The use of animal models in cancer research

The use of animals in research has been a rather emotional issue of discussion in recent years, mostly after an increasing awareness of animal rights has emerged and permeated our western societies. The issue at debate is whether we, as scientists and human beings, can justify today the utilization of individuals of other non-human species for the purpose of advancing knowledge and development of our own human species. Because such an utilization in human research involves manipulation, suffering and finally destruction of living individuals (mostly vertebrates), these issues have been debated in many settings and forums, giving rise to a variety of controversial conclusions.

My personal point of view fully adheres to the principles stated in a recent European Science Foundation Policy Briefing on «Use of animals in research»[1], the content of which, I would hope, represents a consensus opinion for the majority in the scientific community at large. In this document, the ESF states the absolute «need of animal use for the advancement of scientific knowledge and for human and animal health and well being» but also «recognizes that laboratory animals nor only have an instrumental value, but also an intrisic value in themselves, which must be respected». This document states a series of 10 guidelines and ethical recommendations that should control and regulate all aspects of animal experimentation, whereas at the same time endorsing the principles of the «Three Rs», recommending to replace the use of live animals by non animal alternatives whenever possible, to reduce the number of animals used to the minimum required for obtaining meaningful results and to refine the procedures to minimize suffering[1].

From the scientific point of view it is undeniable that, in the past, «the use of animals has significantly contributed to the results obtained in scientific research as well as to the safety and efficiency of biological, chemical and other products»[1]. Regarding the future, we also have to recognize that the use of animals in human research will be fundamentally needed for similar purposes for many years to come. Consistent with this view, an NIH position paper on Public Health Service states that biomedical scientists have «an obligation to inform the general public in a rational way about the need for animal testing to ensure that medications, vaccines, environmental chemicals, and a wide variety of consumer products, including cosmetics, are safe for the public when used appropriately»[2]. Without laboratory animals, scientists would lose a fundamental method for obtaining the data needed to make wise decisions about potential health risks. Of course, any initiatives to develop and validate systems to reduce dependency on animal testing should be supported. However, it is true that although modern tissue, organ and cell culture procedures, computer modelization and other non-animal research tools have reduced our dependence on animals, they cannot completely replace experimental animals for the foreseeable future[2].

Within European Union member states, about 12 million vertebrate animals are used per year for research purposes[1]. Although recent years have documented a substantial decrease in the number of animals used, it is reasonable to infer that this decrease trend will be reversed in the near future, mainly due to increased use of transgenic and/or genetically modified animals[3].

Although the public controversy has focused mostly on the use of higher vertebrates, especially primates, in human research, it should be mentioned that a variety of simpler animal models exist that are as useful and necessary, if not more, for the progress of scientific knowledge. Modern biology owes a lot of its recent progress in understanding cancer, developmental biology and the cell cycle to the use of a variety of simpler animal models including frogs, flies, worms, and even yeast. The NIH Web page on Model Organisms for scientific research lists, and provides information on, a number of these simpler models, including Mammalian models (mouse and rat), Non mammalian models (such as Saccharomyces cerevisiae [budding

yeast], Dictiostelium discoideum [social amoebae], Caenorhabditis elegans [round worm] Drosophila melanogaster [fruit fly], Danio rerio [zebra fish] and Xenopus laevis [clawed frog]), and even plant models such as Arabidopsis, which have obvious relevance in modern genomic studies[4].

The usefulness, and need, of animal models to study the etiology and treatment of various human pathologies is obvious. In addition to the variety of vertebrate animal models used in classic pharmacological and toxicological studies[5-7], the use of mouse models (transgenic or not) for a variety of human diseases (both somatic and mental) is essential nowadays[8]. Recent reviews document the application and relevance of genetic mouse models for the study of physiological and pathological human processes such as reproduction, autoimmune diseases, schizophrenia, alcohol research, cardiovascular processes, neurodege-nerative diseases, Alzheimer´s disease, diabetes, etc.[9-21].

Regarding cancer research, an area of my more direct expertise, the use of animal models has been an essential tool up to now, and will continue to be so for many years to come. Regardless of other areas of work, animal models are essentially needed in two main fields of cancer research: a) mechanistic studies of the genes/proteins/signaling pathways involved in cancer onset and progression and b) design, characte-rization and evaluation of new therapeutic approaches.

The validation and general acceptance of the so called genetic paradigm of cancer, whose basic concepts developed gradually during the last 15-20 years, has relied very heavily on the use of experimental animal models. In particular, our current understanding of the function of dominant and recessive cancer genes, as well as the mechanisms of their participation in cancer onset and progression, was only made possible by a lot of experimental work involving «reverse genetics» approaches requiring the use of scores (millions?) of immunologically suppressed, transgenic or knockout rodents. We provide here a small list of recent reviews describing the use of various animal models for cancer research and the functional study of both dominant oncogenes and tumor suppressor genes[22-25], the analysis of various aspects of human carcinogenesis[26-33], the investigation of various aspects of prevention, etiology and epidemiology of human cancer[34-36], or the pathogenesis of specific forms of human tumors[37-40].

Likewise, only the use of various animal models has made it possible the study and evaluation of novel therapeutic approaches and antitumor drugs arising from the modern advances of cancer molecular biology produced during the last decade. In this regard, we have to mention, among others, a variety of genetically modified rodent animal systems allowing studies on 1) the validity of cancer vaccines and other immunological antitumor approaches; 2) the design of new gene therapy methodologies or 3) the evaluation of the safety and efficacy of new, more specific, drugs of recent design[41-43].

In any event, it is expected that the use of genetically modified animal models in cancer research will not only continue, but significantly increase in future years. This is a direct consequence of both 1) a continuing need for answers to new, emerging, mechanistic questions on the biology and pathogenesis of cancer, and 2) the availability of many new, refined, and much more powerful experimental tools. Some of these newly available technological tools originated from further refinements of the methodologies used with transgenic and knockout animal models, whereas the other main group of tools arised from the recent development of the technologies allowing genomic and proteomic analysis at the systemic level. Because of their tremendous potential, it is worth mentioning here 1) the novel, inducible, systems for conditional gene targeting in mice, as well as 2) the technologies of gene profiling applicable to the analysis of the multiple processes associated whith various aspects of carcinogenesis[44-48]. We can anticipate that the combination of these two distinct —and very powerful— sets of technological tools is bound to produce tremendous advances for cancer research in the near future.

In summary, in the current state of affairs, we have to accept that both 1) the need for use of animals in cancer research, and 2) the ethical controversies derived from such practices will continue for long time into the new century.

On one side, I am convinced that we must continue using animals if we want to advance humankind regarding the knowledge, and possible cure of cancer and other diseases. On the other hand, it is also clear to me that the ethical debate linked to the use of models of human disease will not dissappear, but actually increase significantly in the near future. Consider, for example, how recent developments have dramatically widened the current debate by extending the discussion on the use of «animal» models to the use of «human» model systems in research. The ethical controversies surrounding the recent report describing the first attempts at human cloning[49,50] require an open debate on the acceptability of human embryo cloning for therapeutic or reproductive purposes and, ultimately, an objective evaluation of the dignity of the individual embryos of the human species that will be manipulated, and eventually destroyed, for the purpose of obtaining tutipotential stem

cells.

Since scientific progress will keep taking place at an accelerated rate in these research areas, I would only hope that consensual, clear and enforceable ethi- cal guidelines will arise for the purpose of driving such progress from open discussions within scientific community bodies (scientific and medical academies, professional associations, etc), rather than from frequently seen «lone ranger» attitudes or statements from individual scientists or laboratory enterprises.

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