Progress in Biophysics and Molecular Biology 113 (2013) 231–253

Contents lists available at SciVerse ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

Questions regarding the predictive value of one evolved complex adaptive system for a second: Exemplified by the SOD1 mouse

Ray Greek [a,*], Lawrence A. Hansen [b,1]

[a] Americans for Medical Advancement, 2251 Refugio Road, Goleta, CA 93117, USA
[b] University of California, San Diego, Department of Neurosciences, Mail Code 062 9500, Gilman Drive (MTF 351), La Jolla, CA 92093-0624, USA

ARTICLE INFO

Article history:
Available online 20 June 2013

Keywords:
ALS
Animal models
Complex systems
Evolution
Predictive value
SOD1 mouse

ABSTRACT

We surveyed the scientific literature regarding amyotrophic lateral sclerosis, the SOD1 mouse model, complex adaptive systems, evolution, drug development, animal models, and philosophy of science in an attempt to analyze the SOD1 mouse model of amyotrophic lateral sclerosis in the context of evolved complex adaptive systems.

Humans and animals are examples of evolved complex adaptive systems. It is difficult to predict the outcome from perturbations to such systems because of the characteristics of complex systems. Modeling even one complex adaptive system in order to predict outcomes from perturbations is difficult. Predicting outcomes to one evolved complex adaptive system based on outcomes from a second, especially when the perturbation occurs at higher levels of organization, is even more problematic. Using animal models to predict human outcomes to perturbations such as disease and drugs should have a very low predictive value. We present empirical evidence confirming this and suggest a theory to explain this phenomenon. We analyze the SOD1 mouse model of amyotrophic lateral sclerosis in order to illustrate this position.

Contents

1. Introduction

In this essay, we will examine animal models when they are used to predict human response to drugs and disease (We realize humans are animals, but for convenience will use the term *animal* to mean *nonhuman animal*.). We readily acknowledge that animal models can be used in other, nonpredictive, ways as well (see categories 3–9 in Table 1). For example, animals can be successfully

* Corresponding author. Tel.: +1 805 685 6812.
E-mail addresses: DrRayGreek@gmail.com (R. Greek), lahansen@ucsd.edu (L.A. Hansen).
[1] Tel.: +1 858 534 6212.

0079-6107
http://dx.doi.org/10.1016/j.pbiomolbio.2013.06.002

Table 1
Nine categories of animal use in science and research (Greek and Shanks, 2009).

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

employed to study the basic principles of life, to provide replacement parts for humans, in comparative research, and as bioreactors.

Models can be classified in various ways, and the use of model type varies with purpose. Animal models can also be classified in various ways. For example, another method of categorizing animal models, distinct from Table 1, would be as spontaneous, induced, transgenic, negative, or orphan models. Hau places all classification schemes in perspective when he states: "The majority of laboratory animal models are developed and used to study the cause, nature, and cure of human disorders" [(Hau, 2003) p. 3]. The predictive value of such models is implied but Hau later states it explicitly: "A third important group of animal models is employed as *predictive* models. These models are used with the aim of discovering and quantifying the impact of a treatment, whether this is to cure a disease or to assess toxicity of a chemical compound.... The appropriateness of any laboratory animal model will eventually be judged by its capacity to explain and predict the observed effects in the target species" (Hau, 2003). Numerous scientists use and promote animals as predictive models (Gad, 2007; CSPI, 2008; Huff et al., 2008; Vassar, 2011; Yuen, 2011; Devoy et al., 2012). The relatively recent categorization of systems into simple, complicated, complex, and chaotic also impacts on the discussion of models. Complex systems have historically been thought non-simulable; as a whole, they are difficult if not impossible to model (Lippman et al., 1995; Bickel and Buhlmann, 1996; Williams, 1997).

With that in mind, what are the implications of modeling one evolved complex adaptive system (CAS) with another evolved CAS? Is there predictive value in such modeling and, if so, at what levels of organization is this possible (Greek and Rice, 2012)?

2. Materials and methods

We surveyed the scientific literature regarding relevant aspects of amyotrophic lateral sclerosis (ALS), evolved complex adaptive systems, evolutionary biology, and the SOD1 mouse. We sought to develop a general theme regarding the use of one CAS (animals) to model another, similar CAS (humans), and then apply that theme to the specific case of the SOD1 mouse as a model for human ALS. For this evaluation we needed to understand how evolution has acted on CASs, as one reason species differ is because each has taken a different evolutionary trajectory. We sought to understand how the evolutionary process has resulted in CASs that are *differently complex*. This led us to genetics, evolutionary and developmental biology (evo devo), regulation and expression of genes, gene networks, and convergent evolution, as well as other areas. We then attempted to place these genetic changes in the context of complexity science and discovered that the various properties of CASs, and hence outcomes to perturbations, are greatly influenced by the genetic changes that cause the evolutionary process. This led us to study how animal models are employed in biomedical science and what the term *predict* means in biomedical science.

3. Results and discussion

3.1. Complexity science

We begin with an overview of complex systems. Various aspects complex systems and of modeling complex systems have been addressed in this journal and we refer the reader to these studies, including (Miquel, 2011; Soto et al., 2011; Bard et al., 2012a,b; Durrive, 2012; Melham, 2012; Melham et al., 2012; Bizzarri et al., 2013; Gare, 2013; Nakajima, 2013; Schroederc, 2013).) The study of CASs occurs in many disciplines of science, mathematics, and engineering (Northrop, 2011). Northrop defines a system as "a group of interacting, interrelated, or interdependent elements (also agents, entities, parts, states) forming or regarded as forming a collective entity" [(Northrop, 2011) p. 2]. Northrop defines complexity as: "a subjective measure of the difficulty in *describing and modeling* a system (thing or process), and thus being able to predict its behavior" (Northrop, 2011) (Emphasis added.). Systems, like models, can be categorized using various criteria. For example a system can be understood intuitively or need deeper examination. Similarly, a system can demonstrate linearity or nonlinearity (Northrop, 2011). Braithwaite was conscious of such problems with models, warning that "The price of employment of models is eternal vigilance" (Braithwaite, 1953). Characteristics of complex systems that result in modeling difficulties include the following.

A complex system is composed of many components that exist on various scales. Some of these components are simple systems (electrons and atoms) but others are complex (gene networks, the immune system, and organs). A CAS is a *system of systems*. At the lower levels of organization, the parts are interchangeable: an electron can replace another electron and an atom can replace another atom (provided it is the same element). But at higher levels of organization, the parts are not interchangeable. A heart from a monkey cannot replace a heart from a human, *ceteris paribus*. Alex Novikoff explained this in 1947: "What are wholes on one level become parts on a higher one... both parts and wholes are material entities, and integration results from the interaction of parts as a consequence of their properties." Novikoff observes that some systems must be studied as whole intact entities because living organisms are not "machines made of a multitude of discrete parts (physico-chemical units), removable like pistons of an engine and capable of description without regard to the system from which they are removed" [(Mayr, 1998) p. 18]. One must appreciate the interactions of the parts because, according to Mayr, "a description of the isolated parts fails to convey the properties of the system as a whole. It is the organization of these parts that controls the entire system" [(Mayr, 1998) p. 18].

These components can be grouped into modules that communicate with each other. But the modules may respond differently to the same perturbation. There is a hierarchy of organization among the parts and modules. The upper levels are above the lower levels, and are usually composed of the lower levels; thus there is asymmetry in the relationship between upper and lower levels. Moreover, a component or module may be in several different hierarchies (Ahl and Allen, 1996).

A complex system has feedback loops between components and modules. These feedback loops can inhibit or amplify a response (Kastens et al., 2009).

Complex systems are extremely sensitive to initial conditions such as the genetic make-up with which an individual is born. Complex systems may demonstrate chaotic behavior and exhibit a "non-Gaussian distribution of outputs" (Kastens et al., 2009). A perturbation to the system may have unintended, unanticipated effects far removed from the subsystem or module initially affected.

Complex systems demonstrate nonlinearity, self-organization, and are dynamic; they communicate with their environment. This may lead to epigenetic changes in the case of animals and humans. Complex systems demonstrate redundancy of components as well as robustness — the capacity to resist change. This can be illustrated by the fact that knocking out a gene may produce no noticeable effects in one strain of mouse while it is lethal to another strain (Morange, 2001; Pearson, 2002; Belmaker et al., 2012). Other examples would be gene pleiotropy — when one gene influences multiple traits — such as involvement in multiple diseases. An example of multiple diseases sharing the same genes would be attention deficit-hyperactivity disorder (ADHD), autism, bipolar disorder, major depressive disorder, and schizophrenia, which share four genes (Cross-Disorder Group Of The Psychiatric Genomics Consortium, 2013). This can occur when one gene makes multiple proteins through alternative splicing (Hodgkin, 1998), or simply as a consequence of one protein.

Complex systems are more than the sum of their parts. Williams defines a complex system thusly: "A system is a collection of interacting elements. Behavior of the system is distinct from the behavior of its parts or elements. Output is not proportional to input and output to a perturbation may vary over time" (Williams, 1997). The parts of a complex system are important, but knowledge of the interactions of the parts is also vital for understanding a CAS. This limits what can be learned about CASs through reductionism. CASs demonstrate emergent phenomenon. Therefore the system cannot be fully understood even with total knowledge of its parts. This also limits what can be learned about CASs through reductionism. A complex system has the ability "to switch between different modes of behavior as the environmental conditions are varied." It is adaptive (Nicolis and Prigogine, 1977). CASs as a whole are not thought to be simulable (Lippman et al., 1995; Bickel and Buhlmann, 1996; Williams, 1997). Work on mathematical modeling is challenging this, however.

Besides living systems, other examples of complex systems include ecosystems, climate, and the global economy (Kastens et al., 2009). For more on the characteristics and implications of CASs see previously mentioned references in this journal as well as Novikoff, 1945; Nicolis and Prigogine, 1977; Horgan, 1995; Lewin, 1999; Lombardi, 2000; Seely and Christou, 2000; Goodwin, 2001; Manson, 2001; Noble, 2001; Aird, 2002; Csete and Doyle, 2002; Kitano, 2002b; Sole and Goodwin, 2002; Alm and Arkin, 2003; Ottino, 2004; Noble, 2008; and Bizzarri et al., 2013.

The above characteristics are problematic in terms of studying CASs via reductionism. Mayr defines reductionism as "The belief that the higher levels of integration of a complex system can be fully explained through a knowledge of the smallest components" [(Mayr, 2002) p. 290]. Reductionism has been extremely effective for studying simple, nonliving systems and even for studying some aspects of CASs, such as outcomes at the lower levels of organization. But reductionism cannot explain the totality of a CAS. For an evolved, living CAS to be fully understood, the whole must be studied as a whole (Van Regenmortel, 2002a,b,c, 2004a,b, 2012; Van Regenmortel and Hull, 2002). Bizzarri et al., state: "complex systems exhibit properties and behavior that cannot be understood from laws governing the microscopic parts given that such systems cannot be easily 'reduced' or explained by simple deterministic rules" (Bizzarri et al., 2013).

Gould wrote in 2001: "the collapse of the doctrine of one gene for one protein, and one direction of causal flow from basic codes to elaborate totally marks the failure of reductionism for the complex system that we call biology" (Gould, 2001). Even gene function is not deterministic as gene expression has stochastic aspects within a single cell, in addition, inter-species differences, and even intra-strain differences, are manifest in gene function (Morange, 2001; Elowitz et al., 2002; Pearson, 2002; Gibbs et al., 2007; Holmes, 2007; Belmaker et al., 2012; Bizzarri et al., 2013). Stochasticity is also an aspect of gene networks (Becskei and Serrano, 2000) and protein–protein interactions (Kupiec, 2010). Moreover, cause and effect has been replaced by a *causal chain* thus limiting the role of reductionism even further. Thus, complex systems are examples of nonlinear dynamic systems and their behavior is best modeled by partial differential equations (Noble, 2001, 2008; Kurakin, 2005; Moss, 2006).

Van Regenmortel supports this, stating: "Another defect of reductionist thinking is that it analyses complex network interactions in terms of simple causal chains and mechanistic models. This overlooks the fact that any clinical state is the end result of many biochemical pathways and networks, and fails to appreciate that diseases result from alterations to complex systems of homeostasis" (Van Regenmortel, 2004b). Similarly, Mazzocchi explains: "In modern science reductionism is usually combined with a linear and simplistic idea of causality, where the focus is restricted to the role of a single or few essential causes or factors (occurring at the fundamental physical level), and with determinism. This is the idea whereby any phenomenon in nature is completely determined by pre-existing causes to which it is bound by a relationship of necessity, and that only one possible future exists. Determinism entails the predictability of the evolution of a system, which can be completely established by knowing the initial conditions and the mechanical laws governing its behavior..." (Mazzocchi, 2012).

Even linear systems are not as predictable as many suppose. For example, the three-body problem led to the development of Chaos Theory (Boyd and Mcmillan, 1992; Barrow-Green, 1997). Ironically, Bohm noted in 1969 that physics was abandoning the *reductionism is everything* mentality while biology was embracing it (Bohm, 1969). The realization that reductionism is insufficient for studying complex systems has led to a systems-oriented approach in the biological sciences, known as systems biology (Kitano, 2002a,b, 2007; Noble, 2008; Bard et al., 2012a,b; Melham et al., 2012; Werner, 2012) (see Table 2 [Ahn et al., 2006]).

Some would argue that the human brain is the most complex system known as well as the most difficult to study. Novella stated: "There are approximately 100 billion neurons in the adult human brain. Each neuron makes thousands of connections to other neurons, resulting in an approximate 150 trillion connections in the human brain. The pattern of those connections is largely responsible for the functionality of the brain — everything we sense, feel, think, and do" (Novella, 2011). We see the same problems in studying other complex systems. Koch describes the complexity of the human brain and explains why studying complex systems is difficult: "Such systems are characterized by large numbers of highly heterogenous components, be they genes, proteins, or cells. These components interact causally in myriad ways across a very large spectrum of space–time, from nanometers to meters and from microseconds to years. A complete understanding of these systems demands that a large fraction of these interactions be experimentally or computationally probed. This is very difficult... fields as diverse as neuroscience and cancer biology have proven resistant to facile predictions about imminent practical applications. Improved technologies for observing and probing biological systems have only led to discoveries of further levels of complexity that need to be dealt with. This process has not yet run its course.

Table 2
Reductionism versus a systems-oriented perspective (Ahn et al., 2006).

Characteristic	Reductionism	Systems-oriented approach
Principle	Behavior of a biological system can be explained by the properties of its constituent parts	Biological systems posses emergent properties that are only possessed by the system as a whole and not by any isolated part of the system
Metaphor	Machine, magic bullet	Network
Approach	One factor is singled out for attention and is given explanatory weight on its own	Many factors are simultaneously evaluated to assess the dynamics of the system
Critical factors	Predictors/associated factors	Time, space, content
Model characteristics	Linear, predictable, frequently deterministic	Nonlinear, sensitive to initial condition, stochastic (probabilistic), chaotic
Medical concepts	Health is normalcy	Health is robustness
	Health is risk reduction	Health is adaptation/plasticity
	Health is homeostasis	Health is homeodynamics

We are far away from understanding cell biology, genomes, or brains, and turning this understanding into practical knowledge" (Koch, 2012).

Northrop addresses the question of why complex systems are so difficult for humans to comprehend. He begins by reminding us that *Homo sapiens* are not that far removed from our hunter–gatherer ancestors. We evolved to confront simple problems (a predator, for instance) that usually had simple solutions (move away from the predator). Today we try to resolve problems involving complex systems by assuming there is a simple, single point of contact solution, which we can ascertain using intuition and reductionism. This approach is obviously inadequate. Likewise, we seek solutions based on intervening in one variable when complex systems should be examined in terms of a causal chain and multiple inputs. We need training in order to understand the problems associated with complex systems and appreciate threats that involve complex systems (Northrop, 2011). Wolkenhauer et al., summarized findings from a series of workshops that led to publication of Science Policy Briefing (SPB) Nr. 35. and reinforced Northrop stating: "Conventional modes of medical and biological explanation rely primarily on verbal reasoning and are only suited for dealing with mechanisms that involve small numbers of components and short chains of causality. The diseases most relevant for humankind, however, involve a large number and variety of components interacting through complex networks. New approaches are therefore required to fuel further advances in modern medicine" (Wolkenhauer et al., 2009). Wolkenhauer et al., report that the workshops recommended a systems biology approach and state: "A major breakthrough in systems biology is imminent — medical research is at the crossroads; conventional approaches will no longer work" (Wolkenhauer et al., 2009). They then chastise medical science for not keeping up with times:

- While the need for mathematical modeling and interdisciplinary collaborations is becoming widely recognised in the biological sciences, with substantial implications for the training and research funding mechanisms within this area, the medical sciences have yet to follow this lead.
- To achieve major breakthroughs in Medical Systems Biology, existing academic funding schemes for large-scale projects need to be reconsidered.
- The hesitant stance of the pharmaceutical industry towards major investment in systems biology research has to be addressed.
- Leading medical journals should be encouraged to promote mathematical modeling (Wolkenhauer et al., 2009).

Much remains to be sorted out in terms of research on and for evolved complex systems (Luttge, 2012).

Koch discusses modeling a complex system with a digital computer (Koch, 2012). For a system with 3 components, the Bell's number (B) would be 5. The interactions scale up at a rate that exceeds exponentially. For example, $B_{10} = 115{,}975$ ($\log(\mathbf{Bn}) \approx \mathbf{n}[\log(\mathbf{n}) - 1]$). Koch states that even assuming Moore's law continues to hold true, in "a neural synapse — the presynaptic terminal has an estimated 1000 distinct proteins. Fully analyzing their possible interactions would take about 2000 years. Or consider the task of fully characterizing the visual cortex of the mouse — about 2 million neurons... will take about 10 million years" (Koch, 2012) (see Fig. 1). Koch concludes: "Given the large number of components that cannot be averaged away, any possible technological advance is overwhelmed by the relentless growth of interactions among all components of the system. It is not feasible to understand evolved organisms by exhaustively cataloging all interactions in a comprehensive, bottom-up manner. More is needed" (Koch, 2012).

Koch then describes the idea of Allen and Greeves (2011) who introduced the term "complexity brake" to explain why diverse fields are not amenable to prediction. Their premise is that the more we learn regarding complex systems the more we find that deeper levels exist and this places a brake on how much we can understand about complex systems. The complex systems we understand have a limited number of interactions among components. Living complex systems do not follow this "limited number" rule.

Predicting an outcome to a perturbation to a CAS is very difficult, and using one CAS in order to predict outcomes for a second is even more difficult, if not impossible, when the level of examination is not in the realm of some of the simple systems that comprise a CAS. The history of cancer research is but one example of the failure of reductionism vis-à-vis animal models. When attempting to predict human response to chemicals — be they carcinogens or chemotherapy — using reductionism-based animal models, the failures have been epic (Heng, 2008; Brennan et al., 2010; Editorial, 2006, 2011a,b; Cook et al., 2012; Corry, 1952; Smith et al., 1965; Clemmensen and Hjalgrim-Jensen, 1980; Salsburg, 1983; Di Carlo, 1984; Ennever et al., 1987; Marsoni et al., 1987; Stoloff, 1992; Beniashvili, 1994; Gura, 1997; Kleinman, 1997; Dybing and Sanner, 1999; Rohan et al., 2000; Habeck, 2002; Hahn et al., 2002; Rangarajan and Weinberg, 2003; Kamb, 2005; Dimasi and Grabowski, 2007; Kummar et al., 2007; Dimasi et al., 2010; Arrowsmith, 2011b; Caponigro et al., 2011; Oreskes and Conway, 2011; Begley and Ellis, 2012; Greek, 2013b). Hochachka and Somero summarized the problem with studying complex systems by comparing humans with chimpanzees. They stated that although humans and chimps share 99% of their amino acid sequences, the two species are very different. What accounts for the differences? Hochachka and Somero state: "only exceedingly minimal changes in genome sequences may be necessary to specify separate species,

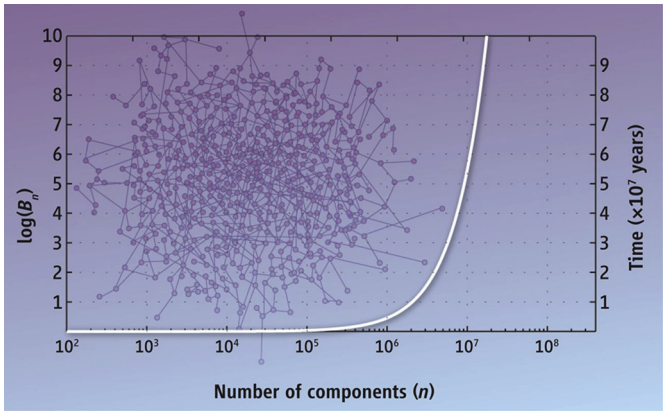

Fig. 1. How long will it take? The logarithm of Bell's number (left axis) and the upper bound on the time it takes to fully analyze all possible partitions of the system (right axis) are shown as a function of the number of components (proteins or cells) (Koch, 2012).

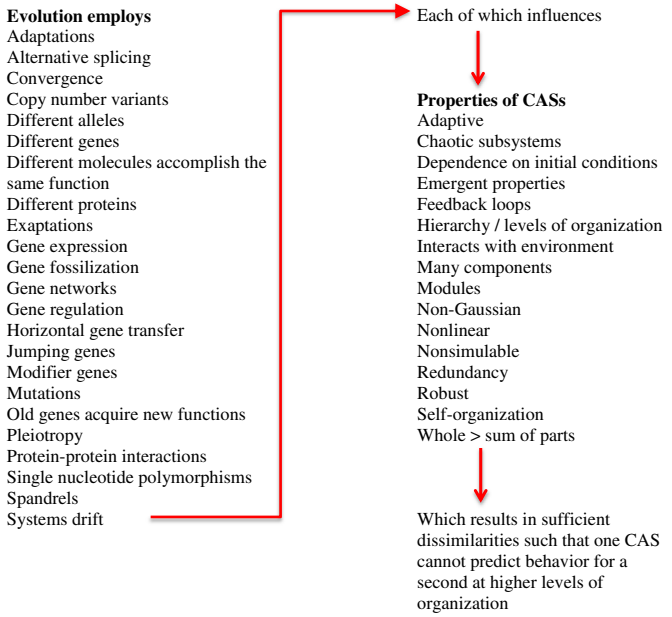

Fig. 2. Dynamics of evolved complex adaptive systems. Each of the tools below employed by evolution is a component or module in a complex system. The changes caused by evolution will affect the CAS in a nonlinear fashion. The differences among species include all of the below. The thousands of differences between two species result in a species that is differently complex from its ancestors and cousins.

possibly with larger percentage changes in gene expression patterns" (Hochachka and Somero, 2002). We should not expect predictive value from modeling one CAS with another that has major genetic differences.

We now turn to the genetics and mechanisms used by the process of evolution that resulted in systems that are differently complex.

3.2. Evolved complex systems

In this article, we are concerned with the use of one evolved CAS to predict drug and disease response in another evolved CAS. In this section we will discuss what tools the process of evolution has used in speciation and why these are important to our discussion.

Dobzhansky states: "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973). The process of evolution has produced the many species we see today and many more that are now extinct. Put simply, evolution is a change in allele frequency over time (an allele being one form of the same gene). Though how evolution accomplishes this is anything but simple. When one nucleotide is wrong, the change is called single nucleotide polymorphism (SNP). SNPs are responsible for sickle cell anemia and cystic fibrosis, among other diseases. Because of differences like SNPs, not all children may be protected by the same vaccine (Yucesoy et al., 2009). Likewise, the bar-headed goose (*Anser indicus*) is very similar to the Greylag goose (*Anser anser*), however the bar-headed goose possesses high-altitude (>30,000 ft) hypoxia adaptation due to a difference in the hemoglobins of the two species involving only four amino acids. Besides SNPs, organisms can change due to other mutations in the genes such as: deletions of chromosomes, genes, or nucleotides; insertions of chromosomes, genes, or nucleotides; inversions, duplications, and copy number variants (CNVs) of genes. See Fig. 2 for other tools used by evolution. CNVs are especially important in the metabolism of drugs. If one individual has one copy of a gene that makes a drug metabolizing enzyme (DME) while another has five copies, the dose will need to be adjusted markedly. What all of these genetic changes have in common is the fact that seemingly small variations can result in dramatically different outcomes to perturbations. Extensive variations simply increase the likelihood of different outcomes.

Perhaps the most important tool in evolution's toolkit is gene regulation and expression. For example, Seok et al., reported that mice and humans were studied for gene response to sepsis, burns, and trauma (Seok et al., 2013). The authors were inspired to conduct the study in part because at least 150 drugs have been shown efficacious for sepsis in mice but have failed in humans. Seok et al., discovered that the genes involved in the human reaction to these inflammatory processes — the genes expressed — were different from the ones activated in mice under similar conditions (see Fig. 3). Dolgin quantifies the magnitude of these failed animal models for sepsis: "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 (see (News, 2012))" (Dolgin, 2013).

By regulating and expressing genes differently, the same genes could be used to make two different species. This can be illustrated by the caterpillar and the butterfly, although, of course, they are not two different species. The same genes are involved in making both the caterpillar and the butterfly, but the two look nothing alike. This is due to the timing of when the genes are turned on or off, and in what proportions they are expressed in the various tissues. Another example would be the development of mice and humans. Each has approximately the same number of genes, with each differing from the other in about 300 genes. Yet the gene that makes a tail in the mouse is turned off in humans during embryogenesis, thus humans have no tail (though exceptions do occur). Venter stated that one could make almost any of the higher vertebrates using the same genes (Cohen and Coghlan, 2001). The notion that regulatory genes are responsible for major changes during evolution is now more or less universally accepted (Lowe et al., 2011). An example of regulatory differences would be that humans have lost 510 sections of regulatory DNA that are vital in other animals, including chimpanzees (Mclean et al., 2011). For more on gene regulation see Ptashne and Gann, 2002; Kirschner and Gerhart, 2006.

Genes also work in networks, which allows for even more variation. If we assume a 100-gene network with each gene switched off or on, then the number of states in which the network

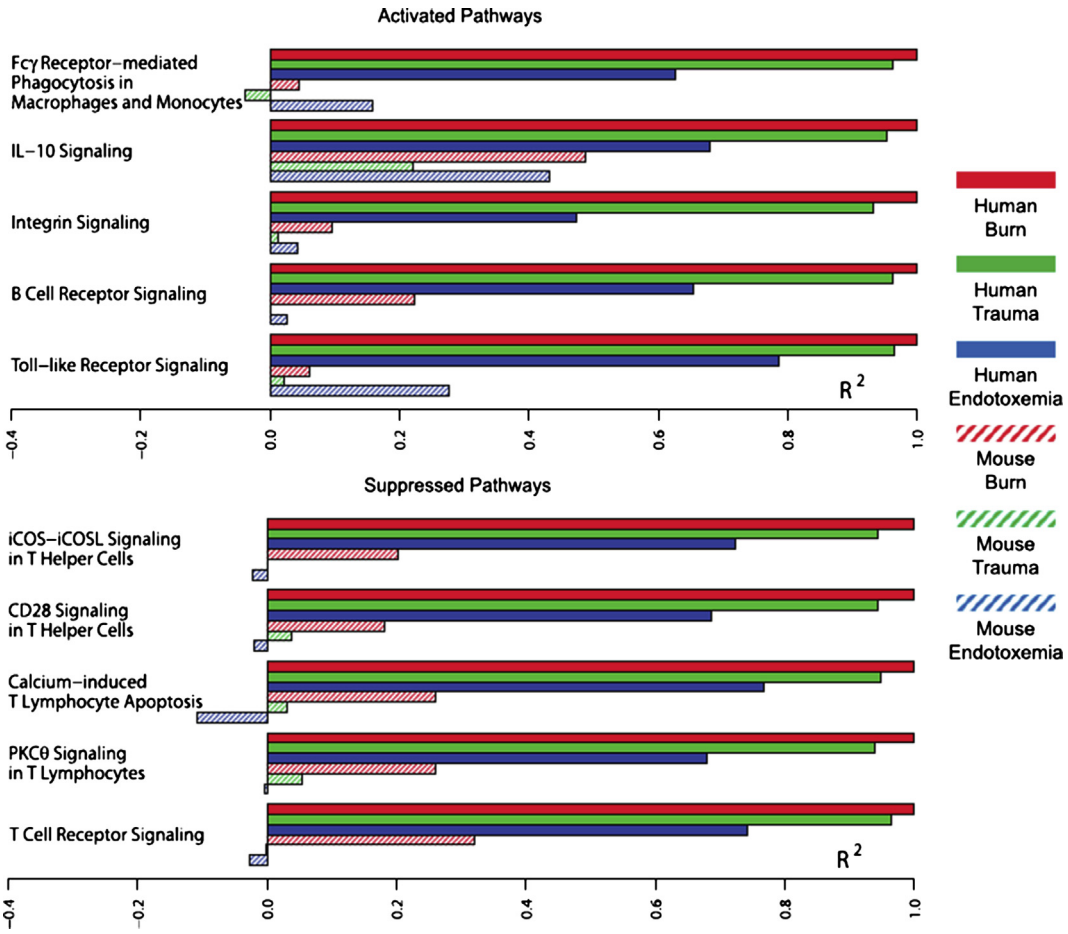

Fig. 3. Comparative gene changes. Pathway comparisons between the human burns, trauma, and endotoxin and mouse models. Shown are bar graphs of Pearson correlations (R^2) for the five most activated and suppressed pathways between the four model systems (human endotoxemia and the three murine models) vs. human trauma and burns. Negative correlations are shown as negative numbers ($-R^2$). Human burn is shown as the reference. In every pathway, human endotoxemia had much higher similarity to human injury than mouse models (Seok et al., 2013).

can exist is 2^{100}. If the network proceeded through every state in some sequence and stayed in that state for one microsecond, it would take billions of billions of years to get through all the states (Goodwin, 2001). Humans have in the neighborhood of 20,000 genes that can be expressed between 0 and 1.0 giving a number of states of at least $2^{20,000}$. With 24,000 genes, even a pairwise matrix would yield 576 million combinations. Other networks include gene–protein networks and protein networks. This should give some idea of the complexity of the system and why small changes in it can have enormous implications (for examples, see Table 3 and Fig. 4).

The above is not to imply that a single gene is unimportant. Bakircioglu et al., discovered that the size and shape of the human cerebral cortex (the outer most layer of the brain) appears to be due to changes in just one gene (Bakircioglu et al., 2011). Bakircioglu et al., arrived at this conclusion after studying three families that have children with very small brains: microcephaly. The children's brains were about 10% of normal size. Mutations in the gene *NDE1* appear to be responsible. This could mean that the difference between the human cerebral cortex and the cerebral cortex of animals is due to this one gene.

Mazzocchi describes the problem of molecular biologists treating evolved CASs as simple systems (Mazzocchi, 2012). When knocking genes out of mice, one can see various effects from deleting the same gene. In part, this is because the gene acts in a "complex macromolecular organization. Gene and their products do not exist and operate, in fact, as isolated and autonomous entities." Proteins also act in networks, and these networks are also complex systems. The full effect of these genes is only appreciated at higher levels of organization. Since CASs exhibit redundancy, such as when gene function is duplicated by other genes, knocking out a gene may lead to no changes in one CAS but be lethal in another. Mazzocchi continues: "Intracellular-signaling networks, initially seen as simple unidirectional pathways, have progressively revealed their complexity. They are now seen as compounded by a multitude of molecular components, which interact in many complex ways, including feedback mechanisms. This implies that [it] is often impossible to predict the effects of their modification" (Mazzocchi, 2012).

Jacques Monod famously stated: "What is true of *Escherichia coli* is also true of the elephant." Unfortunately, Monod was not entirely correct in this. It is true that on the gross morphological level all mammals have hearts, livers, and lungs that perform more or less the same function, that all life is composed of conserved processes, and that the fundamental building blocks of matter are the same. However, at higher levels of organization, or when one delves deeper into the details of conserved processes, tissues, organs, and even biochemistry, there are very important differences. These differences in CASs account for the dissimilarities in response to drugs and disease (Greek and Rice, 2012).

We should take a moment to point out the importance of convergent evolution in this discussion. Organisms can arrive at the

Table 3
Differences between humans and apes in incidence or severity of medical conditions (Varki and Altheide, 2005).

Medical condition	Humans	Great apes
Definite		
HIV progression to AIDS	Common	Very rare
Hepatitis B/C late complications	Moderate to severe	Mild
P. falciporum malaria	Susceptible	Resistant
Myocardial infarction	Common	Very rare
Endemic infectious retroviruses	Rare	Common
Influenza A symptomatology	Moderate to severe	Mild
Probable		
Menopause	Universal	Rare?
Alzheimer's disease pathology	Complete	No neurofibrillary tangles
Epithelial cancers	Common	Rare?
Atherosclerotic strokes	Common	Rare?
Hydatiform molar pregnancy	Common	Rare?
Possible		
Rheumatoid arthritis	Common	Rare?
Endometriosis	Common	Rare?
Toxemia of pregnancy	Common	Rate?
Early fetal wastage (aneuploidy)	Common	Rare?
Bronchial asthma	Common	Rare?
Autoimmune diseases	Common	Rare?
Major psychoses	Common	Rare?

same trait by taking different pathways and using different mechanisms. The current Metazoa provides numerous instances of this. For example, the eyes of humans and octopi resemble each other on the gross morphological scale but the wiring is distinctly different [(Kirschner and Gerhart, 2006) pp. 240–1]. Different species of bats developed different mechanisms by which they now drink nectar (Davalos et al., 2012). Blond hair evolved in Melanesians by a different mechanism than it did in Europeans (Kenny et al., 2012). Ion selectivity in neuronal signaling channels (Gur Barzilai et al., 2012), and clot degradation (Bugge et al., 1996) are other examples of traits that evolved convergently in different animals. Spindle neurons have arisen independently in species as diverse as humans and cetaceans. Spindle neurons, which connect parts of the brain involved in higher cognition, were once thought to only occur in primates, but they also exist in cetaceans, such as humpback whales and fin whales, as well as elephants (Holden, 2006; Hof and Van Der Gucht, 2007; Hakeem et al., 2009).

Shanks and Greek state: "... we note that both Antarctic notothenioids and Arctic cod produce antifreeze glycoproteins that serve similar functions in the respective organisms. Such proteins contribute to the ability of these fish to make a living in their respective (chilly) positions in the economy of nature. The antifreeze glycoproteins are similar in structure and function, but they nevertheless do not arise from a common gene. Different genes are involved and this is a case of convergent biochemical evolution [(Hochachka and Somero, 2002) p. 413]. Similarities can be deceptive. Thus, similar functions can be achieved through very different causal pathways" (Shanks and Greek, 2009). Convergent evolution appears to be ubiquitous in nature, and this limits our ability to assign genes or mechanisms to traits and expect these conditions to hold true for every species. Evolution can use the same parts to make very different organisms. Likewise, it can use different parts to arrive at the same trait. You cannot examine a trait or a part in isolation and determine where or how it came into being. These things must be determined by scientific study.

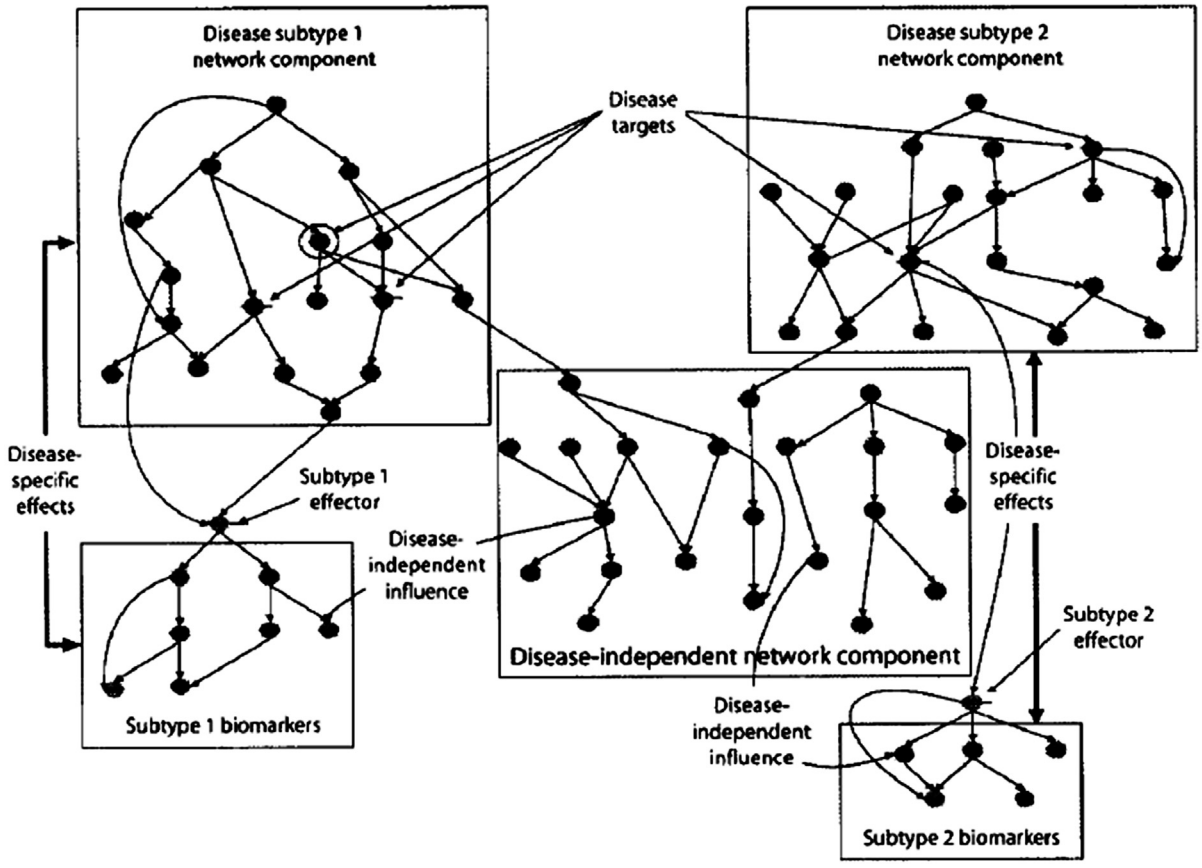

Fig. 4. Disease networks (Schadt et al., 2005).

Lafollette and Shanks labeled the notion that phylogenetic closeness makes a better animal model the "modeler's phylogenetic fallacy" (Lafollette and Shanks, 1996). Caldwell anticipated the fallacy and illustrated it thusly: "It has been obvious for some time that there is generally no evolutionary basis behind the particular-metabolizing ability of a particular species. Indeed, among rodents and primates, zoologically closely related species exhibit markedly different patterns of metabolism" (Caldwell, 1980).

Note that the above does not imply that CASs will always react differently to the same perturbation. The principles of physics and geometry, for example, still apply. But the questions biomedical science is currently asking concern the higher levels of organization of CASs (see Greek and Rice, 2012 for more on this.). Likewise, while much was learned in the 1800s by comparative methods of study, there are several differences between the early study of morphology and the current study of human disease and drug reaction. Firstly, very little was known about phylogeny during the 1800s, whereas today much of what can be learned about the gross similarities among animals and human has been learned. Granted, there are volumes more vis-à-vis genomics and evo devo left to discover, but the gross morphological similarities that have historically been discovered by using intact living organisms are known. This is not an insignificant point despite its tautological nature. In any field involving comparative anatomy and physiology the gross morphological commonalities eventually are exhausted and the research modality must change if more is to be learned in the most efficient way possible.

A second difference between the 1800s and today is the level of examination. This returns us to the characteristics of CASs. Northrop states: "Early bioengineers, biophysicists, and systems physiologists tried to characterize certain physiological regulators as linear and stationary. Initially, linear systems analysis was inappropriately applied to certain complex, physiological regulators and control systems (e.g., pupil regulation and eye movement control), which resulted in 'black-box' closed-loop models in which linear transfer function modules were connected to a nonlinear module in a single feedback loop. These were phenomenological I/0 models that gave little insight into the physiology and complexity of the systems" (Northrop, 2011).

The following from Burggren and Bemis is relevant to our discussion of animal models: "Yet the use of 'cockroach as insect,' 'frog as amphibian,' or 'the turtle as reptile' persists, in spite of clear evidence of the dangers of this approach. Not surprisingly, this type of comparative physiology has neither contributed much to evolutionary theories nor drawn upon them to formulate and test hypotheses in evolutionary physiology" (Burggren and Bemis, 1990). Mazzocchi summarizes the consequences of CASs having evolved: "What is becoming increasingly acknowledged is that life cannot be understood fully at the molecular and genetic level" (Mazzocchi, 2012). Simply knowing that evolved complex systems are differently complex should inform us to the likelihood that one evolved CAS will be of predictive value for another in terms of drug and disease response. We will now examine the empirical evidence.

3.3. Predictive value of animal models in biomedical science

Before we examine the empirical evidence, we need to define *predictive value* and specifically how animal models can be assessed for predictive value. This topic is important because using animal models in order to make our medications safer and more efficacious depends upon the ability of the model to predict human response to drugs and disease.

The usual story told regarding drug development is that it begins in university laboratories where scientists perform basic research using animal models. A pathway is discovered that appears to contain a target that can be reached by a drug. Note the adherence to reductionism here. This knowledge is passed on to Pharma (the pharmaceutical industry), which then develops the idea, synthesizes chemicals that might bind to the target, and ultimately tests the new chemical entity (NCE) on animals, then humans. The ability of animal models to be of predictive value is assumed at two points in this process: the identification of the target from animal data, and go-no go decisions regarding the continuation of development based on tests performed on animals.

If the assumption of predictive value for animal models is false, then there are scientific, business, and societal consequences for using animal models. Giles, writing in *Nature* in 2006, states: "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). An editorial in *Nature* in 2009 reinforced this position: "Animal-research policies need to be guided by a moral compass — a concensus of what people find acceptable and unacceptable" (Editorial, 2009). So how much predictive value do animal models have?

First, we need to analyze the term *prediction*. The term *predict*, in science, does not mean the occasional correct answer, such as: "I predicted the outcome of the football game." Guesses that are sometimes correct but oft times incorrect do not make the person making the guess a predictive modality or make his opinion one of predictive value. The same is true for the use of *predictions* in the form of scientists generating hypotheses that are then evaluated by the predictions the hypotheses make and subsequently fulfill or fail to fulfill. Science uses a binomial classification table and equations to quantify predictive value, be it from a lab test, research modality, or other practice (see Table 4). Positive predictive value (PPV) quantifies the probability that a positive response in the test is a positive in reality (e.g. a test for cancer is positive and the patient really has cancer) whereas negative predictive value (NPV) quantifies the probability that negative test equates with a true negative (if the cancer test is negative, the patient does not have cancer). Medicine is practiced based on PPVs and NPVs, and these values are important in other disciplines as well.

We should again point out that not all animal models are used to predict human response to drugs and disease, and there is scientific merit to these other uses (see categories 3–9 in Table 1). However, we are concerned with the use of animal models for human response to drugs and disease as they are claimed to be of predictive value: categories 1 and 2 in Table 1. Such claims are plentiful. t Hart et al., state: "Nonhuman primates (NHPs) are important models in preclinical research enabling understanding of pathogenic mechanisms in human disease that readily translate into therapy development" (t Hart et al., 2012). Cheng states: "Animal tests are necessary for some research, such as testing drugs for toxicity. It would be, in my opinion, improper to release drugs for human use without animal testing" (Gibson, 2012). Vassar states: "Chronic dosing in mice and monkeys is necessary to show the efficacy and safety of the antibody before it's taken into humans" (Vassar, 2011). Rudczynski wrote in the *New Haven Register*: "Contrary to claims in a letter to the editor, the basic research model used by Yale University and its peer institutions is scientifically valid and predictive of human disease" (Rudczynski, 2011). Yet, the data do not support these claims.

Data from studies where animal and human outcomes can be compared reveals that animal models have little predictive value

Table 4
Binomial table and calculations for predictive value.

		Gold Standard	
		GS+	GS−
Test	T+	TP	FP
	T−	FN	TN

T+ = Test positive
T− = Test negative
T = True
F = False
P = Positive
N = Negative
GS+ = Gold standard positive
GS− = Gold standard negative
Sensitivity = TP/(TP + FN)
Specificity = TN/(FP + TN)
Positive Predictive Value = TP/(TP + FP)
Negative Predictive Value = TN/(FN + TN)

for drug absorption (Gad, 2007) pp. 8–10; (Calabrese, 1991) pp. 5, 9, 45, 50, 66–7, 90, 102–3; (Shah et al., 1991; Barber et al., 1992; Scott et al., 1992; Plos Press Release, 2008), distribution (Fox et al., 1979; Mahmood, 2000), metabolism (Smith and Caldwell, 1977; Walker and Mcelligott, 1981; Weatherall, 1982; Bonati et al., 1984; Abelson, 1992; Caldwell, 1992; Parkinson and Grasso, 1993; Paxton, 1995; BBC News, 2008; Health Day, 2008; Serrano et al., 2011), elimination (Sellers et al., 2004; Walton et al., 2004), toxicity (Litchfield, 1962; Eason et al., 1990; Weaver et al., 2003; Leaf, 2004; Sankar, 2005; Gad, 2006; Dixit and Boelsterli, 2007; Hughes, 2008; Plos Press Release, 2008; Sarkar, 2009; Caponigro et al., 2011; Editors, 2011; Force and Kolaja, 2011; Park et al., 2011), bioavailability (Sietsema, 1989), carcinogenicity (Tomatis et al., 1978; Salsburg, 1983; Anisimov et al., 2005), teratogenicity (Manson and Wise, 1993; Shepard and Lemire, 2004; Greek et al., 2011b), and efficacy (Johnson et al., 2001; Kola and Landis, 2004; Suggitt et al., 2005; Hurko, 2006; Albani and Prakken, 2009; Paul et al., 2010; Arrowsmith, 2011a,b; Buchanan et al., 2011; Cook et al., 2012; Millan et al., 2012; Morgan et al., 2012). For example, Suter compared toxicities for ergoloid mesylates, bromocriptine, ketotifen, cyclosporine, FK 33-824, and clozapine in animals and humans. The positive predictive value was 0.31, or 31% (Suter, 1990). Pathophysiology for diseases also differ among species (Paul, 1971; Gross, 1985; Greek and Pound, 2002; Rangarajan and Weinberg, 2003; Dias et al., 2006; Stump and Vandewoude, 2007; Begley, 2008; Wall and Shani, 2008; Cook et al., 2012; Seok et al., 2013), although accumulating data for Table 4 is challenging. However, one indicator of the predictive value is the frequency with which NCEs translate from basic research. Crowley quantified this at 0.004% of papers published in the top science journals (Crowley, 2003). Moreover, the fact that drug targets identified in animal models fail so frequently to translate to humans in drug development (FDA, 2004; Kola and Landis, 2004; Editorial, 2007; Sarkar, 2009; Paul et al., 2010; Arrowsmith, 2011b; Caponigro et al., 2011; Editorial, 2011b; Begley and Ellis, 2012) is also evidence for questioning the predictive value for pathophysiology translating to humans.

In light of the findings above, among scientists conducting applied research there appears to be consensus on the lack of predictive value of animal models (Fletcher, 1978; Sietsema, 1989; Heywood, 1990; Lumley, 1990; Suter, 1990; Horrobin, 2003; Weaver et al., 2003; Kola and Landis, 2004; FDA, 2009; O'Collins et al., 2006; Dixit and Boelsterli, 2007; Wall and Shani, 2008; Greek and Shanks, 2009; Markou et al., 2009; Shanks and Greek, 2009; Shanks et al., 2009; Greek and Greek, 2010; M.E., 2010; Zielinska, 2010; Collins, 2011; Greek et al., 2011a,b, 2012a; Sharp and Langer, 2011; Cook et al., 2012; Drake III et al., 2012). Despite this, claims of predictive value are commonly made in grant applications for what would otherwise be considered basic research. Roth, in a grant application to NIH, writes: "These data [from monkeys] will aid in the development of novel strategies for ameliorating the neurochemical and behavioral deficits in this potential animal model, and in the cognitive dysfunctions associated with schizophrenia and other psychiatric disorders" (Roth, 2003). Bankiewicz, in a grant application to NIH, states: "This work [on monkeys] will provide insight on the mechanisms behind L-dopa induced dyskinesias and will provide a basis for using gene therapy approaches to treat patients with Parkinson's disease" (Bankiewicz, 2006). Goodlett, also in a grant application to NIH, writes: "The long-term goals of this component are to use rodent models of binge alcohol exposure during the 3rd trimester equivalent to screen and identify molecular agents that may be effective in preventing prenatal alcohol-induced brain damage and neurodevelopmental disorders... A key advantage of integrated approaches across the Consortium is that as promising candidate molecular agents emerge, these animal models can provide in vivo tests of their therapeutic effectiveness" (Goodlett, 2003). These examples could be easily multiplied.

The writers above are clearly claiming that animal models are of predictive value for human response to disease and drugs. First, these claims are inconsistent with the claims for basic research, which has no goals other than to discover more facts concerning the material universe (Greek and Greek, 2010). Second, in light of the fact that even scientists engaging in applied research, vis-à-vis drug development, acknowledge that animal models have no predictive value, assigning predictive value to basic research models is highly suspect. Third, the fact that tax money is being allocated based on what appear to be false claims is a societal concern both in terms of fraud being committed and in terms of taking research money from modalities that have a better track record of success (Rothwell, 2006).

Kirschner addresses the question of improving on drug development by predicting efficacy and safety, a current task assigned to animal models: "The nature of our biological system is that we have relatively few genes — say 20,000 basic core genes — that are used over and over again in different contexts. So when we investigate targets, we need to better appreciate how these function in different contexts. Moreover, there are many overlapping and redundant pathways, so we need to better understand genes not as individual elements with individual functions but within the context of the circuits in which they operate" (Mullard, 2011). He then suggests a quantitative wiring diagram and describes a systems biology approach to drug development. He states: "We need this kind of investigation, rather than the current approach of having a hunch, placing a bet and, if the horse doesn't win, coming back next week to bet on another race" (Mullard, 2011). Similarly, the NIH, with whom Kirschner is working, published a white paper, "Quantitative and Systems Pharmacology," calling for a merger of pharmacology and systems biology (News and Analysis, 2011).

In India, 1725 persons died in clinical drug trials over the four-year period of 2007–2010 (Tandon, 2011). This is concerning on many levels. These deaths should inform those in the animal model community who claim predictive value, in this case the safety of drugs in clinical trials, for animal models in both applied and basic research. The *predictive value* claim for animal models should also be placed in the context of personalized medicine.

3.4. Personalized medicine

Personalized medicine concerns both current medical practice and medical research. Physicians have observed very different

reactions to drugs and disease since at least the 1950s (Willyard, 2007). Even monozygotic twins raised in the same environment do not always suffer from the same diseases or have the same reactions to drugs (Javierre et al., 2010a; Misch et al., 2010; Stankiewicz and Lupski, 2010; Maiti et al., 2011; Ollikainen and Craig, 2011; Chapman and Hill, 2012; Czyz et al., 2012; Halder et al., 2012). Differences in disease and drug response also exist among ethnicities (Gregor and Joffe, 1978; Kalow, 1991; Cheung et al., 1997; Haiman et al., 2006; Couzin, 2007; Spielman et al., 2007; Stamer and Stuber, 2007; Kopp et al., 2011; Wilke and Dolan, 2011), and between the sexes (Holden, 2005; Kaiser, 2005; Simon, 2005; Willyard, 2009; Klein and Huber, 2010; Wald and Wu, 2010; Canto et al., 2012). Likewise there is variation among strains of animals in response to perturbations such as gene modification, drugs, and disease (Morange, 2001; Pearson, 2002; Belmaker et al., 2012). Most drugs are effective in only approximately 50% of patients (Roses, 2000). Because of research like the Human Genome Project, there are now explanations for these differences. Drug and disease response has now been linked to specific genes. Some cancer patients now have their genome sequenced, as well as the genome of their cancer, in order to determine treatment (Daly, 2010) (see Fig. 5 for the goals of personalized medicine.).

Personalized medicine seeks to match drug and disease to individual patients based on the patient's genetic make-up. If gene *XZYQ* causes adverse side effect A, and the patient has a copy of *XZYQ*, then the patient will not be prescribed a drug that triggers gene *XZYQ*. Likewise, if gene *DACS* needs to be present for a drug to be effective, then only patients with that gene will be given the drug. Moreover, a disease of the same name does not manifest exactly the same way in all patients. One group of patients may experience predominantly renal effects from a certain disease, while another group may experience cerebral ischemia. Different drug targets are obviously involved, so different patients will need different drugs even though they ostensibly have the same disease. The drugs will be further broken down by genes for side effects. Hence, per Fig. 5, there will need to be many different types of drugs to treat the same disease.

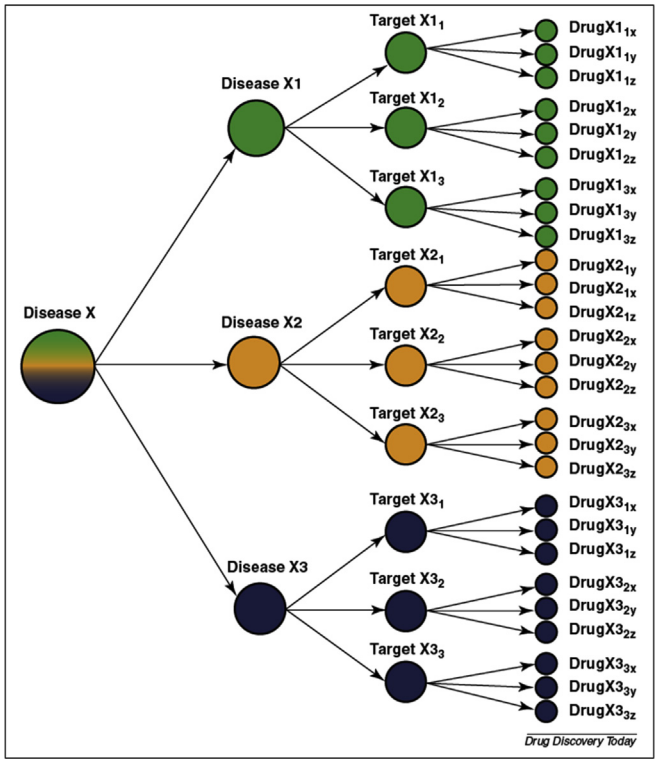

Fig. 5. Personalized medicine. Most diseases are heterogenous and the use of molecular diagnostics can divide them into biological subgroups each with their targets and drugs (Jørgensen, 2011).

We have already covered the reasons for these differences. Small differences between genomes in the form of CNVs, SNPs, background genes, modifier genes, and gene regulation among others result in intra-species differences in outcomes to perturbations. Because animals are evolved CASs, merely substituting a gene or even several genes will not be adequate to replicate the disease in humans. Genes *XZYQ* and *DACS* are not pistons that can be exchanged between systems. In addition, all of this is occurring in a CAS. Personalized medicine cannot be simulated in a mouse. It is however, currently available for scores of drugs and diseases (Meyer, 1990; Kalow, 1991; Gonzalez and Idle, 1994; Nebert, 1997; Nebert et al., 1999; Bhathena and Spear, 2008; Hughes et al., 2008; Blair, 2009; Bates, 2010; Dolgin, 2010; Flaherty et al., 2010; Froehlich et al., 2011; Hudson, 2011; Pirmohamed, 2011; Serrano et al., 2011; Wang et al., 2011; Belmaker et al., 2012). The contrast between employing animal models to predict human outcomes and personalized medicine is stark.

This completes our theoretical examination of using one evolved CAS to model and predict outcomes to perturbations such as disease and drugs for another. As we have seen, it is difficult to predict outcomes for perturbations to single CAS. Using one evolved CAS in order to predict outcomes for a second that is a different species seems untenable in light of the proceeding sections. We now examine a specific and highly touted animal model.

3.5. The use of the SOD1 mouse to model human ALS

Amyotrophic lateral sclerosis (ALS) is a multifactorial, heterogenous group of neurodegenerative diseases characterized by the selective death of upper motor neurons as well as lower motor neurons (see Fig. 6) (Rowland and Shneider, 2001; Redler and Dokholyan, 2012). Described by Charcot in 1865 and 1874 (Charcot, 1865, 1874), ALS is the most common motor neuron disease and the third most common neurodegenerative disease in the developed world (Cleveland and Rothstein, 2001; Hirtz et al., 2007). It is usually fatal in less than 3 years after the onset of symptoms due to paralysis of the respiratory muscles, and is frequently accompanied by cognitive impairment. ALS can be divided into two categories, with 90–95% of cases are termed sporadic ALS (sALS) and 5–10% termed familial ALS (fALS). Mutations in the protein copper–zinc superoxide dismutase (SOD1), an antioxidant protein, are involved in 15–20% of the cases of fALS (Dion et al., 2009).

The pathophysiology of ALS is unknown but there are several interesting hypotheses. The discovery of mechanisms of ALS is complicated by what appears to be multiple candidates for etiology including inflammation, oxidative stress, mitochondrial dysfunction, aberrant RNA processing, misfolding and aggregation of proteins, disruption of axon guidance, glutamate excitotoxicity, and dysregulation of neurotrophic factors. Moreover, no decision has yet been reached on whether the UMN or LMN is the primary site of disease, or whether "variants" effecting only upper or only lower motor neurons are all the same or different diseases (Redler and Dokholyan, 2012). Environmental factors may have a role in the disease (Redler and Dokholyan, 2012).

In both fALS and sALS, the spinal cord of patients contain SOD1-positive proteinaceous inclusions when examined post-mortem. Patients with sALS and fALS also reveal Lewy body-like hyaline inclusions (LBHI) that stain positive for SOD1 (Shibata et al., 1994, 1996; Matsumoto et al., 1996; Watanabe et al., 2001; Stathopulos et al., 2003). LBHIs are also seen in Parkinson's disease,

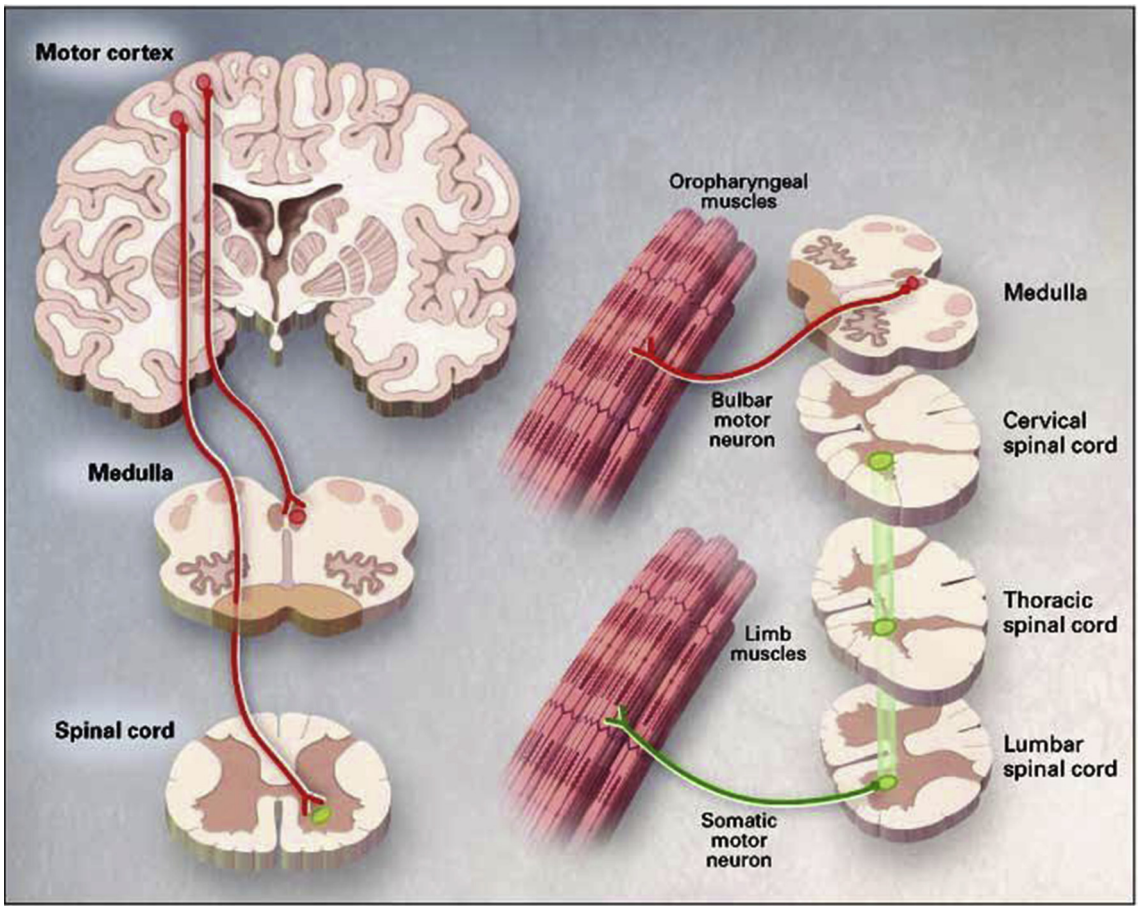

Fig. 6. Upper and lower motor neurons. The upper motor neuron is shown on the left descending from the brain to the spinal cord. The lower motor neuron, shown on the right, descends from the spinal cord to the muscle.

Alzheimer's disease, and Huntington's disease (Watanabe et al., 2001). The SOD1 polypeptide is composed of 153 nucleotides, and 160 mutations in the polypeptide have been linked to ALS (World Federation Of Neurology And European Network To Cure ALS, 2013). The amino acid sequence in wild-type SOD1 protein in mice and humans is 84% identical. One proposed mechanism is a "gain of function toxicity" induced by the mutations, which results in the protein SOD1 aggregating and misfolding. SOD1-rich proteinaceous deposits have been discovered in humans and the SOD1 mouse (Gurney et al., 1994; Wong et al., 1995; Bruijn et al., 2004; Cozzolino et al., 2008). The original research linking SOD1 to ALS was human-based (Deng et al., 1993; Rosen et al., 1993), with the SOD1 mouse model being developed in 1994 (Gurney et al., 1994). Mitochondria were implicated in ALS secondary to human tissue research using microscopic staining in 1966 (Afifi et al., 1966). The main neuropathological findings are illustrated in Table 5 (Kato, 2008).

SOD1 is conserved among species. For example, the three-dimensional structure of SOD1 (a protein dimer) is conserved among yeast (Djinovic et al., 1992; Ogihara et al., 1996; Hart et al., 1999), frogs (Djinovic Carugo et al., 1996), cows (Tainer et al., 1982; Rypniewski et al., 1995), and humans (Parge et al., 1992; Banci et al., 2006; Strange et al., 2006). Moreover, according to Seetharaman et al.: "In mammals, 112 of 153 residues [are] conserved across species and 70 residues are invariant across eukaryotic phyla. Sixty-one of the pathogenic mutations occur at residues conserved in mammals, with 49 occurring at positions that are 'extremely conserved' " (Seetharaman et al., 2010). Seetharaman et al., continue, stating: "Given this high degree of sequence identity [84%], it might be expected that mouse SOD1 would be prone to co-aggregate with mutant human SOD1 in transgenic mice and in cell culture. However... endogenous mouse SOD1 was not a component of these aggregates (Wang et al., 2003; Lambrechts et al., 2009). In contrast, human wild-type SOD1, when coexpressed in mice with the pathogenic SOD1 variants A4V, G85R, G93A, and L126Z, was found co-aggregated with the pathogenic SOD1 variants in the detergent insoluble fractions of spinal cord lysates coming from these animals (Deng et al., 2006; Wang et al., 2009)" (Seetharaman et al., 2010).

Wild-type SOD1 from humans increased disease severity in mouse models, in addition to other changes (Deng et al., 2006; Wang et al., 2009). That the 16% difference in sequence identity is highly significant is not unanticipated. As we discussed in the section on evolution, even one SNP can have lethal ramifications (Seetharaman et al., 2010). Differences also exist in the number of copies of the gene. The SOD1 transgene mouse with a G93A mutation exhibits up to 25 copies of the transgene. This results in a large amount of SOD1 protein produced. A variant of G93A contains fewer copies and exhibits a slower disease course. Differences have also been demonstrated between sexes of mice and among mice with different genetic backgrounds (Acevedo-Arozena et al., 2011). Changes like copy number variations (CNVs) and nucleotide sequence variations, and the influence of background genes, are why speciation results in two species that are differently complex and thus we should expect differences in response to perturbations.

There are numerous differences among strains of the SOD1 mice, including differences secondary to background genes (Kato,

Table 5
Summary of main neuropathological findings in autopsied patients with familial amyotrophic lateral sclerosis (FALS) with characteristic mutations of superoxide dismutase 1 (SOD1) (Kato, 2008) (for references see Kato, 2008.)

SODl mutation	Number of patients	Neuronal inclusion	SODl aggregation	Bunina body	Corticospinal tract involvement	Posterior column involvement
A4V	3	LBHI	+	−	+(slight)	+
	5	ICI	ND	ND	±(mild)	+(asymmetry)
A4T	1	LBHI	+	−	+(mild)	+
G37R	1	LBHI	+	−	+	+
H43R	1	LBHI	+	−	+	+
H46R	1	LBHI	+	−	+(very mild)	+(very mild)
H48Q	1	LBHI&SL1	−	−	+(mild)	minimal
E100G	1	SLI	−	ND	+	+
D101N	2	ICHI	ND	ND	−	−
D101Y	1	LBHI	+	−	+(very mild)	−
LI 06 V	2	LBHI	+	−	+	+
C111Y	1	LBHI	+	−	+	Minimal
I113T	1	NFT	ND	ND	+	−
(Brain and brain stem)						
	1	ICAI	ND	ND	−	ND
	1	ICAI	+	−	ND	ND
	1	HC	ND	ND	+	+
	1	NFCI	−	−	+(slight)	+
L126S	1	LBHI	+	−	+	+
2-bp del	2	LBHI	+	−	+(slight/marked)	+
(L126delTT)	1	LBHI	+	−	+	−
C146R	2	LBHI	+	−	+(slight)	+
Wild type	2	SLI/RHI	−	+	+	−

As controls, FALS siblings with wild-type SOD1 are also tabulated in the bottom row +, present; − absent.
ND: not described; LBHI: Lewy body-like hyaline inclusion; ICI: intracytoplasmic inclusion; SLI: skein-like inclusion; RHI: round hyaline inclusion; ICHI: intracytoplasmic hyaline inclusion; NFT: neurofibrillary tangle (straight filament); ICAI: intracytoplasmic argyrophilic inclusion (neurofilament accumulation); HC: hyaline conglomerate (with neurofilament epitope); NFCI: neurofilamentous conglomerate inclusion; bp, base pair; del deletion.

2008; Joyce et al., 2011; Mancuso et al., 2012; Pan et al., 2012). The A4V mutation represents approximately 50% of all patients with fALS and is associated with a more rapid course. In the SOD1 mouse however, the A4V mutation results in no neurodegeneration during the normal lifespan of the mouse. When the SOD1 A4V mouse is also carrying the wild-type SOD1, then aggressive neurodegeneration is seen (Deng et al., 2006). A similar situation is observed with mutations G93A and LI26Z (Bruijn et al., 1998; Jaarsma et al., 2008), but no such difference is noted for the mutation G85R (Bruijn et al., 1998). Chattopadhyay and Valentine state: "These differences indicate that transgenic mice homozygous for specific mutants do not necessarily reflect aggregation trends and hence, disease mechanisms, observed in fALS patients who are usually heterozygous" (Chattopadhyay and Valentine, 2009). Moreover, when this many differences exist among strains of the same species, we should not expect the model to have predictive value for a different species. Evolved CASs simply do not allow for this many differences without a high probability of dramatic changes in outcomes to perturbations.

Statements like the following by Seetharaman et al., are typical of the claims regarding the SOD1 mouse model: "Although ALS is a human disease, the development of transgenic mouse models that retain many of the pathological features found in human ALS have been extremely valuable" (Seetharaman et al., 2010). Seetharaman et al., discuss the optimism surrounding the discovery of SOD1 and the value of using the SOD1 mouse in order to provide new treatments for ALS. However, they then conclude: "Although a large number of pathogenic SOD1 proteins have been studied intensely by many laboratories over years... the precise molecular mechanism(s) through which these proteins exert their toxic effects remain to be delineated" (Seetharaman et al., 2010). Chattopadhyay and Valentine likewise state: "Transgenic mice expressing mutations in the SOD1 gene have been invaluable tools to investigate disease mechanisms and possible therapeutic applications in ALS" (Chattopadhyay and Valentine, 2009). Yet, they too acknowledge the failure of the model: "However, failure to translate positive preclinical findings achieved in these mice into positive clinical trials in ALS patients has raised concerns about the relevance of SOD1 mouse models to ALS..." (Chattopadhyay and Valentine, 2009).

Pan et al., continue the praise of the SOD1 mouse, stating: "Creation of transgenic mice expressing mutant Cu/Zn superoxide dismutase (SOD1), as ALS models, has made an enormous impact on progress of the ALS studies.... Genetically engineered mice have played a pivotal role not only in the molecular pathogenesis but also in the development of therapeutics for many genetic as well as non-genetic diseases. Indeed, the creation of ALS animal models, namely transgenic mice expressing a mutant SOD1, has made an enormous impact on progress of the ALS studies" (Pan et al., 2012). Rothstein writes: "Transgenic mouse models with mutations in the SOD1 gene and other ALS genes develop pathology reminiscent of the disorder, including progressive death of motor neurons, and have provided insight into the pathogenesis of the disease but have consistently failed to predict therapeutic efficacy in humans" (Rothstein, 2009). Peviani et al., state: "[SOD1 mouse models] replicate many of the clinical, neuropathological and molecular features of ALS patients and have contributed significantly to our understanding of the pathogenic mechanisms of this disease. Although results obtained so far with mutant SOD1 mice have not translated into effective therapies in ALS patients, these models still represent the only experimentally accessible system to study multiple aspects of disease pathogenesis and to provide proof-of-principle for the development of new therapeutic strategies" (Peviani et al., 2010).

Thus we note that the claims for the SOD1 mouse are strong and supportive, yet some simultaneously admit that clinical progress has been slow to nonexistent. This is oxymoronic nevertheless typical of the animal model literature in general. Despite failure after failure of the model in question to aid patients suffering from the disease, advocates of the model make strong claims regarding its value. We acknowledge that animal models such as the SOD1 mouse have aided in advancing science but so has the study of

geology and fault lines. Advances in science are not synonymous with advances in medicine.

Benatar, who reinforces Giles' comment above, is another example: "The scientific and ethical justification for animal models of human disease is that they may provide an opportunity to investigate disease biology and to identify potential therapies that might be beneficial to humans" (Benatar, 2007). However, Benatar follows this by noting the *scientific* success of the SOD1 mouse, stating: "The most popular animal model of amyotrophic lateral sclerosis (ALS) is the mouse that has been genetically engineered to express a mutant form of the human superoxide dismutase (SOD1) gene. The most commonly used SOD1 mouse harbors the glycine to alanine mutation at amino acid 93 (G93A). Since the identification of mutations in the SOD1 gene as an important cause of familial ALS and the generation of the SOD1 mouse model of ALS several years later, there have been dozens of studies of a panoply of therapeutic agents in SOD1 mice. The choice of therapeutic agents in many clinical trials of human ALS has been predicated, at least in part, on the efficacy of these drugs when studied in the SOD1 mouse" (Benatar, 2007).

Benatar then acknowledges the *clinical* success has been less impressive: "Nevertheless, success in human clinical trials has been extremely limited, calling into question the utility of such preclinical data for identifying therapeutic agents that are worthy of further study in humans" (Benatar, 2007). Scott et al., reinforce Benatar, stating: "Identification of SOD1 as the mutated protein in a significant subset of familial amyotrophic lateral sclerosis (FALS) cases has led to the generation of transgenic rodent models of autosomal dominant SOD1 FALS. Mice carrying 23 copies of the human SOD1G93A transgene are considered the standard model for FALS and ALS therapeutic studies. To date, there have been at least 50 publications (see Nirmalananthan and Greensmith, 2005 and Rothstein, 2004) describing therapeutic agents that extend the lifespan of this mouse. However, no therapeutic agent besides riluzole has shown corresponding clinical efficacy" (Scott et al., 2008).

The drug riluzole is the only current treatment that extends life, although only marginally, in ALS patients (Corcia and Gordon, 2012) and it was not discovered because of the SOD1 mouse. Corcia and Gordon note that every drug tested after riluzole has failed in humans (see Table 6 for a list of some of these drugs.). These drugs have included antiglutamatergics, antiapoptotics, anti-inflammatories, immune modulators, and protein-clearing agents (Corcia and Gordon, 2012). However, they then state that "basic and clinical research methods in ALS have become dramatically more sophisticated." They describe the drug Dexpramipexole (RPPX), the R(+) enantiomer of pramipexole, stating that it has the "largest body of pre- and early clinical data that support testing in ALS.... The investigators can be confident that they are proceeding with a drug that is ready for efficacy testing" (Corcia and Gordon, 2012). RPPX was efficacious in the SOD1 mouse model as well as other species (Danzeisen et al., 2006; Corcia and Gordon, 2012). RPPX failed, however, in Phase III human clinical trials (the EMPOWER study) that ended in December 2012, secondary to lack of efficacy (Jeffrey, 2013). Biogen Idec discontinued the Phase III trials involving 943 patients because none showed any improvement. Kerr, of Biogen Idec, states: "Quite simply the drug did not work, not on any measure" (Sinha, 2013).

Despite the above evidence, Kato states: "Of course, human ALS and all ALS animal models share one most important similarity in that both exhibit motor neuron degeneration/death. This important point of similarity has shed much light on the pathomechanisms of the motor neuron degeneration/death at the cellular and molecular levels that would not have been appreciated if only human ALS autopsy samples had been available" (Kato, 2008). In light of the failures of the SOD1 mouse to predict human response to therapeutics, on what basis does Kato conclude the pathophysiology between humans and the mouse model are the same? There are two possibilities:

1. Human data exists to support the claim, in which case the data could have been derived from human-based research without the animal models.
2. Kato is merely making an assumption that has not been shown true.

Both possibilities reveal an unwarranted confidence that animal models are the best way to discover human pathophysiology. We will continue this examination in the following section on rebuttals to our position.

3.6. Response to defenses of animal models

As we have shown, despite the empirical evidence and theory in the form of evolution and CASs, scientists continue to defend the SOD1 model, and animal models in general, as being of predictive value for human response to disease and drugs. Peviani et al., state: "Animal models are an invaluable experimental paradigm to examine the multiple aspects of the pathogenesis of a neurodegenerative disease, particularly when many cellular systems are involved as in ALS" (Peviani et al., 2010). Fomchenko and Holland express confidence in animal models when they state: "GEMs [genetically engineered mice] closely recapitulate the human disease and are used to predict human response to a therapy, treatment or radiation schedule.... GEMs that faithfully recapitulate human brain tumors and will likely result in high-quality clinical trials with satisfactory treatment outcomes and reduced drug toxicities. Additional use of GEMs [include the ability] to establish

Table 6
Clinical failures on ALS drugs (Corcia and Gordon, 2012).

Drug	Trial design	Mechanism	Sample	Endpoint	Outcome
Glatiramer	Phase III	Immune modulator	360	ALSFRS-R	Negative
Lithium	Phase II	Antiglutamatergic, Protein clearance	Up to 171	Survival/ALSFRS-R	Negative
Ceftriaxone	Phase II–III	Antiglutamatergic	600	Survival/ALSFRS-R	Ongoing
Memantine	Phase II	Antiglutamatergic	63	ALSFRS-R	Negative
Arimoclomol	Phase II	Heat shock protein inducer	84	Safety	Adequate safety
Talampanel	Phase II	Antiglutamatergic	59	Arm strength	Nonsignificant improvement
CoQl0	Phase II dose selection/futility	Antioxidant/mitochondrial cofactor	185	ALSFRS-R	Negative
Minocycline	Phase III	Anti-inflammatory/antiapoptotic	412	ALSFRS-R	Negative
Xaliproden	Phase III	Antiapoptotic	Up to 1210	Survival Breathing capacity	Negative
Gabapentin	Phase III	Antiglutamatergic	204	Arm strength	Negative
Celecoxib	Phase III	Anti-inflammatory	300	Arm strength	Negative
Riluzole	Phase III	Antiglutamatergic, unknown	Up to 959	Survival	Positive

Abbreviation: ALSFRS-R, revised version of the Amyotrophic Lateral Sclerosis Functional Rating Scale.

causal links between the presence of various genetic alterations and brain tumor initiation..." (Fomchenko and Holland, 2006). Such examples could be easily multiplied.

Despite the evidence, many in the scientific community simply will not accept that there is anything of scientific concern regarding animal models. Most of the scientists we have encountered, especially in the biological sciences but also in the physical sciences, express the same sentiment the authors of the Seok paper, referred to in Section 3.2, encountered when presenting their data. Kolata writes: "The [Seok] study's investigators tried for more than a year to publish their paper, which showed that there was no relationship between the genetic responses of mice and those of humans. They submitted it to the publications *Science* and *Nature*, hoping to reach a wide audience. It was rejected from both" (Kolata, 2013). Kolata then quotes RW Davis, a coauthor of the Seok article, who said: "reviewers did not point out scientific errors... the most common response was, 'It has to be wrong. I don't know why it is wrong, but it has to be wrong' " (Kolata, 2013).

"It has to be wrong." That is exactly the response we have received from the biomedical research community when we have published our position on modeling evolved CASs (Greek and Pound, 2002; Greek and Shanks, 2009, 2011; Shanks and Greek, 2009; Shanks et al., 2009; Greek and Greek, 2010; Greek et al., 2011a,b, 2012a,b; Greek and Hansen, 2012; Greek and Rice, 2012). The reviewers, and ultimately the readers, do not present counterarguments or point out errors of fact. They offer no data to invalidate our claims nor do they offer theoretical considerations from complexity science or evolutionary biology. They simply do not accept the empirical evidence or theoretical underpinning. Here, we respond to some of the arguments or claims that have been made, as they are relevant to the arguments we have presented in this article.

Many of the arguments against our position are in the form of unsupported claims. In the summary from the March 28 and 29, 2012, workshop on *Animal Models for Nervous System Disorders*, held in Washington, D.C., the authors state: "Ferrante [Professor in the departments of neurological surgery, neurology, and neurobiology at the University of Pittsburgh] suggested that current animal models for Huntington's disease and ALS may accurately reflect not only pathophysiological mechanisms of human disease, but also neuropathology and behavioral phenomena. For other disorders, however, it is much more difficult" (Pankevich et al., 2013). We consider this article to have sufficiently refuted this claim, although, to quote Christopher Hitchens: "What can be asserted without evidence can also be dismissed without evidence" (Hitchens, 2003). Scientists need to remember that the null hypothesis still applies and that the burden of proof is on the one making the claims regarding animal models.

Novella discusses the role of animal models, stating: "Mouse and other animal models are essential to biomedical research. The goal is to find a specific animal model of a human disease and then conduct preliminary research on the animal model in order to determine which research is promising enough to study in humans" (Novella, 2013a). Indeed, that is the goal. Implied in this goal is the notion that animal models are, or can be, of predictive value for humans in terms of responses to drugs and disease. However, as we have shown, such a notion is simply without support. Anecdotes offer nothing in terms of PPV and NPV, and correlations that are only revealed retrospectively do not qualify as being of predictive value. Thus the claim that animal models are *essential* to biomedical research is a case of begging the question. Nevertheless, most defenses of animal models begin just this way.

Novella continues: "I would also point out that it is highly problematic to discuss the utility of animal models in general. Each animal model needs to be considered by itself, in terms of how predictive it is, and for what. For example, there are SOD1 mice who have a mutation that causes familial ALS (FALS). This mouse model has served as a screen for many potential ALS treatments" (Novella, 2013a). Novella neglects to state that all of these potential treatments failed in humans. The National Cancer Institute thinks society may have lost cures for cancer due to animal screening (Gura, 1997), and other scientists have expressed similar concerns regarding other diseases (Weatherall, 1982; Editorial, 2003; Lazzarini et al., 2006). It is not impossible that ALS patients have lost treatments because of animal screening. In terms of the value of animal models in general, we can evaluate the predictive value of animal models as they are currently used, and where such data are available PPVs around 0.3 seem to the norm (Litchfield, 1962, 1965; Fletcher, 1978; Heywood, 1990; Lumley, 1990; Suter, 1990; Sprietz-Pourra and Auriche, 1994). The PPV for neuroprotection, treatments for ALS, cancer, and sepsis as well as a vaccine against HIV, among others, currently have a PPV of zero. When science is evaluating perturbations that occur at lower levels of organization, for example whether an antibiotic will kill a bacterium, animal models do have predictive value. In some of these cases however, so do petri dishes. When studying perturbations that occur at lower levels of organization, animal models have been important. With few exceptions, diseases and drugs do not act at these levels. Antibacterials are affecting a different system, namely the wall of the bacterium, and this can be evaluated without animal models. The CAS in question in terms of efficacy is the bacterium, not the animal infected by it.

Novella continues: "It turns out that the SOD1 mouse is an excellent animal model for SOD1 FALS in humans. This is not surprising considering that it is the same mutation. However, the SOD1 mouse model of ALS is much less predictive for sporadic ALS. Most of the drugs that look promising in the SOD1 model have not shown a significant clinical effect in humans with sporadic ALS (only one drug has actually made it through FDA approval: riluzole)" (Novella, 2013a). Novella, a neurologist who treats ALS, is arguably in a reasonable position to judge the value of an animal model. However, as we should anticipate from the section on evolution, mutations do not result in the same outcomes across species lines. For example, mutations that cause phenylketonuria and Sanfilippo syndrome in humans are normal in macaque monkeys (Gibbs et al., 2007; Holmes, 2007). As we stated, even strains of the same species vary in their response to seemingly potent perturbations such as knocking out a gene. Combine this with convergent evolution and we see no reason to suspect conservation of gene function across species. Conservation *does* happen (Greek and Rice, 2012), but there seems to be no standard method for determining it without comparative studies. Thus again we can only establish validity in retrospect.

Novella's comment also raises the question: what makes an animal model *excellent*? If all treatment attempts based on the model have failed in humans, then that alone is sufficient to suggest the model is not even useful as a heuristic (functioning as a guide in discovery or investigation) and certainly not an *excellent* model. Schnabel, writing in 2008 observed that even then around a dozen drugs had been reported to prolong life in the SOD1 mouse model but none were effective in humans with ALS. As an example, Schnabel cites the antibiotic minocycline, which was efficacious in SOD1 mouse models in four different labs. Minocycline not only failed in humans but made the symptoms of ALS worse in a trial with 400 patients (Schnabel, 2008).

Why did the treatments referred to by Schnabel fail in humans if the model is even adequate? There could be several explanations:

1. The model predicted safety not efficacy. However, the SOD1 mouse did predict efficacy in many of the treatments and efficacy is precisely why the drugs failed in humans.

2. The pathophysiology of human ALS differs, perhaps subtly, from the SOD1 mouse. Perhaps mice and humans share several modules that are involved in ALS, but if even one module differs, then, because both mice and humans are evolved CASs, perturbations to the same module could lead to different outcomes. Therefore, a treatment could be successful mice but fail in humans. However, this would also invalidate the notion of the SOD1 mouse as an excellent model of predictive value.
3. All the modules of ALS pathophysiology are shared by the SOD1 mouse and humans but the background and modifier genes differ, thus placing us back to our theme that small differences between evolved CASs result in the same perturbation giving rise to different responses.

Further, to claim the pathophysiology of ALS is the same in the SOD1 mouse as it is in humans is again a case of begging the question, as the pathophysiology has not been determined in humans. However, let's assume that the general pathophysiology of ALS in the SOD1 mouse mimics that of fALS in humans. What does that achieve in terms of predicting human response to treatments? Very little, as even if mice and humans share all the modules, the modules interact with other modules and with the organism as a whole, thus the same perturbation/drug can affect the two species very differently. Very small differences between evolved CASs can negate a large number of similarities when using one evolved CAS to predict outcomes for a second. Additionally, even if the pathophysiology is identical, we still have the problem of emergent properties and the whole being greater than the sum of its parts.

Novella then discusses the Seok (Seok et al., 2013) paper, which investigated gene response to sepsis, burns, and blunt trauma, and found little correlation between species: "The deeper question is — how similar is the mouse immune system to the human immune system" (Novella, 2013a). As we discussed above, no animal model is going to be *similar enough* to the human system to allow a high PPV and NPV. This is because of differences in initial conditions in terms of genes, genetic regulation and expression, and gene networks. Emergent phenomenon, redundancy and robustness, and other characteristics of evolved CASs will also affect predictive value. Moreover, evolved CASs are also dynamic so we observe differences due to changes in the genome via epigenetics (Mueller and Olsson, 2003; Flintoft, 2005; Fraga et al., 2005; Qiu, 2006; Gosden and Feinberg, 2007; Ballestar, 2010; Javierre et al., 2010b; Meymandi, 2010; Bell and Spector, 2011; Brower, 2011; Gordon et al., 2011; Czyz et al., 2012). Even monozygotic twins fail to respond in the same fashion to diseases like multiple sclerosis and schizophrenia, and small changes in the genome may explain why this is the case (Herndon and Jennings, 1951; Alexanderson and Borga, 1972; Lin et al., 1989; Fraga et al., 2005; Wong et al., 2005; Bruder et al., 2008; Muqit et al., 2008; Javierre et al., 2010a; Misch et al., 2010; Stankiewicz and Lupski, 2010; Bell and Spector, 2011; Dempster et al., 2011; Gordon et al., 2011; Maiti et al., 2011; Ollikainen and Craig, 2011; Chapman and Hill, 2012; Czyz et al., 2012; Halder et al., 2012; Zhao et al., 2012).

Novella recognizes the importance of predictive value. On the podcast *Skeptics Guide to the Universe*, February 9, 2013 (beginning at 1:09:09 into the broadcast), he discusses the predictive values of diagnostic tests. Novella states, we need to pay more attention to "statistical predictability, the base rate and how predictive things are... I'll tell medical students, don't worry about whether or not this symptom is typical of this disease. I want to know how predictive it is that this is the diagnosis" (Novella, 2013b). In light of the above we fail to understand how he can consider animal models, especially the SOD1 mouse, to be of predictive value.

Novella concludes his comments on the Seok paper stating: "The current research appears to be a significant blow to the current mouse models of inflammatory stress, but also contains a wealth of information about which genes become active in humans and mice in response to such stress. This potentially can lead to other useful models or biomarkers, and also to new treatments in this very challenging area of medicine" (Novella, 2013a). Part of this statement is a tautology. If one wishes to draw conclusions about the similarities and differences among species, then comparative research is mandatory. But that is not what researchers using animal models usually claim, as we pointed out in the preceding sections. The SOD1 mouse does appear to mimic humans in terms of some of the characteristics of ALS. While interesting, this does not mean the same mechanisms are involved for reasons alluded to in the section on evolution. The SOD1 mouse has failed in terms of predicting treatment success and we suspect it will do the same for biomarkers. Even if a treatment or biomarker is eventually found because of the SOD1 mouse, the numerous failures will translate to a PPV that is far from adequate in terms of considering it to be of predictive value.

Theory derived from complexity science and evolutionary biology supports the empirical findings that animal models can only be identified retrospectively as responding to perturbations, like drugs and disease, as humans responded. Hau pointed this out years ago: "It is not possible 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]" [(Hau, 2003) p. 6]. This appears to invalidate the concept of *animals as predictive models* for human response to drugs and disease, and we are left with using animals as heuristic devices — a source for new ideas — a use for which they are scientifically valid. It also appears to invalidate the notion that we must evaluate animal models *one at a time* as advocated by Novella and others. Furthermore, even when an animal is discovered that responds to, say, a teratogen, as humans respond, it rarely responds like humans to other teratogens (Greek et al., 2011b). So again, one instance of correlation is an anecdote, not a model with predictive value.

Applying Complexity Theory and the Theory of Evolution to the problem of using one evolved CAS as a model in order to predict responses of a second has resulted in what one of us (Greek) has called Trans-Species Modeling Theory (TSMT): While trans-species extrapolation is possible when perturbations concern lower levels of organization or when studying morphology and function on the gross level, one evolved complex system will not be of predictive value for another when the perturbation affects higher levels of organization. TSMT fulfills Popper's criteria for a theory (Popper, 2002).

1. It is supported by a vast amount of evidence. Where direct comparisons are possible — such as with drug toxicity, efficacy, bioavailability, and so forth — definitive evidence exists to support the concerns raised by trans-species modeling theory (In addition to the previously cited references see (Greek, 2008, 2012, 2013a,b; Greek and Shanks, 2009; Shanks and Greek, 2009; Shanks et al., 2009; Greek et al., 2011b, 2012a; Greek and Rice, 2012.) If two evolved CASs are not predictive for each other in these areas, what changes in evolution would account for their being predictive in other areas such as HIV, ALS, and cancer? Indeed the empirical evidence in these areas agrees with that from the drug development literature.
2. The prediction that such systems should not be of predictive value contained risk in that evolution has followed common pathways and therefore many similarities should and do exist. Based on TSMT, we should expect agreement among species when the perturbation affects only the lower levels of the hierarchy of organization (for example, the laws of physics affect

all mammals equally). However, as one moves into the higher levels of organization the perturbations should be expected to result in varying responses both qualitatively as well as quantitatively (see (Shanks and Greek, 2009; Greek and Rice, 2012) for more on this.). Empirically, we find those two predictions are fulfilled.
3. It prohibits animal models from predictive value at higher levels of organization and this has been quantified.
4. It is refutable. For example, a species or strain that correlated with human data regarding known teratogens >95% of the time and that correctly predicted novel teratogens a similar percentage of the time would falsify the theory.
5. It has been tested many times in disciplines ranging from infectious diseases, cancer, toxicity, neurology, and drug efficacy to teratogenicity.
6. Confirming evidence has come from many and varied disciplines involved in animal use: research on heart disease, sepsis, trauma, and anesthesiology.
7. The theory is straightforward and has no *ad hoc* features.

Suggesting that animal models must be evaluated on a case-by-case basis is like asking that each flora or fauna that fills an ecological niche be evaluated for achieving its position through an act of special creation or evolution. There is no logical reason to assume the trait in question was not the result of a special creation. But in light of theory — the Theory of Evolution — and empirical evidence, there is no reason to ask such questions. Theories and laws in science prohibit certain hypotheses. For example, the Germ Theory of Disease prohibited, and indeed replaced, the notion that rotting organic matter caused disease — miasma. The Germ Theory does not prohibit other causes of disease, such as cancer, vascular abnormalities, and endocrine disorders, but it does mandate the clinician consider bacteria and viruses instead of rotting matter. Likewise, Atomic Theory prohibits an infinite division of matter into smaller and smaller units, and the Theory of Relativity prohibits faster-than-light velocities.

We should also note, yet again, what we are *not* saying. In an article proclaiming the value of animal models in basic research, Carbone stated that Greek and Greek (2004): "would end animal studies, which they find misleading to the point of danger — a 'scientific failure' "(Carbone, 2012). On the contrary, Greek et al., have stated exactly the opposite many times. For example, Shanks and Greek: "This book is not intended to be a criticism of the use of animals in the context of basic biological research. There can be no doubt that careful studies of animals have prompted important hypotheses about basic biological principles, and there can be no doubt that studies of animals have contributed greatly to our scientific understanding of life, and there is little doubt that these studies will continue to illuminate these matters in the future... " [(Shanks and Greek, 2009) p. 30].

What Greek et al., *have* consistently stated is that animal models have no predictive value in terms of human response to drugs and disease. For example, Shanks and Greek: "The purpose of this book is to address the ability, or lack thereof, of animals to predict human response and to see what other roles they may have in research and testing. We will argue that claims concerning the great utility of animals as predictive models of human biomedical phenomena are unsupported by evidence and are compromised by both methodological issues and issues arising from basic biological theory" [(Shanks and Greek, 2009) p. 24].

Carbone's argument is thus a straw man. Gorski also commits this fallacy: "In other words, because animal models have many difficulties and flaws and all too often don't predict human physiology or drug response as well as the critics think that they should, then by implication *all* animal research is bad science" (Orac, 2010). Stemwedel also resorts to a straw man: "Ray Greek, president of Americans for Medical Advancement... asserted that animals are too different from humans to tell us anything useful about humans, and suggested that this is why so few basic research studies end up resulting in knowledge or therapies that are useful in treating human patients" (Stemwedel, 2010).

The argument we have presented regarding the SOD1 mouse is representative of outcomes from animal models. Occasionally an animal will mimic humans in response to a perturbation at higher levels of organization. But this happens at a rate that approaches what we would expect from random chance and hence cannot be consider of predictive value. Moreover, even in retrospect it is difficult to reproduce some aspects of human responses to drugs and disease (Rosenblum et al., 1965a,b,c; Collins et al., 1969; Stolley, 1972; Stolley and Schinnar, 1979; Inman, 1980; Wynn, 1982; Bari, 1996; Gad, 2006). Because animals and humans are evolved CASs, animal models *per se* will never be of predictive value for responses to perturbations that occur at higher levels of organization. This conclusion is not threatened if a drug is discovered tomorrow that cures sepsis or AIDS in humans and in a strain of mouse or a monkey. In order for a model to be of predictive value it must have a high PPV and NPV. It would also facilitate matters if we knew why the model worked when all others do not. Similarities in responses between humans and animal models have, to date, been haphazard and not repeatable for other drugs or species. As stated earlier, if the only way a scientist can know whether the model will reproduce outcomes for humans is in retrospect, then the model has no predictive value.

4. Conclusions

Grove states: "Humans are incredibly complex biological systems, and working with them has to be subject to safety, legal, and ethical concerns.... The result is wide-scale experimentation with animal models of dubious relevance, whose merit principally lies in their short lifespan" (Grove, 2005). Humans and animals have a genome, proteome, transcriptome, interactome, metabolome, regulome, and epigenome and they all interact and modify one another. Understanding the interactions is crucial in a complex system.

Current science has advanced to the place where we are asking very specific questions, the answers to which can only be determined by studying humans with specific genotypes. Medical practice, as well as medical research, is aiming for personalized medicine. The reasons individual humans respond differently to perturbations such as drugs and disease are qualitatively the same reasons different species respond differently. Any two evolved complex adaptive systems are unlikely to experience identical outcomes to the same perturbation provided the perturbation occurs at higher levels of organization. Responses to drugs and disease occur at these higher levels and this accounts for the profound inter-species variation we describe. Modeling one evolved CAS (animals) in order to predict responses to drugs and disease for a second CAS (humans) is not scientifically viable based on the best science we currently have. Trans-species modeling theory accounts for both the successes and failures of animal models and has been verified empirically in a wide variety of areas. That having been stated, animal models have been very useful as a heuristic and in outlining the general contours of mammalian physiology and of life itself. Early studies on animals revealed facts that would have been difficult to obtain without animal use.

Trans-species modeling theory has major implications for the use of animal models in research.

References

Abelson, P.H., 1992. Exaggerated carcinogenicity of chemicals. Science 256, 1609. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1609271.

Acevedo-Arozena, A., Kalmar, B., Essa, S., Ricketts, T., Joyce, P., Kent, R., Rowe, C., Parker, A., Gray, A., Hafezparast, M., Thorpe, J.R., Greensmith, L., Fisher, E.M.C., 2011. A comprehensive assessment of the SOD1G93A low-copy transgenic mouse, which models human amyotrophic lateral sclerosis. Dis. Models Mech. 4, 686–700. http://dmm.biologists.org/content/4/5/686.abstract.

Afifi, A.K., Aleu, F.P., Goodgold, J., MacKay, B., 1966. Ultrastructure of atrophic muscle in amyotrophic lateral sclerosis. Neurology 16, 475–481. http://www.ncbi.nlm.nih.gov/pubmed/5949060.

Ahl, V., Allen, T.F.H., 1996. Hierarchy Theory, a Vision, Vocabulary and Epistemology. Columbia University Press, New York.

Ahn, A.C., Tewari, M., Poon, C.S., Phillips, R.S., 2006. The limits of reductionism in medicine: could systems biology offer an alternative? PLoS Med. 3, e208. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16681415.

Aird, W.C., 2002. Endothelial cell dynamics and complexity theory. Crit. Care Med. 30, S180–S185. http://www.ncbi.nlm.nih.gov/pubmed/12004233.

Albani, S., Prakken, B., 2009. The advancement of translational medicine — from regional challenges to global solutions. Nat. Med. 15, 1006–1009. http://dx.doi.org/10.1038/nm0909-1006.

Alexanderson, B., Borga, O., 1972. Interindividual differences in plasma protein binding of nortriptyline in man — a twin study. Eur. J. Clin. Pharmacol. 4, 196–200. http://dx.doi.org/10.1007/BF00635795.

Allen, P., Greeves, M., 2011. Paul Allen: the Singularity Isn't Near. http://www.technologyreview.com/view/425733/paul-allen-the-singularity-isnt-near/.

Alm, E., Arkin, A.P., 2003. Biological networks. Curr. Opin. Struct. Biol. 13, 193–202. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12727512.

Anisimov, V.N., Ukraintseva, S.V., Yashin, A.I., 2005. Cancer in rodents: does it tell us about cancer in humans? Nat. Rev. Cancer 5, 807–819. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16195752.

Arrowsmith, J., 2011a. Trial watch: phase II failures: 2008–2010. Nat. Rev. Drug Discov. 10, 328–329. http://dx.doi.org/10.1038/nrd3439.

Arrowsmith, J., 2011b. Trial watch: phase III and submission failures: 2008–2010. Nat. Rev. Drug Discov. 10, 87. http://dx.doi.org/10.1038/nrd3375.

Bakircioglu, M., Carvalho, O.P., Khurshid, M., Cox, J.J., Tuysuz, B., Barak, T., Yilmaz, S., Caglayan, O., Dincer, A., Nicholas, A.K., Quarrell, O., Springell, K., Karbani, G., Malik, S., Gannon, C., Sheridan, E., Crosier, M., Lisgo, S.N., Lindsay, S., Bilguvar, K., Gergely, F., Gunel, M., Woods, C.G., 2011. The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis. Am. J. Hum. Genet.. http://www.ncbi.nlm.nih.gov/pubmed/21529752.

Ballestar, E., 2010. Epigenetics lessons from twins: prospects for autoimmune disease. Clin. Rev. Allergy Immunol. 39, 30–41. http://www.ncbi.nlm.nih.gov/pubmed/19653134.

Banci, L., Bertini, I., Cantini, F., D'Amelio, N., Gaggelli, E., 2006. Human SOD1 before harboring the catalytic metal: solution structure of copper-depleted, disulfide-reduced form. J. Biol. Chem. 281, 2333–2337. http://www.ncbi.nlm.nih.gov/pubmed/16291742.

Bankiewicz, K.S., 2006. Focal Dopamine Indicated in Dyskinesias in MPTP Monkeys. UCSF, 1R01NS050156-01A2. http://projectreporter.nih.gov/project_info_description.cfm?aid=7148558&icde=15324344.

Barber, E.D., Teetsel, N.M., Kolberg, K.F., Guest, D., 1992. A comparative study of the rates of in vitro percutaneous absorption of eight chemicals using rat and human skin. Fundam. Appl. Toxicol. 19, 493–497. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1426706.

Bard, J., Melham, T., Noble, D., 2012a. Epilogue: some conceptual foundations of systems biology. Prog. Biophys. Mol. Biol.. http://www.ncbi.nlm.nih.gov/pubmed/23274735.

Bard, J., Melham, T., Werner, E., Noble, D., 2012b. Plenary discussion of the conceptual foundations of systems biology. Prog. Biophys. Mol. Biol.. http://www.ncbi.nlm.nih.gov/pubmed/23276725.

Bari, A., 1996. Severe toxicity of fialuridine (FIAU). N. Engl. J. Med. 334, 1135. author reply 1137-8. http://www.ncbi.nlm.nih.gov/pubmed/8598879.

Barrow-Green, J., 1997. Poincaré and the Three Body Problem. American Mathematical Society, Providence.

Bates, S., 2010. Progress towards personalized medicine. Drug Discov. Today 15, 115–120.

BBC News, November 10, 2008. Window into Cancer-spread Secrets. http://news.bbc.co.uk/2/hi/health/7711650.stm.

Becskei, A., Serrano, L., 2000. Engineering stability in gene networks by autoregulation. Nature 405, 590–593. http://www.ncbi.nlm.nih.gov/pubmed/10850721.

Begley, S., September 15, 2008. We Fought Cancer... and Cancer Won April 24. http://www.newsweek.com/id/157548.

Begley, C.G., Ellis, L.M., 2012. Drug development: raise standards for preclinical cancer research. Nature 483, 531–533. http://dx.doi.org/10.1038/483531a.

Bell, J.T., Spector, T.D., 2011. A twin approach to unraveling epigenetics. Trends Genet. TIG 27, 116–125.

Belmaker, R., Bersudsky, Y., Agam, G., 2012. Individual differences and evidence-based psychopharmacology. BMC Med. 10, 110. http://www.ncbi.nlm.nih.gov/pubmed/23016518.

Benatar, M., 2007. Lost in translation: treatment trials in the SOD1 mouse and in human ALS. Neurobiol. Dis. 26, 1–13. http://www.sciencedirect.com/science/article/pii/S0969996106003287.

Beniashvili, D.S., 1994. Experimental Tumors in Monkeys. CRC Press, Boca Raton.

Bhathena, A., Spear, B.B., 2008. Pharmacogenetics: improving drug and dose selection. Curr. Opin. Pharmacol. 8, 639–646. http://www.ncbi.nlm.nih.gov/pubmed/18762278.

Bickel, P.J., Buhlmann, P., 1996. What is a linear process? Proc. Natl. Acad. Sci. U S A 93, 12128–12131. http://www.ncbi.nlm.nih.gov/pubmed/8901544.

Bizzarri, M., Palombo, A., Cucina, A., 2013. Theoretical aspects of systems biology. Prog. Biophys. Mol. Biol.. http://www.ncbi.nlm.nih.gov/pubmed/23562476.

Blair, E., 2009. Predictive tests and personalised medicine. Drug Discov. World, 27–31.

Bohm, D., 1969. Some remarks on the noting of order. In: Waddington, C.H. (Ed.), Towards a Theoretical Biology, Sketches, vol. 2. Edinburgh Press, Edinburgh, pp. 18–40.

Bonati, M., Latini, R., Tognoni, G., Young, J.F., Garattini, S., 1984. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. Drug Metab. Rev. 15, 1355–1383. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=6543526.

Boyd, P.T., Mcmillan, S.L.W., 1992. Parameter space structure in irregular gravitational scattering. Phys. Rev. A15, 6277–6287.

Braithwaite, R.B., 1953. Scientific Explanation: a Study of the Function of Theory, Probability and Law in Science. Cambridge University Press, Cambridge.

Brennan, R., Federico, S., Dyer, M.A., 2010. The war on cancer: have we won the battle but lost the war? Oncotarget 1, 77–83. http://www.ncbi.nlm.nih.gov/pubmed/20877440.

Brower, V., 2011. Epigenetics: unravelling the cancer code. Nature 471, S12–S13. http://dx.doi.org/10.1038/471s12a.

Bruder, C.E., Piotrowski, A., Gijsbers, A.A., Andersson, R., Erickson, S., De Stahl, T.D., Menzel, U., Sandgren, J., Von Tell, D., Poplawski, A., Crowley, M., Crasto, C., Partridge, E.C., Tiwari, H., Allison, D.B., Komorowski, J., Van Ommen, G.J., Boomsma, D.I., Pedersen, N.L., Den Dunnen, J.T., Wirdefeldt, K., Dumanski, J.P., 2008. Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. Am. J. Hum. Genet. 82, 763–771. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=18304490.

Bruijn, L.I., Houseweart, M.K., Kato, S., Anderson, K.L., Anderson, S.D., Ohama, E., Reaume, A.G., Scott, R.W., Cleveland, D.W., 1998. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science 281, 1851–1854. http://www.ncbi.nlm.nih.gov/pubmed/9743498.

Bruijn, L.I., Miller, T.M., Cleveland, D.W., 2004. Unraveling the mechanisms involved in motor neuron degeneration in ALS. Annu. Rev. Neurosci. 27, 723–749. http://www.ncbi.nlm.nih.gov/pubmed/15217349.

Buchanan, R.W., Keefe, R.S., Umbricht, D., Green, M.F., Laughren, T., Marder, S.R., 2011. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophrenia Bull. 37, 1209–1217. http://www.ncbi.nlm.nih.gov/pubmed/20410237.

Bugge, T.H., Kombrinck, K.W., Flick, M.J., Daugherty, C.C., Danton, M.J., Degen, J.L., 1996. Loss of fibrinogen rescues mice from the pleiotropic effects of plasminogen deficiency. Cell 87, 709–719. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=8929539.

Burggren, W.W., Bemis, W.E., 1990. Studying physiological evolution: paradigms and pitfalls. In: Nitecki, M.H. (Ed.), Evolutionary Innovations. University Of Chicago Press, Chicago, pp. 191–228.

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

Caldwell, J., 1980. Comparative aspects of detoxification in mammals. In: Jakoby, W. (Ed.), Enzymatic Basis of Detoxification. Academic Press, New York, pp. 85–114.

Caldwell, J., 1992. Problems and opportunities in toxicity testing arising from species differences in xenobiotic metabolism. Toxicol. Lett., 64–65. Spec No, 651-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=1471219.

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., Zheng, Z.-J., 2012. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA: J. Am. Med. Assoc. 307, 813–822. http://jama.ama-assn.org/content/307/8/813.abstract.

Caponigro, G., Sellers, W.R., 2011. Advances in the preclinical testing of cancer therapeutic hypotheses. Nat. Rev. Drug Discov. 10, 179–187. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=21358737.

Carbone, L., 2012. The utility of basic animal research. Hastings Center Rep. Suppl., S12–S15. http://www.ncbi.nlm.nih.gov/pubmed/23138422.

Chapman, S.J., Hill, A.V.S., 2012. Human genetic susceptibility to infectious disease. Nat. Rev. Genet. 13, 175–188. http://dx.doi.org/10.1038/nrg3114.

Charcot, J., 1865. Sclérose Des Cordons Latéraux De La Moelle Épinière Chez Une Femme Hystérique Atteinte De Contracture Permanente Des Quatre Membres. Bull. Soc. Méd. Des. Hôpit. Paris 10, 24–35.

Charcot, J., 1874. Amyotrophies Spinales Deuteropathiques Sclérose Latérale Amyotrophique & Sclérose Latérale Amyotrophique. Bureaux Prog. Méd. 2, 234–266.

Chattopadhyay, M., Valentine, J.S., 2009. Aggregation of copper-zinc superoxide dismutase in familial and sporadic ALS. Antioxid. Redox Signal. 11, 1603–1614.

Cheung, D.S., Warman, M.L., Mulliken, J.B., 1997. Hemangioma in twins. Ann. Plast. Surg. 38, 269–274. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=9088466.

Clemmensen, J., Hjalgrim-Jensen, S., 1980. On the absence of carcinogenicity to man of phenobarbital. In: Coulston, F., Shubick, S. (Eds.), Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis. Alex Pub., pp. 251–265.

Cleveland, D.W., Rothstein, J.D., 2001. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS, nature reviews. Neuroscience 2, 806–819. http://www.ncbi.nlm.nih.gov/pubmed/11715057.

Cohen, P., Coghlan, A., 2001. Secrets of the genome: less is more. New Sci. 169, 6.

Collins, F.S., 2011. Reengineering translational science: the time is right. Sci. Transl. Med. 3, 90cm17. http://stm.sciencemag.org/content/3/90/90cm17.abstract.

Collins, J.M., Mcdevitt, D.G., Shanks, R.G., Swanton, J.G., 1969. The cardio-toxicity of isoprenaline during hypoxia. Br. J. Pharmacol. 36, 35–45. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=5768127.

Cook, N., Jodrell, D.I., Tuveson, D.A., 2012. Predictive in vivo animal models and translation to clinical trials. Drug Discov. Today 17, 253–260.

Corcia, P., Gordon, P.H., 2012. Amyotrophic lateral sclerosis and the clinical potential of dexpramipexole. Ther. Clin. Risk Manag. 8, 359–366.

Corry, D.C., 1952. Pain in carcinoma of the breast. Lancet 1, 274–276. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=14889840.

Couzin, J., 2007. Cancer research. Probing the roots of race and cancer. Science 315, 592–594. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17272699.

Cozzolino, M., Ferri, A., Carri, M.T., 2008. Amyotrophic lateral sclerosis: from current developments in the laboratory to clinical implications. Antioxid. Redox Signal. 10, 405–443. http://www.ncbi.nlm.nih.gov/pubmed/18370853.

Cross-Disorder Group Of The Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. http://linkinghub.elsevier.com/retrieve/pii/s0140673612621291.

Crowley Jr., W.F., 2003. Translation of basic research into useful treatments: how often does it occur? Am. J. Med. 114, 503–505. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=12727585.

Csete, M.E., Doyle, J.C., 2002. Reverse engineering of biological complexity. Science 295, 1664–1669. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=11872830.

CSPI, November 17, 2008. Longer Tests on Lab Animals Urged for Potential Carcinogens. http://www.cspinet.org/new/200811172.html.

Czyz, W., Morahan, J., Ebers, G., Ramagopalan, S., 2012. Genetic, environmental and stochastic factors in monozygotic twin discordance with a focus on epigenetic differences. BMC Med. 10, 93. http://www.biomedcentral.com/1741-7015/10/93.

Daly, A.K., 2010. Genome-wide association studies in pharmacogenomics. Nat. Rev. Genet. 11, 241–246. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=20300088.

Danzeisen, R., Schwalenstoecker, B., Gillardon, F., Buerger, E., Krzykalla, V., Klinder, K., Schild, L., Hengerer, B., Ludolph, A.C., Dorner-Ciossek, C., Kussmaul, L., 2006. Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+)2-amino-4,5,6,7-tetrahydro-6-lpropylamino-benzathiazole dihydrochloride]. J. Pharmacol. Exp. Ther. 316, 189–199. http://www.ncbi.nlm.nih.gov/pubmed/16188953.

Davalos, L.M., Cirranello, A.L., Geisler, J.H., Simmons, N.B., 2012. Understanding phylogenetic incongruence: lessons from phyllostomid bats. Biol. Rev. Camb. Philos. Soc..

Dempster, E.L., Pidsley, R., Schalkwyk, L.C., Owens, S., Georgiades, A., Kane, F., Kalidindi, S., Picchioni, M., Kravariti, E., Toulopoulou, T., Murray, R.M., Mill, J., 2011. Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder. Hum. Mol. Genet. 20, 4786–4796. http://www.ncbi.nlm.nih.gov/pubmed/21908516.

Deng, H.X., Hentati, A., Tainer, J.A., Iqbal, Z., Cayabyab, A., Hung, W.Y., Getzoff, E.D., Hu, P., Herzfeldt, B., Roos, R.P., et al., 1993. Amyotrophic lateral sclerosis and structural defects in Cu, Zn superoxide dismutase. Science 261, 1047–1051. http://www.ncbi.nlm.nih.gov/pubmed/8351519.

Deng, H.X., Shi, Y., Furukawa, Y., Zhai, H., Fu, R., Liu, E., Gorrie, G.H., Khan, M.S., Hung, W.Y., Bigio, E.H., Lukas, T., Dal Canto, M.C., O'Halloran, T.V., Siddique, T., 2006. Conversion to the amyotrophic lateral sclerosis phenotype is associated with intermolecular linked insoluble aggregates of SOD1 in mitochondria. Proc. Natl. Acad. Sci. U S A 103, 7142–7147. http://www.ncbi.nlm.nih.gov/pubmed/16636275.

Devoy, A., Bunton-Stasyshyn, R.K.A., Tybulewicz, V.L.J., Smith, A.J.H., Fisher, E.M.C., 2012. Genomically humanized mice: technologies and promises. Nat. Rev. Genet. 13, 14–20. http://dx.doi.org/10.1038/nrg3116.

Di Carlo, F.J., 1984. Carcinogenesis bioassay data: correlation by species and sex. Drug Metab. Rev. 15, 409–413. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=6489158.

Dias, A.S., Bester, M.J., Britz, R.F., Apostolides, Z., 2006. Animal models used for the evaluation of antiretroviral therapies. Curr. HIV Res. 4, 431–446. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17073618.

Dimasi, J.A., Grabowski, H.G., 2007. Economics of new oncology drug development. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 25, 209–216. http://www.ncbi.nlm.nih.gov/pubmed/17210942.

Dimasi, J.A., Feldman, L., Seckler, A., Wilson, A., 2010. Trends in risks associated with new drug development: success rates for investigational drugs. Clin. Pharmacol. Ther. 87, 272–277. http://www.ncbi.nlm.nih.gov/pubmed/20130567.

Dion, P.A., Daoud, H., Rouleau, G.A., 2009. Genetics of motor neuron disorders: new insights into pathogenic mechanisms. Nat. Rev. Genet. 10, 769–782. http://www.ncbi.nlm.nih.gov/pubmed/19823194.

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

Djinovic Carugo, K., Battistoni, A., Carri, M.T., Polticelli, F., Desideri, A., Rotilio, G., Coda, A., Wilson, K.S., Bolognesi, M., 1996. Three-dimensional structure of xenopus laevis Cu, Zn superoxide dismutase B determined by X-ray crystallography at 1.5 A resolution. Acta Crystallogr. Sect. D, Biol. Crystallogr. 52, 176–188. http://www.ncbi.nlm.nih.gov/pubmed/15299740.

Djinovic, K., Gatti, G., Coda, A., Antolini, L., Pelosi, G., Desideri, A., Falconi, M., Marmocchi, F., Rotilio, G., Bolognesi, M., 1992. Crystal structure of yeast Cu/Zn superoxide dismutase. Crystallographic refinement at 2.5 A resolution. J. Mol. Biol. 225, 791–809. http://www.ncbi.nlm.nih.gov/pubmed/1602482.

Dobzhansky, T., 1973. Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. 35, 125–129.

Dolgin, E., 2010. Big pharma moves from 'blockbusters' to 'niche busters'. Nat. Med. 16, 837. http://dx.doi.org/10.1038/nm0810-837a.

Drake III, D.R., Singh, I., Nguyen, M.N., Kachurin, A., Wittman, V., Parkhill, R., Kachurina, O., Moser, J.M., Burdin, N., Moreau, M., Mistretta, N., Byers, A.M., Dhir, V., Tapia, T.M., Vernhes, C., Gangur, J., Kamala, T., Swaminathan, N., Warren, W.L., 2012. In vitro biomimetic model of the human immune system for predictive vaccine assessments. Disruptive Sci. Technol. 1, 28–40.

Durrive, B., 2012. Scientific progress specific to biology: an epistemological overview. Prog. Biophys. Mol. Biol. 110, 17–23. http://www.ncbi.nlm.nih.gov/pubmed/22543274.

Dybing, E., Sanner, T., 1999. Species differences in chemical carcinogenesis of the thyroid gland, kidney and urinary bladder. IARC Sci. Publ., 15–32. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=10457907.

Dolgin, E., 2013. Animal rule for drug approval creates a jungle of confusion. Nat Med. 19, 118–119. http://www.ncbi.nlm.nih.gov/pubmed/23389593.

Eason, C.T., Bonner, F.W., Parke, D.V., 1990. The importance of pharmacokinetic and receptor studies in drug safety evaluation. Regul. Toxicol. Pharmacol. 11, 288–307. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=2196638.

Editorial, 2003. Follow the yellow brick road. Nat. Rev. Drug Discov. 2, 167. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=12619635.

Editorial, 2006. The end of the beginning? Nat. Rev. Drug Discov. 5, 705. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17001798.

Editorial, 2007. Same old story? Nat. Rev. Drug Discov. 6, 97. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17342859.

Editorial, 2009. A slippery slope. Nature 462, 699.

Editorial, 2011a. Cancer drugs: remedy required. Nat. Med. 17, 231. http://dx.doi.org/10.1038/nm0311-231.

Editorial, 2011b. A stronger role for science. Nat. Rev. Drug Discov. 10, 159. http://www.ncbi.nlm.nih.gov/pubmed/21469392.

Editors, 2011. Nat Rev Drug Discov. 10, 239. http://dx.doi.org/10.1038/nrd3411, in this issue.

Elowitz, M.B., Levine, A.J., Siggia, E.D., Swain, P.S., 2002. Stochastic gene expression in a single cell. Science 297, 1183–1186. http://www.ncbi.nlm.nih.gov/pubmed/12183631.

Ennever, F.K., Noonan, T.J., Rosenkranz, H.S., 1987. The predictivity of animal bioassays and short-term genotoxicity tests for carcinogenicity and non-carcinogenicity to humans. Mutagenesis 2, 73–78. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=3331705.

FDA, 2004. Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products. http://www.Nipte.Org/Docs/Critical_Path.Pdf.

FDA, March 7, 2006. FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient. June 18, 2009. http://www.fda.gov/newsevents/newsroom/pressannouncements/2006/ucm108576.htm.

Flaherty, K.T., Puzanov, I., Kim, K.B., Ribas, A., Mcarthur, G.A., Sosman, J.A., O'Dwyer, P.J., Lee, R.J., Grippo, J.F., Nolop, K., Chapman, P.B., 2010. Inhibition of mutated, activated BRAF in metastatic melanoma. N. Engl. J. Med. 363, 809–819. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=20818844.

Fletcher, A.P., 1978. Drug safety tests and subsequent clinical experience. J. R. Soc. Med. 71, 693–696. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=712750.

Flintoft, L., 2005. Epigenetics: identical twins: epigenetics makes the difference. Nat. Rev. Genet. 6, 667.

Fomchenko, E.I., Holland, E.C., 2006. Mouse models of brain tumors and their applications in preclinical trials. Clin. Cancer Res. 12, 5288–5297. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17000661.

Force, T., Kolaja, K.L., 2011. Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes. Nat. Rev. Drug Discov. 10, 111–126. http://dx.doi.org/10.1038/Nrd3252.

Fox, J.G., Thibert, P., Arnold, D.L., Krewski, D.R., Grice, H.C., 1979. Toxicology studies. II. The laboratory animal. Food Cosmet. Toxicol. 17, 661–675. http://www.ncbi.

nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=546701.
Fraga, M.F., Ballestar, E., Paz, M.F., Ropero, S., Setien, F., Ballestar, M.L., Heine-Suner, D., Cigudosa, J.C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aguilera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T.D., Wu, Y.Z., Plass, C., Esteller, M., 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proc. Natl. Acad. Sci. U S A 102, 10604–10609. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=16009939.
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., Kahn, R.S., 2011. Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 50, 1129–1139.E2. http://linkinghub.elsevier.com/retrieve/pii/s0890856711006897?showall=true.
Gad, S., 2006. Model selection and scaling. In: Gad, S. (Ed.), Animal Models in Toxicology, Second ed. Informa Healthcare, pp. 831–862. Drug And Chemical Toxicology.
Gad, S., 2007. Preface. In: Gad, S. (Ed.), Animal Models in Toxicology. CRC Press, Boca Raton, pp. 1–18.
Gare, A., 2013. Overcoming the Newtonian paradigm: the unfinished project of theoretical biology from a Schellingian perspective. Prog. Biophys. Mol. Biol.. http://www.ncbi.nlm.nih.gov/pubmed/23562477.
Gibbs, R.A., Rogers, J., Katze, M.G., Bumgarner, R., Weinstock, G.M., Mardis, E.R., Remington, K.A., Strausberg, R.L., Venter, J.C., Wilson, R.K., Batzer, M.A., Bustamante, C.D., Eichler, E.E., Hahn, M.W., Hardison, R.C., Makova, K.D., Miller, W., Milosavljevic, A., Palermo, R.E., Siepel, A., Sikela, J.M., Attaway, T., Bell, S., Bernard, K.E., Buhay, C.J., Chandrabose, M.N., Dao, M., Davis, C., Delehaunty, K.D., Ding, Y., Dinh, H.H., Dugan-Rocha, S., Fulton, L.A., Gabisi, R.A., Garner, T.T., Godfrey, J., Hawes, A.C., Hernandez, J., Hines, S., Holder, M., Hume, J., Jhangiani, S.N., Joshi, V., Khan, Z.M., Kirkness, E.F., Cree, A., Fowler, R.G., Lee, S., Lewis, L.R., Li, Z., Liu, Y.S., Moore, S.M., Muzny, D., Nazareth, L.V., Ngo, D.N., Okwuonu, G.O., Pai, G., Parker, D., Paul, H.A., Pfannkoch, C., Pohl, C.S., Rogers, Y.H., Ruiz, S.J., Sabo, A., Santibanez, J., Schneider, B.W., Smith, S.M., Sodergren, E., Svatek, A.F., Utterback, T.R., Vattathil, S., Warren, W., White, C.S., Chinwalla, A.T., Feng, Y., Halpern, A.L., Hillier, L.W., Huang, X., Minx, P., Nelson, J.O., Pepin, K.H., Qin, X., Sutton, G.G., Venter, E., Walenz, B.P., Wallis, J.W., Worley, K.C., Yang, S.P., Jones, S.M., Marra, M.A., Rocchi, M., Schein, J.E., Baertsch, R., Clarke, L., Csuros, M., Glasscock, J., Harris, R.A., Havlak, P., Jackson, A.R., Jiang, H., et al., 2007. Evolutionary and biomedical insights from the Rhesus macaque genome. Science 316, 222–234. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17431167.
Gibson, E., May 1, 2012. Q&A: Dr. Keith Cheng, Researcher at Penn State's College of Medicine, Shares Views on Using Animals in Scientific Research. April 22. http://www.pennlive.com/midstate/index.ssf/2012/04/qa_dr_keith_cheng_researcher_a.html.
Giles, J., 2006. Animal experiments under fire for poor design. Nature 444, 981. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17183281.
Gonzalez, F.J., Idle, J.R., 1994. Pharmacogenetic phenotyping and genotyping. Present status and future potential. Clin. Pharmacokinet. 26, 59–70. http://www.ncbi.nlm.nih.gov/pubmed/8137598.
Goodlett, C.R., 2003. Testing Fasd Therapeutic Agents: Neonatal Rodent Models. Indiana Univ-Purdue Univ at Indianapolis, 1U01AA014829-01. http://projectreporter.nih.gov/project_info_description.cfm?aid=6743827&icde=15324375&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=asc.
Goodwin, B., 2001. How the Leopard Changed Its Spots: the Evolution of Complexity. Princeton University Press, Princeton.
Gordon, L., Joo, J.H., Andronikos, R., Ollikainen, M., Wallace, E.M., Umstad, M.P., Permezel, M., Oshlack, A., Morley, R., Carlin, J.B., Saffery, R., Smyth, G.K., Craig, J.M., 2011. Expression discordance of monozygotic twins at birth: effect of intrauterine environment and a possible mechanism for fetal programming. Epigenetics 6, 579–592.
Gosden, R.G., Feinberg, A.P., 2007. Genetics and epigenetics – nature's pen-and-pencil set. N. Engl. J. Med. 356, 731–733. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=17301306.
Gould, S., February 21, 2001. Humbled by the Genome's Mysteries. New York Times.
Greek, R., 2008. Letter. Dogs, genes and drugs. Am. Scientist 96, 4.
Greek, R., 2012. Animal models and the development of an HIV vaccine. J. AIDS Clinic Res.. S8:001.
Greek, R., 2013a. Animal models in drug development. In: Gowder, S. (Ed.), New Insights into Toxicity and Drug Testing. Intech, Manhattan, pp. 124–152.
Greek, R., 2013b. Animal models of cancer. In: Light of Evolutionary Biology and Complexity Science, the Research and Biology of Cancer. Iconcept Press, Hong Kong.
Greek, J., Greek, R., 2004. What Will We Do if We Don't Experiment on Animals? Trafford.
Greek, R., Greek, J., 2010. Is the use of sentient animals in basic research justifiable? Philos. Ethics Humanit. Med. 5, 14. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&dopt=citation&list_uids=20825676.
Greek, R., Hansen, L.A., 2012. The development of deep brain stimulation for movement disorders. J. Clinic Res. Bioeth. 3.
Greek, R., Pound, P., 2002. Animal studies and HIV research. BMJ 324, 236–237.
Greek, R., Rice, M.J., 2012. Animal models and conserved processes. Theor. Biol. Med. Model. 9. http://www.tbiomed.com/content/9/1/40/abstract.
Greek, R., Shanks, N., 2009. Faqs about the use of animals. In: Science: a Handbook for the Scientifically Perplexed. University Press Of America, Lanham.
Greek, R., Shanks, N., 2011. Complex systems, evolution, and animal models. Stud. Hist. Philos. Biol. Biomed. Sci. 42, 542–544. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22035727.
Greek, R., Hansen, L.A., Menache, A., 2011a. An analysis of the Bateson review of research using nonhuman primates. Medicolegal Bioeth. 1, 3–22. Http://www.Dovepress.Com/An-Analysis-Of-The-Bateson-Review-Of-Research-Using-Non human-Primates-Peer-Reviewed-Article-MB.
Greek, R., Shanks, N., Rice, M.J., 2011b. The history and implications of testing thalidomide on animals. J. Philos. Sci. Law 11. http://www6.Miami.Edu/Ethics/Jpsl/Archives/All/Testingthalidomide.Html.
Greek, R., Menache, A., Rice, M.J., 2012a. Animal models in an age of personalized medicine. Personalized Med. 9, 47–64. http://dx.doi.org/10.2217/pme.11.89.
Greek, R., Pippus, A., Hansen, L.A., 2012b. The Nuremberg code subverts human health and safety by requiring animal modeling. BMC Med. Ethics 13, 16. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22769234.
Gregor, Z., Joffe, L., 1978. Senile macular changes in the Black African. Br. J. Ophthalmol. 62, 547–550. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=687553.
Gross, D.R., 1985. Animal Models in Cardiovascular Research. Martinus Nijhoff, The Hague.
Grove, A.S., 2005. Efficiency in the health care industries: a view from the outside. JAMA 294, 490–492. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16046656.
Gur Barzilai, M., Reitzel, A.M., Kraus, J.E.M., Gordon, D., Technau, U., Gurevitz, M., Moran, Y., 2012. Convergent evolution of sodium ion selectivity in metazoan neuronal signaling. Cell Rep.. http://Linkinghub.Elsevier.Com/Retrieve/Pii/S2211124712001908.
Gura, T., 1997. Cancer models: systems for identifying new drugs are often faulty. Science 278, 1041–1042. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=9381203.
Gurney, M.E., Pu, H., Chiu, A.Y., Dal Canto, M.C., Polchow, C.Y., Alexander, D.D., Caliendo, J., Hentati, A., Kwon, Y.W., Deng, H.X., et al., 1994. Motor neuron degeneration in mice that express a human Cu/Zn superoxide dismutase mutation. Science 264, 1772–1775. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/8209258.
Habeck, M., 2002. Of mice and men, and cancer research. Drug Discov. Today 7, 981–982.
Hahn, W.C., Weinberg, R.A., 2002. Modelling the molecular circuitry of cancer. Nat. Rev. Cancer 2, 331–341. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=12044009.
Haiman, C.A., Stram, D.O., Wilkens, L.R., Pike, M.C., Kolonel, L.N., Henderson, B.E., Le Marchand, L., 2006. Ethnic and racial differences in the smoking-related risk of lung cancer. N. Engl. J. Med. 354, 333–342. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16436765.
Hakeem, A.Y., Sherwood, C.C., Bonar, C.J., Butti, C., Hof, P.R., Allman, J.M., 2009. Von economo neurons in the elephant brain. Anat. Rec. 292, 242–248. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/19089889.
Halder, A., Jain, M., Chaudhary, I., Varma, B., 2012. Chromosome 22q11.2 microdeletion in monozygotic twins with discordant phenotype and deletion size. Mol. Cytogenet. 5, 13. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22413934.
Hart, P.J., Balbirnie, M.M., Ogihara, N.L., Nersissian, A.M., Weiss, M.S., Valentine, J.S., Eisenberg, D., 1999. A structure-based mechanism for copper–zinc superoxide dismutase. Biochemistry 38, 2167–2178. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/10026301.
t Hart, B.A., Abbott, D.H., Nakamura, K., Fuchs, E., 2012. The Marmoset monkey: a multi-purpose preclinical and translational model of human biology and disease. Drug Discov. Today 17, 1160–1165. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22728226.
Hau, J., 2003. Animal models. In: Hau, J., Van Hoosier Jr., G.K. (Eds.), Handbook of Laboratory Animal Science, second ed., Animal Models CRC Press, Boca Raton, pp. 1–9.
Health Day, 11/13/2008. Hormone Lowers Glucose Levels in Mice. http://www.Healthday.Com/Article.Asp?AID=620987.
Heng, H.H., 2008. The conflict between complex systems and reductionism. JAMA: J. Am. Med. Assoc. 300, 1580–1581. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/18827215.
Herndon, C.N., Jennings, R.G., 1951. A twin-family study of susceptibility to poliomyelitis. Am. J. Hum. Genet. 3, 17–46. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/13171372.
Heywood, R., 1990. Clinical toxicity – could it have been predicted? Post-marketing experience. In: Lumley, C.E., Walker, S. (Eds.), Animal Toxicity Studies: Their Relevance for Man. Quay, Lancaster, pp. 57–67.
Hirtz, D., Thurman, D.J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A.R., Zalutsky, R., 2007. How common are the "Common" neurologic disorders? Neurology 68, 326–337. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/17261678.
Hitchens, C., 2003. Mommie Dearest. http://www.Slate.Com/Articles/News_And_Politics/Fighting_Words/2003/10/Mommie_Dearest.Html.
Hochachka, P.W., Somero, G.N., 2002. Biochemical Adaptation: Mechanism and Process in Physiological Evolution. Oxford University Press, Oxford.
Hodgkin, J., 1998. Seven types of pleiotropy. Int. J. Dev. Biol. 42, 501–505. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=9654038.

Hof, P.R., Van Der Gucht, E., 2007. Structure of the cerebral cortex of the humpback whale, Megaptera Novaeangliae (Cetacea, Mysticeti, Balaenopteridae). Anat. Rec. 290, 1–31. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/17441195.

Holden, C., 2005. Sex and the suffering brain. Science 308, 1574. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15947170.

Holden, C., 2006. Random samples. Well-wired whales. Science 314, 1363.

Holmes, B., 2007. Monkey genome springs surprise for human origins. New Scientist 15.

Horgan, J.F., 1995. From complexity to perplexity. Scientific Am., 104–109.

Horrobin, D.F., 2003. Modern biomedical research: an internally self-consistent universe with little contact with medical reality? Nat. Rev. Drug Discov. 2, 151–154. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=12563306.

Hudson, K.L., 2011. Genomics, health care, and society. N. Engl. J. Med. 365, 1033–1041. http://www.Nejm.Org/Doi/Full/10.1056/Nejmra1010517.

Huff, J., Jacobson, M.F., Davis, D.L., 2008. The limits of two-year bioassay exposure regimens for identifying chemical carcinogens. Environ. Health Perspect. 116, 1439–1442. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=19057693.

Hughes, B., 2008. Industry concern over EU hepatotoxicity guidance. Nat. Rev. Drug Discov. 7, 719. http://dx.doi.org/10.1038/Nrd2677.

Hughes, A.R., Spreen, W.R., Mosteller, M., Warren, L.L., Lai, E.H., Brothers, C.H., Cox, C., Nelsen, A.J., Hughes, S., Thorborn, D.E., Stancil, B., Hetherington, S.V., Burns, D.K., Roses, A.D., 2008. Pharmacogenetics of hypersensitivity to Abacavir: from Pgx hypothesis to confirmation to clinical utility. Pharmacogenomics J. 8, 365–374. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=18332899.

Hurko, O., 2006. Understanding the strategic importance of biomarkers for the discovery and early development phases. Drug Discov. World, 63–74.

Inman, W.H., 1980. Monitoring for Drug Safety. MTP Press.

Jaarsma, D., Teuling, E., Haasdijk, E.D., De Zeeuw, C.I., Hoogenraad, C.C., 2008. Neuron-specific expression of mutant superoxide dismutase is sufficient to induce amyotrophic lateral sclerosis in transgenic mice. J. Neurosci.: Off. J. Soc. Neurosci. 28, 2075–2088. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/18305242.

Javierre, B.M., Fernandez, A.F., Richter, J., Al-Shahrour, F., Martin-Subero, J.I., Rodriguez-Ubreva, J., Berdasco, M., Fraga, M.F., O'Hanlon, T.P., Rider, L.G., Jacinto, F.V., Lopez-Longo, F.J., Dopazo, J., Forn, M., Peinado, M.A., Carreno, L., Sawalha, A.H., Harley, J.B., Siebert, R., Esteller, M., Miller, F.W., Ballestar, E., 2010a. Changes in the pattern of DNA methylation associate with twin discordance in Systemic lupus erythematosus. Genome Res. 20, 170–179. http://Genome.Cshlp.Org/Content/20/2/170.Abstract.

Javierre, B.M., Fernandez, A.F., Richter, J., Al-Shahrour, F., Martin-Subero, J.I., Rodriguez-Ubreva, J., Berdasco, M., Fraga, M.F., O'Hanlon, T.P., Rider, L.G., Jacinto, F.V., Lopez-Longo, F.J., Dopazo, J., Forn, M., Peinado, M.A., Carreno, L., Sawalha, A.H., Harley, J.B., Siebert, R., Esteller, M., Miller, F.W., Ballestar, E., 2010b. Changes in the pattern of DNA methylation associate with twin discordance in Systemic lupus erythematosus. Genome Res. 20, 170–179. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=20028698.

Jeffrey, S., February 16, 2013. Dexpramipexole Fails in Als. January 4, 2013. http://www.Medscape.Com/Viewarticle/777141.

Johnson, J.I., Decker, S., Zaharevitz, D., Rubinstein, L.V., Venditti, J.M., Schepartz, S., Kalyandrug, S., Christian, M., Arbuck, S., Hollingshead, M., Sausville, E.A., 2001. Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. Br. J. Cancer 84, 1424–1431. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=11355958.

Joyce, P.I., Fratta, P., Fisher, E.M., Acevedo-Arozena, A., 2011. SOD1 and TDP-43 animal models of amyotrophic lateral sclerosis: recent advances in understanding disease toward the development of clinical treatments. Mamm. Genome Off. J. Int. Mamm. Genome Soc. 22, 420–448. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/21706386.

Jørgensen, J.T., 2011. A challenging drug development process in the era of personalized medicine. Drug Discov. Today 16, 891–897.

Kaiser, J., 2005. Gender in the pharmacy: does it matter? Science 308, 1572. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15947169.

Kalow, W., 1991. Interethnic variation of drug metabolism. Trends Pharmacol. Sci. 12, 102–107. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/2053186.

Kamb, A., 2005. What's wrong with our cancer models? Nat. Rev. Drug Discov. 4, 161–165. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15688078.

Kastens, K.A., Manduca, C.A., Cervato, C., Frodeman, R., Goodwin, C., Liben, L.S., Mogk, D.W., Spangler, T.C., Stillings, N.A., Titus, S., 2009. How geoscientists think and learn. EOS Trans. AGU 90. http://dx.doi.org/10.1029/2009EO310001.

Kato, S., 2008. Amyotrophic lateral sclerosis models and human neuropathology: similarities and differences. Acta Neuropathol. 115, 97–114. http://dx.doi.org/10.1007/S00401-007-0308-4.

Kenny, E.E., Timpson, N.J., Sikora, M., Yee, M.-C., Moreno-Estrada, A.S., Eng, C., Huntsman, S., Burchard, E.G.L., Stoneking, M., Bustamante, C.D., Myles, S., 2012. Melanesian Blond hair is caused by an amino acid change in TYRP1. Science 336, 554. http://www.Sciencemag.Org/Content/336/6081/554.Abstract.

Kirschner, M.W., Gerhart, J.C., 2006. The Plausibility of Life. Yale University Press, New Haven.

Kitano, H., 2002a. Computational systems biology. Nature 420, 206–210. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=12432404.

Kitano, H., 2002b. Systems biology: a brief overview. Science 295, 1662–1664. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=11872829.

Kitano, H., 2007. A robustness-based approach to systems-oriented drug design. Nat. Rev. Drug Discov. 6, 202–210. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17318209.

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

Kleinman, C., October 2, 1997. Of Mice and Mandates. http://www.Acsh.Org/Wp-Content/Uploads/2012/04/20040329_Mice.Pdf.

Koch, C., 2012. Systems biology. Modular biological complexity. Science 337, 531–532. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22859475.

Kola, I., Landis, J., 2004. Can the pharmaceutical industry reduce attrition rates? Nat. Rev. Drug Discov. 3, 711–715. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15286737.

Kolata, G., February 16, 2013. Mice Fall Short as Test Subjects for Humans' Deadly Ills. February 11, 2013. http://www.Nytimes.Com/2013/02/12/Science/Testing-Of-Some-Deadly-Diseases-On-Mice-Mislead-Report-Says.Html.

Kopp, J.B., Nelson, G.W., Sampath, K., Johnson, R.C., Genovese, G., An, P., Friedman, D., Briggs, W., Dart, R., Korbet, S., Mokrzycki, M.H., Kimmel, P.L., Limou, S., Ahuja, T.S., Berns, J.S., Fryc, J., Simon, E.E., Smith, M.C., Trachtman, H., Michel, D.M., Schelling, J.R., Vlahov, D., Pollak, M., Winkler, C.A., 2011. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J. Am. Soc. Nephrol. 22, 2129–2137. http://Jasn.Asnjournals.Org/Content/Early/2011/10/06/ASN.2011040388.Abstract.

Kummar, S., Kinders, R., Rubinstein, L., Parchment, R.E., Murgo, A.J., Collins, J., Pickeral, O., Low, J., Steinberg, S.M., Gutierrez, M., Yang, S., Helman, L., Wiltrout, R., Tomaszewski, J.E., Doroshow, J.H., 2007. Compressing drug development timelines in oncology using phase '0' trials. Nat. Rev. Cancer 7, 131–139. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/17251919.

Kupiec, J.J., 2010. On the lack of specificity of proteins and its consequences for a theory of biological organization. Prog. Biophys. Mol. Biol. 102, 45–52. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/19917305.

Kurakin, A., 2005. Self-organization vs watchmaker: stochastic gene expression and cell differentiation. Dev. Genes Evol. 215, 46–52. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/15645318.

Lafollette, H., Shanks, N., 1996. Brute Science: Dilemmas of Animal Experimentation. Routledge, London and New York.

Lambrechts, D., Poesen, K., Fernandez-Santiago, R., Al-Chalabi, A., Del Bo, R., Van Vught, P.W., Khan, S., Marklund, S.L., Brockington, A., Van Marion, I., Anneser, J., Shaw, C., Ludolph, A.C., Leigh, N.P., Comi, G.P., Gasser, T., Shaw, P.J., Morrison, K.E., Andersen, P.M., Van Den Berg, L.H., Thijs, V., Siddique, T., Robberecht, W., Carmeliet, P., 2009. Meta-analysis of vascular endothelial growth factor variations in amyotrophic lateral sclerosis: increased susceptibility in male carriers of the -2578AA genotype. J. Med. Genet. 46, 840–846. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/18413368.

Lazzarini, L., Overgaard, K.A., Conti, E., Shirtliff, M.E., 2006. Experimental osteomyelitis: what have we learned from animal studies about the systemic treatment of osteomyelitis? J. Chemother. 18, 451–460. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17127219.

Leaf, C., 2004. Why we are losing the war on cancer. Fortune, 77–92. http://Money.Cnn.Com/Magazines/Fortune/Fortune_Archive/2004/03/22/365076/Index.Htm.

Lewin, R., 1999. Complexity: Life at the Edge of Chaos. The University Of Chicago Press, Chicago.

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., Hsu, L.C., 1989. Hepatitis B virus markers in Chinese twins. Anticancer Res. 9, 737–741. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/2764519.

Lippman, N., Stein, K.M., Lerman, B.B., 1995. Nonlinear forecasting and the dynamics of cardiac rhythm. J. Electrocardiol. 28 (Suppl.), 65–70. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/8656131.

Litchfield Jr., J.T., 1962. Symposium on clinical drug evaluation and human pharmacology. XVI. Evaluation of the safety of new drugs by means of tests in animals. Clin. Pharmacol. Ther. 3, 665–672. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14465857.

Litchfield Jr., J.T., 1965. Predictability of conventional animal toxicity tests. Ann. N. Y. Acad. Sci. 123, 268–272. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14329209.

Lombardi, F., 2000. Chaos theory, heart rate variability, and arrhythmic mortality. Circulation 101, 8–10. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/10618296.

Lowe, C.B., Kellis, M., Siepel, A., Raney, B.J., Clamp, M., Salama, S.R., Kingsley, D.M., Lindblad-Toh, K., Haussler, D., 2011. Three periods of regulatory innovation during vertebrate evolution. Science 333, 1019–1024. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/21852499.

Lumley, C., 1990. Clinical toxicity: could it have been predicted? Premarketing experience. In: Lumley, C., Walker, S. (Eds.), Animal Toxicity Studies: Their Relevance for Man. Quay, London, pp. 49–56.

Luttge, U., 2012. Modularity and emergence: biology's challenge in understanding life. Plant Biol. 14, 865–871. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23016697.

Mahmood, I., 2000. Can absolute oral bioavailability in humans be predicted from animals? A comparison of allometry and different indirect methods. Drug Metab. Drug Interact. 16, 143–155. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=10962646.

Maiti, S., Kumar, K.H.B.G., Castellani, C.A., O'Reilly, R., 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, E17125. http://dx.doi.org/10.1371%2Fjournal.Pone.0017125.
Mancuso, R., Olivan, S., Mancera, P., Pasten-Zamorano, A., Manzano, R., Casas, C., Osta, R., Navarro, X., 2012. Effect of genetic background on onset and disease progression in the SOD1-G93A model of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Motor Neuron Dis. 13, 302–310. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22424126.
Manson, S.M., 2001. Simplifying complexity: a review of complexity theory. Geoforum 32, 405–414.
Manson, J., Wise, D., 1993. Teratogens, Casarett and Doull's Toxicology, p. 228.
Markou, A., Chiamulera, C., Geyer, M.A., Tricklebank, M., Steckler, T., 2009. Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 34, 74–89. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/18830240.
Marsoni, S., Hoth, D., Simon, R., Leyland-Jones, B., De Rosa, M., Wittes, R.E., 1987. Clinical drug development: an analysis of Phase II trials, 1970–1985. Cancer Treat. Rep. 71, 71–80. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=3791270.
Matsumoto, S., Kusaka, H., Ito, H., Shibata, N., Asayama, T., Imai, T., 1996. Sporadic amyotrophic lateral sclerosis with dementia and Cu/Zn superoxide dismutase-positive Lewy body-like inclusions. Clin. Neuropathol. 15, 41–46. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/8998856.
Mayr, E., 1998. This is Biology: the Science of the Living World. Belknap Press.
Mayr, E., 2002. What Evolution is. Basic Books, New York.
Mazzocchi, F., 2012. Complexity and the reductionism–holism debate in systems biology. Wiley Interdiscip. Rev. Syst. Biol. Med. 4, 413–427. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22761024.
Mclean, C.Y., Reno, P.L., Pollen, A.A., Bassan, A.I., Capellini, T.D., Guenther, C., Indjeian, V.B., Lim, X., Menke, D.B., Schaar, B.T., Wenger, A.M., Bejerano, G., Kingsley, D.M., 2011. Human-specific loss of regulatory DNA and the evolution of human-specific traits. Nature 471, 216–219. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=21390129.
M.E., 2010. Models that better mimic human cancer. Nature Biotechnology 28, vii, in this issue.
Melham, T., 2012. Modelling, abstraction, and computation in systems biology: a view from computer science. Prog. Biophys. Mol. Biol.. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22975313.
Melham, T., Bard, J., Werner, E., Noble, D., 2012. Conceptual foundations of systems biology. Prog. Biophys. Mol. Biol.. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23200782.
Meyer, U.A., 1990. Genetic polymorphisms of drug metabolism. Fundam. Clin. Pharmacol. 4, 595–615. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/1982880.
Meymandi, A., 2010. The science of epigenetics. Psychiatry (Edgmont) 7, 40–41. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=20436775.
Millan, M.J., Agid, Y., Brune, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., Derubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joels, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22293568.
Miquel, P.A., 2011. Extended physics as a theoretical framework for systems biology? Prog. Biophys. Mol. Biol. 106, 348–352. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/21463648.
Misch, E.A., Berrington, W.R., Vary Jr., J.C., Hawn, T.R., 2010. Leprosy and the human genome. Microbiol. Mol. Biol. Rev. MMBR 74, 589–620. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/21119019.
Morange, M., 2001. A successful form for reductionism. The Biochemist 23, 37–39.
Morgan, P., Graaf, P.H.V.D., Arrowsmith, J., Feltner, D.E., Drummond, K.S., Wegner, C.D., Street, S.D.A., 2012. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving phase II survival. Drug Discov. Today 17, 419–424.
Moss, L., 2006. The question of questions: what is a gene? Comments on Rolston and Griffiths & Stotz. Theor. Med. Bioeth. 27, 523–534. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/17139449.
Mueller, G.B., Olsson, L., 2003. Epigenesis and epigenetics. In: Hall, B.K., Olson, W.M. (Eds.), Keywords and Concepts in Evolutionary Developmental Biology. Harvard University Press, p. 120.
Mullard, A., 2011. Marc Kirschner. Nat. Rev. Drug Discov. 10, 894. http://dx.doi.org/10.1038/Nrd3613.
Muqit, M.M., Larner, A.J., Sweeney, M.G., Sewry, C., Stinton, V.J., Davis, M.B., Healy, D.G., Payne, S.J., Chotai, K., Wood, N.W., Lane, R.J., 2008. Multiple mitochondrial DNA deletions in monozygotic twins with OPMD. J. Neurol. Neurosurg. Psychiatry 79, 68–71.
Nakajima, T., 2013. Probability in biology: overview of a comprehensive theory of probability in living systems. Prog. Biophys. Mol. Biol.. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23562914.
Nebert, D., 1997. Pharmacogenetics: 65 candles on the cake. Pharmacogenetics 7, 435–440.
Nebert, D.W., Ingelman-Sundberg, M., Daly, A.K., 1999. Genetic epidemiology of environmental toxicity and cancer susceptibility: human allelic polymorphisms in drug-metabolizing enzyme genes, their Functional importance, and nomenclature issues. Drug Metab. Rev. 31, 467–487. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/10335448.
News & Analysis, 2011. News in brief. Nat. Rev. Drug Discov. 10, 889. http://dx.doi.org/10.1038/Nrd3609.
Nicolis, G., Prigogine, I., 1977. Self-organisation in Nonequilibrium Systems: from Dissipative Structures to Order through Fluctuations. John Wiley & Sons, New York.
Nirmalananthan, N., Greensmith, L., 2005. Amyotrophic lateral sclerosis: recent advances and future therapies. Curr. Opin. Neurol. 18, 712–719. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/16280684.
Noble, D., 2001. From genes to whole organs: connecting biochemistry to physiology. Novartis Found. Symp. 239, 111–123. Discussion 123-8, 150-9. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=11529307.
Noble, D., 2008. Genes and causation. Philos. Transact. A Math. Phys. Eng. Sci. 366, 3001–3015. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=18559318.
Northrop, R.B., 2011. Introduction to Complexity and Complex Systems. CRC Press, Boca Raton.
Novella, S., 2011. Connectomics. http://Theness.Com/Neurologicablog/Index.Php/Connectomics/.
Novella, S., 2013a. Mouse Models of Sepsis Challenged. http://www.Sciencebasedmedicine.Org/Index.Php/Mouse-Model-Of-Sepsis-Challenged/.
Novella, S., 2013b. The Skeptics Guide to the Universe. #395. February 9, 2013. http://www.Theskepticsguide.Org/Archive/Podcastinfo.Aspx?Mid=1&Pid=395.
Novikoff, A.B., 1945. The concept of integrative levels and biology. Science 101, 209–215. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17814095.
News, 2012. Focus on sepsis. Nat Med. 18, 997. http://dx.doi.org/10.1038/nm0712-997.
O'Collins, V.E., Macleod, M.R., Donnan, G.A., Horky, L.L., Van Der Worp, B.H., Howells, D.W., 2006. 1026 experimental treatments in acute stroke. Ann. Neurol. 59, 467–477. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16453316.
Ogihara, N.L., Parge, H.E., Hart, P.J., Weiss, M.S., Goto, J.J., Crane, B.R., Tsang, J., Slater, K., Roe, J.A., Valentine, J.S., Eisenberg, D., Tainer, J.A., 1996. Unusual trigonal–planar copper configuration revealed in the atomic structure of yeast copper–zinc superoxide dismutase. Biochemistry 35, 2316–2321. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/8652572.
Ollikainen, M., Craig, J.M., 2011. Epigenetic discordance at imprinting control regions in twins. Epigenomics 3, 295–306.
Orac, 2010. Answering "Scientific" Arguments of Animal Rights Extremists. http://Scienceblogs.Com/Insolence/2010/03/Answering_Scientific_Arguments_Of_An.Php?Utm_Source=Networkbanner&Utm_Medium=Link. http://Scienceblogs.Com/Insolence/2010/03/Answering_Scientific_Arguments_Of_An.Php?Utm_Source=Networkbanner&Utm_Medium=Link.
Oreskes, N., Conway, E.M.M., 2011. Merchants of Doubt. How a Handful of Scientists Obscrued the Truth on Issues from Tobacco Smoke to Global Warming. Bloomsbury Press, New York.
Ottino, J.M., 2004. Engineering complex systems. Nature 427, 399. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14749808.
Pan, L., Yoshii, Y., Otomo, A., Ogawa, H., Iwasaki, Y., Shang, H.F., Hadano, S., 2012. Different human copper-zinc superoxide dismutase mutants, SOD1G93A and SOD1H46R, exert distinct harmful effects on gross phenotype in mice. Plos ONE 7, E33409. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22438926.
Pankevich, D.E., Wizemann, T.M., Altevogt, B.M., 2013. Improving the Utility and Translation of Animal Models for Nervous System Disorders: Workshop Summary. National Academies Press, Washington DC.
Parge, H.E., Hallewell, R.A., Tainer, J.A., 1992. Atomic structures of wild-type and thermostable mutant recombinant human Cu, Zn superoxide dismutase. Proc. Natl. Acad. Sci. U S A 89, 6109–6113. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/1463506.
Park, B.K., Boobis, A., Clarke, S., Goldring, C.E.P., Jones, D., Kenna, J.G., Lambert, C., Laverty, H.G., Naisbitt, D.J., Nelson, S., Nicoll-Griffith, D.A., Obach, R.S., Routledge, P., Smith, D.A., Tweedie, D.J., Vermeulen, N., Williams, D.P., Wilson, I.D., Baillie, T.A., 2011. Managing the challenge of chemically reactive metabolites in drug development. Nat. Rev. Drug Discov. 10, 292–306. http://dx.doi.org/10.1038/Nrd3408.
Parkinson, C., Grasso, P., 1993. The use of the dog in toxicity tests on pharmaceutical compounds. Hum. Exp. Toxicol. 12, 99–109. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=8096722.
Paul, J.R., 1971. A History of Poliomyelitis. Yale University Press, New Haven.
Paul, S.M., Mytelka, D.S., Dunwiddie, C.T., Persinger, C.C., Munos, B.H., Lindborg, S.R., Schacht, A.L., 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat. Rev. Drug Discov. 9, 203–214. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=20168317.
Paxton, J.W., 1995. The allometric approach for interspecies scaling of pharmacokinetics and toxicity of anti-cancer drugs. Clin. Exp. Pharmacol. Physiol. 22, 851–854. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=8593743.
Pearson, H., 2002. Surviving a knockout blow. Nature 415, 8–9. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=11780081.
Peviani, M., Caron, I., Pizzasegola, C., Gensano, F., Tortarolo, M., Bendotti, C., 2010. Unraveling the complexity of amyotrophic lateral sclerosis: recent advances

from the transgenic mutant SOD1 mice. CNS Neurol. Disord. Drug Targets 9, 491–503. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/20522008.
Pirmohamed, M., 2011. Pharmacogenetics: past, present and future. Drug Discov. Today 16, 852–861.
Plos Press Release, 2008. Dalmatian Bladder Stones Caused by Gene that Regulates Uric Acid in Humans. http://www.Eurekalert.Org/Pub_Releases/2008-11/Plos-Dbs110408.Php.
Popper, K., 2002. Conjectures and Refutations: the Growth of Scientific Knowledge, second ed. (Routledge Classics), Routledge, New York.
Ptashne, M., Gann, A., 2002. Genes & Signals. Cold Springs Harbor Laboratory Press.
Qiu, J., 2006. Epigenetics: unfinished symphony. Nature 441, 143–145. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16688142.
Rangarajan, A., Weinberg, R.A., 2003. Opinion: comparative biology of mouse versus human cells: modelling human cancer in mice. Nat. Rev. Cancer 3, 952–959. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14737125.
Redler, R.L., Dokholyan, N.V., 2012. The complex molecular biology of amyotrophic lateral sclerosis (ALS). Prog. Mol. Biol. Transl. Sci. 107, 215–262. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/22482452.
Rohan, R.M., Fernandez, A., Udagawa, T., Yuan, J., D'Amato, R.J., 2000. Genetic heterogeneity of angiogenesis in mice. FASEB J. 14, 871–876. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=10783140.
Rosen, D.R., Siddique, T., Patterson, D., Figlewicz, D.A., Sapp, P., Hentati, A., Donaldson, D., Goto, J., O'Regan, J.P., Deng, H.X., et al., 1993. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362, 59–62.
Rosenblum, I., Wohl, A., Stein, A.A., 1965a. Studies in cardiac necrosis. 3. Metabolic effects of sympathomimetic amines producing cardiac lesions. Toxicol. Appl. Pharmacol. 7, 344–351. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14298025.
Rosenblum, I., Wohl, A., Stein, A.A., 1965b. Studies in cardiac necrosis. I. Production of cardiac lesions with sympathomimetic amines. Toxicol. Appl. Pharmacol. 7, 1–8. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14256598.
Rosenblum, I., Wohl, A., Stein, A.A., 1965c. Studies in cardiac necrosis. II. Cardiovascular effects of sympathomimetic amines producing cardiac lesions. Toxicol. Appl. Pharmacol. 7, 9–17. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14256610.
Roses, A.D., 2000. Pharmacogenetics and the practice of medicine. Nature 405, 857–865. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=10866212.
Roth, R.H., 2003. Dopamine Deficit and Schizophrenia. Yale, 5R01MH057483-06.
Rothstein, J.D., 2004. Preclinical studies: how much can we rely on? Amyotroph. Lateral Scler. Other Motor Neuron Disord. Off. Publ. World Fed. Neurol., Res. Group Motor Neuron Dis. 5 (Suppl. 1), 22–25. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/15512864.
Rothstein, J.D., 2009. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. Ann. Neurol. 65 (Suppl. 1), S3–S9.
Rothwell, P.M., 2006. Funding for practice-oriented clinical research. Lancet 368, 262–266. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16860680.
Rowland, L.P., Shneider, N.A., 2001. Amyotrophic lateral sclerosis. N. Engl. J. Med. 344, 1688–1700. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/11386269.
Rudczynski, A.B., 2011. Letter. New Haven Register. http://www.Nhregister.Com/Articles/2011/03/25/Opinion/Doc4d8bb9186a82b265857273.Txt.
Rypniewski, W.R., Mangani, S., Bruni, B., Orioli, P.L., Casati, M., Wilson, K.S., 1995. Crystal structure of reduced bovine erythrocyte superoxide dismutase at 1.9 A resolution. J. Mol. Biol. 251, 282–296. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/7643403.
Salsburg, D., 1983. The lifetime feeding study in mice and rats – an examination of its validity as a bioassay for human carcinogens. Fundam. Appl. Toxicol. 3, 63–67. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=6884625.
Sankar, U., 2005. The delicate toxicity balance in drug discovery. The Scientist 19, 32.
Sarkar, S.K., 2009. Molecular imaging approaches. Drug Discov. World, 33–38.
Schadt, E.E., Sachs, A., Friend, S., 2005. Embracing complexity, inching closer to reality. Sci. STKE 2005, Pe40. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16077086.
Schnabel, J., 2008. Neuroscience: standard model. Nature 454, 682–685. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=18685674.
Schroederc, M.J., 2013. Crisis in science: in search for new theoretical foundations. Prog. Biophys. Mol. Biol.. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23541469.
Scott, R.C., Batten, P.L., Clowes, H.M., Jones, B.K., Ramsey, J.D., 1992. Further validation of an in vitro method to reduce the need for in vivo studies for measuring the absorption of chemicals through rat skin. Fundam. Appl. Toxicol. 19, 484–492. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=1426705.
Scott, S., Kranz, J.E., Cole, J., Lincecum, J.M., Thompson, K., Kelly, N., Bostrom, A., Theodoss, J., Al-Nakhala, B.M., Vieira, F.G., Ramasubbu, J., Heywood, J.A., 2008. Design, power, and interpretation of studies in the standard murine model of ALS. Amyotroph. Lateral Scler. 9, 4–15.
Seely, A.J., Christou, N.V., 2000. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit. Care Med. 28, 2193–2200. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/10921540.
Seetharaman, S.V., Taylor, A.B., Holloway, S., Hart, P.J., 2010. Structures of mouse SOD1 and human/mouse SOD1 chimeras. Arch. Biochem. Biophys. 503, 183–190.
Sellers, R.S., Senese, P.B., Khan, K.N., 2004. Interspecies differences in the nephrotoxic response to cyclooxygenase inhibition. Drug Chem. Toxicol. 27, 111–122. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15198071.
Seok, J., Warren, H.S., Cuenca, A.G., Mindrinos, M.N., Baker, H.V., Xu, W., Richards, D.R., Mcdonald-Smith, G.P., Gao, H., Hennessy, L., Finnerty, C.C., Lopez, C.M., Honari, S., Moore, E.E., Minei, J.P., Cuschieri, J., Bankey, P.E., Johnson, J.L., Sperry, J., Nathens, A.B., Billiar, T.R., West, M.A., Jeschke, M.G., Klein, M.B., Gamelli, R.L., Gibran, N.S., Brownstein, B.H., Miller-Graziano, C., Calvano, S.E., Mason, P.H., Cobb, J.P., Rahme, L.G., Lowry, S.F., Maier, R.V., Moldawer, L.L., Herndon, D.N., Davis, R.W., Xiao, W., Tompkins, R.G., 2013. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc. Natl. Acad. Sci. U S A. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23401516.
Serrano, D., Lazzeroni, M., Zambon, C.F., Macis, D., Maisonneuve, P., Johansson, H., Guerrieri-Gonzaga, A., Plebani, M., Basso, D., Gjerde, J., Mellgren, G., Rotmensz, N., Decensi, A., Bonanni, B., 2011. Efficacy of tamoxifen based on cytochrome P450 2D6, CYP2C19 and SULT1A1 genotype in the Italian tamoxifen prevention trial. Pharmacogenomics J. 11, 100–107. http://dx.doi.org/10.1038/Tpj.2010.17.
Shah, V.P., Flynn, G.L., Guy, R.H., Maibach, H.I., Schaefer, H., Skelly, J.P., Wester, R.C., Yacobi, A., 1991. Workshop report on in vivo percutaneous penetration/absorption. Washington D.C., May 1–3, 1989. Skin Pharmacol. 4, 220–228. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=1685087.
Shanks, N., Greek, R., 2009. Animal Models in Light of Evolution. Brown Walker, Boca Raton.
Shanks, N., Greek, R., Greek, J., 2009. Are animal models predictive for humans? Philos. Ethics Humanit. Med. 4, 2. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=19146696.
Sharp, P.A., Langer, R., 2011. Promoting convergence in biomedical science. Science 333, 527. http://www.Sciencemag.Org/Content/333/6042/527.Short.
Shepard, T., Lemire, R., 2004. Catalog of Teratogenic Agents, eleventh ed. Johns Hopkins, Baltimore.
Shibata, N., Hirano, A., Kobayashi, M., Sasaki, S., Kato, T., Matsumoto, S., Shiozawa, Z., Komori, T., Ikemoto, A., Umahara, T., et al., 1994. Cu/Zn superoxide dismutase-like immunoreactivity in Lewy body-like inclusions of sporadic amyotrophic lateral sclerosis. Neurosci. Lett. 179, 149–152. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/7845611.
Shibata, N., Asayama, K., Hirano, A., Kobayashi, M., 1996. Immunohistochemical study on superoxide dismutases in spinal cords from autopsied patients with amyotrophic lateral sclerosis. Dev. Neurosci. 18, 492–498. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/8940623.
Sietsema, W.K., 1989. The absolute oral bioavailability of selected drugs. Int. J. Clin. Pharmacol. Ther. Toxicol. 27, 179–211. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=2654032.
Simon, V., 2005. Wanted: women in clinical trials. Science 308, 1517. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15947140.
Sinha, G., 2013. Another blow for ALS. Nat. Biotechnol. 31, 185. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23471053.
Smith, R.L., Caldwell, J., 1977. Drug metabolism in non-human primates. In: Parke, D.V., Smith, R.L. (Eds.), Drug Metabolism – from Microbe to Man. Taylor & Francis, London, pp. 331–356.
Smith, W.E., Miller, L., Elsasser, R.E., Hubert, D.D., 1965. Tests for carcinogenicity of asbestos. Ann. N. Y. Acad. Sci. 132, 456–488. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=5219568.
Sole, R., Goodwin, B., 2002. Signs of Life: How Complexity Pervades Biology. Basic Books, New York.
Soto, A.M., Sonnenschein, C., Maini, P.K., Noble, D., 2011. Systems biology and cancer. Prog. Biophys. Mol. Biol. 106, 337–339. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/21843772.
Spielman, R.S., Bastone, L.A., Burdick, J.T., Morley, M., Ewens, W.J., Cheung, V.G., 2007. Common genetic variants account for differences in gene expression among ethnic groups. Nat. Genet. 39, 226–231. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17206142.
Spriet-Pourra, C., Auriche, M. (Eds.), 1994. SCRIP Reports. PJB, New York.
Stamer, U.M., Stuber, F., 2007. The pharmacogenetics of analgesia. Expert Opin. Pharmacother. 8, 2235–2245. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17927480.
Stankiewicz, P., Lupski, J.R., 2010. Structural variation in the human genome and its role in disease. Annu. Rev. Med. 61, 437–455.
Stathopulos, P.B., Rumfeldt, J.A., Scholz, G.A., Irani, R.A., Frey, H.E., Hallewell, R.A., Lepock, J.R., Meiering, E.M., 2003. Cu/Zn superoxide dismutase mutants associated with amyotrophic lateral sclerosis show enhanced formation of aggregates in vitro. Proc. Natl. Acad. Sci. U S A 100, 7021–7026. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/12773627.
Stemwedel, J., 2010. Some Preliminary Thoughts on the UCLA Panel Discussion on Animal-based Research. http://Scienceblogs.Com/Ethicsandscience/2010/02/Some_Preliminary_Thoughts_On_T.Php.

Stolley, P.D., 1972. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am. Rev. Respir. Dis. 105, 883–890. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=5032708.

Stolley, P.D., Schinnar, R., 1979. Fatal asthma. Lancet 2, 897. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=90979.

Stoloff, L., 1992. An analysis of the 1987 list of IARC-identified human carcinogens and the correlated animal studies. Regul. Toxicol. Pharmacol. RTP 15, 10–13. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/1553406.

Strange, R.W., Antonyuk, S.V., Hough, M.A., Doucette, P.A., Valentine, J.S., Hasnain, S.S., 2006. Variable metallation of human superoxide dismutase: atomic resolution crystal structures of Cu–Zn, Zn–Zn and as-isolated wild-type enzymes. J. Mol. Biol. 356, 1152–1162. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/16406071.

Stump, D.S., Vandewoude, S., 2007. Animal models for HIV AIDS: a comparative review. Comp. Med. 57, 33–43. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17348289.

Suggitt, M., Bibby, M.C., 2005. 50 years of preclinical anticancer drug screening: empirical to target-driven approaches. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 11, 971–981. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/15709162.

Suter, K., 1990. What can Be learned from case studies? The company approach. In: Lumley, C., Walker, S. (Eds.), Animal Toxicity Studies: Their Relevance for Man. Quay, Lancaster, pp. 71–78.

Tainer, J.A., Getzoff, E.D., Beem, K.M., Richardson, J.S., Richardson, D.C., 1982. Determination and analysis of the 2 A − Structure of copper, zinc superoxide dismutase. J. Mol. Biol. 160, 181–217. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/7175933.

Tandon, A., April 12, 2011. August 8, 2011. http://www.Tribuneindia.Com/2011/20110808/Main1.Htm.

Tomatis, L., Agthe, C., Bartsch, H., Huff, J., Montesano, R., Saracci, R., Walker, E., Wilbourn, J., 1978. Evaluation of the carcinogenicity of chemicals: a review of the monograph program of the International Agency for research on cancer (1971 to 1977). Cancer Res. 38, 877–885. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=346205.

Van Regenmortel, M., 2002a. A paradigm shift is needed in proteomics: 'structure determines function' should Be replaced by binding determines function'. J. Mol. Recognit.: JMR 15, 349–351. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/12501156.

Van Regenmortel, M., 2002b. Pitfalls Otf reductionism in immunology. In: Van Regenmortel, M., Hull, D.L. (Eds.), Promises and Limits of Reductionism in the Biomedical Sciences. John Wiley & Sons Ltd., Chichester, pp. 47–66.

Van Regenmortel, M., 2002c. Reductionism and the search for structure-function relationships in antibody molecules. J. Mol. Recognit.: JMR 15, 240–247. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/12447900.

Van Regenmortel, M., 2004a. Biological complexity emerges from the ashes of genetic reductionism. J. Mol. Recognit. 17, 145–148. http://dx.doi.org/10.1002/Jmr.674.

Van Regenmortel, M., 2004b. Reductionism and complexity in molecular biology. Scientists now have the tools to unravel biological complexity and overcome the limitations of reductionism. EMBO Rep. 5, 1016–1020. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15520799.

Van Regenmortel, M.H.V., 2012. Basic research in HIV vaccinology is hampered by reductionist thinking. Front. Immunol. 3. http://www.Frontiersin.Org/Journal/Abstract.Aspx?S=1247&Name=Immunotherapies_And_Vaccines&ART_DOI=10.3389/Fimmu.2012.00194.

Van Regenmortel, M.H., Hull, D.L., 2002. Promises and Limits of Reductionism in the Biomedical Sciences (Catalysts for Fine Chemical Synthesis). Wiley, West Sussex.

Vassar, R., 2011. Alzheimer's therapy: a BACE in the hand? Nat. Med. 17, 932–933. http://dx.doi.org/10.1038/Nm0811-932.

Wald, C., Wu, C., 2010. Of mice and women: the bias in animal models. Science 327, 1571–1572.

Walker, R.M., Mcelligott, T.F., 1981. Furosemide induced hepatotoxicity. J. Pathol. 135, 301–314. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=7328448.

Wall, R.J., Shani, M., 2008. Are animal models as good as we think? Theriogenology 69, 2–9. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17988725.

Walton, K., Dorne, J.L., Renwick, A.G., 2004. Species-specific uncertainty factors for compounds eliminated principally by renal excretion in humans. Food Chem. Toxicol. 42, 261–274. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14667472.

Wang, J., Slunt, H., Gonzales, V., Fromholt, D., Coonfield, M., Copeland, N.G., Jenkins, N.A., Borchelt, D.R., 2003. Copper-binding-site-null SOD1 causes ALS in transgenic mice: aggregates of non-native SOD1 delineate a common feature. Hum. Mol. Genet. 12, 2753–2764. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/12966034.

Wang, L., Deng, H.X., Grisotti, G., Zhai, H., Siddique, T., Roos, R.P., 2009. Wild-type SOD1 overexpression accelerates disease onset of a G85R SOD1 mouse. Hum. Mol. Genet. 18, 1642–1651. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/19233858.

Wang, D., Guo, Y., Wrighton, S.A., Cooke, G.E., Sadee, W., 2011. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J. 11, 274–286. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=20386561.

Watanabe, M., Dykes-Hoberg, M., Culotta, V.C., Price, D.L., Wong, P.C., Rothstein, J.D., 2001. Histological evidence of protein aggregation in mutant SOD1 transgenic mice and in amyotrophic lateral sclerosis neural tissues. Neurobiol. Dis. 8, 933–941. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/11741389.

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., Hastings, K.L., 2003. Detection of systemic hypersensitivity to drugs using standard guinea pig assays. Toxicology 193, 203–217. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=14599760.

Werner, E., 2012. History of the seminar on the conceptual foundations of systems biology. Prog. Biophys. Mol. Biol.. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/23262312.

Wilke, R.A., Dolan, M.E., 2011. Genetics and variable drug response. JAMA: J. Am. Med. Assoc. 306, 306–307. http://Jama.Ama-Assn.Org/Content/306/3/306.Short.

Williams, G., 1997. Chaos Theory Tamed. Joseph Henry Press, Washington, D.C.

Willyard, C., 2007. Blue's clues. Nat. Med. 13, 1272–1273. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17987010.

Willyard, C., 2009. HIV gender clues emerge. Nat. Med. 15, 830. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=19661976.

Wolkenhauer, O., Fell, D., De Meyts, P., Bluthgen, N., Herzel, H., Le Novere, N., Hofer, T., Schurrle, K., Van Leeuwen, I., 2009. Sysbiomed report: advancing systems biology for medical applications. IET Syst. Biol. 3, 131–136. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/19449974.

Wong, P.C., Pardo, C.A., Borchelt, D.R., Lee, M.K., Copeland, N.G., Jenkins, N.A., Sisodia, S.S., Cleveland, D.W., Price, D.L., 1995. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. Neuron 14, 1105–1116. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/7605627.

Wong, A.H., Gottesman II, , Petronis, A., 2005. Phenotypic differences in genetically identical organisms: the epigenetic perspective. Hum. Mol. Genet. 14, R11–R18. Spec No 1. http://www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=15809262.

World Federation of Neurology and European Network to Cure ALS, February 15, 2013. ALS Online Genetics Database. http://Alsod.Iop.Kcl.Ac.Uk/Als/.

Wynn, J., 1982. What future for regulation? UK Committee's role disputed. Nature 299, 387. http://www.Ncbi.Nlm.Nih.Gov/Pubmed/11643800.

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., Luster, M.I., 2009. Influence of cytokine gene variations on immunization to childhood vaccines. Vaccine 27, 6991–6997.

Yuen, J., October 2, 2011. Ths CEO Criticized for Links to Animal Testing. http://M.Torontosun.Com/2011/09/23/Ths-Ceo-Criticized-For-Links-To-Animal-Testing?Noimage.

Zhao, J., Goldberg, J., Bremner, J.D., Vaccarino, V., 2012. Global DNA methylation is associated with insulin resistance: a monozygotic twin study. Diabetes 61, 542–546.

Zielinska, E., 2010. Building a better mouse. The Scientist 24, 34–38.