Squirrel monkeys (*Saimiri* sp.) in Biomedical Research

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Introduction

Figure 1. *Saimiri boliviensis* can be distinguished from *S. sciureus* by the rounded arch over the eyes.

It has long been recognized that the squirrel monkey (*Saimiri* sp.) is an important nonhuman primate model in biomedical research. Squirrel monkeys are one of the most commonly used neotropical primates in biomedical research.[1-3] In the late 1970's, the NIH recognized that supply and availability of squirrel monkeys from source countries had become very vulnerable and that a self-sustaining breeding resource in the United States was the only way to assure continued availability of squirrel monkeys. For this reason, the Squirrel Monkey Breeding and Research Resource[a] was established through ORIP (then NCRR) to ensure a constant population of pedigreed monkeys with known medical histories. The breeding colonies of the SMBRR include three species/subspecies of squirrel monkeys: Bolivian squirrel monkeys (*Saimiri boliviensis boliviensis*) comprising about 68%; Guyanese or common squirrel monkeys (*Saimiri sciureus sciureus*) comprising about 28%; and Peruvian squirrel monkeys (*Saimiri boliviensis peruviensis*) comprising about 4%.

Natural Biology

Squirrel monkeys are distributed widely in the Amazon basin, with disjunct populations occurring in Central America. Eight species are currently recognized: *S. oerstedii* in Central America, and seven South American forms: *S. boliviensis, S. sciureus, S. collinsi, S. ustus, S. vanzolinii, S. cassiquiarensis,* and *S. macrodon.*[4,5] *S. boliviensis* and *S. sciureus* are the two most commonly used species in biomedical investigations. The species are defined by physiological and behavioral characteristics. For example, adult *S. sciureus* are more susceptible to gallstone formation than *S. boliviensis*, and infant *S. sciureus* are less active and less irritable than *S. boliviensis.*[6]

Squirrel monkeys live in various habitats, including primary or secondary rain forests, and habitats affected by human disturbances.[7-13] They do well in areas of secondary growth due to their high consumption of insects.[14] Squirrel monkey home ranges are large, varying from 150 to 250 hectares,[8,14,15] but these are not defended, and there can be overlap in the ranges of neighboring troops.

Squirrel monkey groups are generally large, ranging from 25-75 individuals.[16] However, unlike patterns of basic ecology, such as diet and habitat use, the social organization in the genus *Saimiri* is extremely diverse. In some species, males are dominant over females (e.g., *S. sciureus*), while others are female-dominant (e.g., *S. boliviensis*), and yet in others, there are

[a] https://www.mdanderson.org/research/departments-labs-institutes/programs-centers/michale-e-keeling-center-for-comparative-medicine-and-research/national-research-resources-program.html

negligible dominance interactions between females and males (*S. oerstedi*). These inter-species differences in social structure have been documented both in wild and captive settings. However, it should be noted that, due to the difficulty of recognizing individual monkeys in the wild, much is unknown about social structure and interactions in the genus.

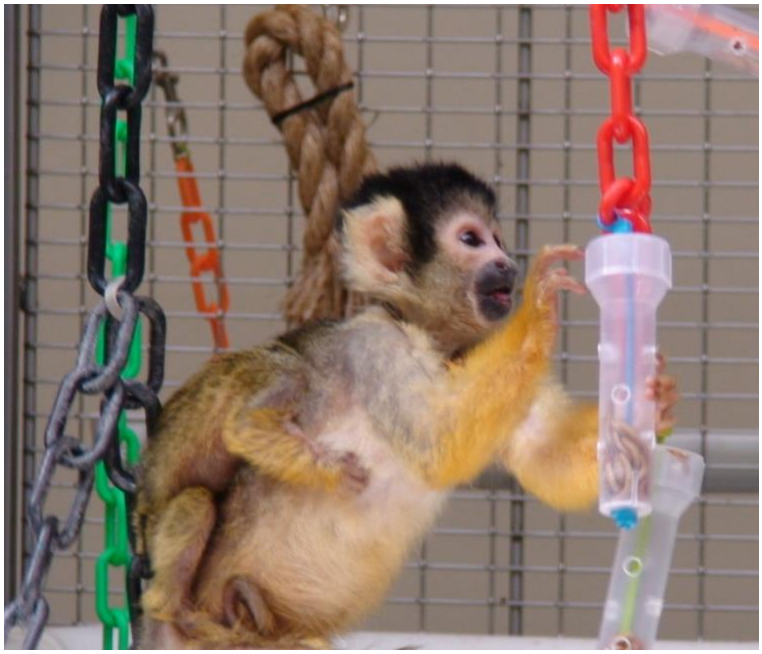

Figure 2. Mealworms provide for nutritional enrichment, and puzzle feeders can be used to promote foraging activity. Note that offspring are carried on the back rather than being held ventrally.

The genus *Saimiri* is characterized by extremely high pre- and post-natal maternal investment. Even though dams usually have single infants, squirrel monkeys rank highest among neotropical primates in infant care costs, including the cost of transporting heavy infants over long day ranges.[17] The gestation period is long in squirrel monkeys (5 months[18]), and is similar to that of the larger capuchins.[19] Neonates are large, usually weighing 16-20% of the mother's body weight[20,21] and have 60% of adult brain mass at birth.[22] Because of this large size, dystocia is common.[23] In the resource setting, squirrel monkeys produce twins at a rate of approximately 1 in 150 pregnancies (Williams, personal observation).

Biomedical Models

Genomics

186 Gbp of sequence data (BioSample: SAMN16846876) has been generated using the PacBio Sequel platform. This represents 69X coverage of the expected 2.7 Gbp squirrel monkey genome. In addition, genetic variation of the different species and subspecies has been studied using sequencing of mitochondria,[4,24] satellite DNA[25,26] and specific genes.[27-29] Cytogenetics (including karyotyping and chromosome painting) is a useful tool in studying the evolution of squirrel monkeys, as different species have different positioning of centromeres within chromosomes.[30-32]

Virology

Squirrel monkeys have been used to study several viral diseases, historically focusing on measles and herpesviruses.[33-40] Squirrel monkeys have been used as a model for polyomavirus viruses.[3,41] In recent years there has been a greater focus on Zika virus, because *Saimiri* is an endemic host for the virus in South America,[42-44] and Zika virus causes prenatal disorders and congenital Zika syndrome in squirrel monkeys.[45,46]

Malaria Vaccine Development

The squirrel monkey is an important animal model for malaria vaccine development studies.[47] Because Plasmodium sp. are host specific, animal models used to study human malaria must be susceptible to the same strains that cause disease in humans. The Bolivian squirrel monkey has been shown to be a superior model for studies of the pathogenesis of P. vivax,[48] developing lesions and clinical signs similar to those reported in

the human disease. Squirrel monkeys are also used to screen P. falciparum vaccine candidates for humans.[49]

Neuroscience and Vision

Squirrel monkeys are used extensively in neuroscience. *Saimiri* are a good model for Alzheimer's Disease (AD),[50,51] and recent work has investigated using CpG oligodeoxynucleotides to ameliorate some AD symptoms in squirrel monkeys.[52] Studies using squirrel monkeys have also contributed to the understanding of injury-induced reorganization of the sensory cortex and somatotopic reorganization of the brain stem and thalamus.[53-55] *Saimiri* and other neotropical non-human primates have contributed to vision research with regard to adaptation of the vestibule-ocular reflex,[56] the topography of cones and rods,[57] and color vision.[58,59] In squirrel monkeys, as in many New World primates, there is a single opsin gene with allelic diversity on the X chromosome, with the result that all males and some females have dichromatic vision.[60] This is in contrast to Old World primates, which are usually trichromatic. Gene therapy has been used to insert a third type of cone pigment into dichromatic retinas, allowing color blind squirrel monkeys to develop color vision, as assessed by a modified Cambridge Colour Test.[61]

Figure 3. The match-to-sample test is used to assess cognitive ability.

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