



Canadians for the Advancement of Health Research

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Scientific Critique of Non-Human Primate Research and Testing

Why the project of the Primate Research Center (Centre national de biologie expérimentale (CNBE), is scientifically irrelevant, costly and irresponsible.

Canadians for the Advancement of Health Research (CAHR) has been informed about the creation, in the area of Laval (Quebec), of a new primate research center designed to house from 150 to 200 non-human primates. These primates are to be used to test vaccines allegedly relevant to malaria, hepatitis, AIDS, and study cardiovascular conditions. As an organization dedicated to the promotion of a sound and modern medical research via human-based strategies and alternatives to outdated and potentially dangerous animal testing and experimentation, CAHR deplores the use of \$22.5 million dollars, including public money, not to mention the operational costs, which the new institution will require. We regret that such amount of money is not engaged to foster human-based research and technologies that do not rely on the use of primates. We are also concerned that the confinement and manipulation of the highly sentient and sociable macaques and marmosets will involve levels of pain and stress, despite claims to the contrary made by INRS. But most of all, we are concerned that this costly project relies on an unscientific, unreliable basis, which might delay real scientific discoveries and might ultimately lead to human death and suffering.

The project of the Primate Research Center (CNBE), indeed, relies on the assumption that animals can be models for human diseases. Thus, one species cannot be a model for another one. Dr. Reiss, former research director of the C.N.R.S. (the National Centre for Scientific Research in France) and at the Jacques Monod's Institute, addresses this point when he writes: "Any individual species is defined by its reproductive isolation, which implies that its chromosomes (genome) cannot match, complement or recombine with those of any other species." Dr. Reiss argues that the control and regulation of gene expression are strictly species-specific. Since the genes determine all biological activities, it follows that the species's molecular events and response to pathologies or external stimuli (e.g. toxins, drugs) are similarly species-specific. Therefore, it can be concluded that one species cannot function as a biological model for another species. Monkeys and humans are examples of animal species showing differences and similarities as a result of evolution. However, important differences at the cell and molecular levels exist, and this is precisely these differences in terms of physiology, anatomy, biochemistry, genetics,



and pharmacokinetics (ADME) that make extrapolations of animal data to humans a game of chance.

The so-called *animal model* is a failed and outdated methodology, which is being replaced by other approaches such as gene-based medicine, and *in vitro* techniques making use of human tissue. Not to mention the refinements of imaging techniques, molecular computerization, in combination with other state-of-the-art methods, all making the use of animal species not just irrelevant but wasteful and misleading. The Human Genome Project and similar studies show that one cannot extrapolate findings from a species to another one. The validity of animal models, and namely the monkey model of human diseases, has been disproved recently by researchers, especially in the fields of neurological disorders. (1) We explore below some substantial evidence found in the scientific literature to prove that having recourse to the animal model, even with animals genetically close to human beings such as monkeys, is unscientific and many times unreliable:

1. We would like to remind INRS that hormone replacement therapy was given to millions of women following research in monkeys. The therapy has recently been found to increase their risk of heart disease, stroke and breast cancer, and has therefore been abandoned. (2)

2. Recently, TGN1412 caused six healthy volunteers to suffer multiple organ failure. Earlier, TGN1412 was shown to be quite safe in monkeys. This clinical trial was approved by the regulatory authority (MHRA) on the basis of experiments using macaque monkeys, who were given 500 times the dose of TGN1412 used in the humans.

3. Earlier, an Alzheimer's vaccine developed by Shenk et al. was withdrawn in 2001, when it caused serious brain inflammation in patients, after proving safe and effective in tests on monkeys.

4. The failure of primate research applies to vaccine development as well: *'...prevention [of polio] was long delayed by the erroneous conception of the nature of the human disease based on misleading experimental models of the disease in monkeys.'* Dr. Albert Sabin, inventor of the polio vaccine said.

5. Decades of work and substantial amounts of resources have been used in AIDS research on non-human primates resulting in needless vaccines. Aidsvaxan, an important vaccine deemed successful in chimpanzees, was announced a failure in 2003 because it could not protect the 8,000 high-risk volunteers who took it, despite proving efficacious in chimpanzees (Wilson, 2003).

6. Vaccines have failed in human trials following success in non-human primates. (3) None of 30-plus vaccines essentially tested in non-human primates has proved safe and effective in over 70 clinical trials. The fact is that some candidate antivirals screened using *in vitro* methods have gone directly into humans with little supportive *in vivo* data from prior animal experiments. INRS claims that animal testing should precede clinical



research, when factual examples show that clinical research can proceed regardless of animal data.

7. Primate research has failed many times to predict dangerous side effects of medications, such as Opren (4) and Vioxx, arguably one the largest drug disasters of all times. Animal testing never revealed the cardiovascular risks posed by Vioxx.

8. Dr. JL Schardein, author of 'Chemically Induced Birth Defects' states : "*Of the 15 listed putative human teratogens tested in non-human primates, only eight were also teratogenic in one or more of the various species...*" Aspirin causes birth defects in monkeys but not in humans. (5)

9. Bailey et al. showed that results obtained from research and testing on non-human primates correlate with known human teratogens only 50% of the time, which they claim is much less than results from species such as rats, hamsters and ferrets. (6)

10. Rather than continuing unchecked, the current use of non-human primates to model humans should be stopped and evaluated scientifically without delay, insofar as the practice leads to human death or suffering. The benefits of animal research are often exaggerated and do not pass the test of meta analyses, as pointed out by Ian Roberts and his team at the London School of Hygiene. In a recent publication, they analyzed six medical interventions tested in both human and animals, and they concluded that the results did not match in half the cases (BMJ 2007 Jan 27;334(7586):197). The review reported that corticosteroids did not improve head injury in clinical trials, but animal studies showed a beneficial effect. Antifibrinolytics reduced bleeding in humans but findings in animals were inconclusive. Trilazad for stroke was harmful in clinical trials, but promising in the animal model; this shows the limitations of animal models and the extrapolation of data between animal species.

11. The US Food and Drug Administration (FDA) has stressed that after years of pre-clinical testing, a novel drug entering a phase I clinical trial has only an 8% chance of reaching the market (7). The 92% failure-rate has resulted from safety concerns and lack of effectiveness in humans, despite tests on non-human primates and other animals. Undeniably, the FDA refers specifically to the limitations of animal toxicology and animal models for assessing drug efficacy. For example, Indinavir, a protease inhibitor drug used against HIV, underwent ADME tests in animal models, including monkeys. Results revealed significant differences between three animal species. Drug absorption was 14% in monkeys, 23% in rats and 72% in dogs. The equivalent values for humans were unknown until the drug could be assessed in volunteers. Studies showed that the livers of monkeys generate a unique metabolite of Indinavir that was not seen in humans; the report concluded that monkeys were not a suitable surrogate species for humans. (8) "*Most of the animal tests we accept have never been validated. They evolved over the past 20 years and the FDA is comfortable with them.*" (Anita O'Connor, Office of Science, FDA, US 1998)



12 AIDS: For years, countless numbers of primates have been infected with SIV or SIV/HIV hybrids in order to create a model of AIDS. This research yielded no meaningful information for the prophylaxis and treatment of AIDS in humans. In fact, the HIV is highly mutable, which makes vaccination avenues difficult. Although SIV and HIV have strong DNA sequence homologies, host-virus interactions are species-specific, therefore translation of animal data to humans remains uncertain. HIV infection, like antiviral therapies, can be studied at the cellular and molecular levels in human cells; ultimately vaccines must be evaluated in the host for which this vaccine is designed. SIV and HIV envelope proteins, which are key targets of neutralizing antibodies, are considerably divergent. Cytotoxic T lymphocytes (CTLs) specific for HIV do not recognize SIV-infected cells and reversely. SIV analogs in monkey models might or might not be comparable to vaccine candidates optimized and manufactured for human trials. Also, SIV isolates use the CCR5 coreceptor for virus uptake into cells. In 40–50% of HIV-infected humans, CCR5 predominates throughout the asymptomatic phase of a typical HIV infection. As distinguished from SIV-infected macaques, a shift of tropism to CXCR4 is observed in patients progressing to AIDS. (9)

13. Human clinical investigation has isolated HIV, defined the disease's natural course and identified risk factors. (10) Cell and tissue culture research using human white blood cells has identified both the efficacy and toxicity of anti-AIDS medicines, including AZT, (11) 3TC (12) and protease inhibitors (13). These are achievements that derived from human-based studies. Peter B. Jahrling, senior research scientist at USAMRIID reported the development of candidate Ebola vaccines that protected rodents but failed in primates. Will any vaccine tested in monkeys hold promise for protection of humans? We can only conclude that experiments in human subjects will confirm or invalidate the findings in monkeys, with incalculable and unforeseeable risks for the volunteers involved. Dr. Mark Feinberg, a leading AIDS researcher, summed it up: *'What good does it do you to test something [a vaccine] in a monkey? You find five or six years from now that it works in the monkey, and then you test it in humans and you realize that humans behave totally differently from monkeys, so you've wasted five years'*. We invite INRS decision-makers to realize that the substantial investment on animal research that is proposed, once again, is unlikely to foster human health research advancement and ultimately, optimum human health.

14. SARS coronavirus: Following the SARS outbreak and the media hype, the experimental infection of a few monkeys with a new coronavirus, later developing a pulmonary disease similar to SARS, was trumpeted as a major feat of science. Comparatively, the pathological and epidemiological observations in humans went underreported. Such observations can't fulfill the 19th-century Koch's postulates that are necessary to "prove" the cause of an infectious disease; postulates that have been unverified for some other infectious diseases (e.g. Tuberculosis, leprosy, HIV, mumps, measles). However, regardless of the monkey tests, the identity of the SARS virus was first revealed to be a novel coronavirus, a virus never before encountered in humans. Animal studies of SARS may be informative to human medicine or not; ultimately only real-life immunization in humans will confirm or invalidate the pre-clinical successes in animals. In particular, unpredictable infection-enhancing antibodies or harmful immune



or inflammatory responses are a major safety concern that no amount of animal study can ever predict. Interestingly, since 2003, international collaboration of researchers has made it possible to decode the genetic sequence of the SARS coronavirus, opening in a span of just two years, several avenues of research to develop diagnostic tests, therapies and vaccines currently under evaluation. In the case of SARS, molecular biology and information technology has been critical, according to Anthony S. Fauci, M.D., director of NIAID. If vaccine challenge in animals remains, regardless of its predictive value, the SARS hype has prompted a sense of urgency that benefited the research and development process in a positive way. Namely, by using the best tools, it was possible to greatly shorten the time needed to produce an uncertain vaccine yet, and consequently to reduce the number of animal tests. Unfortunately, efforts to find the most appropriate animal model for testing novel therapeutics in humans are far from driven by science. Indeed, the regulatory health agencies' often unclear "animal rule" applies to vaccine licensure.

15. Malaria: The anti-malaria drug Mefloquine was responsible for some serious side effects such as mood swings and psychosis in patients. The significant toxicity of many of these agents is difficult to evaluate in non-human primates and psychiatric side effects are common, and animal tests are inappropriate in predicting them with accuracy. It remains to be proven that emotional states in non-human primates are informative of the human condition, whereas human beings can describe their feelings and mental experiences. Considering drug toxicity and lack of efficacy, vaccination strategies would offer a better alternative to drugs. However, none of the animal models of malaria can present the many antigenic variations of *Plasmodium falciporum*, the parasite that is responsible for malaria in human patients. Furthermore, immunization strategies can appear more easily achievable in animal models than in humans (e.g. schistosomes). Even though experimental studies in animal models have shown it possible to produce vaccines for malaria in other animals such as dogs and bovine, in humans, the polymorphism of parasites makes strategies of therapeutic vaccination particularly problematic.

16. Hepatitis: The limited host range of the HBV virus and the lack of cell culture systems in which to grow the virus are well documented, and are obstacles to vaccination avenues. HBV infects the liver and to a lesser extent, the kidney and pancreas of humans and chimpanzees. The disease is determined by the patient's immune response to the infection but the animal model (chimpanzee) is essentially asymptomatic when infected. Unlike humans, chimpanzees continue to produce the virus as long as it is in their body. The liver, which is the organ primarily affected, is not affected in chimpanzees. Liver enzymes, which are measured to assess the progression of the disease, respond differently in humans and chimpanzees making cross-comparison impossible. Let's consider that the first Hepatitis B vaccine was made from blood of infected humans and is now made from bacterial culture. Vaccines against pathogens such as acellular pertussis, *Haemophilus influenzae* type B and *Streptococcus pneumoniae*, were successful in the absence of any useful data from chimpanzees. Clinical research and further *in vitro* work proved that mumps is caused by a virus, and this research made the vaccine possible.



17. Hepatitis B and C viruses are pathogens to which only humans are susceptible. The Handbook of Animal Models of Infection, (Rouse and Wilson, 1999) observed: ‘*Up to this very day, all infectious diseases affecting humans are far from having appropriate animal models and, even in those cases where such infections are possible, the symptoms observed in animals and the course of the disease are often very different from those encountered in humans*’. Non-human primate experiments for treatment of HCV infection, relevant to vaccine development and understanding of the mechanisms of hepatocellular damage have been unproductive (Rosen HR. and Marten P., 2000) while most of the progress has derived from *in vitro* and clinical studies. One recent breakthrough in the development of a successful *in vitro* culture system for the virus has been reported (Sun et al., 2004; Zhong et al., 2005).

18. Recombinant-DNA vaccines, like other biologicals, require proven quality, potency and efficacy controls. There are examples that the production and safety testing of vaccines is shifting to *in vitro* and physicochemical methodologies. Because some vaccines utilize live pathogens (OPV, yellow fever, rabies) or are well defined (e.g. influenza) they can be tested using *in vitro* methods. For example, new neurovirulence tests for OPV, tetanus, and diphtheria vaccines have replaced traditional animal-based tests. For types 1 and 2 Polio vaccines, no batch has ever consistently failed the monkey test. The virus used in these vaccines has been proven to be stable and is unlikely to revert to virulence. Furthermore, it was shown that the monkey neurovirulence test reliably detects mutations in types 1 and 2 polio virus; monkey tests failed to detect vaccine batches with deliberately induced mutations. (14, 15) One non-animal method called *MAPREC* detects and quantifies mutations which can cause the polio vaccine virus to regain virulence. Sadly, it took over 13 years to develop, principally because of a lack of motivation and too much inertia on the part of both governments and industry. (16)

19. While it can be argued that classical methods (animal tests) have not resulted in the release of outright dangerous vaccines (although their effectiveness is a far more controversial issue), there are a number of alternatives (both serological assays and *in vitro* tests) that have been proposed as replacements to current animal tests in Europe. (17) It is accepted that lack of information relevant to the human immune response and the mode of pathogenicity of agent-causing infection delays the development of mechanistically based-assays. Therefore, more emphasis on human-based models is needed. Also, especially for the human vaccines, limited understanding of the relevance to humans of monkey models should call for a reduced reliance on animal tests, instead of an increased emphasis on them. Additionally, McKinlay and McKinlay have analyzed the effect of medical strategies in combating influenza, pneumonia, diphtheria, whooping cough, and poliomyelitis; they estimated that just 3.5% of the total decline in mortality was due to vaccination against those diseases since 1900, questioning the notion that vaccination has resulted greatly in the decline of infectious diseases in the world. (18)

20. **Cardiovascular diseases:** Drug companies and hospitals have hundreds of billions of dollars at stake in investment and future revenues in conventional heart and vascular therapy. But heart disease, arrhythmia, stroke, diabetes, and numerous other circulatory diseases can be treated and prevented with simple and inexpensive strategies



not deriving from animal research. There is no one perfect animal model that commonly replicates the stages of human atherosclerosis. (19) The search for treatments for stroke led to the selection of diverse drugs which appear to exert neuroprotective effects in animal models of brain ischaemia treatment for acute stroke. However, none of these drugs were clinically proven. (20) In experiments in gerbils, rats, rabbits and cebus or rhesus monkeys, none of the animals responded to some cholesterol-raising factor found in boiled coffee or to coffee oil. This cholesterol-raising factor appeared to be specific for humans. (21) Milrinone, a medication designed to aid failing hearts, increased mortality when administered to humans; it had been proven safe in animals. Human studies of pimobendan, flosequinan, and vesrinone indicated that the drugs were effective but only when taken for a shorter period. Cholesterol-lowering agent Baycol was withdrawn by the company Bayer because of safety concerns, not shown in monkeys. Human observations were critical to withdraw or relabeled dangerous products. The drug Vioxx has known the same demise. The first drug to counter high cholesterol, a risk factor for CAD, was triparanol. It was recalled because it produced cataracts in humans, but prior animal tests had shown no signs of this condition. Epidemiological studies showed the dramatically lower incidence of many cancers, neurological, cardiovascular, degenerative and chronic diseases among the Japanese, Chinese, and Singhalese, the people of India and of many other undeveloped nations. These observations strongly support that these conditions, and cardiovascular diseases being not the least in the Western world, are mainly caused by environmental factors rather than genetic ones. (22) Noteworthy, the Japanese are the longest living people in the world (85 years for women and 78 for men in 2002). With regard to cardiovascular conditions, prevention, proper diets and exercise will save more human lives than any amount of research on non-human primates.

21. There are differences between the immune response of laboratory animals and the target species (human). Additionally, wild and laboratory strain antigenicity differ and routes of challenge administration vary from the natural route of administration. The addition of these technical problems shows quite clearly that the ideal situation (testing in the target species) is already compromised. The preference of *in vivo* monkey models over *in vitro* techniques must be proven on a case-by-case basis, and all the more when ethical observations in humans are feasible and/or available and make the case for *in vitro* research stronger. The validation of monkey models has not occurred yet, partly due to perceived good experience and reassurance provided to government and industry by the use of imperfect models. On the other hand, new alternatives have been validated scientifically, sometimes with the use of these very same imperfect animal tests as gold standards for comparative evaluation. Because one cannot extrapolate from one species to another, it is unscientific to use one or several animal species to evaluate some new tests that are intended to give more precise and accurate results and thus replace such poor animal models. Alternative tests that would be validated under the condition that they give results that are comparable and equivalent to animal tests, will not offer reassurance that the new test is reliable to guarantee human safety. Under that flawed principle, a promising alternative test would not pass validation because of conflicting results with a standard animal test.



By endorsing the new research primate center in Laval (CNBE), INRS authorities fail to observe that non-human primates research has already caused a great amount of harm, and the present document has listed just a few of them. Reliance on animal models has caused human suffering and death, indirectly delayed medical progress and diverted research funds away from more scientific methodology. The small genetic differences within the genes account for much of the problems of extrapolative health science that INRS promotes. Although genetic similarities exist, the regulation of genes is very much species-specific and the fine tuning of genes drastically changes their function and the function of the proteins they encode. The complexity of molecular pathways and cascades of reactions has effect upon hundreds of other genes. Therefore one stimulus studied in one species with a known effect, can have unpredictable effects in another. It is noteworthy that differences have been observed in the levels of gene expression between humans and chimps in the brain and liver (Ruvolo, 2004). On an evolutionary point of view, macaques and marmosets are further apart from humans than chimpanzees; predictably, data gathered in macaques and marmosets are very likely to deflect from clinical data. Marmosets, namely, is one species essentially used out of convenience.

The rigorous supervision and respect of international standards of animal care, as claimed by INRS, falls short to improve a methodology with a track record of failure (animal modeling). INRS states that monkeys are representative of the human condition; however INRS fails to prove this statement. INRS's claimed participation in past achievements (vaccines for Tuberculosis, Polio, Influenza, measles), as underlined by Mr. Pierre Lapointe, in his letter to our organization, offers no evidence that: 1) animal models were essential to the discovery, efficacy, safety of such vaccines; and 2) that animal models remains essential, as of today. The fact that one animal model is being used in a particular type of research is no evidence that this animal model is essential. Besides, the use of one animal model over another is seldom justified on scientific grounds. If we look back over 66 years of research at INRS, the literature abounds with studies on animal models that never materialized in useful knowledge and the rationale for using them is often unclear.

With regard to social attitudes, it is also interesting to point out that 88 members in the European Parliament support a complete end to experiments on primates across Europe, a motion which calls for the immediate prohibition in the EU of tests on apes and wild caught monkeys, and a six year phasing out of all experiments on monkeys. Statesmen John Bowis OBE MEP, former Minister of Health for the last Conservative Government and Michel Rocard MEP former Socialist Prime Minister in France, are among the signatories. (23) A survey of 500 general practitioners across the UK, conducted by TNS Healthcare in August 2004, show that 82% of the physicians were concerned that animal data can be misleading when translated to humans. Only 21% would have more confidence in animal tests for new drugs than in a battery of human-based safety tests and 83% would support an independent scientific evaluation of the clinical relevance of animal experimentation. Nonetheless, attitudes and opinions can change from one country to another, but since methods/standards of health research and care are basically the same in the Western world, it would be quite odd that a majority of Canadian doctors would trust animal tests, while so many of their colleagues in the UK



do not, as the survey shows. Are the government and the pharmaceutical industry more persuasive, in North America, in reassuring the public and the medical profession that animal tests provide a safety net? In December 2006, Marius Maxwell MBBChir, DPhil, who studied at Cambridge, Oxford and Harvard and now practises in the USA, wrote: “*Many of my Oxford colleagues in world-class scientific laboratories, and in the humanities, are privately aghast at the ability of a small group of media-savvy vivisectionists to hold the debate hostage and thereby besmirch the international reputation of their University.*” Dr. Marius Maxwell is not the typical animal rights activist that Canadian animal researchers seem to fear; he is one more scientist voicing his concerns about the unchecked reliance on animal tests.

The strategy of animal researchers to defend their discipline, at large, and regardless of its actual value, while avoiding debating and suppressing dissent within their ranks is counterproductive for two reasons. First, it does great harm to the public whose health and welfare it claims to protect. Second, it diminishes the credibility of scientists who refuse to debate with members of the public, and to make matters worse, generally refuse communications with scientifically knowledgeable peers having opposing views. The fear of reprisals by radical animal right activists, which is often invoked as a barrier to discussion, is unfounded and a pale excuse for not engaging in debate. As animal research is growing controversial, the burden of proof lies on researchers seeking research funding. It is disgraceful to demand unscientifically educated members of the public to disprove the claims made by animal researchers and the agencies granting them substantial amounts of money. (e.g., the \$22.5 million dollars attributed by various government bodies to the *Centre national de biologie expérimentale*)

Given: 1) the lack of evidence to support the productivity of animal models in various fields of human medicine, particularly, in neurology, toxicology and virology, 2) the emerging body of non-animal technologies with proven superiority to animal tests, and 3) the financial investments on the project detrimental to other projects (e.g, clinical and alternatives research), Canadians for the Advancement of Health Research asks for the project of the primate research center in Laval, which has been announced via the media just a few months before its realization this summer 2007, to be reconsidered and transformed into a new research center dedicated to the development of alternatives to traditional non-human animal research. Such a center of excellence would place Canada at the forefront of progressive science, and would contribute largely to the knowledge-economy. Such a research center would ultimately satisfy its mission of research and testing for the benefit to human health.

Canadians for the Advancement of Health Research is a non-religious, apolitical and a non-for-profit association of concerned individuals, scientists, and doctors with common interests in sound and humane health research. We offer the INRS’s decision makers the opportunity to respond to our concerns. We strongly advise INRS NOT to proceed with its plan to build a new animal research facility.



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