# Project Proposal: *Artemis* - A "Focused Research Organization" to Establish New Mammalian Models for Predictive Preclinical Research

By Alex Shintaro Araki

***Program Overview –*** Despite representing over 95% of lab animals in biomedical research today[1], the canonical lab rodents still fail to recapitulate our most complex diseases[2]. *Mus* was essential for understanding and treating simple biological phenomena such as hypertension[3] and obesity[4] in early biomedicine. But with complex diseases of pregnancy, menopause, neurological disease, and aging remain unsolved, we are now constrained by the biological limitations of traditional rodents[5,6,7,8]. While AI and *ex vivo*/organoid models are becoming increasingly common for complex disease drug discovery, their predictive validity[9] and clinical translatability remain poorly understood. Although alternative mammals with more human-like adaptations than *Mus* have been identified across various indications, the adoption of new mammals in research is bottlenecked by convenience, cost, and tradition[10]. A robust experimental toolkit for non-model mammals is a public good that, if developed, would enable research in translational mammals to unlock biological discoveries of high predictive validity[9]. The lab mouse was a pivotal system for early biological discovery. Now, we must rely on other mammals for the next breakthroughs.

***The problem*** – Unlike humans, the canonical lab mouse is nocturnal with limited visual acuity[11], dies primarily (>70%) of cancer[12], and neither menstruates[13] nor experiences menopause[14]. With 95% of clinical trials now failing in the clinic[15], poorly predictive animal models are a significant contributor to this phenomenon[2]. Despite increasing recognition of the need for more predictive models, animals that naturally share human physiology remain a critically underdeveloped resource in biomedical research. While mammals have been identified in isolated scientific communities to share human characteristics of menstruation[13], visual acuity[11], and aging[12], widespread adoption of new animals in research has been hindered by a lack of fundamental tools such as antibodies, experimental protocols, and transgenics. We identified three translational animals for complex disease that share these bottlenecks:

**Spiny mouse (*Acomys dimidiatus*)** has recently been characterized as the only naturally menstruating rodent[16] that undergoes perimenopause with aging[14] that more closely resembles the human hormonal cycling patterns than *Mus*[,17,18,19]. Despite its historic use as a regenerative skin model[20,21], the *Acomys* has significant potential as a reproductive disease model of menstruation, pregnancy and aging, but is limited by unique handling and housing protocols[22], a lack of comprehensive species-specific antibodies, transgenics, and vendors for sourcing live animals or sectioned tissues.

**Naked mole rat (*Heterocephalus glaber)*** is the model organism for healthy aging, pioneered by Dr. Rochelle Buffenstein[23]. Their exceptionally long lifespan despite their size, healthy aging, resistance to cancer, and efficient DNA repair mechanisms[24] continues to spark the interest of biologists around the world. However, despite over three decades of research and investment from private companies like

Calico, there remains no comprehensive species-specific antibody list available to researchers, with very limited sources for obtaining live animals or sectioned tissues.

**Tree shrew (*Tupaia belangeri*)** is a diurnal animal model for visual neuroscience that offers unique advantages over *Mus* and *Rattus* due to close phylogeny to primates, as well as anatomically and functionally similar ophthalmology to humans[25,26]. Their well-developed secondary visual pathway supports complex visual processing and behaviors, which, combined with their high visual acuity and motion detection, makes them great models of visual perception[27,28]. However, like the previous mammals, there are few species-specific antibodies, no vendor to procure live animals or tissue sections, and no transgenics.

Despite this need, high-throughput tool development is challenging in academia due to limited funding, talent, incentives, and the long timescales required. Conversely, startups and pharmaceutical companies are also not incentivized due to limited investment returns, lack of precedent for ever-conservative pharma, and logistical challenges around animal housing and handling. Furthermore, animal models are currently a major contributor to the reproducibility crisis in science[29,30]. The institutions responsible for generating these models often operate under misaligned incentives, under-emphasizing 'zeroth order' implicit factors, such as animal housing, handling, and socialization, that can significantly contribute to variability in research outcomes[31]. Continuing to rely on these institutions for new model development risks perpetuating the cycle of unreliable data, hindering their adoption in the field. Establishing new animal models is therefore a public good that is best done through a focused research effort.

***Solution*** – **We propose the centralized, parallel development and distribution of standardized scientific tools to establish three new high-impact mammals to unlock the next biological breakthroughs in aging, female reproduction, and visual neurological diseases.**

*Artemis* will develop a full suite of tools for three non-model mammalian vertebrates: *Acomys dimidiatus, Heterocephalus glaber,* and *Tupaia belangeri.* We will recruit experts in each species to lead the programs, with internal functional teams to develop the suite of tools for each species in parallel. The core functional teams and their objectives are highlighted below.

***1. Antibodies*** – Species-specific antibodies are a critical resource that is lacking across non-model organisms. Academic scientists currently face the time-consuming task of individually identifying effective antibodies by screening those from mice, humans, and adjacent species. Many animal communities like the *Acomys* also have private sheets that circulates through trusted academics listing effective antibodies. However, non-specific antibodies often cannot detect unique molecules of different species, which significantly reduces accessibility as a result. We therefore propose the parallel repurposing and *de novo* synthesis of tissue-specific antibodies across all three animal programs, with an initial emphasis on tissue-types with the highest translational potential such as the *Acomys* endometrium, *Heterocephalus* fibroblasts, and *Tupaia* retina. These standard antibodies will be developed and licensed in collaboration with partners such as Thermo Fisher,

with protocols being continuously uploaded on our portal for all scientists to access and comment on.

***2. Full genome sequencing and annotation*** – Genome assembly and annotation of functional sequences is a critical milestone that will enable novel research in the species through functional genomic experiments in both academia and industry. While non-model organism sequencing efforts are ongoing or completed, it is the annotation of genes and regulatory elements that makes this information truly useful. We will leverage advanced bioinformatics tools and experienced scientists to accurately identify and annotate genes, pathways, and functional elements. We plan to make this information freely available through resources like Ensembl and GenBank.

***3. Transgenic (Cre-Dependent Cas9 Knockin) animal*** – Transgenic animals are a critical resource for genetic overexpression and knockdown for novel biological pathway discovery. Genetic models remain the preferred method of challenge to induce disease models in industry, and developing these systems will greatly facilitate the direct translational impact of the respective species for drug development. We therefore propose the development of Cre-dependent Cas9 knockin animals to enable precise and controlled genetic modifications. Such a model will be instrumental in elucidating complex gene functions and interactions, further improving the species' utility in understanding complex diseases.

***4. Comparative medicine*** – Biological breakthroughs from animals have historically been products of serendipity. The discovery of insulin through the beagle[32], fluorescent proteins from jelly fish[33], nanobodies from camelids[34], ACE inhibitors from snakes[35], all occurred from serendipitous and long-term research on fundamental biomolecular properties of unique animals. While developing standard housing and care protocols for the broader research community, we aim to systematically characterize and publicize the biomolecular properties of core animal phenotypes under our care, inspiring novel applications of these models

***5. Web Portal*** – A centralized portal will serve as the intellectual resource hub to facilitate open collaboration and discussion, serving a major unmet need for the scattered non-model mammal community. This portal will house much of *Artemis'* key deliverables including comprehensive protocols, methods, and more. By consolidating these resources, the portal aims to foster a vibrant, collaborative community, accelerate scientific discoveries, and ultimately advance the use of non-model mammals in research around the world.

***Key deliverables***:

1. Collaborative portal for research methods & tools for open science.

A centralized, GitHub-like public database for effective antibodies, methods, sequences, and other tools will be an essential resource for both novice and experienced scientists working with non-model organisms. An interactive, continuously updated internet portal will allow for scientists to

post both effective and ineffective protocols to help other researchers and allow for de-centralized open science collaboration.

2. Development and ready access to antibodies, sequences, animals and experimental methods through collaborations, licensing or an independent institute.

We plan to make our tools such as antibodies available through collaboration and licensing to large distributors such as Sigma Aldrich who have pre-existing infrastructure for production at-scale. Tissue sections of animals can be produced in-house or licensed to pre-existing institutions such as Zyagen for high-scale production as well. Live animals are currently expected to be distributed through an independent animal vendor spun out directly from *Artemis*. While a colony transfer with existing animal vendors (JAX, CRL, Inotiv) is ideal, these vendors have not been historically receptive to commercializing animals other than *Mus* and *Rattus* due to infrastructure limitations. We will re-engage vendors for colony transfer in later stages.

***Team:***

Alex Araki (CEO) – Expert in complex disease model generation across +3 species with +7yrs of *in vivo* gene delivery experience. Previously *in vivo* team lead, vivarium manager, and early scientist at Gordian Biotechnology.

Christine Arnold (VP Research | Comparative Medicine lead) – Current CEO & Chair of in vivo compliance committees for top biotech's for +8yrs. During her +20 year career she has conducted studies with numerous rodent, bird, and mammal species, including highly regulated sea otters.

Ben Sajdak (Portal | Community Engagement lead) – Director of Non-Model Mammal Discovery at Fauna Bio, a comparative genomics drug discovery startup. Heavily engaged with numerous academic networks across many non-model mammals, with deep knowledge of key bottlenecks preventing their widespread use in research.

*Acomys* lead – TBD. We are currently searching for a lead scientist through Dr. Seifert.

*Heterocephalus* lead – TBD. We are currently searching for a lead scientist through Dr. Buffenstein.

*Tupaia* lead – TBD. We are currently navigating the *Tupaia* academic network through Ben Sajdak.

Antibody lead – TBD. We are currently leveraging our existing network around members of the David Baker and other protein design labs.

Genome assembly lead – TBD. We plan to approach Linda Goodman, CTO of Fauna Bio who was involved in the Zoonomia consortium[36], for introductions to an in-house expert and consultation for non-model organism genome assembly and annotation.

Transgenesis lead – TBD. We are in conversation with transgenesis experts, and plan to first approach Randall Platt and Sidi Chen, co-authors on the CRISPR mouse[37], through our existing network. We also plan to navigate the Zoonomia and related consortia to find an expert in transgenesis.

Scientific Advisors – Ashley Seifert (*Acomys,* U. Kentucky), Rochelle Buffenstein (*Heterocephalus,* U. Illinois Chicago), Jack Scannell (CEO, Etheros Pharmaceuticals), Ashley Zehnder (CEO, Fauna Bio).

***Appendix:***

1. How were these specific animals selected over others?

The selection process began with the development of a comprehensive shortlist, generated through informal surveys and direct polling of scientists at multiple research institutes. Researchers were invited to nominate non-traditional mammalian models they believed had significant promise for translational research. This shortlist was then evaluated using a weighted, multi-criteria analysis.

Key factors included:

- **Robustness of the research community:** Consideration of whether an active and collaborative network of researchers already exists or can be rapidly mobilized around a given model.
- **Publication history:** Review of the number and quality of peer-reviewed publications involving each candidate species, indicating both the maturity and depth of prior research.
- **Projected translational impact:** Assessment of the species' physiological or genetic similarities to humans and their relevance to disease mechanisms that are poorly modeled in standard laboratory animals (*Mus, Rattus,* etc).
- **Shared resource gaps:** Identification of existing bottlenecks, such as the lack of standardized reagents, protocols, or breeding colonies, where focused investment could rapidly accelerate research progress.

This approach allowed us to select a cohort of animal species that balanced maximum potential translational impact with ease of adoption by the broader scientific community.

2. What is the existing market for these tools/new models? Could venture funding support this project instead?

Currently, the limited tools and animals are primarily shared within trusted academic communities, creating barriers for private companies to access these resources. High throughput antibody development is a time consuming, talent- and resource-intensive endeavor that lies outside the scope of academic publications or for-profit companies. Further, the existing market for antibodies, annotated sequences, and methods is too small to be sustainable independently. While online

science platforms like JOVE are useful, their B2B subscription models are often prohibitively expensive for many academics. Although transgenics could become a lucrative asset for licensing or sale to pharmaceutical companies, the associated risks and extended timelines make them unattractive under traditional venture-backed models as well.

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