

Use of Nonhuman Primates in Developing Monoclonal Antibodies

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Nonhuman primates (NHP) are the preferred animal models for pre-clinical research because they approximate humans in physiology and genetics more closely than any other animal species. Vital advances in immunologic research have been made through the use of the NHP model, most notably in AIDS pathogenesis, treatment, and vaccine development. Cytokines and chemokines are soluble mediators of the immune system that play a crucial role in intercellular signaling, and in the recruitment of cells to inflammation sites. Identification of these molecules in NHP is important for the understanding of complex physiological and pathological mechanisms that occur in these species, and to demonstrate whether these mechanisms function similarly in humans. Recently, several antibodies specific for human cytokines that have the capacity to recognize homologous chemokines and cytokines of NHP origin have been identified. Currently, a panel of reagents is available which allows the simultaneous identification of cytokines and chemokines from Chimpanzees, Old World Monkeys, Rhesus Macaques, Baboons, Cynomolgus Macaques, Pig-tailed Macaques, and African Green Monkeys.

Key words: Nonhuman primates, monoclonal antibodies

Introduction:

An important challenge in drug development is the appropriate and justified use of animal in studies to assess efficacy and safety. Though, the clinical relevance of data from animal studies is often difficult to assess, it is crucial to compare the biological responses observed across species used in the nonclinical development program. The NHP is an appropriate model for the evaluation of a compound's effect on numerous organ systems and functions.¹ As a result, nonhuman primates are used for a variety of study types including subchronic and chronic toxicity, reproductive and development toxicity studies, safety pharmacology, and pharmacokinetic evaluations. Recent advances, such as innovative techniques for the marmoset, represent the growing importance of primate models in the study of biologics.²

According to ICH guidance, relevant animal species for testing monoclonal antibodies are those that express the desired epitope and demonstrate a similar tissue cross reactivity profile as for human tissues. In addition, these programs normally include two relevant species. However, in certain cases one relevant species may suffice.³

Although there are significant pros and cons surrounding the use of non-human primates for nonclinical studies, the standard animal species throughout the

biopharmaceutical industry for development of monoclonal antibodies has been the cynomolgus monkey. Comparison of the variable region of cynomolgus monkey antibody to human antibody has revealed extensive identity. However, there are a number of issues with the conduct of safety studies including the availability of animals and the lack of appropriate models of disease. Macular degeneration is being studied with photocoagulation induced choroidal neovascularisation models and diabetes therapies are being studied with obese nonhuman primates.⁴

A comparison of the findings from key rodents and nonhuman primate studies was done to support the clinical development and registration of a bone anabolic agent for the treatment of osteoporosis. These data demonstrate the importance of the animal studies in assessing both the efficacy and safety of the therapeutic agent. It is evident that nonhuman primate studies provide clinically relevant information that cannot be gained from other animal models. Efficacy study was done to assess effects on bone mass, structure, and strength. Nonclinical safety studies are used to assess effects of exaggerated pharmacology and determine if there are unexpected off-target toxicities. Data collected in support of regulatory requirements of parathyroid hormone as a bone anabolic agent includes pharmacologic and toxicological data from rodent and primate studies as well as carcinogenicity

data. The primary modelling species is the rat, with nonhuman primates, canines and sheep being used as a remodelling species. Bone remodelling involves resorption and formation. The rodent data showed improved bone mass, strength and micro-architecture. The nonhuman primate data showed an increase in the bone mineral content of the vertebrae, an increase in trabecular and cortical bone mass, and steady cortical bone quality.³

Transgenic mouse models expressing human Alzheimer related proteins like APP mutations causing autosomal dominant forms of Alzheimer's disease (AD) in humans have greatly contributed to an understanding of the neurodegenerative disease. However, because the nonhuman primate model is physiologically much closer to the human, such a model would be particularly valuable in prevention (and treatment) of neurodegenerative diseases. Aged, nonhuman primates develop human like P-amyloid pathology in the brain. The best models are rhesus, cynomolgus and squirrel monkeys. Testing experimental Alzheimer therapies in biologically optimal models could speed the development of new therapies. More data is available about rhesus monkeys; cynomolgus monkeys are biologically similar to rhesus monkeys with regards to aging.⁵

With age, nonhuman primates develop nearly all of the changes in the brain that occur in elderly humans. Macaque monkeys

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Picture: Marmoset Monkey

are the most thoroughly studied primates genus and (it quite evident that) cytologically and biochemically age associated lesions in the macaque brain closely resemble those in aging humans. In spite of these similarities, no nonhuman primates has been found to develop human like neurofibrillary tangles or show the profound loss of brain substance and consequent dementia that characterizes Alzheimer's disease. Despite the given fact aged nonhuman

primates are quite advantageous model for most of the neuropathological alterations acquired by aging humans. At the same time, phenotypic differences present an opportunity to seek cellular and molecular clues to the uniquely human susceptibility to Alzheimer's disease. Studies show that for cynomolgus monkeys older than 15 years, amyloid plaques and abnormal tau protein were detected in brain tissue. The degree of plaque burden was variable in these animals. However, amyloid β 1-42 levels in cerebrospinal fluid were elevated in the oldest animals and amyloid showed some molecular similarity to those described in patients. These data suggest that aged cynomolgus monkeys may present as useful spontaneous models for age related neurodegenerative diseases. Even though it is unclear as to whether geriatric cynomolgus monkeys also develop dementia and cognitive dysfunction.⁶

Diabetes research has been limited by the lack of availability of good animal models, particularly for the study of chronic diseases associated with diabetes. The use of cynomolgus monkeys in these studies has been looked into and compared to spontaneous diseases with streptozotocin induced diabetes. Various studies including a large number of obese monkeys at various stages of insulin resistance have generated substantial relevant data to support the use nonhuman primates in research related to treatment of diabetes and the role of insulin. Also, diabetes has been reported in many species of nonhuman primates and is best characterized in macaques with incidence estimated at 4% and higher in older animals with indicators similar to those in humans like hyperglycemia, glycosuria and polydipsia.

Conclusion:

Monoclonal antibodies, because of their specificity and unlimited availability, have become one of the most powerful experimental tools available to the biological sciences. It is possible to make monoclonal antibodies that bind to determinants that are monomorphic in one or more species or to determinants that are polymorphic within a species. Few monoclonal antibodies have been made using immunogens derived from nonhuman primates. However, some monoclonal antibodies that recognize monotypic markers in humans can be used to detect polymorphic markers in nonhuman primates. Thus, the rapid development of monoclonal antibodies specific for human proteins significantly increases the potential number of immunogenetic markers useful for studying phylogenetic relationships and for identifying genetic polymorphisms among nonhuman primates.

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