2023 Marmoset Community White Paper

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I. Executive Summary

A. Marmosets are a Cornerstone Biomedical Model System

The common marmoset (*Callithrix jacchus*) has experienced unprecedented growth as an animal model in biomedical research across the United States and is continuing to establish itself as a crucial engine for scientific discovery. *There are now over 25 marmoset research colonies serving over 50+ Principal Investigators (PIs) in the United States.* Since the first Marmoset Community White Paper in 2019, investment in marmoset research by the National Institutes of Health (NIH) has increased considerably, reflective of the growing interest in and importance of the marmoset model. The initial grassroots efforts by Investigators to champion this nonhuman primate model are increasingly receiving support from crucial funding agencies – particularly the NIH and BRAIN Initiative - with both targeted investments in key infrastructure needed to further grow the model in the United States and an increase in support for investigator-initiated proposals. While continued support for these initial investments remain crucial for the field's continued growth, new areas of concern and opportunities to further accelerate the growth of the marmoset model have presented themselves in parallel with the increased use of this species in biomedical research nationwide. Specific strategic investment is now needed by the NIH to address these issues and allow the marmoset model to realize its full potential as a cornerstone species able to accelerate the rate of discovery in biomedical research and better understand human disease.

The goal of this White Paper is to highlight the advantages of marmoset monkeys for accomplishing the stated mission of the NIH and to identify strategic investments needed to accelerate the impact of this model system for biomedical research.

B. Past NIH Investment in Marmoset Research

Over the past 5 fiscal years [2018-2022] the NIH has invested over $268M in marmoset research. The most significant increase in funding has occurred over the past two years. Whereas NIH supported 54 marmoset grants with ~$49.5M in funding in FY2020, funding in FY2022 increased to 71 projects and ~$95M. In other words, NIH nearly doubled its support for marmoset research over only a 2-year period. Notably, the vast majority of these funds were awarded through investigator-initiated funding mechanisms (i.e. R01, R21, U01, R34 etc grants) reflecting the prodigious increase in marmoset use across the United States. While neuroscience continues to be the dominant field driving marmoset use, the model's adoption by other biomedical research fields is increasingly contributing to the observed increase in funding. Because of the strategic creation of four national Marmoset Breeding Centers and the Marmoset Coordination Center in 2020 with funding from the NIH BRAIN Initiative, growth in the use of marmosets in biomedical research – and by extension funding for this work – is expected to increase considerably for the foreseeable future.

C. Recommendations & Priorities for Future NIH investment in Marmoset Research

The marmoset model has witnessed substantial growth over the past decade largely through grassroots, researcher-initiated projects. These foundational efforts are now being complemented by the NIH as marmosets are increasingly recognized as a keystone model organism for addressing NIH's stated goal to enhance health, lengthen life and reduce illness and disability in humans. As a nonhuman primate species with several unique reproductive, physiological and behavioral advantages, marmosets are uniquely positioned to accelerate progress to this end. We are presently at a crucial juncture in the development of the model; substantial investment by the NIH is needed to complement new core resources and

infrastructure for the rapidly growing community of marmoset investigators that will facilitate an accelerated rate of discovery for human diseases.

The biannual Marmoset PI meeting was held in 2022 as an in-person meeting; the first for the community since the Covid-19 Pandemic began. As with previous PI Meetings, the principal goal of the 2022 meeting was to identify current bottlenecks for growth and the crucial resources needed to overcome these challenges. Based on input and feedback from the community, we have identified the following four resource priorities that require immediate investment from the NIH.

- Investment in Viral-based Gene-Editing Technologies in Marmosets.
- Investment to develop robust 3D, multi-animal model of marmosets with markerless pose estimation technologies for precise phenotyping.
- Support for Cross-Institutional Training of Students/Post-Docs

To address these issues, we recommend the NIH support the following identified priorities through several crucial RFA/PARs within the next year to foster the continued development of foundational infrastructure and resources for marmoset research to flourish in the United States.

D. Marmoset Community Initiatives

Grass roots efforts by marmoset investigators is a pivotal foundation of our community's future success. We have established both a website – www.marmohub.org – and a Slack workspace for PIs to coordinate efforts and facilitate communication across laboratories. During the 2022 Marmoset PI meeting, the community identified one key initiative that we expect to implement in 2023.

- Establish a Career Development Committee for Post-Docs

E. Marmosets are a Keystone Model to Understand and Cure Human Disease in the 21st Century.

The principal long-term goal of the marmoset research community is to expand the use of this model organism to accelerate our rate of discovery for understanding human disease. The recommendations in this White Paper for immediate strategic investments by the NIH supporting crucial resources and infrastructure are needed to maximize the impact of marmosets as a cornerstone model organism to study human diseases. Marmosets offer unique opportunities to study and understand biomedical processes that have not been feasible to model in other nonhuman primates. The species' rapid development and aging, for example, make it possible to longitudinally examine diseases that afflict humans at specific times in life, both during ontogeny and senescence. Likewise, the small size and high fecundity provide logistical advantages for the development and implementation of next-generation gene-editing technologies. For example, besides development of transgenic lines, higher animal numbers are a huge benefit to testing viral-based approaches where there are typically a larger number of parameters to optimize (viral constructs, titer, or method of delivery) before efficient expression is achieved. The marmoset is well poised to fill gaps for viral-based testing given the limited supply of macaques post-pandemic. Furthermore, due to the notable similarities in their social behavior, cognition and communication with humans, as well as the shared functional brain architecture of all primates - this nonhuman primate species is uniquely suited to model the neuropsychological disorders that afflict humans. The marmoset model has the potential to transform our understanding of the myriad of genetic, physiological and environmental factors affecting human disease as a keystone biomedical model in the next chapter of scientific inquiry.

II. Introduction

A. The marmoset is establishing itself as a keystone animal model for biomedical research

The common marmoset (*Callithrix jacchus*) is a New World monkey that has been used as a model system in biomedical research for several decades. As outlined in the 2019 Marmoset Community White Paper, the use of marmosets has rapidly increased in the past decade. While only 7 marmoset colonies existed in the United States in 2008, there are nearly 40 colonies that have been established by 2021 that support over 50+ Investigators. The growth of the marmoset model is also not restricted to the United States. In North America, three Institutions in Canada – Western University, McGill University, and most recently York University – have heavily invested in marmoset research by building needed research infrastructure and establishing large breeding colonies that each support multiple Investigators. Biomedical research with marmosets has also continued to expand in Asia (China and Japan), Australia, UK, Europe (France, Germany) and Israel. The proliferation of marmosets on an international stage indicates that the model's ascension in the United States is not occurring in isolation, but rather reflects the broader recognition of the species' valuable and unique attributes as a powerful animal model for biomedical research on a global scale. Continued strategic investment in marmosets by the NIH will further demonstrate the United States' role as an international leader in nonhuman primate research.

The growing interest in marmosets both domestically and internationally has occurred as the awareness of the species scientific and logistical advantages that this species of New World primates offers biomedical research. For example, marmosets have a relatively short gestation of only ~150 days and typically birth fraternal twins, which establishes marmosets as having amongst the highest fertility of any primate (S. D. Tardif et al. 2003). Likewise, marmoset development is notably rapid – reaching adulthood in ~14-18 months and becoming aged at ~8yo (Yamamoto 1993; Schiel and Souto 2017) Marmosets are similar in body size as rodents – weighing ~300-400g – making it possible for large populations to be housed in smaller facilities than larger primates. Yet in stark contrast to rodents, marmosets exhibit the shared physiological, behavioral and cognitive characteristics that distinguish primates from all other animals, including the core functional architecture and organization of our nervous system (Miller et al. 2016). This unique complement of characteristics affords the exciting opportunity to feasibly utilize a primate species to model many of the diseases that afflict humans, ranging from those that affect humans at specific times in life – including both developmentally and during aging – to neuropsychiatric disorders that impact uniquely primate properties of our brain.

A related advantage of marmosets has been the species' amenability to modern molecular gene-editing technologies. Following Dr. Erika Sasaki and colleague's pioneering work in marmosets demonstrating the first germline transmission of a transgene in a nonhuman primate (Sasaki et al. 2009) efforts to implement modern gene-editing technologies in marmosets have accelerated (K. Sato et al. 2016; Park et al. 2016; Feng et al. 2020). This includes efforts to develop the most modern gene-editing approaches for use in marmosets, such as CRISPR (Kumita et al. 2019; Yoshimatsu et al. 2019; Vermilyea et al. 2020), as well as viral based approaches that make it possible to more selectively target specific cell types and circuits in the brain (Mehta et al. 2019; D. Vormstein-Schneider et al. 2020; Watakabe et al. 2017, 2015; Dimidschtein et al. 2016) . These viral technologies include the intravenous delivery of AAV capsids designed to cross the blood-brain barrier in marmosets and are particularly promising because of their clear advantages for translational work (Flytzanis et al. 2020; Chen et al. 2022). Researchers are increasingly leveraging the advantages of optogenetic and chemogenetic techniques to selectively manipulate circuits in the marmoset brain (Ebina et al. 2019; MacDougall et al. 2016; Nurminen et al. 2018; Mimura et al. 2021; Jendritza, Klein, and

Fries 2023), while also implementing calcium-imaging approaches in an effort to better understand large populations of neurons in the marmoset brain (Yamada et al. 2016; Sadakane et al. 2015; Zeng et al. 2019; Santisakultarm, Kresbergen, et al. 2016). As this critical line of research and technical development continues to evolve, the promise of marmosets as primate model that can leverage genetic technologies is beginning to be realized.

B. The significance of marmosets as a NHP model in the 21st Century in the United States.

Nonhuman primates are crucial to biomedical research across the globe. In addition to functioning as key animal models for the basic sciences, primates are indispensable for disease modeling and clinical trials. A recent report by the US National Academies of Sciences, Engineering and Medicine entitled 'Nonhuman primate models in biomedical research: State of the science and future needs' emphasizes this point by outlining the critical role NHP models play in developing disease treatments and their increasing significance in the years to come.

Rhesus macaques have been and currently remain the dominant nonhuman primate model for biomedical research in the United States. For the past few decades, biomedical research in the US that uses macaques have relied on importing animals from international sources, primarily from China. Recently, the availability of these monkeys for import into the US has rapidly declined since China declared these animals a key resource and has invested heavily in expanding their own research using rhesus monkeys, including in the Neurosciences (https://www.economist.com/international/2021/07/24/attitudes-towards-experimenting-on-monkeys-are-diverging). Given the enormous expense domestically to produce large quantities of rhesus monkeys, there are likely to be considerable challenges ahead to meet the needs of US researchers. The shortage of macaques is already impacting medical discoveries and treatments (https://unherd.com/2021/02/chinas-plan-for-medical-domination/) with further challenges expected in the years to come.

Marmosets offer an opportunity to bridge this gap for overall NHP needs in the United States. Because of their small body size (~300-400g) marmosets can be housed in relatively large numbers in standard facilities. This fact coupled with their high fecundity and rapid development, this primate species offers clear logistical advantages to increasing the number of NHPs in US for biomedical research. The four newly established NIH/BRAIN Initiative funded marmoset breeding centers in the US are strategically important to meet these growing needs. While no single primate model – including marmosets - is likely to be ideal for all disease models, the availability of marmosets can help to diversify the NHP species used for this purpose and reduce our overall reliance on foreign sources for animals.

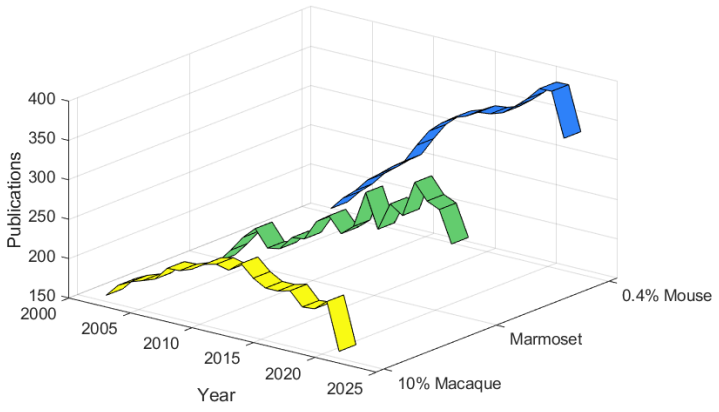

Figure 1. Plots the total number [#] of peer-reviewed publications with marmosets listed on PubMed each year over the last 20 years in Green. Mouse (Blue) and Macaque (Yellow) are shown as a fraction of their total publications to illustrate the relative rate of change in manuscripts published on the same scale with marmosets.

Current Uses of Marmosets in Biomedical Research

Marmosets are utilized as animal models in a wide diversity of biomedical research disciplines, ranging from infectious disease to

reproductive biology but neuroscience remains the dominant area in which this New World primate is used. The increasing interest in marmosets is also reflected in the notable rise in marmoset publications since 2015, excluding the very most recent year which showed a drop across all species likely due to the pandemic. As shown in Figure 1, using 'marmoset' as a keyword search in PubMed for each of the past two decades shows a steady increase in number of marmoset publications in peer-reviewed scientific journals. Figure 1 also plots the publication rate of research for Macaque monkeys and Mouse models over the same period as a percentage of their total publications. As is evident in this plot, the total number of Macaque and Mouse publications is considerably more than in marmosets, but of note, publications with marmosets are increasing at a similar rate over time as papers with Mouse models. By contrast, though the Macaque still dominates as the primary non-human primate model with the most publications per year, it is of concern that their publication rate has dropping in proportion to the Mouse. This trend highlights the increasing importance of the marmoset as a growing non-human primate model which could fill gaps if other models are impacted by increasing costs or infrastructural issues.

Listed below are representative publications in marmosets over this same period of time. The selective list only encompasses peer-reviewed research papers using marmosets in high-profile scientific journals.

Representative Publications [2021-2022]

Systems Neuroscience.

1. Behavioral context affects social signal representations within single primate prefrontal cortex neurons.
   Jovanovic V, Fishbein AR, de la Mothe L, Lee KF, Miller CT. Neuron. 2022 Apr 20;110(8):1318-1326.e4. doi: 10.1016/j.neuron.2022.01.020. Epub 2022 Feb 1. PMID: 35108498
2. Distinct neuronal types contribute to hybrid temporal encoding strategies in primate auditory cortex.
   Liu XP, Wang X. PLoS Biol. 2022 May 25;20(5):e3001642. doi: 10.1371/journal.pbio.3001642. eCollection 2022 May. PMID: 35613218
3. Remodeling of lateral geniculate nucleus projections to extrastriate area MT following long-term lesions of striate cortex.
   Atapour N, Worthy KH, Rosa MGP. Proc Natl Acad Sci U S A. 2022 Jan 25;119(4):e2117137119. doi: 10.1073/pnas.2117137119. PMID: 35058366
4. Active neural coordination of motor behaviors with internal states.
   Zhang YS, Takahashi DY, El Hady A, Liao DA, Ghazanfar AA. Proc Natl Acad Sci U S A. 2022 Sep 27;119(39):e2201194119. doi: 10.1073/pnas.2201194119. Epub 2022 Sep 19. PMID: 36122243
5. Constructing the hierarchy of predictive auditory sequences in the marmoset brain.
   Jiang Y, Komatsu M, Chen Y, Xie R, Zhang K, Xia Y, Gui P, Liang Z, Wang L. Elife. 2022 Feb 17;11:e74653. doi: 10.7554/eLife.74653. PMID: 35174784
6. Cortical neural dynamics unveil the rhythm of natural visual behavior in marmosets. Kaneko T, Komatsu M, Yamamori T, Ichinohe N, Okano H. Commun Biol. 2022 Feb 3;5(1):108. doi: 10.1038/s42003-022-03052-1. PMID: 35115680
7. Lévy walk dynamics explain gamma burst patterns in primate cerebral cortex.
   Liu Y, Long X, Martin PR, Solomon SG, Gong P. Commun Biol. 2021 Jun 15;4(1):739. doi: 10.1038/s42003-021-02256-1. PMID: 34131276

Molecular Neuroscience.

1. Molecular and cellular evolution of the primate dorsolateral prefrontal cortex.
   Ma S, Skarica M, Li Q, Xu C, Risgaard RD, Tebbenkamp ATN, Mato-Blanco X, Kovner R, Krsnik Ž, de Martin X, Luria V, Martí-Pérez X, Liang D, Karger A, Schmidt DK, Gomez-Sanchez Z, Qi C, Gobeske KT, Pochareddy S, Debnath A, Hottman CJ, Spurrier J, Teo L, Boghdadi AG, Homman-Ludiye J, Ely JJ, Daadi EW, Mi D, Daadi M, Marín O, Hof PR, Rasin MR, Bourne J, Sherwood CC, Santpere G, Girgenti MJ, Strittmatter SM, Sousa AMM, Sestan N. Science. 2022 Sep 30;377(6614):eabo7257. doi: 10.1126/science.abo7257. Epub 2022 Sep 30. PMID: 36007006
2. Spatial profiling of early primate gastrulation in utero.
   Bergmann S, Penfold CA, Slatery E, Siriwardena D, Drummer C, Clark S, Strawbridge SE, Kishimoto K, Vickers A, Tewary M, Kohler TN, Hollfelder F, Reik W, Sasaki E, Behr R, Boroviak TE. Nature. 2022 Sep;609(7925):136-143. doi: 10.1038/s41586-022-04953-1. Epub 2022 Jun 16. PMID: 35709828
3. Temporally divergent regulatory mechanisms govern neuronal diversification and maturation in the mouse and marmoset neocortex.
   Yuan W, Ma S, Brown JR, Kim K, Murek V, Trastulla L, Meissner A, Lodato S, Shetty AS, Levin JZ, Buenrostro JD, Ziller MJ, Arlotta P. Nat Neurosci. 2022 Aug;25(8):1049-1058. doi: 10.1038/s41593-022-01123-4. Epub 2022 Aug 1. PMID: 35915179
4. Engineered AAVs for non-invasive gene delivery to rodent and non-human primate nervous systems.
   Chen X, Ravindra Kumar S, Adams CD, Yang D, Wang T, Wolfe DA, Arokiaraj CM, Ngo V, Campos LJ, Griffiths JA, Ichiki T, Mazmanian SK, Osborne PB, Keast JR, Miller CT, Fox AS, Chiu IM, Gradinaru V. Neuron. 2022 Jul 20;110(14):2242-2257.e6. doi: 10.1016/j.neuron.2022.05.003. Epub 2022 May 27. PMID: 35643078
5. AAV capsid variants with brain-wide transgene expression and decreased liver targeting after intravenous delivery in mouse and marmoset.
   Goertsen D, Flytzanis NC, Goeden N, Chuapoco MR, Cummins A, Chen Y, Fan Y, Zhang Q, Sharma J, Duan Y, Wang L, Feng G, Chen Y, Ip NY, Pickel J, Gradinaru V. Nat Neurosci. 2022 Jan;25(1):106-115. doi: 10.1038/s41593-021-00969-4. Epub 2021 Dec 9. PMID: 34887588

Functional Neuroanatomy.

1. Spatial signatures of anesthesia-induced burst-suppression differ between primates and rodents.
   Sirmpilatze N, Mylius J, Ortiz-Rios M, Baudewig J, Paasonen J, Golkowski D, Ranft A, Ilg R, Gröhn O, Boretius S. Elife. 2022 May 24;11:e74813. doi: 10.7554/eLife.74813. PMID: 35607889
2. Cortical basis for skilled vocalization.
   Cerkevich CM, Rathelot JA, Strick PL. Proc Natl Acad Sci U S A. 2022 May 10;119(19):e2122345119. doi: 10.1073/pnas.2122345119. Epub 2022 May 4. PMID: 35507879
3. Neural network of social interaction observation in marmosets.
   Cléry JC, Hori Y, Schaeffer DJ, Menon RS, Everling S. Elife. 2021 Mar 31;10:e65012. doi: 10.7554/eLife.65012. PMID: 33787492
4. An integrated resource for functional and structural connectivity of the marmoset brain.
   Tian X, Chen Y, Majka P, Szczupak D, Perl YS, Yen CC, Tong C, Feng F, Jiang H, Glen D, Deco G, Rosa MGP, Silva AC, Liang Z, Liu C. Nat Commun. 2022 Dec 1;13(1):7416. doi: 10.1038/s41467-022-35197-2. PMID: 36456558.
5. Diffusion MRI anisotropy in the cerebral cortex is determined by unmyelinated tissue features.
   Reveley C, Ye FQ, Mars RB, Matrov D, Chudasama Y, Leopold DA. Nat Commun. 2022 Nov 5;13(1):6702. doi: 10.1038/s41467-022-34328-z. PMID: 36335105
6. Multimodal analysis demonstrating the shaping of functional gradients in the marmoset brain.

Tong C, Liu C, Zhang K, Bo B, Xia Y, Yang H, Feng Y, Liang Z. Nat Commun. 2022 Nov 3;13(1):6584. doi: 10.1038/s41467-022-34371-w. PMID: 36329036
7. Frontoparietal connectivity as a product of convergent evolution in rodents and primates: functional connectivity topologies in grey squirrels, rats, and marmosets.
Schaeffer DJ, Gilbert KM, Bellyou M, Silva AC, Everling S. Commun Biol. 2022 Sep 17;5(1):986. doi: 10.1038/s42003-022-03949-x. PMID: 36115876
8. Simultaneous functional MRI of two awake marmosets.
Gilbert KM, Cléry JC, Gati JS, Hori Y, Johnston KD, Mashkovtsev A, Selvanayagam J, Zeman P, Menon RS, Schaeffer DJ, Everling S. Nat Commun. 2021 Nov 16;12(1):6608. doi: 10.1038/s41467-021-26976-4. PMID: 34785685
9. Interspecies activation correlations reveal functional correspondences between marmoset and human brain areas.
Hori Y, Cléry JC, Selvanayagam J, Schaeffer DJ, Johnston KD, Menon RS, Everling S. Proc Natl Acad Sci U S A. 2021 Sep 14;118(37):e2110980118. doi: 10.1073/pnas.2110980118. PMID: 34493677

Behavior.

1. Problem-solving in groups of common marmosets (*Callithrix jacchus*): more than the sum of its parts.
Sehner S, Willems EP, Vinicus L, Migliano AB, van Schaik CP, Burkart JM. PNAS Nexus. 2022 Sep 14;1(4):pgac168. doi: 10.1093/pnasnexus/pgac168. eCollection 2022 Sep. PMID: 36714869
2. Active vision during prey capture in wild marmoset monkeys.
Ngo V, Gorman JC, De la Fuente MF, Souto A, Schiel N, Miller CT. Curr Biol. 2022 Aug 8;32(15):3423-3428.e3. doi: 10.1016/j.cub.2022.06.028. Epub 2022 Jun 23. PMID: 35750054
3. Marmoset core visual object recognition behavior is comparable to that of macaques and humans.
Kell, A. J., Bokor, S. L., Jeon, Y. N., Toosi, T., & Issa, E. B. iScience. 2022 Dec 10;26(1):105788. doi: 10.1016/j.isci.2022.105788. eCollection 2023 Jan 20. PMID: 36594035
4. Prenatal development of neonatal vocalizations.
Narayanan DZ, Takahashi DY, Kelly LM, Hlavaty SI, Huang J, Ghazanfar AA. Elife. 2022 Jul 26;11:e78485. doi: 10.7554/eLife.78485. PMID: 35880740

Genetics.

1. Comparative cellular analysis of motor cortex in human, marmoset and mouse.
Bakken TE, Jorstad NL, Hu Q, Lake BB, Tian W, Kalmbach BE, Crow M, Hodge RD, Krienen FM, et. al.. Nature. 2021 Oct;598(7879):111-119. doi: 10.1038/s41586-021-03465-8. Epub 2021 Oct 6. PMID: 34616062
2. Evolutionary and biomedical insights from a marmoset diploid genome assembly.
Yang C, Zhou Y, Marcus S, Formenti G, Bergeron LA, Song Z, Bi X, Bergman J, Rousselle MMC, Zhou C, Zhou L, Deng Y, Fang M, Xie D, Zhu Y, Tan S, Mountcastle J, Haase B, Balacco J, Wood J, Chow W, Rhie A, Pippel M, Fabiszak MM, Koren S, Fedrigo O, Freiwald WA, Howe K, Yang H, Phillippy AM, Schierup MH, Jarvis ED, Zhang G. Nature. 2021 Jun;594(7862):227-233. doi: 10.1038/s41586-021-03535-x. Epub 2021 Apr 28. PMID: 33910227
3. Transcriptomic architecture of nuclei in the marmoset CNS.
Lin JP, Kelly HM, Song Y, Kawaguchi R, Geschwind DH, Jacobson S, Reich DS. Nat Commun. 2022 Sep 21;13(1):5531. doi: 10.1038/s41467-022-33140-z. PMID: 36130924
4. Efficient marmoset genome engineering by autologous embryo transfer and CRISPR/Cas9 technology.
Abe Y, Nakao H, Goto M, Tamano M, Koebis M, Nakao K, Aiba A. Sci Rep. 2021 Oct 12;11(1):20234. doi: 10.1038/s41598-021-99656-4. PMID: 34642413

5. Cellular-resolution gene expression profiling in the neonatal marmoset brain reveals dynamic species- and region-specific differences.
   Kita Y, Nishibe H, Wang Y, Hashikawa T, Kikuchi SS, U M, Yoshida AC, Yoshida C, Kawase T, Ishii S, Skibbe H, Shimogori T. Proc Natl Acad Sci U S A. 2021 May 4;118(18):e2020125118. doi: 10.1073/pnas.2020125118. PMID: 33903237

Disease Models.

1. The age-related pattern of inner retinal thickening is affected by myopia development and progression.
   Ablordeppey, R. K., Lin, C., & Benavente-Perez, A. (2022). Sci. Reports 2022 Dec 23;12(1):22190. doi: 10.1038/s41598-022-26598-w. PMID: 36564498
2. NogoA-expressing astrocytes limit peripheral macrophage infiltration after ischemic brain injury in primates.
   Boghdadi AG, Spurrier J, Teo L, Li M, Skarica M, Cao B, Kwan WC, Merson TD, Nilsson SK, Sestan N, Strittmatter SM, Bourne JA. Nat Commun. 2021 Nov 25;12(1):6906. doi: 10.1038/s41467-021-27245-0. PMID: 34824275
3. Functional and molecular characterization of a non-human primate model of autism spectrum disorder shows similarity with the human disease.
   Watanabe S, Kurotani T, Oga T, Noguchi J, Isoda R, Nakagami A, Sakai K, Nakagaki K, Sumida K, Hoshino K, Saito K, Miyawaki I, Sekiguchi M, Wada K, Minamimoto T, Ichinohe N. Nat Commun. 2021 Sep 15;12(1):5388. doi: 10.1038/s41467-021-25487-6. PMID: 34526497
4. Location and temporal memory of objects declines in aged marmosets (Callithrix jacchus).
   De Castro V, Girard P. Sci Rep. 2021 Apr 28;11(1):9138. doi: 10.1038/s41598-021-88357-7. PMID: 33911122

Novel Methodology.

1. An integrated resource for functional and structural connectivity of the marmoset brain. Tian X, Chen Y, Majka P, Szczupak D, Perl YS, Yen CC, Tong C, Feng F, Jiang H, Glen D, Deco G, Rosa MGP, Silva AC, Liang Z, Liu C. Nat Commun. 2022 Dec 1;13(1):7416. doi: 10.1038/s41467-022-35197-2. PMID: 36456558
2. Mesoscopic landscape of cortical functions revealed by through-skull wide-field optical imaging in marmoset monkeys.
   Song X, Guo Y, Li H, Chen C, Lee JH, Zhang Y, Schmidt Z, Wang X. Nat Commun. 2022 Apr 26;13(1):2238. doi: 10.1038/s41467-022-29864-7. PMID: 35474064
3. Flexible auditory training, psychophysics, and enrichment of common marmosets with an automated, touchscreen-based system.
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Here we outline the current use and advantages of marmosets for specific NIH Institutes, Centers, and Initiatives that support nonhuman primate research to further emphasize the unique advantages and broad potential of this species in the next chapter of biomedical research.

- Appendix 1 | NIH BRAIN Initiative
- Appendix 2 | NIH Office of Research Infrastructure Programs
- Appendix 3 | National Institute of Mental Health
- Appendix 4 | National Institute Neurological Disorders and Stroke
- Appendix 5 | National Institute Deafness and other Communication Disorders
- Appendix 6 | National Institute of Aging
- Appendix 7 | National Institute Child Health and Human Development
- Appendix 8 | National Eye Institute

III. Past NIH Investment in Marmoset Research

Funding support for marmoset research has increased over the past decade. The most dramatic increase has occurred over the past 5 years [2018-2022] in which the NIH has invested over $268M in marmoset research.

A search of NIH RePort Database using the term 'Marmoset' for 'Project Title' and 'Project Abstracts' revealed that in FY 2020 the NIH supported 54 projects with $49,700,000 in funding. Only two year laters (FY 2022), the NIH supported 71 projects with **$94,600,000** in funding. This represents a near doubling of NIH investment in this primate model over two years. Furthermore, the number of NIH ICs funding marmoset research increased from 10 to 12 from 2020-2022. While some of this increase can be attributed to funding by the NIH BRAIN Initiative for marmoset infrastructure related efforts, the vast majority relate to investigator-initiated proposals from more traditional NIH funding mechanisms (i.e. R01, U01, R24, U24, R21 etc), including several young investigator training awards (i.e. F32, K99, etc).

IV. Outcome of 2021 Community Priorities & Recommendations

The 2021 Marmoset Community White Paper outlined four following Recommendations & Priorities for NIH Investment. Below we list each of these and the respective outcome of the NIH.

- Investment in Developing Marmoset Behavioral Techniques & Technologies.
- Investment in Viral-based Genetic Technologies in Marmosets.
- Support for Cross-Institutional Training of Student/Post-Docs.
- Centralized Resource for Cataloging and Distributing Aging Marmosets.

Unlike the outcome of the 2019 Marmoset Community White Paper, the priorities outlined in the 2021 Community White Paper did not result in significant investments by the NIH. The likely reason for this is that the infrastructure investments of our initial White Paper were still not completed and required continued investment. For example, funding for the four Marmoset Breeding Centers and Marmoset Coordination Center had only begun in mid-2020 and significant planning and investment were dedicated to establishing each component of this

considerable infrastructure plan and their collective integration. Likewise, the two rounds of submissions for the BRAIN Initiative RFA DA-21-006 (Tools for Germline Gene Editing in Marmosets) were not completed until 2022. As outlined below, the priorities in 2023 are like those described in the 2021 White Paper as the marmoset community continues to regard these as the most critical needs for the next chapter of research with this model system.

V. Recommendations & Priorities for future NIH Investment in Marmoset Research.

The third Marmoset Principal Investigators meeting took place in 2022 and included ~45 Investigators. Attendance was significantly impacted by Covid as several attendees had to cancel travel plans due to the sickness. This meeting was attended by both PIs and post-docs to include the thoughts and perspectives of the next generation of marmoset researchers in shaping the priorities of the field. The principal aim of the marmoset PI meeting is to [1] identify key bottlenecks facing marmoset research in the United States and [2] establish the strategic plans to address these issues. Listed below are the most critical priorities discussed by the investigators at the 2022 PI meeting along with recommendations that should factor heavily for strategic plans in the next phase of marmoset research.

1. Investment in Viral-based Gene-Editing Technologies in Marmosets.
2. Investment to develop robust 3D, multi-animal model of marmosets with markerless computer vision technologies for precise phenotyping.
3. Support for Cross-Institutional Training of Students/Post-Docs

1. Investment in Viral-based Genetic Technologies in Marmosets.

In our 2021 White Paper, we listed the need to invest in viral based genetic technologies as one of our key priorities. Although the NIH Brain Initiative generously had two RFAs (RFA-DA-21-006) to address the need to generate germ-line gene-editing in marmosets, the need for viral based technologies remains high. Viral-based gene-editing approaches remain a powerful and likely keystone technologies for marmoset research in the coming years for several reasons. The most significant pertains to the likelihood that the number of marmoset transgenic lines is almost certain to be dwarfed by the catalog available for other genetically tractable animal models (i.e. mice, zebrafish, etc) due to sheer cost of development and housing of these populations. As a result, viral-based approaches are likely to be critical to performing precise, functional genetic manipulations in marmosets to address a wide range of research questions in the coming years. Further, viral-based approaches provide the most promise for future translation of gene-editing technology to humans for potential therapies to mental disease. While advances in these technologies continue to occur (Mehta et al. 2019; D. Vormstein-Schneider et al. 2020; Chen et al. 2022), strategic investment is needed to accelerate this process and maximize its benefits for explicating the functional circuitry of the primate brain. Investing in these technologies as the marmoset model continues to grow would offer a key foundation to accelerate the rate of discovery for many years to come.

Solution. A Resource PAR/RFA is needed to directly fund the development and expansion of the molecular tool kit available for use in marmosets using viral based gene-editing technologies,

including the intravenous delivery of AAV capsids because of their significant benefits for translational research with humans.

2. Investment to Develop 3D, multi-animal model of marmosets with markerless pose estimation technologies for precise phenotyping.

Owing to their relatively small body size (~300-400g), a notable advantage of marmosets for biomedical research is their amenability to a wide range of behavioral techniques. This ranges from traditional primate cognitive methodologies (i.e. Wisconsin card sorting task) to the use of modern markerless tracking technologies (i.e. SLEAP, DeepLabCut, etc) to quantify fine behavioral details in freely-moving animals across a range of contexts in a manner not previously possible using traditional head-fixed/restrained approaches (Pereira et al. 2022; Pereira, Shaevitz, and Murthy 2020; Pereira et al. 2019). These latter quantification tools have revolutionized many areas of research as they afford the opportunity to measure a suite of naturally occurring biomechanical actions in single animals or concurrently across multiple animals in social contexts. We recommend a key investment to optimize modern pose-estimation technologies for behavioral analysis in marmosets.

There is a critical need to develop standardized 3D models of marmoset pose-estimation that generalize to multi-camera test environments. This investment is both significant to the field and timely for at least the following two reasons. First, the increased development and usage of genetically modified marmosets for disease modelling will necessitate accurate phenotyping. These quantification tools will allow an unprecedented capacity to explicate key differences in behavioral phenotypes between wild type and genetically modified animals not only at a general level, but in the more nuanced properties necessary to fully characterize primate behavior, particularly in social contexts. This level of quantification is likely to ultimately be necessary to fully understand critical relationships between genes and behaviors. Second, the temporal resolution at which these technologies quantify behavior is on the same timescale as modern technologies used to record and manipulate the brain. As neuroscience remains a cornerstone of marmoset research, the optimization of these technologies would serve to accelerate the rate of discovery in this area.

Solution. One or more PAR/RFAs are needed to accelerate the advancement on marmoset behavioral techniques and technologies. Given the difficulty of funding pure behavioral research through more conventional NIH funding mechanisms, PAR/RFAs specifically for developing behavioral methodologies in marmosets would be particularly impactful to the field.

3. Support for Cross-Institutional Training of Students/Post-Docs.

The accelerated growth of marmoset research highlights its growing importance as a NHP model. Because of the scarcity of institutions with active marmoset researchers only a decade ago, the majority of researchers who have adopted marmosets as a model organism in recent years did not receive formal training during graduate school or post-doctoral periods. Instead, many new researchers previously gained their primary training either in rodents or macaque monkeys and have faced considerable challenges adapting their research program to marmosets. To address this issue, we propose immediate investment to support the cross-institutional training of new students and post-docs from established laboratories in the field. While this environment has

grown organically amongst marmoset researchers, investment in such a system would allow researchers at smaller institutions or new investigators with limited funding to have these training opportunities for their trainees.

Solution. A Resource PAR/RFA is needed that awards funds to graduate students and post-docs for the explicit purpose that they receive training in management, husbandry, surgical approaches, and experimental techniques. This funding would support training periods at Institutions with established marmoset laboratories and scientific leaders of different cutting-edge technologies to accelerate research efforts and reduce the need for single labs to develop approaches in isolation.

VI. Marmoset Community Initiatives

During the PI meeting, the Community also identified initiatives that could be undertaken by the Investigators to further strengthen marmoset research. The following project was determined to be the most pressing concern for the community.

Establish a Career Development Committee for Post-Docs

Marmoset research is rapidly growing, and by extension the number of trainees is likewise increasing. The future of the marmoset model hinges on the advancement of junior scientists to faculty positions nationwide. To facilitate senior post-docs approaching and entering the job market, we will establish a Career Development Committee. The purpose of this committee is to serve as a resource to marmoset researchers at this critical career stage. They will be available for consultation and advice about all facets of navigating the faculty job market. This Committee will also serve as a liaison between the broader marmoset community and institutions that may have questions regarding the details of establishing new marmoset laboratories at Institutions that currently lack them.

VII. Contributors.

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Appendix 1

National Institute of Health BRAIN Initiative

2023 Marmoset Community White Paper

Central to the mission of the BRAIN initiative is the creation and application of innovative technologies and gathering of information for understanding how individual cell types and complex neural circuits interact in space and time to generate normal brain function and dysfunction in the diseased brain. Priority research areas of the BRAIN Initiative include the generation of brain cell atlases, understanding circuit wiring, the function of specific cell types and circuits via causal manipulations, large scale multi-area interactions, and the link between brain function and behavior. Marmosets offer unique advantages for both developing new technologies and expanding our knowledge of the brain. As non-human primates, this New World species is within the same taxonomic family as humans (Order: Primates) and share the core brain architecture and broad behavioral repertoire. For example, marmosets have an extensively developed prefrontal cortex, and their motor control, sensory perception and social cognition is very similar to those of humans. In contrast to the more commonly used macaque monkey, however, they offer the advantage of a much smaller body (300-400gr in weight), a small lissencephalic brain, a shorter gestational period (5-6 months) and life span (8-12 yrs of age), a faster maturational period (sexual maturity is reached around 1.5 yrs of age), and high fecundity (producing litters of 2-3 offspring). These advantages make marmosets an ideal non-human primate species to address many goals of the BRAIN Initiative. For example, the fast maturation and high fecundity of the marmoset is a great advantage for the generation of transgenic lines. Indeed, recent advances in genetic engineering in marmosets have opened new pathways to study the brain, allowing modeling of disorders with a genetic component, such as Alzheimer's disease, Schizophrenia, Autism and Huntington's disease, in which mouse models have so far been unsuccessful in translation to humans. Moreover, the marmoset small brain size is ideal for studying circuit wiring and connectomics in a complex non-human primate brain that is several orders of magnitudes smaller than the macaque brain, whose large brain size still poses a big data challenge for computational tools. Additionally, in contrast to the large and convoluted macaque brain, the marmoset's small lissencephalic brain allows the accessibility needed for brain-wide, high resolution *in vivo* imaging techniques, such as two-photon microscopy.

Breadth of Current Research. There are several research questions within the BRAIN Initiative mission currently being addressed using the marmoset as a model species. Following the initial development of calcium imaging in the marmoset brain (Ding et al. 2017; Yamada et al. 2016; Sadakane et al. 2015), several laboratories are applying this technique to image network dynamics in real time in behaving marmosets (Ebina et al. 2018; Zeng et al. 2019; Kondo et al. 2018). Similarly, following the initial development of *in vivo* optogenetics in the marmoset (MacDougall et al. 2016), reports are rapidly accumulating on its application to study marmoset cortical function and behavior (Ebina et al. 2019; Macknik et al. 2019; Nurminen et al. 2018; Tremblay et al. 2020). These approaches will advance our knowledge of the neural basis of cognition and behavior, a major goal of the BRAIN Initiative. Studies are currently underway to produce a spatially specific catalog of cell types in the marmoset brain, using single-cell RNA sequencing; using this approach a recent study has profiled RNA expression in a large number of inhibitory neurons across several species, including marmosets (Krienen et al. 2020). These

approaches will pave the way for future studies of primate genetics and circuits. BRAIN Initiative funds have been, and continue to be, used successfully for the development of new viral tools for targeting specific cell types in the non-human primate brain. For example, novel recombinant adeno-associated virus (rAAV) vectors that restrict gene expression to GABAergic interneurons in many vertebrate species including marmosets using the mDlx enhancer (Dimidschtein et al. 2016) or the h56D promoter (Mehta et al. 2019) have recently been developed. Moreover, over the past year, two laboratories have developed viral vectors for selective transgene expression in specific inhibitory neuron subtypes (parvalbumin and somatostatin-positive interneurons) in marmoset cortex (Mehta et al. 2019; D. C. Vormstein-Schneider et al. 2020). Studies of the auditory system have successfully leveraged the aforementioned advantages of marmosets to pioneer numerous neural recording and behavioral techniques to make new discoveries about the physiological mechanisms underlying sensory perception and social communication in the primate brain (Song et al. 2016; Johnson, Della Santina, and Wang 2016; Zhou and Wang 2014; Issa and Wang 2011; Bendor and Wang 2010; S. J. Eliades and Wang 2008; Bendor and Wang 2008; Wang et al. 2005; Bendor and Wang 2005; Gao et al. 2016; Roy, Zhao, and Wang 2016; Toarmino et al. 2017; S. Nummela et al. 2017; Miller et al. 2015). More recently, researchers have also begun to take advantage of the marmoset natural tendency to orient towards visual stimuli, perform visual tasks, and the accessibility of the middle temporal (MT) visual area and frontal eye field on the cortical surface of this species, to study a diverse range of visual behaviors in marmosets (J. Mitchell, Priebe, and Miller 2015; Ghodrati et al. 2019; Mundinano, Kwan, and Bourne 2019; Davis et al. 2020; Samonds, Geisler, and Priebe 2018; J. Mitchell, Reynolds, and Miller 2014; Knöll, Pillow, and Huk 2018; S. U. Nummela et al. 2019).

The Future. The marmoset is a unique model to investigate the non-human primate brain in ways that are not allowed by other primate species. Promising future research areas are briefly discussed below. First, the marmoset small lissencephalic brain is ideally suited for the development of wide-field calcium imaging to enable imaging of millions of neurons across cortical layers and multiple brain areas. Future efforts are directed towards increasing the width and depth capabilities of imaging in this primate species Second, the marmoset small brain size is also ideal for the development of large-scale manipulations of cortical circuit activity, to understand interareal interactions. Future efforts are directed towards developing large-area manipulations throughout the cortical depth, and performing spatiotemporally patterned photostimulation to mimic the spatiotemporal patterns of neuronal activity. Third, efforts are under way to couple single-cell RNA sequencing with behavioral studies in marmoset (as previously done in mouse (Moffitt et al. 2018)), to establish computational tools that allow linking gene expression in specific cell types to behaviorally relevant circuits in a primate. Fourth, current and future efforts are under way for further development of viral tools for cell specific targeting in non-human primate brains; for example, rAAV vectors that can specifically infect additional subtypes of inhibitory neurons in marmoset cortex, beyond those recently reported. Finally, a revolution in understanding the human brain in health and disease will require non-invasive real-time mapping of neurotransmitter and calcium signaling. New vasoactive imaging probes with high sensitivity and resolution have been developed in rodents (Okada et al. 2018; Hai et al. 2016) and are currently being developed for marmosets.

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Appendix 2

National Institutes Office of the Director
Office of Research Infrastructure Programs

2023 Marmoset Community White Paper

The core mission of the Office of Research Infrastructure Programs (ORIP) within the Office of Director (OD) is to advance the NIH mission by supporting research infrastructure and research-related resource programs and by coordinating NIH's science education efforts. Specifically, ORIP's Strategic Plan supports the NIH-Wide Strategic Plan by funding the "scientific human and physical resources that will help to ensure the Nation's capability to prevent disease." ORIP awards grants to support research resources, such as animal models of human disease and state-of-the-art biomedical instrumentation. ORIP plans, organizes, and conducts workshops, both independently and in collaboration with NIH Institutes and Centers, to identify and pursue scientific opportunities. ORIP supports research-training opportunities for veterinary scientists to capitalize on their distinct perspective and expertise based in a deep understanding of comparative medicine and insight into animal models of human diseases. In the last several decades, the mouse system has been a powerful model for medical research due to, in large part, an array of sophisticated gene-editing techniques to manipulate the mouse genome and strategies for cell-type specific, inducible, or spatiotemporal regulation. However, considerable anatomical, physiological, cognitive, and behavioral differences between mice and humans limit the degree to which insights from mouse models shed light on human diseases. This is reflected in the high number of failed clinical trials for drugs that were effective in treating mouse models of human disease. Thus, non-human primates (NHPs) may serve as better models for studying human disease with the macaque being the traditional choice. However, the common marmoset (*Callithrix jacchus*) has emerged recently as a complementary species with advantageous characteristics over the macaque. First, marmosets share with other primates, including humans, similar physiology, brain organization, and sophisticated social and cognitive behaviors. For example, like humans, marmosets are diurnal and housed in social groups consistent with the size and composition of groups in the wild. This is particularly important because the range of sophisticated social and cognitive behaviors that emerge naturally within social groups can be effectively studied under more controlled laboratory conditions. Second, marmosets are among the shortest-lived NHPs with small body size and strong reproductive power, making them highly economical and scalable for housing and generating the number of marmosets needed for preclinical evaluation. Third, in contrast to rhesus macaques, marmosets are free of Herpes B viruses, making the species safer to work with. Finally, technologies for generating genetically modified marmosets have already been developed, and their short generation time represents a distinct advantage for creating and expanding transgenic lines over larger nonhuman primate species.

Breadth of Current Research. Ongoing research in the marmoset is focused on modeling various human diseases and investigating in a wide range of systems and at multiple levels of analysis, including infectious disease, aging, Alzheimer's disease, Parkinson disease, Schizophrenia, Huntington's disease and multiple sclerosis. Furthermore, the marmoset has been used to develop a model system to evaluate various gene-editing approaches and strategies for gene therapy. Research efforts are also ongoing to characterize the effects of pharmacological and life-style interventions on health span in the marmoset.
The Future. ORIP can play an essential role in addressing numerous resources issues that impede the progress in using marmosets as a biomedical model. Here are some examples. First, one of major bottlenecks in using marmosets to model human disease is the extreme short supply of marmosets available for sale to research community. Second, the genetic diversity of marmoset population in this country is largely unknown. The information is critical in better maintaining high population diversity and modeling human disease. For example, it will be extremely informative to know the divergence and frequency of marmoset alleles relevant to human mutations such as major risk factors ApoE and Trem2 for AD and other diseases. As marmosets are purposely kept as out-bred to maintain diversity, the

database will provide information to understand (Goodroe et al. 2020) the extent of genetic diversity and ancestral relationship of different populations; (Singh et al. 2021) assist the analysis of fidelity of genome following gene editing and (Feng et al. 2020) facilitate the genome-based interpretation and comparisons of variations in phenotypes across different populations. Third, it is not known if immunological reagents and protocols for analytic experiments in the marmoset are available. Database for these reagents and, if needed, developing these reagents will become critical for the success of modeling human disease. Fourth, it is critical to develop genetic viral tools that work in the marmoset. Fifth, it will be important to develop and standardize a suit of state-of-art behavioral tests for marmosets Sixth, it will be advantageous to establish an aging marmoset colony and its related resources for the community. Finally, ORIP can offer workshops to advance above endeavors and disseminate the resulting resources.

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Appendix 3

National Institute of Mental Health

2023 Marmoset Community White Paper

The core mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illness through basic and clinical research. Traditionally, research funded by the NIMH has taken advantage of three main species – namely the mouse, the macaque monkey, and the human. This combination has led to a series of important discoveries that has gradually expanded our understanding of how the brain supports a range of higher cognitive processes. However, progress towards understanding and treating mental health and behavioral disorders has slowed, marking the need for a substantial paradigm shift in the scientific approach toward more human-relevant experimental-models. The recent emphasis on the common marmoset as a promising model for neuroscience heralds a broadening of experimental paradigms to study brain mechanisms of cognition, including those whose failure underlies prevalent mental disorders. Traditionally, research in cognitive neuroscience has also taken advantage of the three aforementioned main species: the mouse, the macaque monkey, and the human. This has led to a series of important discoveries, gradually transforming our understanding of how the brain supports a range of higher cognitive processes. The marmoset adds new and important dimensions to our understanding of brain function, with great relevance to mental health and disease within an animal model whose brain shares many of its primate specializations with the human. Importantly, new experimental opportunities are rooted in marmosets' gregarious social behavior, which, together with their relative ease in breeding and handling, invite investigation into interactive and developmental aspects of primate cognition. Marmosets are particularly well suited for studying the brain in paradigms involving interactive social behavior. Several aspects of their behavior closely resemble that of humans, including their cooperative foraging and defense, reciprocal communication, and allomaternal rearing of offspring. The marmoset brain shares many of its primate features with the human brain, including specializations for social perception and vocal communication. These scientific factors, together with practical considerations such as the relative ease in breeding and handling marmosets compared to macaques, opens the door to a range of naturalistic experimental paradigms. Recent advances in miniaturization and telemetry make it possible to measure and manipulate brain circuits during natural social exchanges, such as affiliative, competitive, and reproductive behaviors. Further, the marmoset is an ideal species for studying mechanisms of prenatal and postnatal brain development relevant to mental illness. Similar to other primates, marmoset brain development diverges from other mammals by the inclusion of additional zones of neural progenitors, the preservation of neural stem cells after birth, and an unusually protracted childhood during which the brain matures slowly amid abundant social experience. The systematic investigation into the anatomy and physiology of primate brain development and its bearing on cognition, from the cellular and molecular processes in the embryo to the brain's circuit development during critical periods in early life, requires a high degree of control over a species' reproductive biology, breeding, rearing, and weaning. Marmosets breed easily in captivity and can be housed in multigenerational families that cooperate in the rearing of infants. Moreover, marmosets exhibit routine twinning, typically with two reproductive cycles each year, with offspring reaching sexual maturity at the age of eighteen months. Together, these factors provide a much needed opportunity to study unique features of primate brain development whose failure is suspected to be at the core of psychiatric disorders.

Breadth of research. In the past several decades, marmosets have been used in experimental neuropsychology programs to study aspects of executive function (Dias, Robbins, and Roberts 1996; Clarke et al. 2007) and emotion (Roberts 2006; Roberts and Wallis 2000). This work has demonstrated that the organization of the prefrontal cortex is similar to that found in macaques and humans. In parallel,

systematic mapping studies of the sensory systems have illustrated that the cortical blueprint of the marmoset is also fundamentally similar to that of the macaque and human (Solomon and Rosa 2014; Kaneko et al. 2020; Cloherty et al. 2019; Ma et al. 2020). Additional work has demonstrated specializations in the marmoset brain for the perception of faces (Hung et al. 2015; Cléry et al. 2021; David J. Schaeffer et al. 2020), the production and perception of vocal behavior (S. Nummela et al. 2017; S. J. Eliades and Miller 2017; Miller et al. 2015; S. J. Eliades and Wang 2008; Tsunada and Eliades 2020; Steven J. Eliades and Tsunada 2018; Roy, Zhao, and Wang 2016), and more recently begun to uncover circuits underlying curiosity driven behavior (Tian, Silva, and Liu 2021). Technological advances in optical imaging using genetically encoded calcium indicators (Kondo et al. 2018; Santisakultarm, Kresbergen, et al. 2016), as well as viral based optogenetic approaches (Ebina et al. 2019; MacDougall et al. 2016; Nurminen et al. 2018) have rapidly begun to import technology developed in the mouse into the marmoset. This, together with emerging transgenic methods (K. Sato et al. 2016; Park et al. 2016; Sasaki et al. 2009), chronic wireless recordings (Walker et al. 2021; Roy and Wang 2012) and interactive behavioral paradigms (Toarmino, Wong, and Miller 2017; Miller and Thomas 2012), have expanded conceptions of the types of experiments currently feasible in nonhuman primates.

Future. Future marmoset research holds great promise both for increasingly precise basic science research into cognitive circuits, as well as the generation of primate models of neuropsychiatric disease. In both cases, the creation of transgenic animals is likely to figure prominently into the research. For basic scientific research, transgenic animals will serve as valuable tools for experiments in the domains of both neurodevelopment and social interaction, providing, for example, cell-type specific reporters indicating activity level or maturation state. The recent generation of transgenic marmosets expressing genetically encoded calcium indicators at the NIH (Park et al. 2016) is an important step in enabling chronic *in vivo* monitoring of neural activity using high-resolution optical imaging. Regarding translational neuropsychiatric research, preclinical models are beginning to yield deeper understanding into underlying mechanisms and potential treatments for autism spectrum disorder (Mimura et al. 2019), depression (Alexander et al. 2019), stress response (Ash, Smith, and Buchanan-Smith 2021), and fear memory relevant for PTSD in humans (Philippens et al. 2021). In the creation of disease models, transgenic animals will enable translational studies aimed at understanding the complex neural mechanisms of human brain function, with the ultimate goal of molecular targeting for pharmacotherapy and brain stimulation. Taken together, the remarkable similarities between marmosets' brain architecture and cognitive and social capacities with humans, as well as the species wide array of cutting-edge molecular and genetic tools, this primate model provides a promising bridge between basic science research and clinical psychiatry.

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Appendix 4

National Institute of Neurological Disorders and Stroke

2023 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 neurologicaldiseases. In support of its mission, NINDS performs and funds basic, translational, and clinical neuroscience research on more than 600 neurological diseases afflicting humans, including genetic diseases (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 high spatial resolution. In support of the second component, marmosets are excellent models of 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 (Donadieu et al. 2021; Perez-Munoz et al. 2021; Werneburg et al. 2020; Lefeuvre et al. 2020; Lee et al. 2019). Marmoset models of MS haveclinicopathologic correlation patterns, lesion heterogeneity, immunologic mechanisms, and disease markers more closely mimic the human condition. Marmoset models of stroke (Le Friec et al. 2021; Teo et al. 2018) 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 (Rothwell et al. 2021), and the recent evidence that aging marmosets shows the biological hallmarks for Alzheimer's disease, including amyloid-beta (Ludlage et al. 2005; Geula, Nagykery, and Wu 2002; Palazzi, Switzer, and George 2006), hyperphosphorylated tau, and dystrophic microglia (Sharma et al. 2019; Rodriguez-Callejas, Fuchs, and Perez-Cruz 2016), strongly elevates the marmoset as a superior model for the study of aging and age-related diseases (S. D. Tardif et al. 2011). Transgenic marmoset models of stroke (Park and Silva 2019), Parkinson's disease (Okano and Kishi 2017), polyglutamine diseases (Tomioka et al. 2017), spinocerebellar ataxia (Tomioka, Nagai, and Seki 2020), and severe combined immunodeficiency (K. Sato et al. 2016) 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 (C. Liu et al. 2021; Cirong Liu et al. 2020; C. Liu et al. 2018; Woodward et al. 2018), gene-expression (Shimogori et al. 2018), and neuronal connections (P. Majka et

al. 2021; Piotr Majka et al. 2020). Finally, the use of high-resolution fMRI for mapping sensory and social regions of the marmoset brain (Clery et al. 2021; D. J. Schaeffer et al. 2021; Clery et al. 2020; Yen, Papoti, and Silva 2018), resting-state brain networks (Hori et al. 2020; Cirong Liu et al. 2019), and neurophysiological, behavioral (Yabumoto et al. 2019) and calcium imaging (Yamamori 2021; Yamada et al. 2016; Santisakultarm, Kersbergen, et al. 2016) 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 techniquesin 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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Appendix 5

National Institute of Deafness and Other Communication Disorders

2023 Marmoset Community White Paper

The core mission of the National Institute of Deafness and Other Communication Disorders (NIDCD) to understand normal and disordered processes of hearing, balance, taste, smell, voice, speech and language as well as to improve the treatment of communication impairment and other sensory disorders. The common marmoset (*Callithrix jacchus*) has contributed significantly to research designed to address these key issues for several decades and will remain a cornerstone model to significantly advance the core missions of the NIDCD in the years to come. With their complex and human-like social behavior and brain organization, marmosets are an ideal model for studies of normal and disordered hearing. As a non-human primate with hearing ranges and auditory brain structures similar to that of humans, marmosets can provide greater insight into basic mechanisms of hearing than studies in more evolutionarily distant rodent models can. Because they can be easily bred and raised in laboratory conditions, have an average lifespan of 10 years, and exhibit age-related hearing loss, marmosets provide a unique opportunity to longitudinally study the effects of development and aging upon hearing over the entire lifespan. Because they are amenable to genetic manipulation as well as more genetically similar to humans than other species, marmosets may provide better understanding of genetic causes of hearing loss and their rehabilitation. Marmosets are also a valuable non-human primate model for studying vocal and social communication. Even in the laboratory colony, marmosets are highly social primates in constant interactive vocal contact with each other facilitated by the ability to be kept in natural social and family groups. Even in the laboratory colony, marmosets are highly social primates in constant interactive vocal contact with each other facilitated by the ability to be kept in natural social and family groups. As a result, marmosets can provide critical insight into normal mechanisms of communication, the evolutionary origins of speech, and disorders in communication that can arise from deafness, neurologic disease, or social isolation. Notably, work in the marmoset auditory system was the first to leverage the many advantages of this model organism to explore core questions of systems neuroscience research with nonhuman primates, such as sensory coding in neocortex (Wang et al. 2005) and the cortical basis of vocal communication (S. J. Eliades and Wang 2005, 2008; S. J. Eliades and Miller 2017; S. Nummela et al. 2017; Jovanovic et al. 2022). The potential of the marmoset model also extends beyond hearing, but includes less well investigated facets of the NIDCD mission. As prolific scent markers, marmosets are amenable to studying the neural mechanisms of olfaction in a non-human primate. As a species that naturally moves rapidly in three dimensions and relies more heavily on head than eye movements(Pandey, Simhadri, and Zhou 2020), marmosets are potentially useful in studying both the peripheral and central aspects of the vestibular system, in particular less-well understood encoding of gravity and tilt.

Expansion and Breadth of Latest Marmoset Research. Recent work in marmosets has begun to address many fundamental questions central to the mission of the NIDCD. In basic hearing research, recent behavioral research has revealed that marmosets exhibit human-like pitch perceptual patterns(Song et al. 2016), complementing previous work showing that pitch-selective area in marmoset auditory cortex (Bendor and Wang 2005). Additional recent work has also shown that marmosets use the same cues as humans to perceptually localize sound, complementing previous work showing physiologic mechanisms of sound localization(Chen,

Remington, and Wang 2023), mechanisms that have also been shown to be affected by manipulations of the cortical and thalamic activity(Steven J. Eliades and Tsunada 2023). Marmosets are beginning to be used to understand therapies for hearing loss, having recently become a model species for studying the neural effects of Cochlear Implants, revealing critical similarities and differences from normal sensory processing REFS. Marmosets have also shown recent advances in our understanding of hearing loss genetics and cochlear development, with recent studies of the marmoset cochlea showing patterns of hearing-related gene expression that are distinct from that in mice and more similar to humans REF, thus suggesting marmosets may be a better model for genetic hearing loss. Marmosets also exhibit patterns of early cochlear development that are distinctly different than rodents, and more human-like, suggesting that marmosets may be a better future model for understanding inner ear development, biology, and rehabilitation(Hosoya, Fujioka, et al. 2022; Hosoya, Kitama, et al. 2022). Furthermore, recent evidence has now shown that marmosets, like humans, exhibit age-related hearing loss (Sun et al. 2021). Marmosets are also proving themselves to be an excellent model for vocal communication and its disorders (S. J. Eliades and Miller 2017). Marmosets engage in cooperative, turn-taking vocal conversations with rules similar to that of human communication (Chow, Mitchell, and Miller 2015; Takahashi, Narayanan, and Ghazanfar 2013). Some evidence also suggests that infant marmosets babble, similarly to human babies, and their vocal development may be dependent, in part, on interactions with their parents (Chow, Mitchell, and Miller 2015) . Like humans, marmosets use their hearing to help them control their vocalizations on a moment-to-moment basis, and can exhibit long-lasting vocal plasticity, and that the auditory cortex is necessary for this vocal control (Steven J. Eliades and Tsunada 2023), evidence of the intimate relationship between hearing and vocal production(Steven J. Eliades and Tsunada 2018; Steven J. Eliades and Wang 2019), with implications for human speech and vocal disorders. Marmosets are also able to learn and detect artificial grammars, and ability that may be an ancestral trait for the evolution of language (Watson et al. 2020; Reber et al. 2019). The breadth of current work is not limited to the auditory-vocal domain, with recent anatomic studies of marmoset olfaction showing human-like connections between the olfactory bulb and cortex (Moriya-Ito et al. 2015), and genetic analysis of the marmoset olfactory system have been used in comparative evolutionary studies (Saraiva et al. 2019), as well as to understand and treat olfactory dysfunction in SARS-CoV-2 (Brann et al. 2020; Pande, Rudick, and Walter 1970). Finally, emerging research has begun to examine the marmoset vestibular system. Unlike rodents, marmoset exhibit rapid head movements (Pandey, Simhadri, and Zhou 2020), and may provide an ideal model for studying vestibular coding during natural locomotion and freely-moving behavior, something difficult in larger primate species more traditionally used in vestibular studies.

The Future. Marmosets are uniquely suited for future advances in our understanding of critical open questions in disordered hearing and communication. For example, what are the long-term effects of hearing loss and hearing restoration on the brain and what are the mechanisms by which this can contribute to cognitive decline? This association has garnered significant recent interest and attention, but the underlying mechanisms remain uncertain. Because of marmosets' lifespan, reproductive patterns, and social behavior, they are an ideal model for studying age-related hearing loss and its consequences on cognitive decline and social isolation that have been revealed as critically important in humans. Furthermore, marmosets would be amenable to more rapid testing of hearing or other rehabilitation to determine its effects on future age-related changes. Marmosets may also be a better model for studies of auditory development, hearing loss, and rehabilitation than current murine models because they exhibit more human-like patterns of cochlear development, and, and social and communicative behaviors. A second

line of critical forthcoming research pertains to genetic and neuroanatomical origins of speech and other vocal communication disorders. Although marmosets do not possess human language, their vocalizations exhibit many similarities and they are the only non-human primate species in which vocal communication can readily be studied in the laboratory, including greater homology with humans than other non-primate research models. When combined with the potential for genetic manipulations and longitudinal studies during development, marmosets are an ideal model for understanding these disorders and potential therapies.

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Appendix 6

National Institute of Aging

2023 Marmoset Community White Paper

The core mission of the National Institute of Aging (NIA) is to support and conduct genetic, biological, clinical, behavioral, and social research on aging. Common marmosets (*Callithrix jacchus*) share with other primates, including humans, many aspects of physiology, a complex brain organization, and sophisticated social and cognitive behaviors, facilitating translational research on human conditions. With an average lifespan of about 10 years and a maximum lifespan of 21, marmosets are also among the shortest-lived anthropoid primates. This characteristic makes them uniquely suited for studies of aging, as the dynamics of the aging process can be studied longitudinally throughout the entire lifespan, an approach not feasible in more long-lived primates. Thus, marmoset models of human aging have the potential to advance the NIA mission in multiple areas. First, the short lifespan of the marmoset provides the opportunity to track the progression of normal aging and age-related disorders and study their underlying mechanisms in order to achieve better prevention and prognosis. Interestingly, marmosets develop several age-related changes of specific relevance to human late-life phenotypes. For example, they exhibit age-related declines in basic biological markers, such as a decrease in lean muscle mass, that are similar to those observed in humans. They also show a marked age-related increase in cancers, amyloidosis, pathogenic tau accumulation, diabetes and renal diseases, typical of human late-life disorders. Many aspects of functional decline during normative aging in marmosets are also similar to those of humans, with marmosets exhibiting hearing loss as well as declines in cognitive and motor function with increased age. Aging is the greatest risk factor for many diseases including Alzheimer's Disease (AD), and understanding how age-related changes at both the system and cellular levels predispose the primate brain to these diseases will be critical to developing effective prevention and treatment strategies. Of particular interest, aged marmosets spontaneously develop β-amyloid deposition and tauopathies, both implicated in the pathogenesis of AD. Because the high rate of failure in AD clinical trials has been ascribed, in part, to the inadequacy of rodent models that recapitulate only limited aspects of AD pathology, these features of marmoset biology position the species as an excellent primate model for advancing our understanding of AD. In addition, advances in genetic engineering are leading to the generation of genetically modified marmosets as models for AD and other age-related neurodegenerative conditions, such as Parkinson's disease. Thus, the marmoset has substantial potential for the development of novel strategies to prevent and treat neurological diseases of aging. Moreover, because the marmoset is a highly social primate who forms long-lasting bonds and can be maintained in a social group in the laboratory, it should also prove particularly valuable to study social influences on the aging process and their impact on the pathogenesis of age-associated diseases. Finally, this short-lived primate offers the opportunity to test the safety and efficacy of interventions against age-related burden in a compressed time-frame relative to long-term studies in macaques or humans, thus allowing for the evaluation of specific interventions to extend human healthspan.

Breadth of research. Recent work in the marmoset has documented age-related changes in a wide range of biological systems (C. N. Ross 2019), including the microbiome (Reveles et al. 2019) immune system (Mietsch et al. 2020) and metabolome (Hoffman et al. 2016), likely to have important consequences for aging trajectories. At the CNS level, efforts are ongoing to characterize age-related changes in the marmoset brain (Freire-Cobo et al., n.d.; Rodriguez-Callejas, Fuchs, and Perez-Cruz 2016), associated changes in perception, cognition and motor function (Phillips et al. 2019; Sadoun et al. 2019), and their neuroendocrine mechanisms (Garber et al. 2020; Gervais et al. 2019). A rapidly growing area of research focuses on developing genetically modified marmosets to model AD (Kenya Sato et al. 2020), Parkinson's disease (Vermilyea et al. 2020) and other age-related brain disorders (Feng et al. 2020). Capitalizing on the relatively short lifespan of the marmoset, research evaluating the effects of pharmacological (e.g, rapamycin, (Sills et al. 2019) metformin and acarbose (Fernandez et al. 2019))

and environmental (e.g., exercise (Phillips et al. 2015)) interventions on healthspan in this species is underway.

Future. Offering key advantages for aging research, the marmoset provides a unique model to advance our understanding of aging at multiple levels of analysis. Studies focused on the basic biology of aging will help elucidate how age-related changes in immune function, mitochondrial function, DNA damage repair and epigenetic processes may increase the brain's vulnerability to neurodegeneration. Complementary *in vitro* studies of marmoset neuron and astrocyte cultures (Dorigatti et al. 2021) will enable better understanding of the basic processes involved in aging and neurodegenerative disorders. At the system level, advances in neuroscience techniques applicable to behaving marmosets, such as chemogenetics, optogenetics, 2-photon imaging, and high field functional MRI, will be critical to identify the neural changes that underlie perceptual and cognitive deficits in healthy and pathological aging. Longitudinal studies integrating behavioral, physiological and neural assessments in naturally aging marmosets, marmosets with induced pathology, and genetically modified models for neurodegenerative diseases will provide better tools for understanding the mechanisms underlying neurodegeneration and designing new treatment strategies with high translational potential to humans. The marmoset will also be an ideal animal model to study the effects of early life interventions (e.g., diet, caloric restriction) on the development of late-life diseases. Finally, the rich social behavior of the marmoset, now amenable to functional neuroimaging (Cléry et al. 2021), will offer the opportunity to study the mechanisms by which social influences impact the aging process. Given the unique advantages of the marmoset model for advancing fundamental questions of human aging, we urge NIA to support aging marmoset colonies, to facilitate their distribution to Investigators and to support marmoset aging research.

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Appendix 7

National Institute of Child Health and Human Development

2023 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 (Bethea et al. 2015; Kraynak et al. 2017) 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 (Power et al. 2013; Riesche et al. 2018; Corinna N. Ross et al. 2013; Suzette D. Tardif et al. 2013) 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 (Julienne N. Rutherford et al. 2014; J. N. Rutherford and Tardif 2009; Narapareddy et al. 2020; Julienne N. Rutherford et al. 2021) 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 (Dettling, Feldon, and Pryce 2002). This work has led to the further development of the model by French and colleagues (Cavanaugh, Mustoe, and French 2018; Cavanaugh et al. 2018; Taylor, Carp, and French 2020), 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 (Gultekin and Hage 2018, 2017; Chow, Mitchell, and Miller 2015; Koshiba et al. 2021). Importantly, there is evidence that marmosets are appropriate models for both autism (Nakako et al. 2014; Santana-Coelho et al. 2021) and Zika virus infection (C. Y. et al. 2017).

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 (Ausderau et al. 2017; Ash, Ziegler, and Colman 2020) and brain development from infancy to adulthood (Sawiak et al. 2018) 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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Appendix 8

National Eye Institute

2023 Marmoset Community White Paper

The core mission of the National Eye Institute (NEI) is to support research on the mechanisms underlying visual perception, from the early stages of processing in the eye to downstream processes in the lateral geniculate nucleus, primary visual and extra-striate cortex, and including areas involved in higher order visual processes such as visual attention and the control of eye movements. Natural selection has endowed primates, including humans, with specializations that affect visual processing in all these areas such as, critically, the fovea. The primate fovea has an outsized impact on the way visual information is processed, not simply because it yields higher acuity than any other mammal, leading to fine spatial form (shape) processing (J. Mitchell, Reynolds, and Miller 2014; S. U. Nummela et al. 2019; Knöll, Pillow, and Huk 2018), but because it fundamentally changes how primates use their eyes to acquire information about the world. The primate brain has a network of oculomotor areas (Krauzlis 2005) and efficient strategies for moving the eyes so that the fovea is rapidly positioned over targets of interest. Rapid eye movements (saccades), are made two to three times every second as the brain samples the visual scene, and these signals are smoothly integrated across time so that it looks to the observer as though a wide visual field is seen crisply during a period of viewing. The areas governing the planning of saccades also play a critical role in the deployment of visuospatial attention, which strongly influences visual processing (Reynolds and Chelazzi 2004). Eye movements are also critical for visuo-motor manipulations during tool use and face recognition during social interactions. Relative to other mammals, primate vision is defined by these specializations along the full extent of the visual pathway from enhanced low-level retinal processing through high-level visual abilities. Thus vision research in non-human primates affords clear advantages over rodents. Both Old- and New-world monkeys have critical roles to play in the study of primate vision, but marmosets have several practical advantages: they are economical to house and easy to handle, and lack B-virus, making them safer to work with. Further, as detailed below, the marmoset has additional advantages over other primate models for vision research in multiple areas:

Development **-** Their short developmental timescale (reaching sexual maturity ~3x faster than macaques) allows study of postnatal development in the early visual system, and they offer interesting opportunities for developmental studies of color vision, as they exhibit genetic polymorphisms that affect the long-wavelength sensitive cones, yielding both dichromats (all males, some females) and some trichromats (some females) (Jacobs, Neitz, and Crognale 1987).

Mapping - The lissencephalic brain of the marmoset places multiple areas (such as V2, MT, face patches in IT, FEF) on the surface of the brain, where they are readily accessible for laminar recordings, array recordings, intrinsic imaging, fluorescent calcium imaging, and surface-based optogenetics (Nassi et al. 2015; Sadakane et al. 2015; Kondo et al. 2018; MacDougall et al. 2016; Nurminen et al. 2018; Santisakultarm, Kresbergen, et al. 2016). The smaller brain of the marmoset makes large-scale mapping more efficient. Studies in Japan have already shown the promise of large-scale mapping techniques such as diffusion tensor imaging and widefield imaging.

Behavior – Like macaques, marmosets readily accept head restraint, a prerequisite for some approaches to electrophysiology and imaging (J. Mitchell, Reynolds, and Miller 2014; S. U. Nummela et al. 2019) and can readily perform tasks requiring sensory discrimination (J. Mitchell, Reynolds, and Miller 2014). Marmosets make saccadic and smooth pursuit eye movements (Samonds, Geisler, and Priebe 2018; J. Mitchell, Priebe, and Miller 2015) and preserve the use of eye movements to explore visual scenes and the relationship between saccadic velocity and displacement (J. Mitchell, Reynolds, and Miller 2014; S. U. Nummela et al. 2019; Knöll, Pillow, and Huk 2018). Marmosets naturally exhibit a rich visuo-social behavior that in many respects parallels human.

Disease – Treatments for debilitating diseases like blindness and retinal degeneration benefit from studying animals whose retinae are similar to those of humans. Marmosets, macaques, and humans have very similar foveal cone densities though marmosets also have higher cone density in the

visual periphery (Troilo, Rowland, and Judge 1993). The rapid reproductive cycle of the marmoset and lower cost of housing relative to the macaque is an advantage when testing novel treatments such as gene therapy and neuroprosthetics where costs may be prohibitive in a macaque.

Breadth of Current Research. The breadth of research related to the mission of NEI Eye currently underway in marmosets is notable, ranging from disease modeling of the visual periphery to higher level visual processing. For example, myopia (nearsightedness) is a prevalent disease of the eye that affects >20% of the human population and can develop throughout life. Work has been done in marmosets studying how corrective optics early in development can affect the evolution of nearsightedness (Troilo & Judge, *Vision Research* 1993). Ongoing work in marmoset is studying the genetic markers and the molecular signaling pathways involved in myopia so that potential therapeutic targets can be identified (Tkatchenko et al. 2018). Recent work in marmosets has also begun to show how interactions between cortical areas affect visual processing elucidating the long-debated role of cortical feedback in vision. Using novel optogenetic techniques for circuit dissection, the specific effects of long-range projections from V2 on V1 function were demonstrated advancing on work using more classical techniques in macaques (Nurminen et al. 2018). Moreover, visual face processing is important in primate social interactions and developmental prosopagnosia and autism are examples of specific disorders of face recognition afflicting a large fraction of the human population. Marmosets are highly social (Miller et al. 2016) and, like humans, are highly attentive to faces (J. Mitchell, Reynolds, and Miller 2014; S. U. Nummela et al. 2019) because they convey meaningful social information (Kemp and Kaplan 2013) and exhibit specialized regions for face processing in high-level visual cortex (Hung et al. 2015). Studies of this face-patch network are poised to expand with ongoing efforts to developed transgenic marmoset models of autism disorder. Close parallels are being established between marmoset and human visual and oculomotor behavior, including comparable performance on object recognition tasks (Kell et al. 2020) and motion perception (Cloherty et al. 2019). The Frontal Eye Fields, which play a critical part in oculomotor planning have been functionally characterized in marmoset, helping to establish the marmoset as a model for studying eye movements (Selvanayagam et al. 2019). Advances are being made in studying foveal vision in marmoset using high precision eye tracking (J. Yates et al. 2020) and there is also evidence for pre-saccadic enhancement in marmoset V1 (J. L. Yates, Coop, and Mitchell 2019). Marmosets were key to the discovery that traveling waves occur in the extra-striate visual cortex in the awake state, and that these waves strongly regulate sensitivity to visual stimuli (Davis et al. 2020). Detection and tracking of these waves in Area MT was only possible because unlike macaque MT, which is at the bottom of the Superior Temporal Sulcus, in marmoset MT rests on the surface of the largely lissencephalic marmoset cortex.

The Future. As a rapidly emerging model system, marmosets are likely to play a critical role in elucidating the intricacies of the primate visual system for decades to come and increase the range of studies for which the species is employed. Marmosets, for example, are an attractive species for studying diseases with a developmental component because of their fast life cycle and high reproduction rates (Homman-Ludiye and Bourne 2017). The rapid sexual maturation of marmosets (18 months) will be critical for studying schizophrenia, autism-spectrum disorders, and attention-deficit hyperactivity disorder in which psychopathology is manifest in childhood. Furthermore, visual deficits, particularly in the magnocellular (M) pathway of early vision are well documented in schizophrenia and because of conserved early visual pathways in New World primates can be studied in marmosets as well as studying oculomotor, face processing, and visual attention deficits in autism. Marmosets are the shortest-lived anthropoid primates, with a typical lifespan of 9–12 years as compared with 25–40 years for rhesus macaques. Their shorter lifespan makes them better suited to longitudinal studies of age-related vision loss. Finally, an acute need exists throughout neuroscience for means of targeting the elements of cortical circuits in the non-human primate. Viral targeting strategies have been developed for highly selective expression of proteins, such as opsins in non-genetically engineered species, and validated in marmoset (Mehta et al. 2019; D. Vormstein-Schneider et al. 2020; Dimidschtein et al. 2016). The benefits of the development of these capacities, both through the establishment of genetically engineered Cre and Flp lines and through the development of enhanced viral targeting capacities (Dimidschtein et al. 2016) will be particularly impactful in the visual system due to the over 50 years of foundational research on visual circuits.

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