Japanese Macaques (*Macaca fuscata*) in Biomedical Research

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Macaca fuscata (Japanese macaques), also called Japanese snow monkeys, have served as unique models of human disease for over fifty years. Due to their relatively homogeneous genetic background both in captivity and in the wild, and the fact that field researchers have accumulated abundant information on the social behavior of wild Japanese macaques, these animals offer unique opportunities as models or laboratory research.[1] This summary outlines the natural history of snow monkeys and summarizes recent, important research supported by these animals.

Japanese snow monkey in the wild

Japanese macaques are terrestrial Old World monkeys that are native to Japan. Other than humans, they are the most northern-living primates. They are called “snow monkeys” because they are the only non-human primate species whose habitat is covered by snow for many months of the year. Their lifespan in the wild is 28-32 years[2] and up to nearly 40 years in captivity. Japanese macaques are seasonal breeders. Females stay in their natal groups for life, while males leave their natal groups before they are sexually mature. [3,4] JMs are omnivorous, eating many species of plants, fungi, and invertebrates.

History of JMs at the Oregon National Primate Research Center (ONPRC)

A troop of 55 JMs who were considered pests in Hiroshima prefecture were brought to the ONPRC from Japan in 1965. The troop has been housed in outdoor corrals and has thrived, serving as a resource for behavioral and laboratory research. Because the animals have a long life span (and reach very old age at ONPRC), they have been part of an aging resource and have served in studies aimed at understanding the cellular and molecular changes underlying normative primate aging.[5]

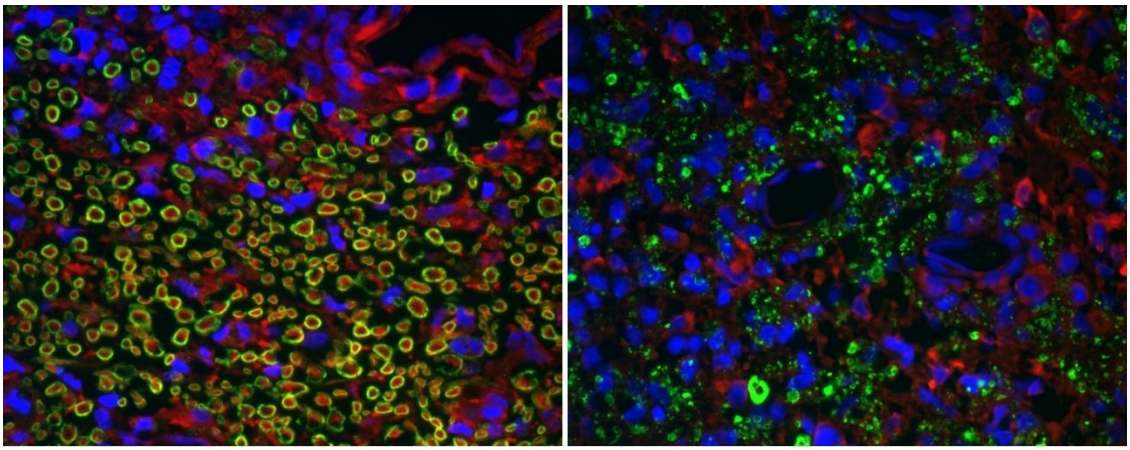
Japanese macaques at the ONPRC

Japanese macaques at the ONPRC have maintained their social structure. As a result, genetic changes in the colony over time have tended to remain in specific matrilineages, allowing for the development and targeted breeding of genetic models of human disease (outlined below). These JMs have also served as subjects in numerous primate behavior, veterinary, and induced disease model studies[6-8].

Inflammatory Demyelinating Disease

In the mid-1980s, veterinary staff at the ONPRC started to observe animals demonstrating motor weakness that sometimes progressed to paralysis, often accompanied by ocular disturbances. The disease only occurs in certain family groups who become infected with a novel rhadinovirus suggesting that it is induced by a viral trigger in animals with a genetic liability, similar to the proposed etiology for multiple sclerosis in humans. This condition, called Japanese macaque encephalomyelitis, involves multi-focal areas of inflammatory demyelination in the brain and spinal cord[9]. More recent studies demonstrated that these animals share many features of multiple sclerosis in humans including the presence of oligoclonal bands in their

cerebrospinal fluid and myelin reactive T cells[10,11]. These animals are currently being used in studies to understand the etiology and pathogenesis of multiple sclerosis and related diseases, and in preclinical studies of drugs that promote remyelination.



Demyelinating lesions in animals with Japanese macaque encephalomyelitis. On the left is an area of normal appearing white matter immunostained for myelin basic protein (green), neurofilament (red), and DAPI. On the right a section through a demyelinating lesion, showing the loss of myelin basic protein and reduced neurofilament staining consistent with axon damage.

Neuronal ceroid lipofuscinosis

In the past several years, a small number of Japanese macaques housed at the ONPRC have arisen bearing acquired mutations in the *CLN7* gene[12], resulting in a fatal and inherited disorder of the nervous system called Batten Disease or Neuronal ceroid lipofuscinosis (NCL). This genetic disorder is characterized clinically by a decline of cognitive function, epilepsy, and vision loss through retinal degeneration. Histopathologically, the disease is characterized by intracellular accumulation of an autofluorescent material, ceroid lipofuscin, in neurons in the brain and in the retina. NCL affects 2 to 4 of every 100,000 children in the United States. At least 10 genetic NCL disorders have been reported and are designated as CLN1 to CLN10. The majority of NCLs are inherited in an autosomal recessive manner. The CLN7 mutant Japanese macaques at the ONPRC are currently being used in studies to understand disease pathophysiology and as models for potential disease therapies.

Age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness in people over fifty years of age. The early stages of AMD are characterized by an increased frequency of drusen - small yellow deposits of fatty proteins (lipids) that accumulate under the retinal pigment epithelium. A line of Japanese macaques that develop drusen have been identified at the ONPRC[13]. In these animals, drusen begin to appear early in life and increase in number and size with age. This phenotype displays an autosomal dominant inheritance pattern. This AMD model is being used in studies of disease progression and as a platform for experimental AMD therapies.

Obesity

The ONPRC Japanese macaque colony has proven to be highly amenable to studies of primate obesity. Animals fed a diet high in saturated fat, simple carbohydrates and cholesterol develop many of the obesity-related conditions observed in humans and have led to numerous studies

that reveal the progression of obesity and its associated metabolic disorders[14-16]. This model has also provided opportunities to explore novel ways of treating these disorders.

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