

PUBLISHED BY

INTECH

open science | open minds

World's largest Science,
Technology & Medicine
Open Access book publisher



3,350+
OPEN ACCESS BOOKS



108,000+
INTERNATIONAL
AUTHORS AND EDITORS



114+ MILLION
DOWNLOADS



BOOKS
DELIVERED TO
151 COUNTRIES

AUTHORS AMONG

TOP 1%
MOST CITED SCIENTIST



12.2%
AUTHORS AND EDITORS
FROM TOP 500 UNIVERSITIES



Selection of our books indexed in the
Book Citation Index in Web of Science™
Core Collection (BKCI)

WEB OF SCIENCE™

Chapter from the book *New Insights into Toxicity and Drug Testing*

Downloaded from: <http://www.intechopen.com/books/new-insights-into-toxicity-and-drug-testing>

Interested in publishing with IntechOpen?
Contact us at book.department@intechopen.com

Animal Models in Drug Development

Ray Greek

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53893>

1. Introduction

The use of specific chemicals to treat specific diseases and disorders dates to 1910 when Paul Ehrlich and Sahachiro Hata discovered that salvarsan, also known as arsphenamine and compound 606, killed the microorganism that caused syphilis. Their research relied on animal models of syphilis as, even currently, syphilis cannot be grown in culture medium. Arsphenamine was the first synthetic drug to actually target and kill a disease-causing organism and is credited with starting the pharmaceutical age. Ehrlich is also credited with coining the term *magic bullet* in reference to a drug that would kill a microorganism without damaging or otherwise affecting the host of the microorganism: the patient. As I will explain, despite being an inspirational concept that led to advances in science and medicine, the notion of a magic bullet proved incomplete. Salvarsan and Ehrlich's concept of a magic bullet are important to current concepts in drug testing because: 1) salvarsan was initially called compound 606 as it was the 606th compound tested on animals in an attempt to find a treatment for syphilis; and 2) the concept of a magic bullet was based on the scientific process known as reductionism. In this chapter, I will explore the reductionist approach of using animal models in drug development, especially in toxicity testing.

2. Reductionism and complexity

The use of animals as models for human anatomy and pathophysiology dates back millennia but the modern version began with Claude Bernard in the 19th century. Bernard was a firm believer in the reductionist approach to medical science and that approach has indeed served biomedical science well for decades. A review of reductionism will allow us to contrast this approach to understanding the material universe with systems biology, which is needed in order to fully understand complex living systems. [1-13]

Ernst 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." [[14] p290] For example, physics attempts to describe the universe in terms of a few elementary particles, and the relationships among them. Reductionism has been very successful in describing many aspects of the material universe, including allowing successful predictions to be made. Reductionism is associated with Newton, Descartes, and determinism and the reliance on animal models in medical science arose during the time of Newtonian physics vis-à-vis reductionism and determinism. Newton said: "Therefore to the same natural effects we must, as far as possible, assign the same causes" and went on to explain that this rule applies "to respiration in a man and in a beast, the descent of stones in Europe and America, the light of our culinary fire and of the sun, the reflection of light in the earth and in the planets."[[15] p3-5] Both Newton and Claude Bernard subscribed to the position that similar causes yield similar effects. Indeed, this concept was one of the breakthroughs that led to the systematic method of inquiry known as the *resoluto-compositiva method* or method of analysis and synthesis. This concept of causal determinism rests on two claims. First, all events have causes, and second, for qualitatively identical systems, the same cause is followed by the same effect. Causal determinism is a presupposition of much scientific activity. The idea that results in the laboratory can be extended to form expectations about qualitatively similar systems outside the laboratory is embodied in this idea, as is the claim that experiments should be replicable. [16] This was how science viewed the universe, including animate bodies, when the animal model was embraced by science in the 19th century.

Claude Bernard was a strict causal determinist, meaning that if X caused Y in a monkey it was also cause Y in a human. Bernard stated: "Physiologists... deal with just one thing, the properties of living matter and the mechanism of life, in whatever form it shows itself. For them genus, species and class no longer exist. There are only living beings; and if they choose one of them for study, that is usually for convenience in experimentation."[[17] p 111] Further complicating matters, Bernard and many of his colleagues rejected the notion of evolution put forth by Darwin. [17-19] Bernard thought that organs and other tissues were interchangeable among animals and that all differences could be accounted for based on scaling; the chief difference between humans and animals being a soul.[19] This thinking persists even in recent times as exemplified by the baboon heart transplant in to the recipient Baby Fae, performed by the creationist surgeon Leonard Bailey of Loma Linda University in 1984. [[20] p162-3]

However, recent advances in other disciplines of science, namely chaos and complexity along with evolutionary biology, have called into question the use of reductionism as the sole factor in studying complex systems. Moreover, the developments in evolutionary biology and genetics are cause for further concern regarding the use of one complex evolved system, say a mouse, to predict responses to perturbations such as disease and drugs for another differently evolved complex system, say a human. For example, we now understand that the same gene can be used in different ways among species and that knocking out a gene in one species is not predictive for the function of that gene in another species.[21-27] This has implications for drug development.

Reductionism was used to study simply systems as opposed to complex systems. Animals, including humans, are complex systems and as such exhibit the characteristics listed below [from [28]].

1. Complex systems are robust, meaning they have the capacity to resist change. [8, 9, 29-35] This can be illustrated by the fact that knocking out a gene in one strain of mouse may produce no noticeable effects.
2. Redundancy tends to be a part of complex systems and may explain some aspects of robustness. For example, many members of the kingdom Animalia exhibit gene redundancy. [8, 9, 29-35]
3. Different parts of a complex system are linked to and affect one another in a synergistic manner. In other words, there is positive and negative feedback in a complex system. [36] This is why overloading one part of a complex system with say vitamins, may not result in a healthier individual. The feedback system results in the rest of the system acting to simply excrete the unneeded vitamins.
4. Complex systems are also modular. But failure in one module does not necessarily spread to the system as a whole as redundancy and robustness also exist. [37-40]
5. The modules do communicate though. For example, genes tend to be part of networks, genes interact with proteins, proteins interact with other proteins and so on.
6. Complex systems communicate with their environment—are dynamic. [37-40]
7. Complex systems are very dependent upon initial conditions. [39] For example, very small changes in genetic makeup can result in dramatic differences in response to perturbations of the living system.
8. The causes and effects of the events that a complex system experiences are not proportional to each other. Perturbations to the system have effects that are nonlinear, in other words large perturbations may result in no change while small perturbations may cause havoc. [37-40]
9. The whole is greater than the sum of the parts. [1, 8, 9, 30, 39]
10. Complex systems have emergent properties. An emergent property cannot be predicted by full knowledge of the component parts. For example, the formation of a flock of birds and hurricanes are examples of emergent phenomenon as is perhaps consciousness. [39]

Reductionism is essentially *divide and conquer*. By dividing a system into its parts and ascertaining the functions of all the parts of the system, one can deduce the function of the entire system. The gears of a Swiss watch, for example, are capable of description on their own, without reference to the system from which they are removed. Conversely, the individual components of a complex system must be described based on the *interaction* of the parts. Describing individual components in isolation, regardless of how detailed such a description is, cannot fully describe the complex system as a whole. The whole is greater than the sum of the parts. A complex system must be described based on the *organization* of the individual components. [41, 42]

Miska states:

The basic analytical method that is behind most biomedical research can be traced back over 300 years to Descartes's essay Discourse on Method, which argued that an animal is a clock-like machine in which the parts and their relationships to one another are precise and unchangeable, and in which causes and effects can be understood by taking the pieces apart. This so-called 'reductionist' approach to understanding biology and medicine has been very productive, but is now up against problems that require different frameworks, institutionally and intellectually. [43]

Nicolis & Prigogine defined complexity as the ability of a system "to switch between different modes of behavior as the environmental conditions are varied." [44] In other words, complex systems are able to adapt to their environments just as life on this planet has adapted resulting in different species. But these adaptations mean that two complex systems that were originally identical would now be less similar and behave differently in certain circumstances. An example of this would be the susceptibility to disease between monozygotic twins. [45-56] Van Regenmortel states:

Reductionists tend to disregard the fact that all biological systems possess so-called emergent properties that arise through the multiple interconnections and relations existing between individual components of the system. These emergent, relational properties do not exist in the constituent parts and they cannot be deduced or predicted from the properties of the individual, isolated components [157]p258]. Examples of emergent properties are the viscosity of water (individual water molecules have no viscosity), the colour of a chemical, a melody arising from notes, the saltiness of sodium chloride, the specificity of an antibody and the immunogenicity of an antigen. [58]

Living complex systems are the result of various evolutionary processes and as such are arguably the *most complex* of all complex systems. Species differ because of the presence of different genes, mutation in the same genes, a difference in the number of the same allele (copy number variants), the same genes may be regulated or expressed differently, alternative splicing, the presence of modifier or background genes, differences in gene networks and protein networks, and convergent evolution where two species share a trait but the trait evolved independently in each. Individuals of the same species may differ for many of the above reasons but also because of dissimilarities in environmental exposures. [50] Importantly, each of the above means that different species as well as individuals of the same species manifest differences in the initial conditions of their complex system. The above also translates into differences in other characteristics of a complex system such as robustness and redundancy.

The progress in these two areas of science, complexity science and evolutionary biology, results in strong theoretical concerns regarding the use of animals as predictive models in drug development. We should expect animals and humans to share responses to perturbations at the level of organization where complex systems can be described as simple systems but not for perturbations occurring at the level of organization where the system as a whole is studied or where parts of the systems that are themselves complex are studied. I will next examine the empirical evidence and place it in the context of these theoretical concerns.

3. Prediction in science

The third relevant advance in science since animal models were mandated for use in drug development is the formal evaluation of animal models in terms of their predictive value for humans. Animal models are used for ascertaining the properties of absorption, distribution, metabolism, elimination and toxicity (ADMET). As all of these properties influence toxicity, an examination of the ability of animal models to predict these properties is important, as is the straightforward examination of animal models for toxicity itself. The answer to the question of the predictive ability of animal models was hinted at by the fact that Ehrlich and Hata ultimately tested the 606th compound of a series in their attempt to find a treatment for syphilis. Previous compounds had successfully treated syphilis in animal models but had failed for various reasons in humans. Even salvarsan resulted in side effects in humans that were unforeseen in animal models.

The ability to predict facts about the material universe is a hallmark of science. Hypotheses are generated that make predictions about the phenomena under study and the success or failure of these predictions can falsify or strengthen the hypothesis. This use of the term *predict* differs from determining whether a modality, practice, or test is *predictive* for its purpose. For example, a CT scan of the chest is a predictive test for diagnosing a pneumothorax, because the CT scan, as opposed to a chest x-ray, is successful in locating the pneumothorax essentially 100% of the time. In order to evaluate a modality like CT scans, a blood test for cancer, or even the use of dogs for catching drug smugglers in airports, the calculations in table 1 are employed.

When evaluating the predictive value of methods, practices, or tests for use in biomedical science, positive predictive value (PPV) and negative predictive value (NPV) > 0.9 are sought. If a single test alone cannot yield such high values then a combination of tests can be evaluated in hopes that the combination will meet the criteria. Such evaluations have been made for toxicity testing using animal models as well as other animal model-based tests in drug development. Profound *inter*-species differences, as well as inter-individual human differences, have been revealed for absorption [[59] p 8-10] [[60] pp 5, 9, 45, 50, 66-7, 90, 102-3,] [61-64], distribution [65, 66], metabolism [67-77], elimination [78, 79], and toxicity [64, 80-91], which results in predictive values for these animal models that are far below those required in biomedical science. For example, Litchfield conducted a classic study in 1962 comparing toxicity among three species: humans, rats, and

dogs. The positive predictive values for the animal models were between 0.49 and 0.55. [92] Similarly, Suter compared toxicities for ergoloid mesylates, bromocriptine, ketotifen, cyclosporine, FK 33-824, and clozapine in animals and humans. The sensitivity for toxicity for the animal tests was 0.52 and the predictive value positive was 0.31. [93] Fourches et al. evaluated animal human data for 1061 compounds known to cause hepatotoxicity in humans and found that the concordance or sensitivity among species was around 39-44%. [94] The positive and negative predictive values could not be calculated from the article but would be well below 0.39. Smith and Caldwell studied twenty-three chemicals and discovered that only four were metabolized the same in humans and rats. [70] Sietsema [95], compared the oral bioavailability of 400 drugs in humans with three other species (see Figure 1) and concluded the data was consistent with a “scatter-gram.” Similar results have been obtained from other studies. [84, 96-101]

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 = $TN / (FN + TN)$			

Table 1. Binomial classification method for calculating sensitivity, specificity, positive predictive value, and negative predictive value when comparing a modality, practice, or test with a gold standard.

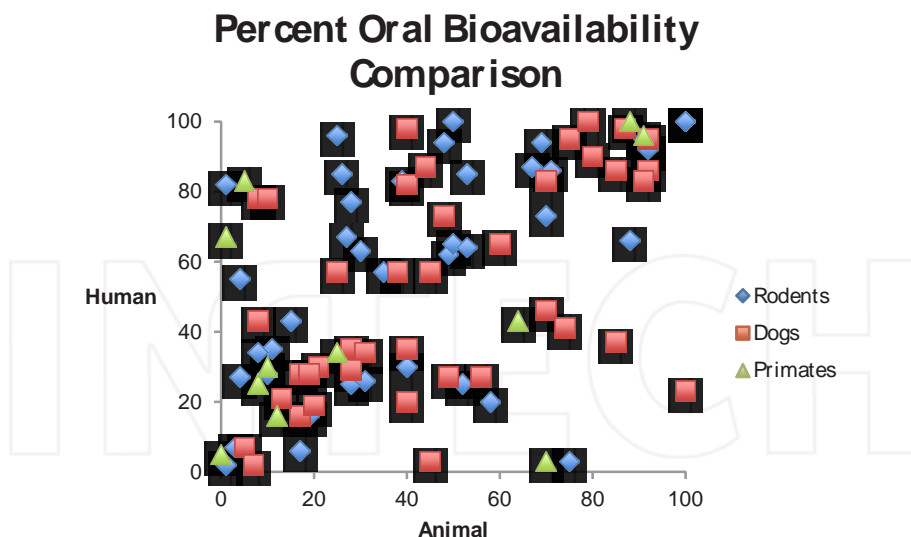


Figure 1. Variation in bioavailability among species. (Based on data from [95].)

The fact that animal models lack predictive ability is well known.[102-110] This shortcoming includes the inability of animal models to be predictive modalities for carcinogenicity.[111, 112] Salsburg stated: "Thus the lifetime feeding study in mice and rats appears to have less than a 50% probability of finding known human carcinogens. On the basis of probability theory, we would have been better off to toss a coin..."[111]

The general attitude in the drug development-related sciences reflects the empirical evidence. Cook et al:

Over many years now there has been a poor correlation between preclinical therapeutic findings and the eventual efficacy of these [anti-cancer] compounds in clinical trials [109, 110].... The development of antineoplastics is a large investment by the private and public sectors, however, the limited availability of predictive preclinical systems obscures our ability to select the therapeutics that might succeed or fail during clinical investigation. [108]

Reuters quoted Francis Collins, Director of the NIH, as stating that: "about half of drugs that work in animals may turn out to be toxic for people. And some drugs may in fact work in people even if they fail in animals, meaning potentially important medicines could be rejected."[113] Alan Oliff, former executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania asserted in 1997: "The fundamental problem in drug discovery for cancer is that the [animal] model systems are not predictive at all."[114] Björ-

quist and Sartipy stated: “Furthermore, the compound attrition rate is negatively affected by the inability to predict toxicity and efficacy in humans. These shortcomings are in turn caused by the use of experimental pre-clinical model systems that have a limited human clinical relevance...”[115] In 2006, then U.S. Secretary of Health and Human Services Mike Leavitt declared: “Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies.”[116] Zielinska, writing in *The Scientist* supported the above, stating:

Mouse models that use transplants of human cancer have not had a great track record of predicting human responses to treatment in the clinic. It's been estimated that cancer drugs that enter clinical testing have a 95 percent rate of failing to make it to market, in comparison to the 89 percent failure rate for all therapies... Indeed, "we had loads of models that were not predictive, that were [in fact] seriously misleading," says NCI's Marks, also head of the Mouse Models of Human Cancers Consortium... [117]

The inability of animal models to predict human response has also increased the cost of drug development as the cost for the 90-95% of drugs that fail must be recouped from the ones that go to market.[91, 118-121] Lost revenue has also resulted from the drugs that would have been marketable had animal models not derailed them in development. This lack of predictive ability for animal models is largely to blame for the cost of new medications and for the fact that the drug development pipeline is drying up.[115, 122, 123] Because animal models fail to predict drugs destined to fail, these drugs go to clinical trials and marketing which consumes roughly 95% of the cost for drug development.[124, 125] Catherine Shaffer, Contributing Editor of *Drug Discovery & Development*, wrote in 2012: “Drug development is an extremely costly endeavor. Estimates of the total expense of advancing a new drug from the chemistry stage to the market are as high as \$2 billion. Much of that cost is attributable to drug failures late in development, after huge investments have been made. Drugs are equally likely to fail at that stage for safety reasons, as for a lack of efficacy, which is often well-established by the time large trials are launched.”[120] Roy estimates the real cost is even higher: “The true amount that companies spend per drug approved is almost certainly even larger today. Matthew Herper of Forbes recently totaled R&D spending from the 12 leading pharmaceutical companies from 1997 to 2011, and found that they had spent \$802 billion to gain approval for just 139 drugs: a staggering \$5.8 billion per drug.”[125] Kenneth Kaitin, director of Tuft’s Center for the Study of Drug commenting on Pharma’s drying pipeline in the March 7, 2011 *New York Times*, stated: “This is panic time, this is truly panic time for the industry.” Even when a drug does reach the market, there is a great amount of uncertainty regarding safety. For example, over 1000 drugs that reached the market were discovered to result in hepatotoxicity. [126]

Kirschner addressed this issue, asking: “could we develop a better way of predicting whether a drug will work or have intolerable side effects?” He then explains the problem in terms similar to what I have presented above:

In part, this problem stems from the fact that we rarely have a situation in which one gene can be linked to one disease and targeted by one drug. 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. This approach requires not just a wiring diagram, but a quantitative wiring diagram... [127]

4. This leads us to current efforts at improving drug development

4.1. Twenty-first century science

Today we have options for drug development and toxicity testing that did not exist until the 21st century, for example microdosing and pharmacogenomics. Two points need be emphasized before I address these two advances, however. First, animal models fail to meet the ends for which they are used; they are not predictive modalities for human response. Therefore using animal models is akin to relying on bloodletting as a treatment for cancer when oncologists have no cures for the cancer in question. Just as bloodletting is not effective as a treatment for cancer, regardless of whether or not other options are available, so employing animal models as they are currently utilized is nonsensical.

Second, technology is available, or is being developed, that will at least predict human response for certain properties important in drug development. However, regardless of how much time is needed in order for these technologies to be developed, animal models are simply ineffective and hence should be abandoned. Lack of effective technology does not justify the utilization of methods proven to be ineffective. Regardless of the technologies available, drug development must be human-based both when reductionism is used and when complexity is relevant. Basing drug development decisions on drug targets identified from animal models has not been effective. Human tissues can be studied instead and this will allow targets to be established in a more reliable manner. Humans must also be studied when responses to drugs are occurring at higher levels of organization; where the system is complex.

In 2006, the FDA approved microdosing for Phase 0 clinical trials.[128, 129] Microdosing is the process whereby very small doses of a drug are administered to human volunteers after which positron emission tomography (PET) and accelerator mass spectrometry (AMS) are used to assess pharmacokinetic (PK) data.[130-132] While animal models are used to inform the dose for the first administration of the drug, the usual range for drugs is 100ng to 100µg. If all drugs were initially administered at a dose of 1ng and subsequently increased, this would obviate the use of unreliable animal models and en-

sure that the first-in-human dose was lower than the most toxic substance currently known.[133, 134] This would be a reliably safe method for conducting first-in-human trials. Although in practice microdosing is currently only used to evaluate PK (as opposed to pharmacodynamics, which is abbreviated as PD), it could be used for evaluating the other properties of interest. For example, by increasing the dose incrementally, the drug could be evaluated for toxicity. This solves the problem of unanticipated catastrophic reactions such as occurred in the TGN1412 trial [135] and allows toxicity to be determined very early in the drug development process. Long term carcinogenicity studies could not be conducted in this fashion however animal models are not predictive for carcinogenicity and human data from long terms use is the *de facto* method now used. Nothing would be lost by eliminating long-term carcinogenicity studies in animals until predictive technologies are developed. According to the Centers for Disease Control and Prevention (CDC): "Most of what we know about chemicals and cancer in humans comes from scientists' observation of workers. The most significant exposures to cancer-causing chemicals have occurred in workplaces where large amounts of toxic chemicals have been used regularly." [136]

The concept of microdosing, used in combination with pharmacogenomics (see below) would allow go-no go decisions to be made early and reliably in drug development as well as matching drug to patient. The transition to full-scale clinical trials would also be seamless. As the dose was increased, an evaluation of efficacy could be made. By starting the dose at 1ng and increasing, the entire clinical trial could be conducted much more reliably and efficiently, drugs destined to fail could be eliminated earlier thus saving money, and the drugs could be matched to genotype before being marketed thus further saving money and decreasing side effects. This leads us to the concepts of pharmacogenomics and personalized medicine.

Personalized medicine seeks to individualize medicine both in terms of treatment and diagnosis while pharmacogenomics matches drugs to patients. Rashmi R Shah, previous Senior Clinical Assessor, Medicines and Healthcare products Regulatory Agency, London stated in 2005: "During the clinical use of a drug at present, a prescribing physician has no means of predicting the response of an individual patient to a given drug. Invariably, some patients fail to respond beneficially as expected whereas others experience adverse drug reactions (ADRs)." [137] Shah echoed comments by Allen Roses, then-worldwide vice-president of genetics at GlaxoSmithKline (GSK), who stated that fewer than half of the patients prescribed some of the most expensive drugs derived any benefit from them: "The vast majority of drugs - more than 90% - only work in 30 or 50% of the people." [138] That individual humans respond very differently to disease and drugs [139, 140], including vaccines [141, 142], has long been appreciated. During the Korean War, Alving observed that black soldiers had an increased probability, compared with white soldiers, of developing anemia when from antimalarials. This was discovered to be secondary to a commonly occurring enzyme deficiency in the black soldiers.[143] Variation in disease susceptibility and response to drugs has been noted to exist between sexes [144-150] and ethnic groups [151-159] as well as between monozygotic twins.[45-52, 56]

Many advances have been made in linking drugs to genes, in part because of spin-offs from the Human Genome Project. Differences between humans including single nucleotide polymorphisms, copy number variants, differences the regulation and expression of the same genes, differences in gene networks, and the influence of background genes can result in a drug being efficacious for one patient but not another. Diseases vary intra-species as well. Michael Snyder, chair of genetics at Stanford University School of Medicine, recently stated: "However, the bulk of the differences among individuals are not found in the genes themselves, but in regions we know relatively little about. Now we see that these differences profoundly impact protein binding and gene expression." [160, 161] Hunter et al studied a mouse model of cancer and discovered differences in metastatic efficiency secondary to background genes. Hunter et al:

Because all tumors were initiated by the same oncogenic event, differences in the metastasis microarray signature and metastatic potential are probably due to genetic background effects rather than different combinations of oncogenic mutations. Consistent with our observations in metastasis, several laboratories have shown similar strain differences with regard to oncogenesis, aging and fertility in transgenic mouse models.[162-164] Data on both primary tumors and metastases reinforce the notion that tumorigenesis and metastasis are complex phenotypes involving both inherent genetic components and cellular responses to extrinsic stimuli. [165]

Thein likewise stated: "As the defective genes for more and more genetic disorders become unravelled, it is clear that patients with apparently identical genotypes can have many different clinical conditions even in simple monogenic disorders." Thein assessed β -thalassaemia and noted that the clinical manifestations are very diverse, ranging from life threatening to asymptomatic. Thein: "The remarkable phenotypic diversity of the β -thalassemias is prototypical of how a wide spectrum of disease severity can be generated in single gene disorders.... relating phenotype to genotype is complicated by the complex interaction of the environment and other genetic factors at the secondary and tertiary levels..." [166]

Agarwal and Moorchung reinforce the above stating: "It is now increasingly apparent that modifier genes have a considerable role to play in phenotypic variations of single-gene disorders." This is due to factors such as: "Oligogenic disorders occur because of a second gene modifying the action of a dominant gene. It is now certain that cancer occurs due to the action of the environment acting in combination with several genes." [167] Friedman and Perriemon explain that there are "hundreds of potential regulators of known signaling pathways." [168] *PLoS Biology*, in an editorial said the following about mouse models of autoimmune diseases: "These results fall in line with mounting evidence that background genes are not silent partners in gene-targeted disease models, but can themselves facilitate expression of the disease. This finding underscores the notion that genes are not solitary, static entities; their expression often depends on context. With genetically complex diseases, having the requisite combination of susceptibility genes does not always lead to disease." [169]

Liu et al explain why the same genes can result in very outcomes:

A general view is that critical genes involved in biological pathways are highly conserved among species. To understand human autoimmune diseases, a great deal of effort has been devoted to the study of murine models that mirror many pathologic properties observed in the human disease. We have found that lymphocytes from humans with different autoimmune disease all carry a common conserved gene expression profile. Therefore, we wanted to determine if lymphocytes from common murine models of autoimmune disease carried a gene expression profile similar to the human profile and if both mouse models carried a shared gene expression profile. We identified numerous differentially expressed genes (DEGs) in the autoimmune strains compared to non-autoimmune strains. However, we found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models. Our research further confirms that murine models of autoimmunity do not perfectly match human autoimmune diseases. [26]

Weiss et al continues this theme:

In contrast to these single gene effects, many drug treatment response phenotypes are complex, produced by multiple coding and regulatory variants in multiple genes that often interact in a signalling pathway. In these cases, each variant could contribute to the variance in the phenotype and there is no clear model of genetic inheritance. Genetic factors that influence whether a drug treatment response is complex include mode of inheritance (recessive versus dominant or additive); pleiotropy; incomplete penetrance; and epistasis, due to gene–environment interactions and environmental phenocopies. All of these factors contribute to the complexity of the response phenotypes. [170]

Gabor Miklos states:

There is enormous phenotypic variation in the extent of human cancer phenotypes, even among family members inheriting the same mutation in the adenomatous polyposis coli (APC) gene believed to be causal for colon cancer. In the experimental mouse knockout of the catalytic gamma subunit of the phosphatidyl-3-OH kinase, there can be a high incidence of colorectal carcinomas or no cancers at all, depending on the mouse strain in which the knockout is created, or into which the knockout is crossed... [27]

Because of advances alluded to above, society is seeing the death of the blockbuster and the arrival of the “niche buster.” [171] Herscu et al write: “The era of the ‘blockbuster drug mod-

el' is ending, and the development of personalized pharmaceutical system is on the rise." [172] This is also due to the fact that diseases are being categorized into more types and individuals even within the same type react differently to drugs. Herscu et al write:

Diabetes mellitus, for example, was simply divided into juvenile or adult onset types for many years. Now we have pre-diabetes; Type 1, broken into immune-related and other causes; Type 2, broken into secretory defect and insulin-resistant types; and more than 11 types that have been linked to specific genetic defects. However, even diabetic patients in a precisely defined category with shared genetic markers differ because they exist at different points along the continuum of the disease depending on their diet, exercise, comorbid conditions and other factors. These phenotypic dissimilarities are the source of inter-patient variability, which confounds both clinical trials and treatment results. [172]

Iressa was one of the first medications administered to patients based on genotype. Iressa did not perform well in clinical trials and was to be abandoned but clinicians were adamant that it helped some people with cancer. By genotyping the patients that responded well to Iressa, researchers were able to confirm that, in certain genotypes, Iressa was efficacious. Numerous drug responses have been matched to specific mutations. [77, 173-176] The Personalized Medicine Coalition notes that personalized medicine will allow patients and physicians to:

- select optimal therapy and reduce "trial-and-error" medicine;
- reduce adverse drug reactions;
- improve the selection of drug targets;
- increase patient compliance with therapy;
- reduce the time, cost, and failure rate of clinical trials;
- revive drugs that failed clinical trials or were withdrawn from the market;
- avoid withdrawal of marketed drugs;
- shift the emphasis in medicine from reaction to prevention; and
- reduce the overall cost of healthcare.[177]

5. Conclusion

We are currently living in what will become known as the Age of Personalized Medicine. While much has yet to be discovered, society is already benefitting from personalized medicine applied to specific drugs and diseases. Contrast this with using a different species in an

attempt to predict human response to drugs and disease. While animals can be used in basic science pursuits, empirical evidence from drug development, placed in the context of the scientific theories of Complexity and Evolution, demands that animal testing be replaced with human-based drug development. Implementing human-based testing early in the development process is how drugs should be developed now and it will be how drugs are developed in the future.

Author details

Ray Greek*

Address all correspondence to: AFMA@AFMA-curedisease.org

Americans For Medical Advancement, Goleta, CA, USA

References

- [1] Ahn AC, Tewari M, Poon CS, Phillips RS. The limits of reductionism in medicine: could systems biology offer an alternative? *PLoS Med.* 2006 May;3(6):e208. Digital Object Identifier: 05-PLME-ES-0675R1 [pii] 10.1371/journal.pmed.0030208. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16681415
- [2] Bornholdt S. Systems biology. Less is more in modeling large genetic networks. *Science.* 2005 Oct 21;310(5747):449-51. Digital Object Identifier: 310/5747/449 [pii] 10.1126/science.1119959. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16239464
- [3] Butcher EC. Can cell systems biology rescue drug discovery? *Nat Rev Drug Discov.* 2005 Jun;4(6):461-7. Digital Object Identifier: nrd1754 [pii] 10.1038/nrd1754. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15915152
- [4] Department of Systems Biology. Harvard Medical School. Systems Biology. Boston: Harcard; 2010 [cited 2011 August 22]; Available from: <https://sysbio.med.harvard.edu/>.
- [5] Editorial. End of the interlude? *Nat Biotechnol.* 2004 Oct;22(10):1191. Digital Object Identifier: nbt1004-1191 [pii] 10.1038/nbt1004-1191. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15470438
- [6] Editorial. In pursuit of systems. *Nature.* 2005 May 5;435(7038):1. Digital Object Identifier: 435001a [pii] 10.1038/435001a. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15874978

- [7] Hood L. Leroy Hood expounds the principles, practice and future of systems biology. *Drug Discov Today*. 2003 May 15;8(10):436-8. Digital Object Identifier: S1359644603027107 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12801791
- [8] Kitano H. Computational systems biology. *Nature*. 2002 Nov 14;420(6912):206-10. Digital Object Identifier: 10.1038/nature01254 nature01254 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12432404
- [9] Kitano H. Systems biology: a brief overview. *Science*. 2002 Mar 1;295(5560):1662-4. Digital Object Identifier: 10.1126/science.1069492 295/5560/1662 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11872829
- [10] Oltvai ZN, Barabasi AL. Systems biology. Life's complexity pyramid. *Science*. 2002 Oct 25;298(5594):763-4. Digital Object Identifier: 10.1126/science.1078563 298/5594/763 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12399572
- [11] Schaffner KF. Theories, Models, and Equations in Systems Biology. In: Boogerd F, Bruggeman FJ, Hofmeyr J-HS, Westerhoff HV, editors. *Systems Biology: Philosophical Foundations*. Netherlands: Elsevier; 2007. p. 145-62.
- [12] Strange K. The end of "naive reductionism": rise of systems biology or renaissance of physiology? *Am J Physiol Cell Physiol*. 2005 May;288(5):C968-74. Digital Object Identifier: 288/5/C968 [pii] 10.1152/ajpcell.00598.2004. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15840560
- [13] Vidal M. A unifying view of 21st century systems biology. *FEBS Lett*. 2009 Dec 17;583(24):3891-4. Digital Object Identifier: 10.1016/j.febslet.2009.11.024. <http://www.ncbi.nlm.nih.gov/pubmed/19913537>
- [14] Mayr E. *What evolution Is: Basic Books*; 2002.
- [15] Thayer HS. *Newton's Philosophy of Nature: Selections from His Writings*: Dover Publications; 2005.
- [16] Shanks N, Greek R. *Animal Models in Light of Evolution*. Boca Raton: Brown Walker; 2009.
- [17] Bernard C. *An Introduction to the Study of Experimental Medicine*. 1865. New York: Dover; 1957.
- [18] Elliot P. Vivisection and the Emergence of Experimental Medicine in Nineteenth Century France. In: Rupke N, editor. *Vivisection in Historical Perspective*. New York: Croom Helm; 1987. p. 48-77.

- [19] LaFollette H, Shanks N. Animal Experimentation: The Legacy of Claude Bernard. *International Studies in the Philosophy of Science*. 1994;8(3):195-210. Digital Object Identifier:
- [20] Milner R. *Darwin's Universe: Evolution from A to Z*: University of California Press; 2009.
- [21] Darlison MG, Pahal I, Thode C. Consequences of the evolution of the GABA(A) receptor gene family. *Cell Mol Neurobiol*. 2005 Jun;25(3-4):607-24. Digital Object Identifier: 10.1007/s10571-005-4004-4. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16075381
- [22] Enna SJ, Williams M. Defining the role of pharmacology in the emerging world of translational research. *Advances in pharmacology*. [Historical Article]. 2009;57:1-30. Digital Object Identifier: 10.1016/S1054-3589(08)57001-3. <http://www.ncbi.nlm.nih.gov/pubmed/20230758>
- [23] Geerts H. Of mice and men: bridging the translational disconnect in CNS drug discovery. *CNS Drugs*. 2009 Nov 1;23(11):915-26. Digital Object Identifier: 10.2165/11310890-000000000-00000. <http://www.ncbi.nlm.nih.gov/pubmed/19845413>
- [24] Jankovic J, Noebels JL. Genetic mouse models of essential tremor: are they essential? *J Clin Invest*. 2005 Mar;115(3):584-6. Digital Object Identifier: 10.1172/JCI24544. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15765140
- [25] Kiebertz K, Olanow CW. Translational experimental therapeutics: The translation of laboratory-based discovery into disease-related therapy. *Mt Sinai J Med*. 2007 Apr;74(1):7-14. Digital Object Identifier: 10.1002/msj.20006. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17516559
- [26] Liu Z, Maas K, Aune TM. Comparison of differentially expressed genes in T lymphocytes between human autoimmune disease and murine models of autoimmune disease. *Clin Immunol*. 2004 Sep;112(3):225-30. Digital Object Identifier: 10.1016/j.clim.2004.03.017 S1521661604001081 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15308114
- [27] Miklos GLG. The human cancer genome project--one more misstep in the war on cancer. *Nat Biotechnol*. 2005 May;23(5):535-7. Digital Object Identifier: nbt0505-535 [pii] 10.1038/nbt0505-535. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15877064
- [28] Greek R, Menache A, Rice MJ. Animal models in an age of personalized medicine. *Personalized Medicine*. 2012 2012/01/01;9(1):47-64. Digital Object Identifier: 10.2217/pme.11.89. <http://dx.doi.org/10.2217/pme.11.89>
- [29] Csete ME, Doyle JC. Reverse engineering of biological complexity. *Science*. 2002 Mar 1;295(5560):1664-9. Digital Object Identifier: 10.1126/science.1069981 295/5560/1664

- [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11872830
- [30] Kitano H. A robustness-based approach to systems-oriented drug design. *Nat Rev Drug Discov.* 2007 Mar;6(3):202-10. Digital Object Identifier: nrd2195 [pii] 10.1038/nrd2195. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17318209
- [31] Morange M. *The misunderstood gene.* Cambridge: Harvard University Press; 2001.
- [32] Morange M. A successful form for reductionism. *The Biochemist.* 2001;23:37-9. Digital Object Identifier:
- [33] Pearson H. Surviving a knockout blow. *Nature.* 2002 Jan 3;415(6867):8-9. Digital Object Identifier: 10.1038/415008a 415008a [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11780081
- [34] Horrobin DF. Modern biomedical research: an internally self-consistent universe with little contact with medical reality? *Nat Rev Drug Discov.* 2003 Feb;2(2):151-4. Digital Object Identifier: 10.1038/nrd1012 nrd1012 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12563306
- [35] Monte J, Liu M, Sheya A, Kitami T. Definitions, Measures, and Models of Robustness in Gene Regulatory Network. Report of research work for CSSS05. 2005 [cited 2007 March 30]; Report of research work for CSSS05, 2005]. Available from: http://www.santafe.edu/education/csss/csss05/papers/monte_et_al_csss05.pdf.
- [36] Jura J, Wegrzyn P, Koj A. Regulatory mechanisms of gene expression: complexity with elements of deterministic chaos. *Acta Biochim Pol.* 2006;53(1):1-10. Digital Object Identifier: 20061177 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16505901
- [37] Alm E, Arkin AP. Biological networks. *Curr Opin Struct Biol.* 2003 Apr;13(2):193-202. Digital Object Identifier: S0959440X03000319 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12727512
- [38] Ottino JM. Engineering complex systems. *Nature.* 2004 Jan 29;427(6973):399. Digital Object Identifier: 10.1038/427399a 427399a [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14749808
- [39] Sole R, Goodwin B. *Signs of Life: How Complexity Pervades Biology: Basic Books;* 2002.
- [40] Kauffman SA. *The Origins of Order: Self-Organization and Selection in Evolution* Oxford University Press; 1993.
- [41] Van Regenmortel M. Reductionism and complexity in molecular biology. Scientists now have the tools to unravel biological complexity and overcome the limitations of reductionism. *EMBO Rep.* 2004 Nov;5(11):1016-20. Digital Object Identifier: 7400284

- [pii] 10.1038/sj.embor.7400284. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15520799
- [42] Van Regenmortel MHV. Basic Research in HIV vaccinology is hampered by reductionist thinking. *Frontiers in Immunology*. [Review]. 2012 2012-July-9;3. Digital Object Identifier: 10.3389/fimmu.2012.00194. http://www.frontiersin.org/Journal/Abstract.aspx?s=1247&name=immunotherapies_and_vaccines&ART_DOI=10.3389/fimmu.2012.00194
- [43] Miska D. Biotech's twentieth birthday blues. *Nat Rev Drug Discov*. 2003 Mar;2(3):231-3. Digital Object Identifier: 10.1038/nrd1036 nrd1036 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12612649
- [44] Nicolis G, Prigogine I. *Exploring complexity: An introduction*. New York: W.H. Freeman and Co; 1989.
- [45] Bell JT, Spector TD. A twin approach to unraveling epigenetics. *Trends Genet*. 2011 Mar;27(3):116-25. Digital Object Identifier: 10.1016/j.tig.2010.12.005.
- [46] Bruder CE, Piotrowski A, Gijsbers AA, Andersson R, Erickson S, de Stahl TD, et al. Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. *Am J Hum Genet*. 2008 Mar;82(3):763-71. Digital Object Identifier: S0002-9297(08)00102-X [pii] 10.1016/j.ajhg.2007.12.011. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18304490
- [47] Dempster EL, Pidsley R, Schalkwyk LC, Owens S, Georgiades A, Kane F, et al. Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder. *Human molecular genetics*. 2011 Sep 22;20(24):4786-96. Digital Object Identifier: 10.1093/hmg/ddr416. <http://www.ncbi.nlm.nih.gov/pubmed/21908516>
- [48] Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A*. 2005 Jul 26;102(30):10604-9. Digital Object Identifier: 0500398102 [pii] 10.1073/pnas.0500398102. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16009939
- [49] Gordon L, Joo JH, Andronikos R, Ollikainen M, Wallace EM, Umstad MP, et al. Expression discordance of monozygotic twins at birth: effect of intrauterine environment and a possible mechanism for fetal programming. *Epigenetics*. 2011 May;6(5):579-92. Digital Object Identifier:
- [50] Halder A, Jain M, Chaudhary I, Varma B. Chromosome 22q11.2 microdeletion in monozygotic twins with discordant phenotype and deletion size. *Mol Cytogenet*. 2012;5(1):13. Digital Object Identifier: 10.1186/1755-8166-5-13. <http://www.ncbi.nlm.nih.gov/pubmed/22413934>

- [51] Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JJ, Rodriguez-Ubrea J, et al. Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. *Genome Research*. 2010 February 1, 2010;20(2):170-9. Digital Object Identifier: 10.1101/gr.100289.109. <http://genome.cshlp.org/content/20/2/170.abstract>
- [52] Maiti S, Kumar KHBG, Castellani CA, O'Reilly R, Singh SM. Ontogenetic De Novo Copy Number Variations (CNVs) as a Source of Genetic Individuality: Studies on Two Families with MZD Twins for Schizophrenia. *PLoS ONE*. 2011;6(3):e17125. Digital Object Identifier: <http://dx.doi.org/10.1371/journal.pone.0017125>
- [53] Muqit MM, Larner AJ, Sweeney MG, Sewry C, Stinton VJ, Davis MB, et al. Multiple mitochondrial DNA deletions in monozygotic twins with OPMD. *J Neurol Neurosurg Psychiatry*. 2008 Jan;79(1):68-71. Digital Object Identifier: 10.1136/jnnp.2006.112250.
- [54] Ollikainen M, Craig JM. Epigenetic discordance at imprinting control regions in twins. *Epigenomics*. 2011 Jun;3(3):295-306. Digital Object Identifier: 10.2217/epi.11.18.
- [55] Stankiewicz P, Lupski JR. Structural variation in the human genome and its role in disease. *Annu Rev Med*. 2010;61:437-55. Digital Object Identifier: 10.1146/annurev-med-100708-204735.
- [56] Wong AH, Gottesman, II, Petronis A. Phenotypic differences in genetically identical organisms: the epigenetic perspective. *Hum Mol Genet*. 2005 Apr 15;14 Spec No 1:R11-8. Digital Object Identifier: 14/suppl_1/R11 [pii] 10.1093/hmg/ddi116. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15809262
- [57] Holland J. *Emergence*: Perseus Publishing; 1999.
- [58] Van Regenmortel M. Reductionism and the search for structure-function relationships in antibody molecules. *J Mol Recognit*. [Review]. 2002 Sep-Oct;15(5):240-7. Digital Object Identifier: 10.1002/jmr.584. <http://www.ncbi.nlm.nih.gov/pubmed/12447900>
- [59] Gad S. Preface. In: Gad S, editor. *Animal Models in Toxicology*. Boca Rotan: CRC Press; 2007. p. 1-18.
- [60] Calabrese EJ. *Principles of Animal Extrapolation*. Boca Rotan: CRC Press; 1991.
- [61] Shah VP, Flynn GL, Guy RH, Maibach HI, Schaefer H, Skelly JP, et al. Workshop report on in vivo percutaneous penetration/absorption. Washington D.C., May 1-3, 1989. *Skin Pharmacol*. 1991;4(3):220-8. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1685087
- [62] Barber ED, Teetsel NM, Kolberg KF, Guest D. A comparative study of the rates of in vitro percutaneous absorption of eight chemicals using rat and human skin. *Fundam*

- Appl Toxicol. 1992 Nov;19(4):493-7. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1426706
- [63] Scott RC, Batten PL, Clowes HM, Jones BK, Ramsey JD. 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.* 1992 Nov;19(4):484-92. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1426705
- [64] PLoS Press Release. Dalmatian bladder stones caused by gene that regulates uric acid in humans. http://www.eurekalert.org/pub_releases/2008-11/plos-dbs110408.php. 2008(November 6). Digital Object Identifier:
- [65] Mahmood I. Can absolute oral bioavailability in humans be predicted from animals? A comparison of allometry and different indirect methods. *Drug Metabol Drug Interact.* 2000;16(2):143-55. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10962646
- [66] Fox JG, Thibert P, Arnold DL, Krewski DR, Grice HC. Toxicology studies. II. The laboratory animal. *Food Cosmet Toxicol.* 1979 Dec;17(6):661-75. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=546701
- [67] Paxton JW. The allometric approach for interspecies scaling of pharmacokinetics and toxicity of anti-cancer drugs. *Clin Exp Pharmacol Physiol.* 1995 Nov;22(11):851-4. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8593743
- [68] Parkinson C, Grasso P. The use of the dog in toxicity tests on pharmaceutical compounds. *Hum Exp Toxicol.* 1993 Mar;12(2):99-109. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8096722
- [69] Abelson PH. Exaggerated carcinogenicity of chemicals. *Science.* 1992 Jun 19;256(5064):1609. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1609271
- [70] Smith RL, Caldwell J. Drug metabolism in non-human primates. In: Parke DV, Smith RL, editors. *Drug metabolism - from microbe to man*. London: Taylor & Francis; 1977. p. 331-56.
- [71] Walker RM, McElligott TF. Furosemide induced hepatotoxicity. *J Pathol.* 1981 Dec; 135(4):301-14. Digital Object Identifier: 10.1002/path.1711350407. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7328448
- [72] Weatherall M. An end to the search for new drugs? *Nature.* 1982;296:387-90. Digital Object Identifier:

- [73] Bonati M, Latini R, Tognoni G, Young JF, Garattini S. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. *Drug Metab Rev.* 1984;15(7):1355-83. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6543526
- [74] Health Day. Hormone Lowers Glucose Levels in Mice. <http://www.healthday.com/Article.asp?AID=620987>. 11/13/2008. Digital Object Identifier:
- [75] BBC News. Window into cancer-spread secrets. 2008 [November 10].
- [76] Caldwell J. Problems and opportunities in toxicity testing arising from species differences in xenobiotic metabolism. *Toxicol Lett.* 1992 Dec;64-65 Spec No:651-9. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1471219
- [77] Serrano D, Lazzeroni M, Zambon CF, Macis D, Maisonneuve P, Johansson H, et al. Efficacy of tamoxifen based on cytochrome P450 2D6, CYP2C19 and SULT1A1 genotype in the Italian Tamoxifen Prevention Trial. *Pharmacogenomics J.* 2011;11(2):100-7. Digital Object Identifier: <http://dx.doi.org/10.1038/tpj.2010.17>
- [78] Sellers RS, Senese PB, Khan KN. Interspecies differences in the nephrotoxic response to cyclooxygenase inhibition. *Drug Chem Toxicol.* 2004 May;27(2):111-22. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15198071
- [79] Walton K, Dorne JL, Renwick AG. Species-specific uncertainty factors for compounds eliminated principally by renal excretion in humans. *Food Chem Toxicol.* 2004 Feb;42(2):261-74. Digital Object Identifier: S0278691503002722 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14667472
- [80] Dixit R, Boelsterli U. Healthy animals and animal models of human disease(s) in safety assessment of human pharmaceuticals, including therapeutic antibodies. *Drug Discovery Today.* 2007;12(7-8):336-42. Digital Object Identifier:
- [81] Hughes B. Industry concern over EU hepatotoxicity guidance. *Nat Rev Drug Discov.* 2008;7(9):719-. Digital Object Identifier: <http://dx.doi.org/10.1038/nrd2677>
- [82] Weaver JL, Staten D, Swann J, Armstrong G, Bates M, Hastings KL. Detection of systemic hypersensitivity to drugs using standard guinea pig assays. *Toxicology.* 2003 Dec 1;193(3):203-17. Digital Object Identifier: S0300483X03002671 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14599760
- [83] Force T, Kolaja KL. Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes. *Nat Rev Drug Discov.* [10.1038/nrd3252]. 2011;10(2):111-26. Digital Object Identifier: <http://dx.doi.org/10.1038/nrd3252>
- [84] Eason CT, Bonner FW, Parke DV. The importance of pharmacokinetic and receptor studies in drug safety evaluation. *Regul Toxicol Pharmacol.* 1990 Jun;11(3):288-307.

- Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2196638
- [85] Sankar U. The Delicate Toxicity Balance in Drug Discovery. *The Scientist*. 2005 Aug 1;19(15):32. Digital Object Identifier:
- [86] Caponigro G, Sellers WR. Advances in the preclinical testing of cancer therapeutic hypotheses. *Nat Rev Drug Discov*. 2011 Mar;10(3):179-87. Digital Object Identifier: nrd3385 [pii] 10.1038/nrd3385. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21358737
- [87] Editors. In this issue. *Nat Rev Drug Discov*. [10.1038/nrd3411]. 2011;10(4):239-. Digital Object Identifier: <http://dx.doi.org/10.1038/nrd3411>
- [88] Leaf C. Why we are losing the war on cancer. *Fortune*. 2004(March 9):77-92. Digital Object Identifier: http://money.cnn.com/magazines/fortune/fortune_archive/2004/03/22/365076/index.htm
- [89] Park BK, Boobis A, Clarke S, Goldring CEP, Jones D, Kenna JG, et al. Managing the challenge of chemically reactive metabolites in drug development. *Nat Rev Drug Discov*. [10.1038/nrd3408]. 2011;10(4):292-306. Digital Object Identifier: <http://dx.doi.org/10.1038/nrd3408>
- [90] Gad S. Model Selection and Scaling. In: Gad S, editor. *Animal Models in Toxicology, Second Edition (Drug and Chemical Toxicology)*: Informa Healthcare; 2006. p. 831-62.
- [91] Sarkar SK. Molecular imaging approaches. *Drug Discovery World*. 2009(Fall):33-8. Digital Object Identifier:
- [92] Litchfield JT, Jr. 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*. 1962 Sep-Oct;3:665-72. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14465857
- [93] Suter K. What can be learned from case studies? The company approach. In: Lumley C, Walker S, editors. *Animal Toxicity Studies: Their Relevance for Man*. Lancaster: Quay; 1990. p. 71-8.
- [94] Fourches D, Barnes JC, Day NC, Bradley P, Reed JZ, Tropsha A. Cheminformatics analysis of assertions mined from literature that describe drug-induced liver injury in different species. *Chem Res Toxicol*. 2010 Jan;23(1):171-83. Digital Object Identifier: 10.1021/tx900326k. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20014752
- [95] Sietsema WK. The absolute oral bioavailability of selected drugs. *Int J Clin Pharmacol Ther Toxicol*. 1989 Apr;27(4):179-211. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2654032

- [96] Fletcher AP. Drug safety tests and subsequent clinical experience. *J R Soc Med.* 1978 Sep;71(9):693-6. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=712750
- [97] Lumley C. Clinical toxicity: could it have been predicted? Premarketing experience. In: Lumley C, Walker S, editors. *Animal Toxicity Studies: Their Relevance for Man*: Quay; 1990. p. 49-56.
- [98] Spriet-Pourra C, Auriche M, (Eds). *SCRIP Reports*: PJB; 1994.
- [99] Heywood R. Clinical Toxicity--Could it have been predicted? Post-marketing experience. In: CE Lumley, Walker S, editors. *Animal Toxicity Studies: Their Relevance for Man*. Lancaster: Quay; 1990. p. 57-67.
- [100] Igarashi Y. Report from the Japanese Pharmaceutical Manufacturers Association 1994 Seiyakukyo data.
- [101] Lin JH. Species similarities and differences in pharmacokinetics. *Drug Metab Dispos.* 1995 Oct;23(10):1008-21. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8654187
- [102] Garattini S. Toxic effects of chemicals: difficulties in extrapolating data from animals to man. *Crit Rev Toxicol.* 1985;16(1):1-29. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3910353
- [103] Heywood R. Target organ toxicity II. *Toxicol Lett.* 1983 Aug;18(1-2):83-8. Digital Object Identifier: 0378-4274(83)90075-9 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6623552
- [104] Wall RJ, Shani M. Are animal models as good as we think? *Theriogenology.* 2008 Jan 1;69(1):2-9. Digital Object Identifier: S0093-691X(07)00598-5 [pii] 10.1016/j.theriogenology.2007.09.030. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17988725
- [105] Markou A, Chiamulera C, Geyer MA, Tricklebank M, Steckler T. Removing obstacles in neuroscience drug discovery: the future path for animal models. *Neuropsychopharmacology* : official publication of the American College of Neuropsychopharmacology. 2009 Jan;34(1):74-89. Digital Object Identifier: 10.1038/npp.2008.173. <http://www.ncbi.nlm.nih.gov/pubmed/18830240>
- [106] Mullane K, Williams M. Translational semantics and infrastructure: another search for the emperor's new clothes? *Drug Discovery Today* 2012;17(9/10):459-68. Digital Object Identifier:
- [107] Rice J. Animal models: Not close enough. *Nature.* [10.1038/nature11102]. 2012;484(7393):S9-S. Digital Object Identifier: <http://dx.doi.org/10.1038/nature11102>
- [108] Cook N, Jodrell DI, Tuveson DA. Predictive in vivo animal models and translation to clinical trials. *Drug Discovery Today.* 2012;17(5/6):253-60. Digital Object Identifier:

- [109] Johnson JI, Decker S, Zaharevitz D, Rubinstein LV, Venditti JM, Schepartz S, et al. Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. *Br J Cancer*. 2001 May 18;84(10):1424-31. Digital Object Identifier: 10.1054/bjoc.2001.1796 S0007092001917963 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11355958
- [110] Suggitt M, Bibby MC. 50 years of preclinical anticancer drug screening: empirical to target-driven approaches. *Clinical cancer research : an official journal of the American Association for Cancer Research*. [Research Support, Non-U.S. Gov't Review]. 2005 Feb 1;11(3):971-81. Digital Object Identifier: <http://www.ncbi.nlm.nih.gov/pubmed/15709162>
- [111] Salsburg D. The lifetime feeding study in mice and rats--an examination of its validity as a bioassay for human carcinogens. *Fundam Appl Toxicol*. 1983 Jan-Feb;3(1):63-7. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6884625
- [112] Tomatis L, Agthe C, Bartsch H, Huff J, Montesano R, Saracci R, et al. 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*. 1978 Apr;38(4):877-85. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=346205
- [113] Reuters. U.S. to develop chip that tests if a drug is toxic. *Reuters*; 2011 [updated September 16; cited 2011 October 6]; Available from: http://www.msnbc.msn.com/id/44554007/ns/health-health_care/-To5AMnPaixF.
- [114] Gura T. Cancer Models: Systems for identifying new drugs are often faulty. *Science*. 1997 Nov 7;278(5340):1041-2. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9381203
- [115] Björquist P, Sartipy P, Raimund Strehl and Johan Hyllner. Human ES cell derived functional cells as tools in drug discovery. *Drug Discovery World*. 2007(Winter):17-24. Digital Object Identifier:
- [116] FDA. FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient. *FDA*; 2006 [updated June 18, 2009; cited 2010 March 7]; *FDA News Release*. Available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108576.htm>.
- [117] Zielinska E. Building a better mouse. *The Scientist*. 2010 April 1;24(4):34-8. Digital Object Identifier:
- [118] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003 Mar;22(2):151-85. Digital Object Identifier: S0167-6296(02)00126-1 [pii] 10.1016/S0167-6296(02)00126-1. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12606142

- [119] Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov.* 2004 Aug;3(8):711-5. Digital Object Identifier: 10.1038/nrd1470 nrd1470 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15286737
- [120] Shaffer C. Safety Through Sequencing. *Drug Discovery & Development* 2012 [updated January 1, 2012; cited 2012 January 30]; Available from: http://www.dddmag.com/article-Safety-Through-Sequencing-12412.aspx?et_cid=2450547&et rid=45518461&linkid=http%3a%2f%2fwww.dddmag.com%2farticle-Safety-Through-Sequencing-12412.aspx
- [121] Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov.* 2010 Mar;9(3):203-14. Digital Object Identifier: nrd3078 [pii] 10.1038/nrd3078. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20168317
- [122] Cressey D. Traditional drug-discovery model ripe for reform. *Nature.* 2011 Mar 3;471(7336):17-8. Digital Object Identifier: 471017a [pii] 10.1038/471017a. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21368796
- [123] Giri S, Bader A. Foundation review: Improved preclinical safety assessment using micro-BAL devices: the potential impact on human discovery and drug attrition. *Drug Discovery Today.* 2011;16(9/10):382-97. Digital Object Identifier:
- [124] Unknown. *Drug Discovery & Development.* 2002(November):35. Digital Object Identifier:
- [125] Roy ASA. *Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials.* New York: Manhattan Institute for Policy Research 2012 March
- [126] Makarova SI. Human N-acetyltransferases and drug-induced hepatotoxicity. *Current drug metabolism.* [Review]. 2008 Jul;9(6):538-45. Digital Object Identifier: <http://www.ncbi.nlm.nih.gov/pubmed/18680474>
- [127] Mullard A. Marc Kirschner. *Nat Rev Drug Discov.* [10.1038/nrd3613]. 2011;10(12): 894-. Digital Object Identifier: <http://dx.doi.org/10.1038/nrd3613>
- [128] Alonso-Zaldivar R. Earlier Drug Testing on Humans OKd. Los Angeles: LA Times; 2006 [updated January 13; cited 2010 March 8]; Available from: <http://articles.latimes.com/2006/jan/13/nation/na-fda13>.
- [129] Waldman M. Drive for drugs leads to baby clinical trials. *Nature.* 2006 Mar 23;440(7083):406-7. Digital Object Identifier: 440406a [pii] 10.1038/440406a. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16554774
- [130] Lappin G, Garner RC. Big physics, small doses: the use of AMS and PET in human microdosing of development drugs. *Nat Rev Drug Discov.* 2003 Mar;2(3):233-40. Dig-

- ital Object Identifier: 10.1038/nrd1037 nrd1037 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12612650
- [131] Lappin G, Garner RC. The utility of microdosing over the past 5 years. *Expert Opinion on Drug Metabolism & Toxicology*. [Review]. 2008 Dec;4(12):1499-506. Digital Object Identifier: 10.1517/17425250802531767. <http://www.ncbi.nlm.nih.gov/pubmed/19040326>
- [132] Lappin G, Kuhnz W, Jochemsen R, Kneer J, Chaudhary A, Oosterhuis B, et al. Use of microdosing to predict pharmacokinetics at the therapeutic dose: experience with 5 drugs. *Clin Pharmacol Ther*. 2006 Sep;80(3):203-15. Digital Object Identifier: S0009-9236(06)00200-1 [pii] 10.1016/j.clpt.2006.05.008. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16952487
- [133] Gill DM. Bacterial toxins: a table of lethal amounts. *Microbiol Rev*. [Review]. 1982 Mar;46(1):86-94. Digital Object Identifier: <http://www.ncbi.nlm.nih.gov/pubmed/6806598>
- [134] National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances (R-TECS). Cincinnati: National Institute of Occupational Safety and Health; 1996.
- [135] Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? *Nat Rev Drug Discov*. 2010 Nov;9(11):856-65. Digital Object Identifier: nrd3227 [pii] 10.1038/nrd3227. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20847743
- [136] ATSDR. Cancer Fact Sheet. Atlanta: CDC. Agency for Toxic Substances & Disease Registry; 2002 [updated August 30, 2002; cited 2012 May 22]; Available from: <http://www.atsdr.cdc.gov/com/cancer-fs.html>.
- [137] Shah RR. Pharmacogenetics in drug regulation: promise, potential and pitfalls. *Philos Trans R Soc Lond B Biol Sci*. 2005 Aug 29;360(1460):1617-38. Digital Object Identifier: 3VfVUVCNBUK20M3Q [pii] 10.1098/rstb.2005.1693. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16096112
- [138] Roses AD. Pharmacogenetics and the practice of medicine. *Nature*. 2000 Jun 15;405(6788):857-65. Digital Object Identifier: 10.1038/35015728. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10866212
- [139] Angst MS, Chu LF, Tingle MS, Shafer SL, Clark JD, Drover DR. No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. *Pain*. 2009 Mar;142(1-2):17-26. Digital Object Identifier: 10.1016/j.pain.2008.11.001. <http://www.ncbi.nlm.nih.gov/pubmed/19135798>
- [140] Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data.

- British journal of anaesthesia. [Review]. 2005 Nov;95(5):584-91. Digital Object Identifier: 10.1093/bja/aei227. <http://www.ncbi.nlm.nih.gov/pubmed/16169893>
- [141] Yucesoy B, Johnson VJ, Fluharty K, Kashon ML, Slaven JE, Wilson NW, et al. Influence of cytokine gene variations on immunization to childhood vaccines. *Vaccine*. 2009 Nov 23;27(50):6991-7. Digital Object Identifier: S0264-410X(09)01423-6 [pii] 10.1016/j.vaccine.2009.09.076. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19819209
- [142] King C. Personalised vaccines could protect all children *New Scientist*. 2009 December 5(2737):11. Digital Object Identifier:
- [143] Willyard C. Blue's clues. *Nat Med*. 2007 Nov;13(11):1272-3. Digital Object Identifier: nm1107-1272 [pii] 10.1038/nm1107-1272. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17987010
- [144] Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, et al. Association of Age and Sex With Myocardial Infarction Symptom Presentation and In-Hospital Mortality. *JAMA: The Journal of the American Medical Association*. 2012 February 22/29, 2012;307(8):813-22. Digital Object Identifier: 10.1001/jama.2012.199. <http://jama.ama-assn.org/content/307/8/813.abstract>
- [145] Holden C. Sex and the suffering brain. *Science*. 2005 Jun 10;308(5728):1574. Digital Object Identifier: 308/5728/1574 [pii] 10.1126/science.308.5728.1574. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15947170
- [146] Kaiser J. Gender in the pharmacy: does it matter? *Science*. 2005 Jun 10;308(5728):1572. Digital Object Identifier: 308/5728/1572 [pii] 10.1126/science.308.5728.1572. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15947169
- [147] Klein S, Huber S. Sex differences in susceptibility to viral infection. In: Klein S, Roberts C, editors. *Sex hormones and immunity to infection*. Berlin: Springer-Verlag; 2010. p. 93-122.
- [148] Simon V. Wanted: women in clinical trials. *Science*. 2005 Jun 10;308(5728):1517. Digital Object Identifier: 308/5728/1517 [pii] 10.1126/science.1115616. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15947140
- [149] Wald C, Wu C. Of Mice and Women: The Bias in Animal Models. *Science*. 2010;327(5973):1571-2. Digital Object Identifier:
- [150] Willyard C. HIV gender clues emerge. *Nat Med*. 2009 Aug;15(8):830. Digital Object Identifier: nm0809-830b [pii] 10.1038/nm0809-830b. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19661976

- [151] Cheung DS, Warman ML, Mulliken JB. Hemangioma in twins. *Ann Plast Surg*. 1997 Mar;38(3):269-74. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9088466
- [152] Couzin J. Cancer research. Probing the roots of race and cancer. *Science*. 2007 Feb 2;315(5812):592-4. Digital Object Identifier: 315/5812/592 [pii] 10.1126/science.315.5812.592. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17272699
- [153] Gregor Z, Joffe L. Senile macular changes in the black African. *Br J Ophthalmol*. 1978 Aug;62(8):547-50. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=687553
- [154] Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med*. 2006 Jan 26;354(4):333-42. Digital Object Identifier: 354/4/333 [pii] 10.1056/NEJMoa033250. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16436765
- [155] Kalow W. Interethnic variation of drug metabolism. *Trends in Pharmacological Sciences*. [Review]. 1991 Mar;12(3):102-7. Digital Object Identifier: <http://www.ncbi.nlm.nih.gov/pubmed/2053186>
- [156] Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 Genetic Variants in Focal Segmental Glomerulosclerosis and HIV-Associated Nephropathy. *Journal of the American Society of Nephrology*. 2011 October 13, 2011. Digital Object Identifier: 10.1681/asn.2011040388. <http://jasn.asnjournals.org/content/early/2011/10/06/ASN.2011040388.abstract>
- [157] Spielman RS, Bastone LA, Burdick JT, Morley M, Ewens WJ, Cheung VG. Common genetic variants account for differences in gene expression among ethnic groups. *Nat Genet*. 2007 Feb;39(2):226-31. Digital Object Identifier: ng1955 [pii] 10.1038/ng1955. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17206142
- [158] Stamer UM, Stuber F. The pharmacogenetics of analgesia. *Expert Opin Pharmacother*. 2007 Oct;8(14):2235-45. Digital Object Identifier: 10.1517/14656566.8.14.2235. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17927480
- [159] Wilke RA, Dolan ME. Genetics and Variable Drug Response. *JAMA: The Journal of the American Medical Association*. 2011 July 20, 2011;306(3):306-7. Digital Object Identifier: 10.1001/jama.2011.998. <http://jama.ama-assn.org/content/306/3/306.short>
- [160] HealthDay. Gene Sequences May Make You Unique. *HealthDay_News*; 2010 [updated March 18; cited 2010 March 18]; Available from: <http://health.yahoo.com/news/healthday/genesequencesmaymakeyouunique.html>.

- [161] Kasowski M, Grubert F, Heffelfinger C, Hariharan M, Asabere A, Waszak SM, et al. Variation in Transcription Factor Binding Among Humans. *Science*. 2010 Mar 18;328(5975):232-5. Digital Object Identifier: science.1183621 [pii] 10.1126/science.1183621. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20299548
- [162] Herzig M, Christofori G. Recent advances in cancer research: mouse models of tumorigenesis. *Biochim Biophys Acta*. 2002 Jun 21;1602(2):97-113. Digital Object Identifier: S0304419X02000392 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12020798
- [163] Ingram DK, Jucker M. Developing mouse models of aging: a consideration of strain differences in age-related behavioral and neural parameters. *Neurobiol Aging*. 1999 Mar-Apr;20(2):137-45. Digital Object Identifier: S0197458099000330 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10537023
- [164] Raineri I, Carlson EJ, Gacayan R, Carra S, Oberley TD, Huang TT, et al. Strain-dependent high-level expression of a transgene for manganese superoxide dismutase is associated with growth retardation and decreased fertility. *Free Radic Biol Med*. 2001 Oct 15;31(8):1018-30. Digital Object Identifier: S0891584901006864 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11595386
- [165] Hunter K, Welch DR, Liu ET. Genetic background is an important determinant of metastatic potential. *Nat Genet*. 2003 May;34(1):23-4; author reply 5. Digital Object Identifier: 10.1038/ng0503-23b ng0503-23b [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12721549
- [166] Thein SL. Genetic modifiers of beta-thalassemia. *Haematologica*. 2005 May;90(5):649-60. Digital Object Identifier: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15921380
- [167] Agarwal S, Moorchung N. Modifier genes and oligogenic disease. *J Nippon Med Sch*. 2005 Dec;72(6):326-34. Digital Object Identifier: JST.JSTAGE/jnms/72.326 [pii]. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16415512
- [168] Friedman A, Perrimon N. Genetic screening for signal transduction in the era of network biology. *Cell*. 2007 Jan 26;128(2):225-31. Digital Object Identifier: S0092-8674(07)00063-3 [pii] 10.1016/j.cell.2007.01.007. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17254958
- [169] Editorial. Deconstructing Genetic Contributions to Autoimmunity in Mouse Models. *PLoS Biology*. 2004 August 01, 2004;2(8):e220. Digital Object Identifier: <http://dx.doi.org/10.1371/journal.pbio.0020220>
- [170] Weiss ST, McLeod HL, Flockhart DA, Dolan ME, Benowitz NL, Johnson JA, et al. Creating and evaluating genetic tests predictive of drug response. *Nat Rev Drug Dis*

cov. 2008 Jul;7(7):568-74. Digital Object Identifier: nrd2520 [pii] 10.1038/nrd2520. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18587383

- [171] Dolgin E. Big pharma moves from 'blockbusters' to 'niche busters'. *Nat Med.* [10.1038/nm0810-837a]. 2010;16(8):837-. Digital Object Identifier: <http://dx.doi.org/10.1038/nm0810-837a>
- [172] Herscu P, Hoover TA, Randolph AG. Clinical prediction rules: new opportunities for pharma. *Drug Discov Today.* 2009 Dec;14(23-24):1143-9. Digital Object Identifier: S1359-6446(09)00341-9 [pii] 10.1016/j.drudis.2009.09.012. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19853059
- [173] The Medical Letter. Invader UGT1A1 Molecular Assay for Irinotecan Toxicity. *The Medical Letter.* 2006 May 8;48(1234):39-40. Digital Object Identifier:
- [174] Hudson KL. Genomics, Health Care, and Society. *New England Journal of Medicine.* 2011;365(11):1033-41. Digital Object Identifier: doi:10.1056/NEJMra1010517. <http://www.nejm.org/doi/full/10.1056/NEJMra1010517>
- [175] Hughes AR, Spreen WR, Mosteller M, Warren LL, Lai EH, Brothers CH, et al. Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility. *Pharmacogenomics J.* 2008 Dec;8(6):365-74. Digital Object Identifier: tpj20083 [pii] 10.1038/tpj.2008.3. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18332899
- [176] Blair E. Predictive tests and personalised medicine. *Drug Discovery World.* 2009(Fall):27-31. Digital Object Identifier:
- [177] PMC. Personalized Medicine. Personalized Medicine Coalition; 2006 [cited 2006 October 30]; Available from: http://www.ageofpersonalizedmedicine.org/personalized_medicine/today_case.asp.