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May 19, 2021

Jesse Mager, Ph.D.
Chair
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University of Massachusetts Amherst

Via e-mail: jmager@vasci.umass.edu

Dear Dr. Mager,

I am writing on behalf of People for the Ethical Treatment of Animals (PETA) and our more than 6.5 million members and supporters to express our concerns regarding experiments on vulnerable marmosets conducted by Agnès Lacreuse at the University of Massachusetts Amherst (UMass Amherst). We are deeply concerned that the extreme harms inflicted on marmosets in these experiments far outweigh any perceived benefit that the results might have for humans; and respectfully ask that the UMass Amherst Institutional Animal Care and Use Committee (IACUC) suspend its approval of these experiments.

Severity of the Experiments

In an attempt to study the complex interaction of aging and hormonal changes on cognition in humans, Lacreuse and her colleagues subject male and female marmosets to various harmful and unnatural biological and behavioral manipulations. To artificially induce age-related hormonal changes, experimenters subject marmosets to multiple invasive surgeries. They surgically remove the testes in males and the ovaries in females to manipulate sex hormones. Males are also vasectomized. They then inject these middle-aged marmosets with hormones and monitor sleep, cognition, and thermoregulation in the animals over time.

Additional major surgeries and stress-inducing behavioral procedures are often carried out to allow for the collection of specific measurements. For example, in one set of experiments, marmosets were placed in a stereotaxic frame to keep their heads entirely immobile. Two burr holes were drilled into the skull and an incision was cut into the neck to expose the muscle below. Electrodes were implanted in the scalp and the neck, and electrode leads were threaded from the scalp and neck beneath the skin to the abdomen. In other experiments, Lacreuse uses plastic cable ties to fasten marmosets into a semi-cylindrical plastic cover that immobilizes the animal's head and body; fully awake, the marmosets are then placed in an MRI machine, in which the noise and the ordeal are frightening and confusing to them. While marmosets do not experience menopause in nature, in the Lacreuse laboratory, experimenters used hand warmers to simulate hot flashes. In multiple experiments, Lacreuse and her colleagues remove individual marmosets from their colony and place the animal alone in an unfamiliar room for seven hours; during this time of social separation, the monkeys cannot see, smell or hear their family members or friends. Eventually, the marmosets used in Lacreuse's experiments are killed and their bodies dissected.

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Irrelevant to Human Health

While there is no circumstance in which the torment and killing of marmosets described above could be considered acceptable, the conduct is particularly reprehensible when we consider that several critical limitations inherent in the experiments severely limit their applicability to human beings. Experimenters may emphasize some of the similarities between marmosets and humans, but there are numerous species differences that impact the translatability of these experiments that also need to be considered. For example, there are fundamental differences in gene expression and protein function,[1] immune system functioning,[2] neurodevelopment,[3] neuroanatomy,[4] and reproductive physiology[5] between humans and marmosets that limit the applicability of data obtained from these experiments to humans. Moreover, critical differences between humans and marmosets in age-related changes in hormone production, age-related neurodegeneration, and tao isoform expression[6] make marmosets a poor model for the conditions and symptoms associated with aging in humans that Lacreuse is attempting to study.

Furthermore, artificially induced, oversimplified versions of hormone and age related changes in cognition in a laboratory setting do not adequately simulate the complex and variable etiology, symptomatology, and hormone replacement responsivity found in humans. Marmosets in laboratories cannot mimic the complex genetic, environmental, or epigenetic factors known to influence human aging and age-related neurodegeneration. Coupled with the lack of available and adequate molecular, genomic, and imaging tools[7] and the impact that international capture and trade is having on wild populations,[8] continuing to experiment on marmosets is problematic on numerous fronts.

Failure of Institutional Oversight

As you know, Dr. Mager, the IACUC is responsible for ensuring that UMass Amherst is in compliance with humane standards and regulations and is an important last line of defense for animals confined in laboratories and used in experiments. In its review of activities involving

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[1]Bailey J. (2014). Monkey-based research on human disease: the implications of genetic differences. Alternatives to laboratory animals : ATLA, 42(5), 287–317. https://doi.org/10.1177/026119291404200504

[2]Kametani, Y., Shiina, T., Suzuki, R., Sasaki, E., & Habu, S. (2018). Comparative immunity of antigen recognition, differentiation, and other functional molecules: similarities and differences among common marmosets, humans, and mice. *Experimental animals*, *67*(3), 301–312. https://doi.org/10.1538/expanim.17-0150

[3]Sakai, T., Komaki, Y., Hata, J., Okahara, J., Okahara, N., Inoue, T., ... & Okano, H. (2017). Elucidation of developmental patterns of marmoset corpus callosum through a comparative MRI in marmosets, chimpanzees, and humans. *Neuroscience research*, *122*, 25-34.

[4]Charvet, C. J., Palani, A., Kabaria, P., & Takahashi, E. (2019). Evolution of Brain Connections: Integrating Diffusion MR Tractography With Gene Expression Highlights Increased Corticocortical Projections in Primates. *Cerebral cortex (New York, N.Y. : 1991)*, *29*(12), 5150–5165. https://doi.org/10.1093/cercor/bhz054

[5]Müller, T., Simoni, M., Pekel, E., Luetjens, C. M., Chandolia, R., Amato, F., Norman, R. J., & Gromoll, J. (2004). Chorionic gonadotrophin beta subunit mRNA but not luteinising hormone beta subunit mRNA is expressed in the pituitary of the common marmoset (Callithrix jacchus). *Journal of molecular endocrinology*, *32*(1), 115–128. https://doi.org/10.1677/jme.0.0320115

[6]Sharma, G., Huo, A., Kimura, T., Shiozawa, S., Kobayashi, R., Sahara, N., Ishibashi, M., Ishigaki, S., Saito, T., Ando, K., Murayama, S., Hasegawa, M., Sobue, G., Okano, H., & Hisanaga, S. I. (2019). Tau isoform expression and phosphorylation in marmoset brains. *The Journal of biological chemistry*, *294*(30), 11433–11444. https://doi.org/10.1074/jbc.RA119.008415

[7]Ash, H., Smith, T. E., Knight, S., & Buchanan-Smith, H. M. (2018). Measuring physiological stress in the common marmoset (Callithrix jacchus): Validation of a salivary cortisol collection and assay technique. *Physiology & behavior*, *185*, 14-22.

[8]National Academies of Sciences, Engineering, and Medicine. (2019). Care, Use, and Welfare of Marmosets as Animal Models for Gene Editing-Based Biomedical Research: Proceedings of a Workshop.

animals, part of the IACUC's mandate is to ensure that procedures involving animals will avoid or minimize discomfort, distress, and pain to the animals.[9] Moreover, the IACUC also bears the responsibility of ensuring that studies on animals will contribute in a meaningful way to the body of research. Principle II of the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training states that "[p]rocedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society." Indeed, IACUC expert Dr. Stephen Schiffer, former director of the Division of Comparative Medicine at Georgetown University, stated, "External funding reviews should be viewed as additional assurance, rather than the only assurance, that the research has value. … Since humane animal use implies morally appropriate animal use, IACUCs must determine that the procedures before them are expertly planned and necessary. It is inhumane to use animals for bad science" (emphasis in original).[10]

The experiments described in Lacreuse's publications demonstrate a pattern of failure to diminish pain and suffering in animals and a lack of adherence to humane standards. Moreover, her experiments lack relevance to the impact of hormones and aging in human cognition, as manipulations of marmosets in a laboratory cannot capture the multiple factors involved in the human condition.

Marmosets are Particularly Sensitive and Vulnerable

Primates, including marmosets, are highly intelligent, complex, social animals. Those held captive in laboratories and subjected to experimental procedures exhibit signs of extreme distress, including pacing, rocking, head-twisting, and eating their own feces. Highly traumatized primates will bite their own flesh, pull out their own hair, and engage in other forms of severe self-mutilation.[11,12,13,14] Current standards for social housing and enrichment do not meet marmosets' need to problem-solve, forage, climb, and engage in complex social interactions, including caring for their offspring.[15] The lack of mental and social stimulation, as well as exposure to common laboratory procedures, leads to chronic stress that affects primates not only psychologically but also physiologically. It is well documented that primates in laboratories display aberrant immune system functioning, including increased stress-related hormones, dysregulation of the hypothalamic-pituitary-adrenal axis, and depressed immune system

[9]9 Code of Federal Regulations §2.31(d)(1)(i)

[10]Schiffer, S. P. (1999). IACUC issues in academia. In M. Podolsky & V. Lukas (Eds.), The care and feeding of an IACUC (pp. 33-48). CRC Press.

[11]Novak, M. A. (2003). Self-injurious behavior in rhesus monkeys: new insights into its etiology, physiology, and treatment. *American Journal of Primatology*, *59*(1), 3-19.

[12]Lutz, C., Well, A., & Novak, M. (2003). Stereotypic and self-injurious behavior in rhesus macaques: a survey and retrospective analysis of environment and early experience. *American Journal of Primatology*, *60*(1), 1-15.

[13]Gottlieb, D. H., Capitanio, J. P., & McCowan, B. (2013). Risk factors for stereotypic behavior and self-biting in rhesus macaques (*Macaca mulatta*): animal's history, current environment, and personality. *American Journal of Primatology*, *75*(10), 995-1008.

[14]Lutz, C. K., Coleman, K., Worlein, J., & Novak, M. A. (2013). Hair loss and hair-pulling in rhesus macaques (*Macaca mulatta*). *Journal of the American Association for Laboratory Animal Science*, *52*(4), 454-457.

[15]Duarte, M. H. L., Goulart, V. D. L. R., & Young, R. J. (2012). Designing laboratory marmoset housing: what can we learn from urban marmosets? *Applied Animal Behaviour Science*, *137*(3-4), 127-136.

functioning.[16] Additionally, marmosets are prone to bone disease[17] as well as a condition known as "marmoset wasting disease," a systemic inflammatory disorder that leads to weight loss, diarrhea, alopecia, weakness, intestinal inflammation, paralysis, and death.[18] The numerous consequences of laboratory life on marmosets' mental and physical health are not just ethically unacceptable; they also introduce several crucial confounds into data with already minimal human relevance, severely limiting the applicability these experiments will have to human health.

In a National Academies of Sciences, Engineering, and Medicine workshop dedicated to discussing the care, use, and welfare of marmosets in biomedical experiments, experts drew the following conclusion:

> [Marmosets] have unique requirements in terms of housing, feeding, social interactions, and other facets, many of which remain poorly understood. There is no standardized diet for captive marmosets, and there are very few people who have expertise in working with them. Marmosets in captivity are susceptible to a range of diseases and are particularly prone to Marmoset Wasting Syndrome, which is not one disease but a perplexing composite of multiple conditions and etiologies that could be due to poor nutrition, stress, infection, or a combination of these factors. Their breeding and parenting behavior is also poorly understood, and although marmosets are easier to handle than tamarins (as they tend to be less easily stressed and are more easily habituated to handling), their multiple births can lead to poor parenting performance.[19]

The current lack of knowledge regarding the provision of standard care for marmosets is concerning. This is particularly the case given that in just a few years, U.S. Department of Agriculture inspectors found violations of federal animal welfare laws in relation to the treatment of marmosets at UMass Amherst, including the following:

- The university caused the death of a marmoset because of "thermal injuries" after severely burning the animal as he was recovering from a vasectomy.
- The university did not have a communication mechanism in place to ensure that the attending veterinarian was aware of problems regarding the health, behavior, or well-being of the animals, including a marmoset named Pat who was repeatedly observed to be shaky and moving more slowly than usual.
- A marmoset escaped from an acclimation device, and his tail was injured during recapture by UMass staff.

Conclusion

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[16]Novak, M. A., Hamel, A. F., Kelly, B. J., Dettmer, A. M., & Meyer, J. S. (2013). Stress, the HPA axis, and nonhuman primate well-being: a review. *Applied Animal Behaviour Science*, *143*(2-4), 135-149.

[17]Olson, E. J., Shaw, G. C., Hutchinson, E. K., Schultz-Darken, N., Bolton, I. D., Parker, J. B., … & Carlson, C. S. (2015). Bone disease in the common marmoset: radiographic and histological findings. *Veterinary Pathology*, *52*(5), 883-893.

[18]Otovic, P., Smith, S., & Hutchinson, E. (2015). The use of glucocorticoids in marmoset wasting syndrome. *Journal of Medical Primatology*, *44*(2), 53-59.

[19]National Academies of Sciences, Engineering, and Medicine. (2019). *Care, Use, and Welfare of Marmosets as Animal Models for Gene Editing–Based Biomedical Research: Proceedings of a Workshop*. Washington, D.C.: The National Academies Press.

Given the level of suffering inflicted on marmosets confined and used in UMass Amherst's laboratories, it is particularly important that the IACUC ensure the experiments are scientifically sound and relevant to human health.

Thank you for your consideration of our concerns. May we present our concerns—virtually or in person—at an upcoming IACUC meeting? We look forward to your response.

Sincerely,

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