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Rodent models for human diseases

Thierry F. Vandamme *

Université de Strasbourg, Faculté de pharmacie, UMR 7199 CNRS, Laboratoire de Conception et Application de Molécules Bioactives, 74 Route du Rhin, B.P. 60024, 67401 Illkirch Cedex, France

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ABSTRACT

One of the factors limiting the translation of knowledge from preclinical studies to the clinic has been the limitations of *in vivo* diseases models. Except in the case of highly controlled and regulated clinical trials, geneticists and scientists do not use humans for their experimental investigations because of the obvious risk to life. Instead, they use various animal, fungal, bacterial, and plant species as model organisms for their studies. Amongst these model organisms, rodent models are the most used due to the easiness for the experiments and the possibility to modify genetically these model animals. Nevertheless, due to the fact that animal models typically do not contract the same genetic diseases as people, so scientists must alter their genomes to induce human disease states and to know what kind of mutation causes the disease. In this brief review, we will discuss the interests of rodent models that have been developed to simulate human pathologies, focusing in models that employ xenografts and genetic modification. Within the framework of genetically engineered mouse (GEM) models, we will review some of the current genetic strategies for modeling diseases.

1. Introduction

A multi-disciplinary approach to improve medical treatments can catalyze scientific developments and enable clinical translation beyond what we currently utilize. Engineers, chemists, and physical scientists are teaming up with biologists, physiologists and clinical physicians to attack the vast array of human diseases using new drug developments, materials and conventional or targeted dosage forms.

The challenge is not other than to identify new therapeutic targets in keeping with a pathology. Classically, they are receivers or enzymes on which are fixed the drugs in order to modify the cellular functions. Once the validated target, its biological operation should then be deciphered. Thanks to the exploration of the human genome, the potential of new targets increased these last years considerably and, in the future, the treatments will gain in specificity. The current challenge consists in identifying the embarrassments predisposing with such or such disease in the objective to find new ways of therapeutic.

Even if bioinformatics, high-throughput screening, cell cultures, *in vitro* and *ex vivo* experiments are able to orientate the interests for a lead compound, a drug or a new formulation, it does not remain about it less than the animal experimentation remains necessary before considering the first human tests.

In many cases, while computers provide terrific resources for researchers all over the world, they do have limitations. For instance, computers are only able to provide informations or models known as “phenomena.” Because research consistently seeks answers to unknowns, a computer is unable to simulate how a particular cell might interact or react with a medical compound, or how a complex biological system such as the circulatory system will react to a new drug directed to improve organ function. A single living cell is many times more complex than even the most sophisticated computer program. There are an estimated 50–100 trillion cells in the human body, all of which communicate and interact using a complicated biochemical language – a language researchers have only just begun to learn. Studies using isolated cells or tissues almost always precede animal-based research, but researchers must study whole living systems to understand the effectiveness of treatments and, their potential benefits and dangers.

Despite claims by animal rights activists, it is undeniable that animal-based research has contributed to significant improvement in the length and quality of human lives. Nevertheless, each species in the animal kingdom is unique. But just as there are differences, there are also key similarities. This is what comparative medicine is about: researchers use both similarities and differences to gain insight into the many complex human biological systems.

Researchers often work with animal models that have biological systems similar to that of a human. For instance, swine and humans share similar cardiovascular and skin systems. By working

* Tel.: +33 3 68 85 41 06; fax: +33 3 68 85 43 25.
E-mail address: vandamme@unistra.fr

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with swine, researchers are better able to develop and study new heart medicines and treatments for skin diseases.

To study genetic disorders such as Down Syndrome or Parkinson's Disease, researchers might study a mouse model which shares 94% of its DNA with humans. Organisms that look very different can be very similar genetically. Chimpanzees share 98.7% of their DNA with humans. Zebra fish share 75–80% of their DNA with humans. Bananas share 50%.

The differences exhibited in a research model can also provide great insights. For instance, sharks and pigs rarely get cancer, cockroaches can regenerate damaged nerves, and some amphibians can regrow lost limbs. By studying these animals we may learn how they accomplish these remarkable feats and apply the principles to human medicine.

2. Animal models

In vitro assays typically rely on simple interactions of (bio) chemicals with a drug target, such as receptor binding or enzyme activity inhibition. However, *in vitro* results often poorly correlate with *in vivo* results because the complicated physiological environment is absent in the *in vitro* testing system. Although cell-based assays can provide some information, cultured cells still do not provide physiological conditions and complex interactions among different cell types and tissues. Moreover, cell lines are usually transformed, exhibiting different gene expression and cell cycle profiles than those of cells in the living organism.

For these reasons, there is a growing trend of using human tissues for drug discovery research. Tissues, however, only provide an isolated *ex vivo* condition, which is not completely representative of *in vivo* response because drug action often involves metabolism and interplay among different tissues. For instance, the effects of a drug on muscle may involve absorption by the intestine and metabolism by the liver. Therefore, results in animal studies are essential to validate HTS (high-throughput screening) hits and exclude compounds with unfavorable ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, which are responsible for more than half of compound attrition in costly clinical trials.

It is generally estimated that rodents and fish comprise well over 95% of all animals used in clinical research. When animal models are employed in the study of human disease, they are frequently selected because of their similarity to humans in terms of genetics, anatomy, and physiology. Also, animal models are often preferable for experimental disease research because of their unlimited supply and ease of manipulation (Simmons, 2008). For example, to obtain scientifically valid research results, the conditions associated with an experiment must be closely controlled. This often means manipulating only one variable while keeping others constant, and then observing the consequences of that change. In addition, to test hypotheses about how a disease develops, an adequate number of subjects must be used to statistically test the results of the experiment. Therefore, scientists cannot conduct research on just one animal or human, and it is easier for scientists to use sufficiently a large numbers of animals (rather than people) to attain significant results (Simmons, 2008).

The advantages and limitations by using animal models are shown in Figs. 1 and 2.

2.1. Xenografts model animals

Also called heterograft, xenograft is a graft obtained from a member of one species and transplanted to a member of another species. Investigating the metastatic behavior of cancer stem cells (CSCs) is critical for the development of more effective therapies to

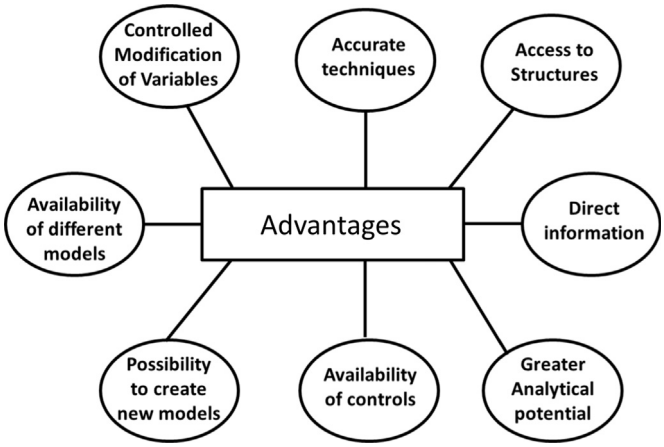

Fig. 1. Main advantages of animal models used in preclinical studies.

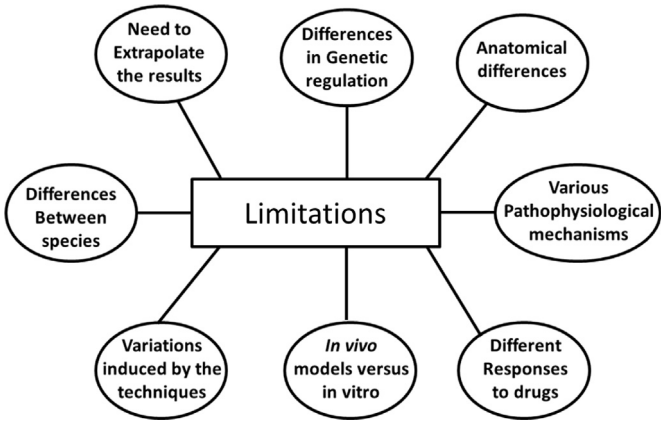

Fig. 2. Limitations of animal models used in preclinical studies.

prevent or delay the progression of malignant diseases. Animal models have been developed to mimic the multistep process of metastasis to various target organs. To do this, several xenograft methods have been studied to introduce human cancer cells into nude mice in order to generate spontaneous and experimental metastases.

By the past, numerous murine models have been developed to study human cancer. These models are used to investigate the factors involved in malignant transformation, invasion and metastasis, as well as to examine response to therapy. One of the most widely used models is the human tumor xenograft. In this model, human tumor cells are transplanted, either under the skin or into the organ type in which the tumor originated, into immunocompromised mice that do not reject human cells. For example, the xenograft will be readily accepted by athymic nude mice, severely compromised immunodeficient (SCID) mice, or other immunocompromised mice (Morton and Houghton, 2007). Depending upon the number of cells injected, or the size of the tumor transplanted, the tumor will develop over 1–8 weeks (or in some instances 1–4 months, or longer), and the response to appropriate therapeutic regimes can be studied *in vivo* (Richmond and Su, 2008).

Even if heterotransplantation of human cancer cells or tumor biopsies into immunodeficient rodents (xenograft models) has, for the past two decades, constituted the major preclinical screen for the development of novel cancer therapeutics, at present time genetically engineered model animals are preferred. Despite limitations, these models have identified clinically efficacious agents, and remain