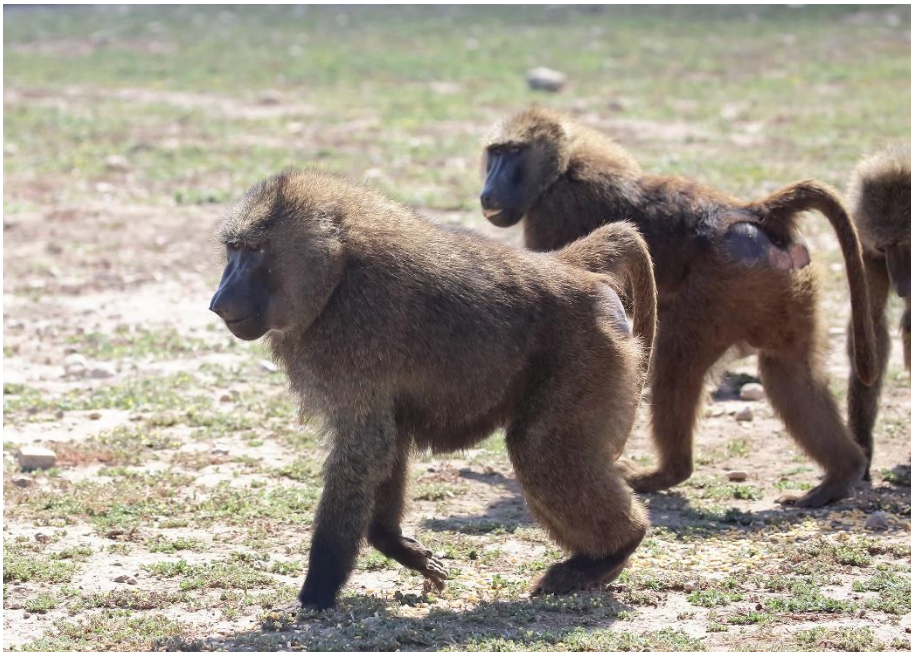
Baboons (*Papio* sp.) in research

Ken Sayers, Chris Chen and Deepak Kaushal

Baboons (*Papio* sp.) have played a critical role in basic and translational research. Their large size and close genetic relationship to humans models many normative aspects of human biology. This makes baboons an excellent species to study reproductive biology, infectious diseases (including SARS-CoV-2), physiology, neuroscience, psychology, transplantation, skeletal biology, and evolution.

Natural history

Baboons are native to much of Sub-Saharan Africa. While baboon taxonomy is continually revised, most researchers accept six groupings of baboons, genus *Papio*, that are classified as separate at either the subspecies[1] or species level.[2, 3] These include olive (*anubis*), yellow (*cynocephalus*), hamadryas (*hamadryas*), Kinda (*kindae*), Guinea (*papio*), and chacma (*ursinus*) baboons.[4] There are extensive hybrid zones in areas where the assorted baboons overlap in their natural ranges—baboon varieties can produce fertile offspring with all others—reflecting an interesting and complicated evolutionary history. Social organization generally involves multi-male, multi-female groups with males usually leaving their natal group near puberty (male-biased dispersal). The predominate exceptions are hamadrayas and Guinea baboons, where basic social organization usually involves single-male, multi-female units that travel together in bands made up of many such units, with female-biased dispersal.[5] Baboons are largely terrestrial or ground-living, and partly due to this are excellent models to **study locomotion,** skeletal disorders such as **osteoporosis,** and development of devices aiding **human mobility** such as artificial vertebral discs.[6] Baboons are extraordinarily generalist animals, among the most ecologically flexible of all primates,[7] inhabiting a wide range of environments and having a diverse diet—including fruits and seeds, tubers, leaves, flowers, invertebrate and vertebrate animals, and fungi. Indeed, they have been described as “eclectic omnivores,” [8] making them an ideal model for research in which **dietary interventions** are needed or where the **microbiome** is involved; for example, to examine the effects of diet on obesity or gut health, or to contrast dietary-related health outcomes for particular diseases, such as diabetes.



Reproduction

Baboons differ from rhesus macaques in that they breed continuously throughout the year. This facet of baboon reproductive physiology and behavior facilitated the first major theoretical accounting for the origins of primate and human sociality.[9] It is also a striking advantage in research requiring a consistent supply of new pregnancies or infants. Female baboons exhibit a prominent, colorful anogenital swelling that reaches peak tumescence near the time of ovulation; this allows reliable, non-invasive, and low-cost daily assessment of ovarian status and pregnancy. Baboons can develop spontaneous **endometriosis**[10] and provide a natural model for investigating this condition, which can also be experimentally induced. They also have reproductive anatomy that closely approximates the human condition and the larger size and extended gestation is useful for studying pregnancy. For these reasons, baboons are an excellent model for investigations involving **contraception, the physiology of ovulation, pregnancy and placentation, fetal development, developmental programming, gynecologic procedures** and **maternal-fetal transfer**.[11]

Immunology and Infectious Disease

Like humans, baboons have four immunoglobulin G (IgG 1-4) subclasses with close genetic identity to their human counterparts.[12] As IgG is the only antibody class to show marked crossing of the placenta, providing fetal protection[13]—and given the similarities in baboon-human reproductive physiology mentioned above—baboons are an ideal animal model for evaluating methods to enhance maternal-fetal transfer of IgG, including during vaccine administration. It is beneficial that baboons do not carry the herpes B virus (*Macacine herpesvirus 1*), an occupational hazard.[14] Furthermore, the ontogeny of the baboon immune system is similar to that of humans, including age-associated but individually-variable immune senescence.[15]

Not surprisingly, baboons are superb models for many infectious diseases and for vaccine development. In particular baboons have been used extensively to study respiratory diseases like pneumonia, whooping cough, and most recently COVID-19. Infant baboons were shown to be infectable with respiratory syncytial virus (RSV) and develop pneumonia. This model has been used to test whether pregnant baboons could transfer maternal RSV antibodies to infants for protection against severe respiratory disease. Baboons have become the primary animal model to study **pertussis,** the bacteria that causes **whooping cough**. Baboons are the only research animal that faithfully recapitulates all major elements of human infection, including paroxysmal cough and transmission. Baboons have proved vital in the development and production of more potent acellular pertussis vaccines.[16] Recently, it was found that baboons are susceptible to infection with **SARS-CoV-2,** and that they develop more severe **COVID-19 disease** than macaques or marmosets. Baboons harbor higher viral titers, have longer viremia, and have more pronounced lung pathology than macaques infected with SARS-CoV-2.[17] These results indicate that baboons, which develop moderate-to-severe COVID-19, will be very useful for the assessment of antivirals and host-directed therapeutics against this important public health issue.

Like several other nonhuman primate species, baboons are susceptible to *T. cruzi* infection which causes **Chagas disease**. Ineffective translation of treatments to human clinical trials based on rodent data has resulted in the need for a better preclinical animal model for Chagas disease.[18] Baboon response to these same treatments has since been shown to predict human response,[19]

suggesting future studies of promising therapies in baboons will likely predict effective therapies in clinical trials.

Left: Olive baboon at the Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, Texas.

Physiology

The baboon has long been an important model for human physiology, including genetic, epigenetic, and environmental contributors to conditions such as **obesity**, **cardiovascular disease**,[20] and **diabetes**,[21] and their correlates with various health outcomes. One comprehensive study explored the genetic variants affecting response to high fat, high protein diets in over 3,000 pedigreed baboons.[22] This has led to follow up studies on associated liver pathology like non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), and liver cancer – all of which have alarming increasing rates in the United States.[23] Other recent work has utilized baboons to assess novel methods for assessing resting energy expenditure and body temperature, as well as deploying tissue-specific ultrasound-targeted microbubble destruction gene-based therapy for aids in weight loss and to improve immunometabolism.[24]

Transplant Biology

The large size and human-like anatomy of baboons has been useful in the field of transplant biology and the testing of medical devices. Pig to baboon heart xenotransplants are being used to determine both the immunomodulatory regimens humans will need and genetic modification pigs will need to make pig to human transplants a viable possibility. Toward this end, successful pig heart transplant into baboons has now been sustained for more than 900 days.[25] Similar transplant studies are also allowing for research into methods of prolonging the survival of the organ between harvest and transplant. In addition to live organ transplants, there is increasing interest in studying decellularized tissue and organ grafts. For these studies, the comparable sizes of human and baboon organs and vasculature is being utilized.

Neuroscience and psychology

Baboons have brains with extensive cortical folding. They are flexible in behavior and frequently manipulate objects with their hands. As a stand-in for humans, they are excellent models for studies of brain function, brain physiology, and cognitive and social behaviors, including the investigation and treatment of neurocognitive-related disorders including **Alzheimer's** and **Parkinson's diseases**.[26] Baboons have been instrumental in elucidating **genetic contributions** to brain architecture,[27] in studying **hemispheric brain specialization** and novelty detection,[28] in **evaluating psychotropic drugs**,[29] and in many related areas of research.

Biological anthropology

The use of nonhuman primates, including baboons, in human-relevant research is predicated on our close evolutionary relationship with these animals—greater than 90% overall DNA sequence conservation. Thus, describing such relationships and understanding the similarities and differences between nonhuman primates and humans is a tantamount topic in **evolutionary medicine**. Baboons have been a predominate player in these types of investigations, and have shed light on aspects of anatomy, physiology, ecology, and behavior that are homologous, shared due to common descent, or analogous, shared due to common function, with humans. Baboons, for reasons described above, were the initial model used to closely describe normative anthropoid, including human, reproductive physiology and its influences on the evolution of social relationships.[30] In recent years, baboons have been utilized to describe the evolution and genetic development of primate, including human, teeth,[31] have provided insights on genetic and epigenetic contributors to skeletal joint formation, with key application to pathology such as osteoporosis,[32] and proved a key comparator for interpretation of the locomotion of the 4.4 million-year-old hominid *Ardipithecus ramidus*. *Ardipithecus ramidus* is a crucial fossil form in early human evolution, especially relevant to the appearance and modification of obligate bipedal or two-footed posture and movement—the uniquely human form of locomotion that is unfortunately associated with many potential health risks, such as back, hip, knee, and foot problems.[33]

Other models and considerations

This article gives only a broad overview of research areas where baboon models have proved influential. For example, among the many topics yet uncovered are many medical devices for human use that were first developed with baboons, such as high-frequency ventilators now used all over the world to treat infant **respiratory distress syndrome**.[34] Some baboons are naturally afflicted with congenital **epilepsy** and can be studied with regards to treatments in that area.[35] And there are established or emerging baboon applications to other pathologies such as **cancer**. Among all nonhuman primate models, baboons are especially notable for being appropriate for an exceptionally broad spectrum of research, including novel and exploratory investigations. If you are a researcher interested in human biology or health, baboons may very well be the optimal model for your area of interest. This overview provides some basic information on the model; for additional information please consider reviewing some of the literature (e.g., ref 36).[36]

We believe that the African-origin baboon is an underutilized nonhuman primate model that can recapitulate the conditions of human life-span at the intersection of infectious diseases, inflammation and human diseases of the brain, central organs and metabolism.

References and notes.

[1] Gilbert, C.C., et al. Evolution of the modern baboon (*Papio hamadryas*): A reassessment of the African Plio-Pleistocene record. *Journal of Human Evolution* 122:38-69, 2018.

[2] Rogers, J., et al., The comparative genomics and complex population history of *Papio* baboons. *Science Advances* 5: eaau6947, 2019.

[3] Jolly, C.J., Species, subspecies, and baboon systematics, in *Species, Species Concepts and Primate Evolution*, W.H. Kimbel and L.B. Martin, Editors. 1993, Plenum Press: New York. p. 67-107.

[4] In the subspecies perspective, for example, olive baboons would be designated as *Papio hamadrayas anubis* and hamadrayas baboons would be *Papio hamadryas hamadryas*. In the "separate species" perspective these same forms would receive the names *Papio anubis* and *Papio hamadryas*.

[5] Fischer, G. H. et al. Charting the neglected West: The social system of Guinea baboons. *American Journal of Physical Anthropology* 162 (suppl. 63): 15–31, 2017.

[6] For example, Malinin T. & Brown M.D. Changes in vertebral bodies adjacent to acutely narrowed intervertebral discs: observations in baboons. Spine 32:E603–E607, 2007.

[7] Sayers K. On folivory, competition, and intelligence: generalisms, overgeneralizations, and models of primate evolution. *Primates* 54:111-124, 2013.

[8] Altmann S.A. *Foraging for Survival: Yearling Baboons in Africa*. Chicago: University of Chicago Press. 1998.

[9] Zuckerman S. *The Social Life of Monkeys and Apes*. London: Kegan Paul, Trench, Trubner & Co. Ltd. 1932.

[10] D'Hooghe T.M. et al. Development of spontaneous endometriosis in baboons. *Obstetrics & Gynecology* 88:462-466, 1996.

[11] Reviewed in Bauer C. The baboon (*Papio* sp.) as a model for female reproduction studies. *Contraception* 92:120-3, 2015.

[12] Attanasio R. et al. Baboon immunoglobulin constant region heavy chains: identification of four IGHG genes. Immunogenetics 54:556-61, 2002.

[13] Palmeira P. et al. IgG placental transfer in healthy and pathological pregnancies. *Clinical and Developmental Immunology* 2012: Article ID 985646, 2012.

[14] Eberle R. & Jones-Engel L. Understanding primate herpesviruses. *Journal of Emerging Diseases and Virology* 3:10.16966/2473-1846.127, 2017.

[15] McFarlane D. et al. Age-associated alteration in innate immune response in captive baboons. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 66:1309-17, 2011.

[16] For example, Merkel T.J. Toward a controlled human infection model of pertussis. *Clinical Infectious Diseases*. 2019:ciz842, https://doi.org/10.1093/cid/ciz842, 2019.

[17] Singh, D.K. et al. Responses to acute infection with SARS-CoV-2 in the lungs of rhesus macaques, baboons and marmosets. *Nature Microbiology* 6:73–86, 2021.

[18] Urbina J.A. Ergosterol biosynthesis and drug development for Chagas disease. *Mem. Inst. Oswaldo Cruz* 104 (Suppl. 1): 311–318, 2009.

[19] Molina I. et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med* 370:1899-1908, 2014.

[20] Comuzzie A.G. et al. The baboon as a nonhuman primate model for the study of the genetics of obesity. *Obesity Research* 11:75– 80, 2003.

[21] Chavez A.O. et al. Physiological and molecular determinants of insulin action in the baboon. *Diabetes* 57:899–908, 2008.

[22] Blangero,J. et al. Genetic analysis of apolipoprotein AI in two dietary environments. *Am.J.Hum.Genet.* 47:414-428, 1990; Mahaney M.C. et al. Pleiotropy and genotype by diet interaction in a baboon model for atherosclerosis: A multivariate quantitative genetic analysis of HDL subfractions in two dietary environments. *Arterioscler. Thromb. Vasc. Biol.* 19:1134–1141, 1999.

[23] Higgins P.B. et al. Eight week exposure to a high sugar high fat diet results in adiposity gain and alterations in metabolic biomarkers in baboons (*Papio hamadryas* sp.). *Cardiovasc Diabetol*. 9:71-77, 2010.

[24] Frost P.A. et al. Research methodology for in vivo measurements of resting energy expenditure, daily body temperature, metabolic heat and non-viral tissue-specific gene therapy in baboons. *Research in Veterinary Science* 133: 136-145, 2020.

[25] Mohiuddin, M. M. et al. Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO.hCD46.hTBM pig-to primate cardiac xenograft. *Nature Communications, 7:* 11138, 2016.

[26] For example, Navara C.S. et al. Optimization of culture conditions for the derivation and propagation of baboon (*Papio anubis*) induced pluripotent stem cells. *PloS One* 13:e0193195, 2018.

[27] Rogers J. et al. Heritability of brain volume, surface area and shape: an MRI study in an extended pedigree of baboons. *Human Brain Mapping* 28: 576–583, 2007.

[28] Fagot, J., & Vauclair, J. Video-task assessment of stimulus novelty effects on hemispheric lateralization in baboons (*Papio papio*). *Journal of Comparative Psychology, 108*, 156–163, 1994.

[29] Wu M.V. et al. Impact of social status and antidepressant treatment on neurogenesis in the baboon hippocampus. *Neuropsychopharmacology* 39, 1861–1871, 2014.

[30] Zuckerman S. *The Social Life of Monkeys and Apes*. London: Kegan Paul, Trench, Trubner & Co. Ltd. 1932.

[31] Hlusko L.J. et al. The integration of quantitative genetics, paleontology, and neontology reveals genetic underpinnings of primate dental evolution. *Proceedings of the National Academy of Sciences USA* 113:9262–9267, 2016.

[32] Housman G. et al. An evolutionary perspective of DNA methylation patterns in skeletal tissues using a baboon model of osteoarthritis. *Journal of Orthopaedic Research*. In press, published online 16 December 2020.

[33] Lovejoy C.O. et al. Combining prehension and propulsion: The foot of *Ardipithecus ramidus*. *Science* 326, 72, 2009.

[34] Yoder B.A. et al High-frequency oscillatory ventilation: effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. *American Journal of Respiratory Critical Care Medicine* 162:1867–1876, 2000.

[35] Szabo C.A. et al. Mortality in captive baboons with seizures: a new model for SUDEP? *Epilepsia* 50:1995–1998, 2009.

[36] VandeBerg J.L. et al. *The Baboon in Biomedical Research*. New York: Springer Verlag. 2008.