National Institute of Neurological Disorders and Stroke

2021 Marmoset Community White Paper

The core mission of the National Institute of Neurological Disorders and Stroke (NINDS) is twofold. First, NINDS seeks fundamental knowledge about the brain and nervous system. Second, NINDS aims to use that knowledge to reduce the burden of neurological diseases. In support of its mission, NINDS performs and funds basic, translational, and clinical neuroscience research on more than 600 neurological diseases afflicting humans, including geneticdiseases (e.g., Huntington's disease; muscular dystrophy), developmental disorders (e.g., cerebral palsy), neurodegenerative diseases (e.g., Parkinson's disease; Alzheimer's disease; multiple sclerosis), metabolic diseases (e.g., Gaucher's disease), cerebrovascular diseases (e.g., stroke; vascular dementia), trauma (e.g., spinal cord and head injury), convulsive disorders (e.g., epilepsy), infectious diseases (e.g., AIDS dementia) and brain tumors. Common marmosets (*Callithrix jacchus*) offer unique,powerful advantages to both components of the NINDS mission. In support of the first component, marmosets are particularly well suited for neuroanatomical and functional brain studies, as their brains retain the typical anatomical and functional organization of the primate brain. A significant advantage is that the marmoset is a lissencephalic primate, which greatly facilitates the mapping of functional brain areas by neuroimaging techniques, such as fMRI and optical imaging, as well as by electrophysiology, with highspatial resolution. In support of the second component, marmosets are excellent modelsof neurological disorders. Unlike rodents, marmosets are outbred, and every individual isgenetically different. Further, the marmoset brain has a gray-to-white matter ratio comparable to humans, which strongly facilitates modeling diseases such as multiple sclerosis and small vessel disease. The species also exhibits the breadth of cognitive sophistication that distinguishes primates from other taxonomic groups. Finally, gene-edited marmosets can be generated with an intergeneration time and establishment of transgenic lines 2-3 times faster than other primate species, which makes marmosets bethe ideal primate species for the development of genetically engineered lines. For all of the aforementioned reasons, marmosets are poised to be a central player to advance the core mission of the NINDS.

Breadth of Current Research. Marmosets are currently being used to elucidate pathogenetic mechanisms of multiple sclerosis (121-125). Marmoset models of MS haveclinicopathologic correlation patterns, lesion heterogeneity, immunologic mechanisms, and disease markers more closely mimic the human condition. Marmoset models of stroke (126, 127) have been developed as the marmoset brain features cell types and behavioral deficits that most closely mimic human stroke. Marmosets are advantageous models of neurodegenerative diseases due to their many anatomical, functional, metabolic, and social similarities with humans. Marmosets are an ideal model in longitudinal studies of cognitive decline (128), and the recent evidence that aging marmosets shows the biological hallmarks for Alzheimer's disease, including amyloid-beta (129-131), hyperphosphorylated tau, and dystrophic microglia (132, 133), strongly elevates the marmoset as a superior model for the study of aging and age-related diseases (134). Transgenic marmoset models of stroke (135), Parkinson's disease (136), polyglutamine diseases (137), spinocerebellar ataxia (138), and severe combined immunodeficiency (139) have been developed to allow better modeling of neurological disorders. Meanwhile, we know more about the organization of the primate brain thanks to the very high-resolution anatomical, neurophysiological, and functional imaging efforts being made in marmosets, with the development of brain atlases based on MRI (140-143), gene-

expression (144), and neuronal connections (145, 146). Finally, the use of high-resolution fMRI for mapping sensory and social regions of the marmoset brain (147-150), resting-state brain networks (151, 152), and neurophysiological, behavioral (153) and calcium imaging (62, 154, 155) studies in freely-moving marmosets are significantly advancing our understanding of marmoset behavior in ways to understand their changes due to neurological disorders.

The Future. There's a bright future for biomedical research, as marmosets are poised tomake a tremendous, potentially revolutionary contribution both to our currentunderstanding of brain anatomy and function and to the causes and mechanisms of neurological disorders. The small marmoset brain allows, for the first time in a primate species, the integration of whole-brain morphological (MRI, fMRI, and neuronal tracing) studies performed at the microscale with cell-specific gene expression. This will enable the construction of a comprehensive atlas/database that will contain completely novel knowledge about the primate brain. The development of genetic-engineering techniques in marmosets will enable the study of a broad range of neurological and neuropsychiatricdisorders as well as spur the development of precision medicine and gene-therapy approaches to manage and treat these diseases. In particular, being among the shortest-lived primate species, marmosets are uniquely suited to provide crucial information about primate brain development and about the mechanisms of neurodegenerative diseases inwhich aging is a major comorbidity and contributing factor.

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