applied Toxicology*. London: Butterworth- Heinemann, pp. 309–329.

van Meer, P. J. K., Kooijman, M., Gispen-de Wied, C. C., Moors, E. H. M., and Schellekens, H. 2012. "The ability of animal studies to detect serious post marketing adverse events is limited," *Regulatory Toxicology and Pharmacology* 64(3): 345–349.

van Regenmortel, M. 2004. "Biological complexity emerges from the ashes of genetic reductionism," *Journal of Molecular Recognition* 17(3): 145–148.

van Zutphen, L. F. 2000. "Is there a need for animal models of human genetic disorders in the post- genome era?," *Comparative Medicine* 50(1): 10–11.

Varki, A., and Altheide, T. K. 2005. "Comparing the human and chimpanzee genomes: Searching for needles in a haystack," *Genome Research* 15(12): 1746–1758.

Vernon, J. A., Golec, J. H., and Dimasi, J. A. 2010. "Drug development costs when financial risk is measured using the Fama-French three-factor model," *Health Economics* 19(8): 1002–1005.

Wald, C., and Wu, C. 2010. "Of mice and women: The bias in animal models," *Science* 327(5973): 1571–1572.

Walker, R. M., and McElligott, T. F. 1981. "Furosemide induced hepatotoxicity," *Journal of Pathology* 135(4): 301–314.

Wall, R. J., and Shani, M. 2008. "Are animal models as good as we think?," *Theriogenology* 69(1): 2–9.

Walshaw, S. O. 1994. "Animal death and human emotion in the laboratory," *Lab Animal* 23(6): 24–25.

Wang, D., Guo, Y., Wrighton, S. A., Cooke, G. E., and Sadee, W. 2011. "Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs," *Pharmacogenomics Journal* 11(4): 274–286.

Warren, H. S., Tompkins, R. G., Moldawer, L. L., Seok, J., Xu, W., Mindrinos, M. N., Maier, R. V., Xiao, W., and Davis, R. W. 2014. "Mice are not men," *Proceedings of the National Academy of Sciences* 112(4): E347–E348.

Wax, P. M. 1995. "Elixers, dilutants, and the passage of the 1938 Federal Food, Drug and Cosmetic Act," *Annals of Internal Medicine* 122, 456–461.

Weatherall, M. 1982. "An end to the search for new drugs?," *Nature* 296, 387–390.

Weaver, J. L., Staten, D., Swann, J., Armstrong, G., Bates, M., and Hastings, K. L. 2003. "Detection of systemic hypersensitivity to drugs using standard guinea pig assays," *Toxicology* 193(3): 203–217.

Wilke, R. A., and Dolan, M. E. 2011. "Genetics and variable drug response," *JAMA: The Journal of the American Medical Association* 306(3): 306–307.

Willyard, C. 2009. "HIV gender clues emerge," *Nature Medicine* 15(8): 830.

Wong, A. H., Gottesman, I. I., and Petronis, A. 2005. "Phenotypic differences in genetically identical organisms: The epigenetic perspective," *Human Molecular Genetics* 14(Spec No 1): R11–8.

Xu, H., Cheng, C., Devidas, M., Pei, D., Fan, Y., Yang, W., Neale, G., et al. 2012. "ARID5B genetic polymorphisms contribute to racial disparities in the incidence and treatment outcome of childhood acute lymphoblastic leukemia," *Journal of Clinical Oncology* 30(7): 751–757.

Xu, H., Yang, W., Perez-Andreu, V., Devidas, M., Fan, Y., Cheng, C., Pei, D., et al. 2013. "Novel susceptibility variants at 10p12.31-12.2 for childhood acute lymphoblastic leukemia in ethnically diverse populations," *Journal of the National Cancer Institute* 105(10): 733–742.

Young, M. 2008. "Prediction vs attrition," *Drug Discovery World Fall* 9–12.

Yucesoy, B., Johnson, V. J., Fluharty, K., Kashon, M. L., Slaven, J. E., Wilson, N. W., Weissman, D. N., Biagini, R. E., Germolec, D. R., and Luster, M. I. 2009. "Influence of cytokine gene variations on immunization to childhood vaccines," *Vaccine* 27(50): 6991–6997.

Yukhananov, A. 2011. "U.S. to develop chip that tests if a drug is toxic," *Reuters*, September 16, http://www.reuters.com/article/2011/09/16/us-drugs-chip-idUSTRE78F5KX20110916, accessed February 2, 2018.

Zbinden, G. 1993. "The concept of multispecies testing in industrial toxicology," *Regulatory Toxicology and Pharmacology* 17(1): 85–94.

Zhang, Q., Bhattacharya, S., Andersen, M. E., and Conolly, R. B. 2010. "Computational systems biology and dose-response modeling in relation to new directions in toxicity testing," *Journal of toxicology and environmental health. Part B, Critical reviews* 13(2–4): 253–276.

Zhang, W., Duan, S., Kistner, E. O., Bleibel, W. K., Huang, R. S., Clark, T. A., Chen, T. X., et al. 2008. "Evaluation of genetic variation contributing to differences in gene expression between populations," *American Journal of Human Genetics* 82(3): 631–640.

Zhao, J., Goldberg, J., Bremner, J. D., and Vaccarino, V. 2012. "Global DNA methylation is associated with insulin resistance: A monozygotic twin study," *Diabetes* 61(2): 542–546.

Zielinska, E. 2010. "Building a better mouse," *The Scientist* 24(4): 34–38. http://www.the-scientist.com/?articles.view/articleNo/28860/title/Building-a-Better-Mouse/, accessed February 2, 2018.