National Institute of Child Health and Human Development

2021 Marmoset Community White Paper

The principal mission of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is to ensure that every person is born healthy, that women suffer no harmful effects from the reproductive process, that children have the chance to fulfill their potential to live healthy and productive lives free from disease, and the well-being of all people through optimal rehabilitation. Animal models of disease have significantly contributed to the quests meeting the NICHD mission. The common marmoset (*Callithrix jacchus*) – a small monomorphic New World monkey – has a number of critical advantages to accelerate the rate of discovery in this research area. Like other primates, marmosets share the core physiological properties and brain architecture with humans. However, it is the species' small size, short life span, high fecundity, and human-like social structure that distinguish them from other primates and make them a particularly powerful biomedical model of child health and human development. Adult common marmosets average 300-450 grams, about the weight of a rat. They are reproductively competent at approximately 1.5 years of age, produce litters of 2-3 offspring every 5-6 months, and are considered aged at 8-12 years of age. The small size and fast life history of marmosets represents an advantage in many types of studies, including those involving reproduction, child-rearing, child health, impact of early life interventions, chronic disease effects, and testing compounds for which only small volumes may be affordably available. In particular, within a 5-year grant period, a marmoset can be followed from its own conception through to adulthood and reproduction in its offspring. Furthermore, the frequent production of twins and triplets enables study designs that can effectively control for genetic contribution by using siblings in different study groups. In addition, common marmosets are cooperative breeders with shared parenting responsibilities, a social structure very similar to humans. This similarity facilitates use of the common marmoset to model parenting and family effects on child development. Tools that further enhance the value of this species include complete sequencing, assembly, and annotation of the marmoset genome, generation of iPS cells, and production of transgenic marmosets – the first successful production of a transgenic nonhuman primate with germline transmission. For transgenic production, the fast maturation and high fecundity of the marmoset is a great advantage. The use of marmosets may bring transgenic line production within an acceptable financial range for areas of interest to NICHD in which the primate is a particularly compelling model such as autism spectrum disorder, Fragile X syndrome, and osteogenesis imperfecta.

Breadth of Current Research. Ongoing common marmoset research covers many areas of interest to NICHD. Several studies (183, 184) have documented a greatly diminished role for ovarian estradiol in metabolism and have established the relationship between estradiol depletion and diminished negative feedback in the development of polycystic ovarian syndrome (PCOS). A group of studies (185-188) have described marmoset pediatric obesity and its metabolic consequences as well as the role of both developmental programming and the establishment of feeding phenotypes during weaning on the development of pediatric obesity. Rutherford and colleagues (189-192) have taken advantage of litter size variation in marmosets to model the effects of varying intrauterine environments on developmental programming on a female's future reproductive success. Ongoing studies are investigating the role of dietary fat, puberty, and metabolism in the development of adolescent mood disorders. Pryce and colleagues established a model for examining the impact of separation on infant attachment and affective behavior during early development (193). This work has led to the further development of the model by French and colleagues (194-196), who have examined the role of oxytocin in modulating mate-guarding behavior and reunion affiliation following social separation in an attempt to understand the critical

behavioral processes that contribute to the preservation of long-lasting relationships. Marmosets are a well-established model for vocal development. Their cooperative breeding system has been a major asset in research showing the crucial role of social interaction in vocal development (164-166, 197). Importantly, there is evidence that marmosets are appropriate models for both autism (198, 199) and Zika virus infection (200).

The Future. The marmoset is a unique and valuable nonhuman primate model to investigate human development throughout the entire life process. Given their short lifespan and their short generation time, they are particularly important for evaluating the impact of developmental processes and programming on future generations. The development of tools allowing assessment of neurobehavioral developmental milestones (201, 202) and brain development from infancy to adulthood (203) will greatly facilitate this work, as will the ability to create transgenic models. There is great potential for the development of genetically modified models for diseases that have dramatic impacts on child health and development, such as autism spectrum disorder and Fragile X syndrome. Given the emergence of devastating neotropical diseases, such as Zika, we also anticipate increasing interest in marmoset disease models, particularly for diseases endemic to marmoset natural habitats and that may have prolonged latencies or unexpected later life effects. Finally, there is increasing appreciation for the role of social interactions in disease development and this is an area in which marmosets are a particularly valuable model over other potential models due to their human-like family structure.

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