



Summary Statement from the WNPRC P51 2017 Renewal review:

“With respect to the marmoset breeding, additional expansion of the breeding will be necessary to keep pace with needs in view of new gene editing technologies, as well as the value of this model in aging, lifespan and metabolism studies. This species is and will continue to be in demand within the NPRCs and nationally in the foreseeable future.”

Marmosets in demand...

- Anecdotal evidence strongly suggests that demand for the common marmoset in biomedical research is surging...
 - University of Pittsburgh
 - University of Rochester
 - University of Chicago
 - OHSU
 - Biomedical Research Models, Inc.
 - IIT Research Institute
 - Western University, Ontario
 - McGill University
 - AlphaGenesis
 - University of Utah
 - MIT
 - SUNY College of Optometry
 - Northeastern University
 - University of Texas at Austin
 - University of Miami
 - University of Nebraska
 - Salk Institute
 - USAMRID
 - SRI International
 - Etc., etc., etc.....
- Demand is outstripping the ability of individual academic and commercial institutions and NIH-supported Centers to produce sufficient numbers of animals

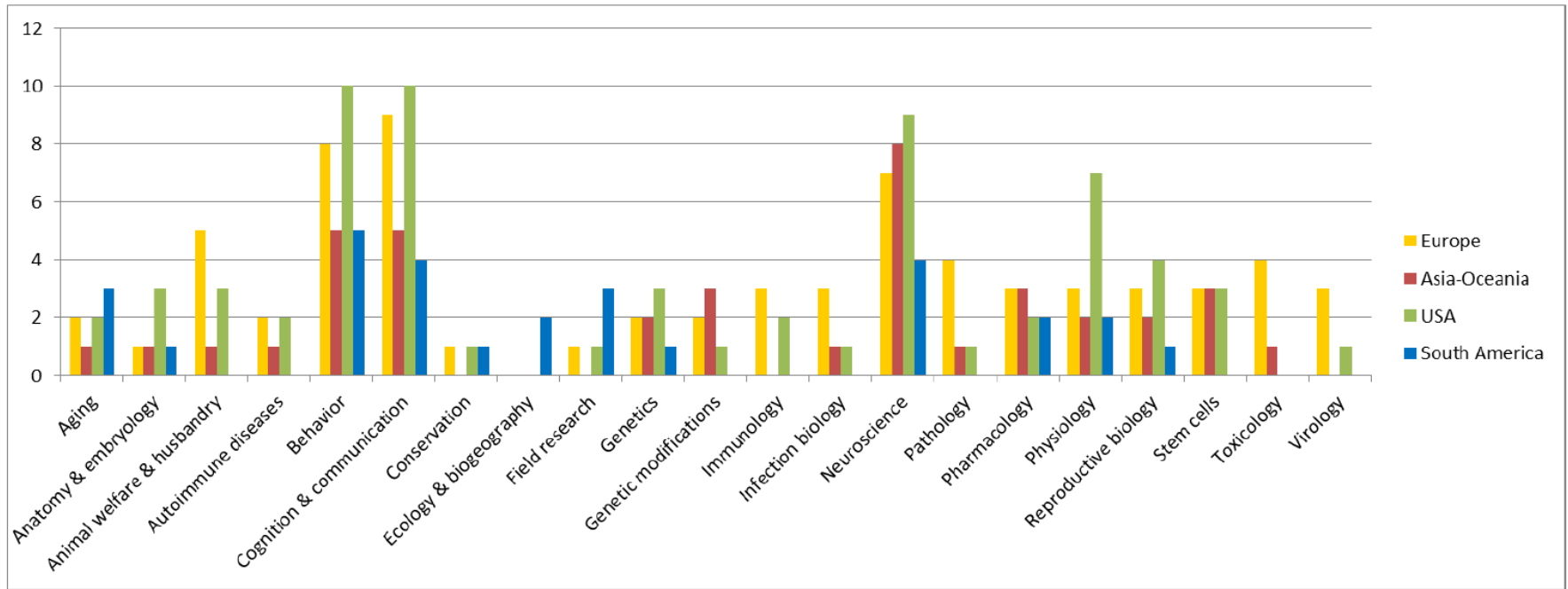
Why Marmosets?

- Shorter lifespan
 - Ease of handling
 - Ease of maintenance
 - No issue with disease transmission
 - More cost effective
 - Require less space
 - Short generation time
 - Multiple births
-

Why Marmosets Now?

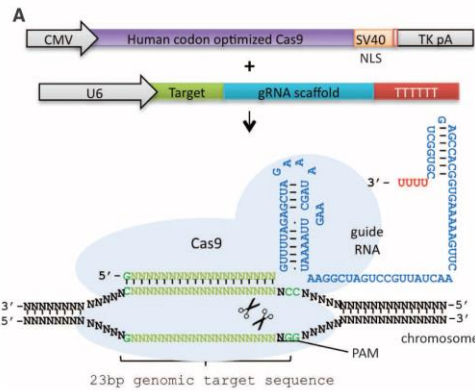
- **New generation of transgenesis/genomic editing methods available**
 - **Primate model in high priority areas, e.g. cognition, neurodevelopmental disorders, neurodegenerative diseases, metabolic diseases**
 - **Reduced funding levels make a cost-efficient primate model more desirable**
-

Summary research areas



The y-axis indicates the number of laboratories /institutes working in this research area.

Germline Genomic Editing for New Animal Models of Disease



“A CRISPR approach”

Genomic edited offspring

LRRK2 G2019S

LRRK2 S2019G

Zygotic cytoplasmic injection

IVF/ICSI



Embryo Transfer recipient

iPSC

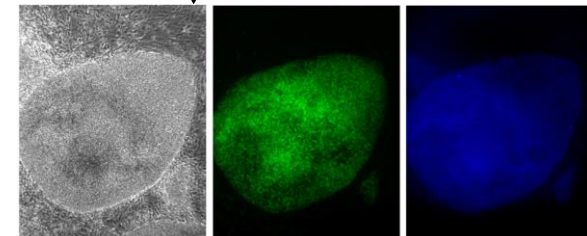
Therapeutic cells

G6055A (G2019S)

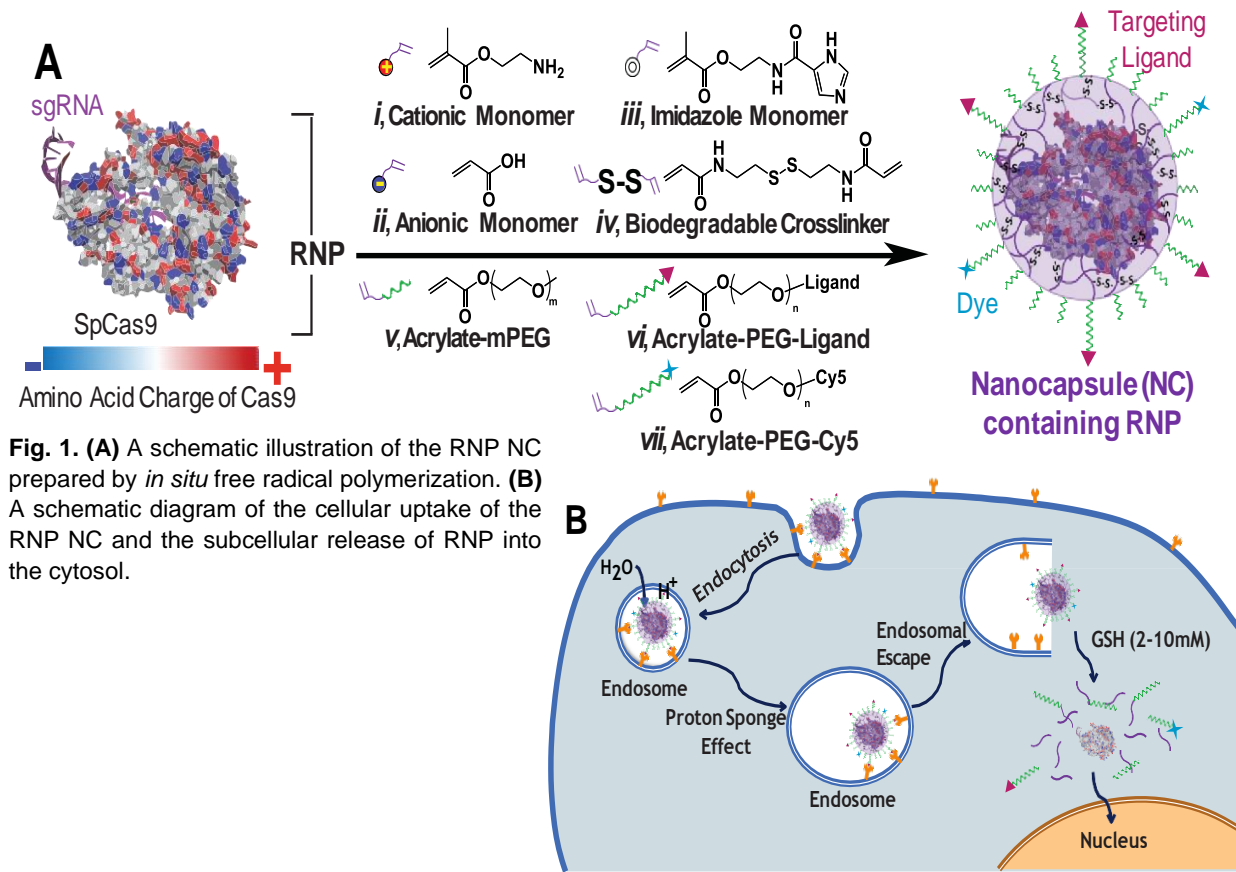
WT: CACAATGTGCTGCTTTTCACCCTGTATCCCAATGCTGCC

5' - TGCTGACTAC **AGC** ATTGCTCAGTACTGCTGTAGAA **TGGG** GATA -
3' - ACGA ACCCTTAT -
CTGATGCCGTAACGAGTCATGACGACATCTT
gRNA 5' - GACUACGGCAUUGCUCAGUACUGCUGUAGAA **NNNN** ... - 3'.

1: CACAATGTGCTGCTTTTC-----CAATGCTGCC
2: CACAATGTGCTGCTTTTCACCCTGTAT**T**-CAATGCTGCC
3: CACAATGTGCTGCTTTTCACCCTGTAT**AT**CCCAATGCTGCC
4: CACAATGTGCTGCTTTTCA-----TCCCAATGCTGCC
5: CACAATGTGCTGCTTTTCACCC-----AATGCTGCC



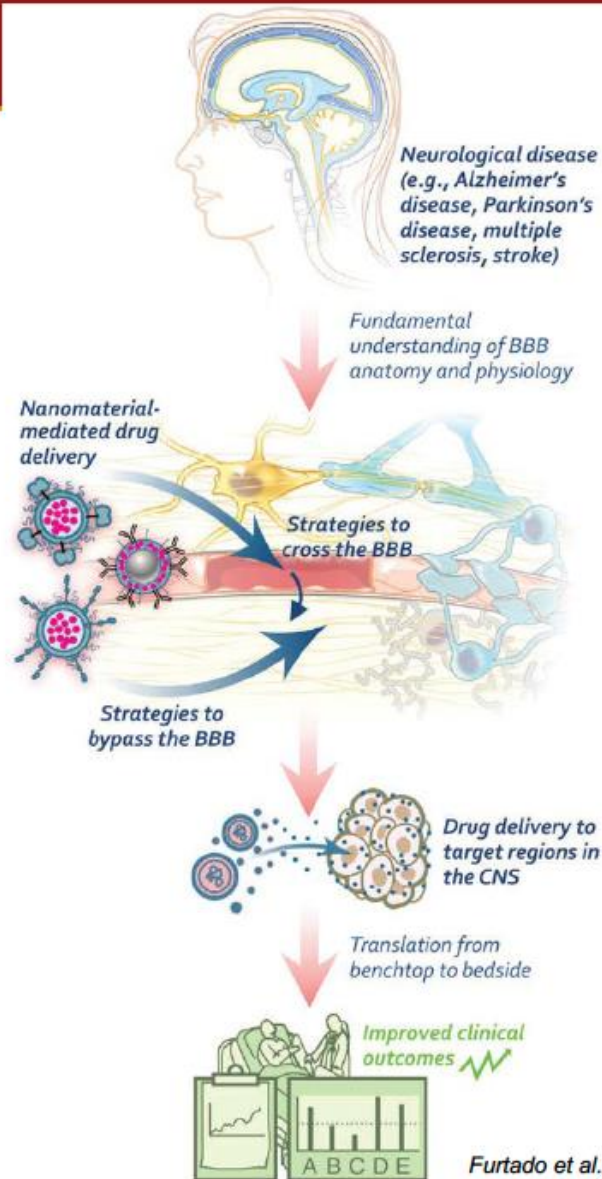
Somatic Cell Genomic Editing: New Non-Viral Delivery Systems



Somatic Cell Genomic Editing in the CNS

Furtado et al., 2018

Nanoparticles and genomic editing



The combination of nanoparticles with genomic editing has possibilities for both Therapies AND Modeling

Current projects:

- UG3 TR002659-01: Enabling Nanoplatforms for Targeted in vivo Delivery of CRISPR/Cas9 Ribonucleoproteins in the Brain
- PA-18-591: Nanoplatforms for targeted in vivo LRRK2 genomic editing in nonhuman primates



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WISCONSIN
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Marmoset Breeding In the U.S.

Location	Total # Animals	Breeding Pairs
SWNPRC	337	30
WNPRC	267	23
NIH (NINDS)	163	16
NIH (NIAID)	125	11
MIT	132	19
Johns Hopkins	126	13
University of Pittsburgh	99	6
Barshop Inst.	108	26
Salk Institute	40	?
Total	1397	144

Brain/MINDS: A Japanese National Brain Project for Marmoset Neuroscience

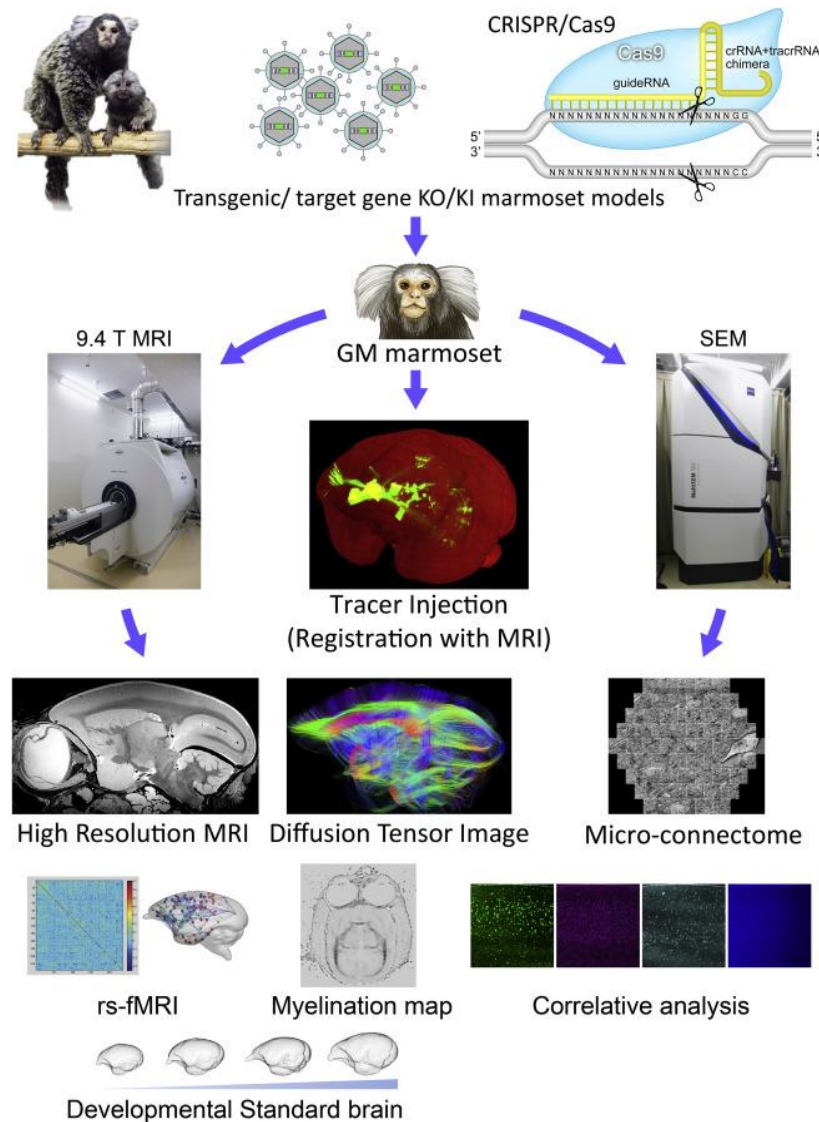


Figure 1. Genetically Modified Marmoset Models for Brain/MINDS Project. Genetically modified (GM) marmosets are being produced by viral vector and genome editing techniques. Rapid breeding methods for GM and cloned marmosets are ongoing in the SRBPS project.



Issues for ORIP/Comparative Medicine/NPRCs to consider...

- Can we more accurately monitor national demand and supply of marmosets for NIH-supported biomedical research?
- Should we develop a coordinated strategic plan to adjust our breeding targets, expand facilities, and increase resources?
- Can we pool and/or distribute expertise and/or core services more efficiently?
- Are there concerns about the genetic composition of marmoset colonies that should be addressed at a national level?

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Nonhuman Primate Evaluation and Analysis Part 1: Analysis of Future Demand and Supply

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October 12, 2018

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Ensuring an adequate supply of NHPs to sustain research progress has been an ongoing challenge, with periodic shortages and surpluses being experienced at various times over the past several years. The NHP Evaluation and Analysis was conducted to provide the NIH and the research community with an improved understanding of the demand for and supply of NHPs within the United States, with particular emphasis on the NPRCs and other NHP centers supported by the ORIP, which support research across the NIH Institutes, Centers, and Offices. [View the full report here.](#)

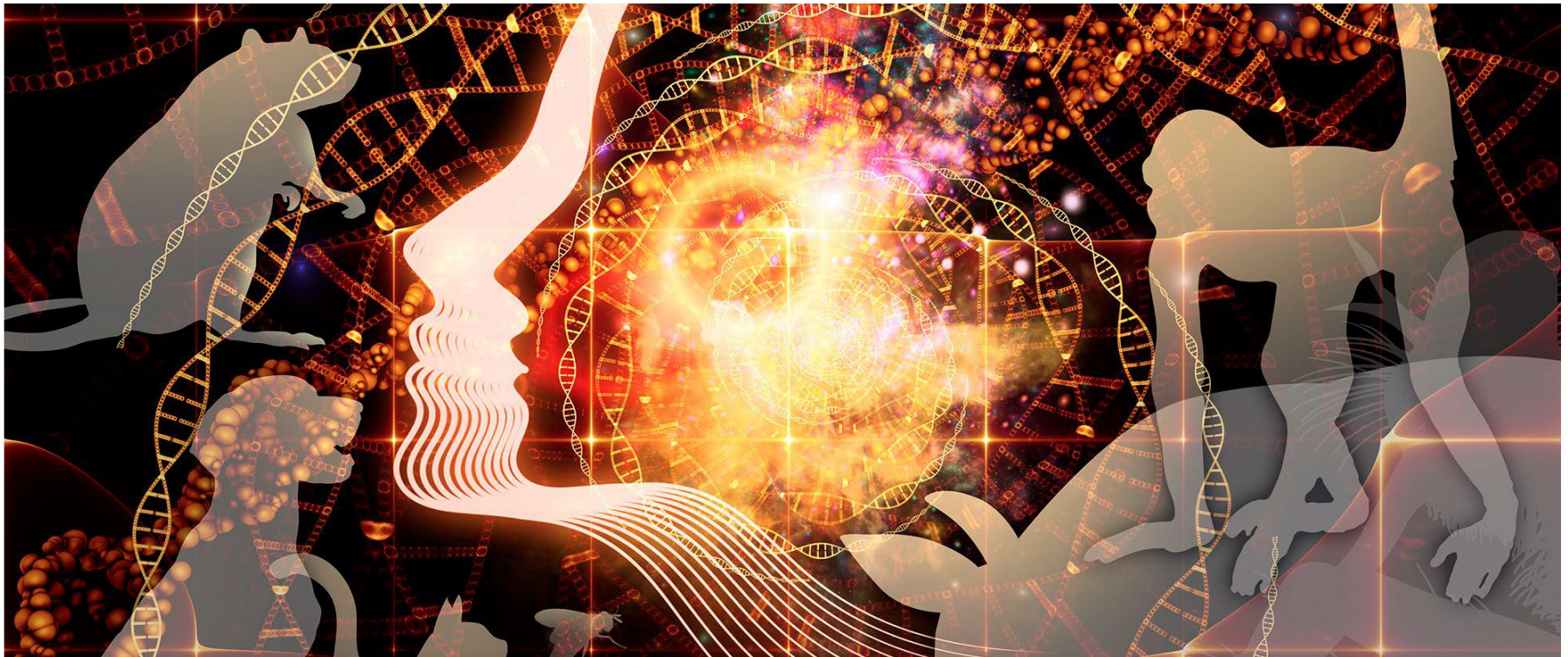
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Challenges in Assessing Nonhuman Primate (NHP) Needs and Resources for Biomedical Research

Sheri Hild, PhD, DCM, ORIP, DPCPSI, NIH



NHP Needs Analysis: Directive

- **Panel Objectives:**

- Forecast the future uses of NHPs in biomedical research
- Discuss and determine the scientific advances that are driving the future research
- Define the relevant and emerging NHP models that will be required for future biomedical advances
- Assess the capabilities of the existing resources and their ability to shift with future needs. Examine what timeframe is needed for expansion and if expansion is not possible, what additional resources or infrastructure would be required
- Address the challenges in the resource planning process

Planning Committees

- **Conference Organizing Committee:**

- Jon Levine (Chair), WNPRC, WI
- Chris Abee, MD Anderson, TX
- Sallie Permar, Duke University, NC
- Jon Hennebold, ONPRC, OR
- James Pickel, NIMH, NIH

- **NIH Organizing Committee:**

- Sheri Hild, DCM, ORIP, DPCPSI, NIH
- Miguel Contreras, DCM, ORIP, DPCPSI, NIH
- Desiree Vonkollmar, ORIP, DPCPSI, NIH
- Lola Ajayi, ORIP, DPCPSI, NIH
- Alan Feister, Leidos, NIH contractor

Meeting Agenda

- **Session 1: Future NIH Research Priorities**
- **Session 2: Scientific Factors Impacting on Demand for NHPs and NHP-Associated Services**
- **Session 3: Factors Impacting on Supply of NHPs for NIH-Sponsored Research**

Challenges

- **Animal Shortages**
- **Limitations of Award Mechanisms (limits on funds and period of support)**
- **Infrastructure and Space Limitations**
- **Peer Review and Award Practices**
- **Scientific Barriers:**
 - Limited high-quality reference genomes
 - Need for standardized methods for collecting and reporting phenotypic data
 - Limited availability of NHP reagents for specific species
 - All scientific research areas identified an on-going need to train the next generation of researchers and support staff in the use of NHP models
 - Limitations on exploiting emerging transgenic NHP models

Potential Solutions

- **Improving Communication - Multi-faceted approaches within the national NHP research community:**
 - Improve reporting of planned NHP use in NIH applications. Projections resulting from analyses of application data could be communicated to suppliers in aggregate.
 - Improve communication on NHP availability and expertise for more efficient use of existing animals.
 - Unique identifiers to track individual animals and link them with data that has previously been collected on them would eliminate unnecessary rework and expense
 - A central system to communicate animal needs and availability would promote efficient use of limited resources
 - Establishment of a national consortium for NHP breeding colonies
 - Promote tissue and organ sharing of existing biobanks that exist at the NPRCs
 - Promote visiting scientist programs at the NPRCs
 - Creation of a trans-NIH NHP working group to promote NHP models and allow identification of initiatives involving NHP research that are being considered by multiple ICs.
 - NIH should encourage the establishment of an annual interagency “NHP Summit”

Potential Solutions

- **Expanding Rhesus Macaque Colonies**
- **Expanding Access to Marmosets**
- **Establish Domestic Cynomolgus Macaque Resources**

Potential Solutions

— Enhancing the Utility and Value of Existing NHP Colonies

- Whole genome sequencing of U.S. colonies or establishing a standardized set of genetic markers incorporated into a genotyping chip to characterize all animals
- Establishing centralized facilities for NHP breeding technology, genomic editing, and transgenic animal production.
- Increasing the utilization of the Caribbean Primate Research Center (CPRC)
- Promoting the use of minimally invasive research techniques to reduce morbidity and enable the productive re-use of animals

— Promoting Training in NHP Research

Potential Solutions

- **Address Award Mechanisms**

- IC-specific NHP resource grants or contracts to support institute-specific needs
- Increasing funding for NHP resource awards, include a “Strategic NHP Reserve”
- Utilizing the P01 mechanism to promote NHP model development
- Increasing the \$500,000 cap on annual direct costs in R01 awards that utilize NHPs
- Expanding research resource grants to support development of reagents that are specific to major NHP species beyond rhesus macaques
- Allowing flexibility in the timing of grant start dates
- Providing supplemental or short-term funding within ICOs to support unforeseen costs associated with NHP acquisition

Disorders of the Nervous System

Transgenic Monkey Model of the Polyglutamine Diseases Recapitulating Progressive Neurological Symptoms

Ikuo Tomioka,¹ Hidetoshi Ishibashi,¹ Eiko N. Minakawa,² Hideyuki H. Motohashi,¹ Osamu Takayama,¹  Yuko Saito,³ H. Akiko Popiel,² Sandra Puentes,¹ Kensuke Owari,¹ Terumi Nakatani,¹ Naotake Nogami,¹ Kazuhiro Yamamoto,⁴  Satoru Noguchi,⁵ Takahiro Yonekawa,⁵ Yoko Tanaka,³ Naoko Fujita,¹ Hikaru Suzuki,¹  Hisae Kikuchi,² Shu Aizawa,² Seiichi Nagano,⁶ Daisuke Yamada,²  Ichizo Nishino,⁵  Noritaka Ichinohe,⁷ Keiji Wada,² Shinichi Kohsaka,⁸  Yoshitaka Nagai,² and  Kazuhiko Seki¹

Table 1. Production rates of transgenic marmosets

	CMV-Ataxin3-120Q-IRES-Venus	CMV-Ataxin3-120Q-2A-Venus	Total
Number of embryos transferred to surrogates	29	37	66
Number of surrogates	17	23	40
Number of pregnancies	7	7	14
Number of deliveries	3	2	5
Number of births (percentage of births per embryos transferred)	5 (17.2)	2 (5.4)	7 (10.6)
Number of transgenic animals (percentage of transgenic animals per birth)	5 (100)	2 (100)	7 (100)

A high titer of lentiviral vector was injected into a total of 66 embryos, followed by embryo transfer to 40 surrogate mothers. A total of 14 surrogates became pregnant, and five surrogates delivered seven offspring.

SCIENTIFIC REPORTS

OPEN

Generation of transgenic marmosets expressing genetically encoded calcium indicators

Received: 12 May 2016
Accepted: 20 September 2016
Published: 11 October 2016

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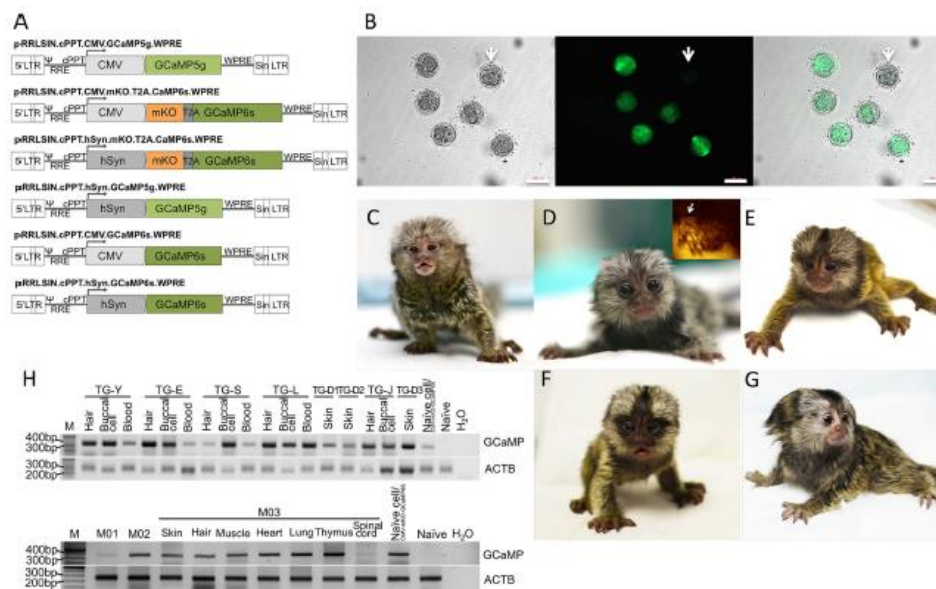


Figure 1. Generation of GCaMP-expressing transgenic marmosets derived by infection of wild-type zygotes with lentiviral vectors. **(A)** Schematic diagram of the lentiviral vectors used. Only the relevant portions of the plasmid are shown. **(B)** Verification of transgene expression in IVF embryos 4 days after lentiviral injection. Left, bright field image. Middle, green fluorescence image shows clear expression of GCaMP. Right, merged image. The arrow shows a naïve embryo. Scale bar = 100 μ m. **(C–G)** Photographs of the infant transgenic marmosets. Shown are: **(C)** TG-Y (CMV-GCaMP5g); **(D)** TG-E (CMV-mKO-GCaMP6s). The inset shows an epifluorescence image of the left front paw of TG-E (left, arrow) placed against that of a wild-type animal. Note mosaic expression of the inert orange tag mKO in the fur of the digits; **(E)** TG-S (hSyn-mKO-GCaMP6s); **(F)** TG-L (hSyn-mKO-GCaMP6s); and **(G)** TG-J (CMV-GCaMP6s). **(H)** PCR products of the transgene in animals born alive (TG-Y, E, S, L, D1, D2, J, and D3) and aborted fetuses (M01-03) showing the presence of the GCaMP transgene in different tissues. M: DNA marker; Naïve cell/CMV-mKO-GCaMP6s: genomic DNAs extracted from wild type marmoset fibroblasts infected with CMV-mKO-GCaMP6s lentiviruses for positive control; Naïve: genomic DNAs extracted from wild type marmoset fibroblasts for negative control.