JOINN Laboratories NEWS

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The Importance of NHP Quality in Preclinical Studies

Overview

As the non-human primate laboratory animals (NHP) are closest to humans, they play an irreplaceable role in the field of preclinical research and evaluation of biomedicine.

Laboratory animals refer to animals that are artificially bred to control the microorganisms they carry, have clear genetic backgrounds or known sources, and are used for scientific research, teaching, production, testing and other scientific experiments. Ordinary-level laboratory NHPs must comply with the negative requirements for pathogens such as Salmonella, Shigella, Mycobacterium tuberculosis (TB), and simian herpes virus type 1 (BV) as stipulated in GB 14922-2022 "Laboratory Animal – Microbiological and Parasitological Standards and Monitoring." This is the minimum requirement for ordinary-level laboratory NHPs in the laboratory animal industry.

In addition to the above-mentioned pathogens, there are also some opportunistic pathogenic microorganisms such as simian immunodeficiency virus (SIV), simian retrovirus (SRV), and simian T-cell tropism virus (STLV). These typically do not show obvious clinical symptoms after infecting animals. When subject to environmental stress or experimental procedures, the animals' resistance may decrease, potentially leading to symptoms occurring. This could amplify the toxicity of the test product or confuse it with the clinical toxicity symptoms of the test product. The main manifestations include abnormal clinical symptoms, abnormal clinical pathological data, abnormal histopathology, and abnormal physiological indicators.

Moreover, the invasion of these microorganisms can also lead to immune suppression, subsequently causing issues such as hair loss, dermatitis, diarrhea, and trauma. In severe cases, mixed multiple infections and malnutrition may occur, causing cachexia or death, and ultimately resulting in deviation or loss of experimental data, thus affecting the accuracy of research, hindering the progress of project submissions.

Main Characteristics and Biological Effects of Retroviruses that May Occur in Commonly Used Experimental NHPs

	SRV	STLV	SIV
Natural Host	Asian NHPs (Macaca spp.)	Asian NHPs, African NHPs, apes	African NHPs, apes
Related Diseases	Subclinical to fatal immunodeficiency diseases; tumor lesions.	Subclinical; rare lymphoproliferative diseases.	Subclinical; immunodeficiency syndrome.
Transmission Route	Direct contact (saliva, urine, blood), can be transmitted via placenta	Direct contact (blood, sexual contact)	Direct contact
Prevalence Rate	0-50%	0->80%	Asian NHPs 0%; African NHPs 0-50%
Cell Tropism	Lymphoid and non-lymphoid tissues	T cells: CD4+、CD8+	T cells: CD4+
Cytokine Changes	IL-4 ↑ IL-17 ↑ MIP-1 α ↑ IL-2 ↓ IL-6 ↓	↑ IFN-γ ↑ TNF-α ↑ IL-2 ↑ IL-6 ↑ IL-10	↑ IFN-γ ↑ IFN-α , β ↑ IL -12 ↑ IL -18

The Necessity of SPF (Specific Pathogen-Free) NHPs in Preclinical Experiments

In 2000, M.A. Schroder and others published an article disclosing that in two studies conducted by a US pharmaceutical company, experimental data for drug safety evaluation were compromised due to animal infection with SRV virus. After identifying the cause, the company adopted internal screening and culling measures, strictly screening newly purchased animals for SRV before they were introduced.

In 2003, Nicholas W. et al. stated that viruses such as SRV, STLV, and SIV have a broad pathogenic potential, ranging from highly pathogenic to non-pathogenic, depending on different hosts, viruses, and environmental factors. Latent or subclinical infections are common, and various procedural operations related to experimental protocols may lead to viral reactivation and disease. These viruses pose potential risks in toxicology studies, and their occurrence may seriously affect the accuracy of evaluations.

Therefore, to eliminate interference in preclinical evaluation trials, it is essential to select high-quality experimental NHPs, which at a minimum must be free from the five pathogenic microorganisms: TB, BV, SIV, SRV, and STLV. These NHPs are commonly referred to as SPF (Specific Pathogen-Free) NHPs. NHPs are natural hosts of exogenous retroviruses such as SIV, SRV, and STLV. These viruses can become important confounding variables and seriously affect the applicability of the animals. Therefore, these viruses are pathogenic microorganisms that SPF-level experimental NHPs are required to eliminate.

China's SPF (Specific Pathogen-Free) NHPs Are in Short Supply

In 2021, the China Laboratory Primate Breeding and Development Association conducted a survey on 46 NHP farms with experimental animal production qualifications. The survey results showed that the total inventory of cynomolgus NHPs in the country is about 190,000. Excluding breeding populations, young NHPs, and reserved populations, it is estimated that about 20,000 NHPs meet the SPF (Specific Pathogen-Free) standard every year. Statistics were also collected on 59 entities in China with licenses for NHP use. Among these, CROs used about 26,000 NHPs, NHP farm laboratories used about 3,000 NHPs, and scientific research institutions used about 1,000 NHPs.

According to statistical data, there is still a gap between the annual supply capacity and the demand for SPF (Specific Pathogen-Free) NHPs. Considering the high market demand and tight supply from 2020 to 2021, NHP prices surged, leading to substantial profits. As a result, some NHP farms sold off all eligible young adult NHPs that met the requirements without adequately planning for breeding stock retention. With the aging of the breeding populations, this gap is likely to widen further.

Although the enthusiasm for new drug development has waned and demand has decreased, the supply of high-standard NHPs (Non-Human Primates) has not increased. The recent decline in NHP prices is a concession made by CROs in response to reduced market demand. However, excessive price compression will inevitably lead to a compromise in animal quality. Lowering animal quality standards to gain a competitive edge in new drug development projects is not advisable and goes against the principles of drug development. Therefore, regardless of changes in supply and demand dynamics or fluctuations in market prices, the quality requirements for NHPs should not be compromised.

JOINN Always Adheres to Source Control & Strict Quality Screening Procedures of High-quality NHP

First, it is necessary to conduct qualification review of potential suppliers, including but not limited to business licenses, production permits, personnel allocation, health check status, facility operations, frequency and results of microbial testing for the population, and frequency and results of microbial testing for the nursery area. Purchases should only be made following satisfactory review results.

Second, there are clear requirements for pathogenic microorganisms and parasites in laboratory NHPs. It is essential to exclude BV, STLV-1, SRV, SIV, shigella, mycobacterium tuberculosis, salmonella, and internal and external parasites, among others. Additional testing items may be added based on project needs. All tests must be conducted by qualified testing agencies, and the results must be negative for the animals to be accepted.

Next, after the animals are received, there is a quarantine period in which the animals undergo tuberculosis testing, body temperature and weight measurements, detailed clinical observations, as well as hematological, biochemical, and coagulation tests. Only after these indicators confirm the animals' health will they enter the trial.

Finally, JOINN supports testing agencies recognized by both parties to conduct another virus test on the laboratory animals before dosing to ensure the reliability of the animal resources. Although test reports or results are available before purchasing with only negative results leading to procurement, any testing method can have false positives or negatives. If clients require retesting, JOINN will actively cooperate, although this will incur additional costs, including testing fees and time.

Both CROs and project sponsors must fully recognize the profound impact of NHP retroviruses on animal health and experimental research. It is essential to consistently monitor and verify the quality of laboratory animals to ensure the reliability of research data, promote the steady progress of drug development, and safeguard the advancement of pharmaceutical research.

1. Schroder M A, Fisk S K, Lerche N W. Eradication of simian retrovirus type Dfrom a colony of cynomolgus, rhesus, and stump-tailed macaques by using serial testing and removal.[J]. Contemporary Topics in Laboratory Animal science, 2000, 39(4):16.

2. Nicholas W L, Kent G O. Simian Retrovirus Infections: Potential Confounding Variables in Primate Toxicology Studies. Toxicologic Pathology, vol 31(Suppl.), pp 103–110, 2003

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