National Institutes of Health

WORKSHOP PROGRAM

National Institute on Aging Workshop

Determinants of Species Differences in Human and Nonhuman Primate Life Spans and Health Spans

Potential Roles in Developing Interventions to Extend Human Longevity and Health Span

August 10-11, 2021

August 10 (*All times Eastern Daylight Time)*

Time	Topic	Presenter
9:30 am	• **Welcome and introductions**	Richard Hodes, Director, National Institute on Aging
9:50 am	• **Goals of workshop**	Evan Hadley, Director, Division of Geriatrics and Clinical Gerontology
10:10 am	• **Workshop Proceedings Communications**	Kathleen Mercure, National Institute on Aging
	• **Human studies of determinants of longevity and health span, and approaches for target identification for human interventions**	(Moderator: Evan Hadley)
10:15 am	✓ ***Longitudinal studies***	Luigi Ferrucci
10:30 am	✓ ***Genetics and omics approaches and findings***	Paola Sebastiani
10:45 am	✓ ***Integrative approaches to identify candidate targets and drugs using human and nonhuman data***	Nik Schork
11:00 am	***Questions and Answers***	
11:15 am	**BREAK**	
	• **Multiple phyla comparisons in studies on longevity** ***(with special focus on primate data)***	(Moderator: Evan Hadley)
11:30 am	✓ ***Potential insights into determinants of longevity from comparing primate species; considerations for selecting species***	Steven Austad
11:45 am	✓ ***Comparative studies in multiple clades, candidate mechanisms***	Richard Miller
12:00 pm	✓ ***Molecular and metabolic signatures of longevity from cross-species comparisons; correlations of species life span with other life history traits***	Vadim Gladyshev

Time	Topic	Presenter
12:15 pm	*Questions and Answers*	
12:30 pm	**BREAK**	
	• **Biodemography of primate longevity and life histories**	(Moderator: Melissa Gerald, NIA, Division of Behavioral and Social Research)
1:20 pm	✓ ***Human and nonhuman primate species differences in biodemographic parameters; evolutionary and historical changes in hominid longevity***	Annette Baudisch
1:35 pm	✓ ***Human and nonhuman primate differences in the biodemographic pace and shape of aging***	Susan Alberts
1:50 pm	✓ ***Relationships of primate species variation in reproductive strategies to aging and life span***	Melissa Emery Thompson
2:05 pm	*Questions and Answers*	
	• **Biologic and evolutionary differences that might be related to primate species life spans**	(Moderator: Luci Roberts, NIA, Division of Neurosciences)
2:20 pm	✓ ***Primate species bioenergetic difference in relation to brain and life history***	Herman Pontzer
2:35 pm	✓ ***Rates of age-related physiologic dysregulation across primate species***	Alan Cohen
2:50 pm	**BREAK**	
3:05 pm	✓ ***Comparative pathology of chimpanzee and human age-related conditions***	M. Lon Lammey
3:20 pm	✓ ***Variation in lifespans and pace of aging among monkeys in the Americas (Platyrrhini), and capuchins in a comparative context***	Amanda Melin
3:35 pm	*Questions and Answers*	
3:55 pm	• **Discussion: Ideas on research needs and opportunities arising from Day 1 presentations.**	
4:35 pm	**End Day 1 session**	

August 11, Day 2

Time	Topic	Presenter
9:30 am	**Logistics updates, etc.**	
	• **Biologic and evolutionary differences that might be related to primate species life spans, continued.**	(Moderator: Julie Mattison, NIA, Intramural Research Program)
9:40 am	✓ ***Evolution of primate-specific, hominoid-specific, and human-specific genes and relationships to phenotypes***	Yong Zhang
9:55 am	✓ ***Genes and pathways related to evolution of primate species longevity; developmental factors influencing primate species longevity***	J. Pedro de Magalhaes
10:10 am	✓ ***Interrelationships among evolutionary changes in brain regions, socially transmitted behavior, and extended life histories in primates***	Robert Barton
10:25 am	***Questions and Answers***	
10:40 am	✓ ***Evolutionary genetic changes in hominoids influencing multiple functions, behavioral plasticity, and responses to environmental factors***	Courtney Babbitt
10:55 am	✓ ***Non-coding genetic regions of accelerated human evolutionary change; relationships of human-specific traits to alterations in development***	Lucia Franchini
11:10 am	✓ ***Genomics of human evolution in relation to the exposome***	Caleb Finch
11:25 am	***Questions and Answers***	
11:40 am	**BREAK**	
	• **Evolutionary brain differences that might be related to cognitive aging changes**	(Moderator: Janine Simmons, NIA, Division of Behavioral and Social Research)
11:55 am	✓ ***Human neurobiology in comparative perspective***	Chet Sherwood

Time	Topic	Presenter
12:10 pm	✓ ***The exceptional vulnerability of humans to Alzheimer's disease: A comparative primate perspective***	Lary Walker
12:25 pm	✓ ***Costs of human brain neoteny***	Manu Goyal
12:40 pm	*Questions and Answers*	
12:55 pm	**BREAK**	
1:45 pm	• **Resources for human-nonhuman primate comparisons**	Sheri Hild, John Morrison, Jeffrey Rogers, Chet Sherwood, Susan Alberts, Nik Schork, Thomas Girke (Moderator: Manuel Moro, NIA, Division of Aging Biology)
2:45 pm	• **Discussion of research questions and opportunities (including resource needs)**	
3:30 pm	• **Mechanisms to support sustained planning and development of integrative projects**	Evan Hadley, other NIA staff
3:45 pm	• **Topics for more detailed workshops or research planning**	
4:15 pm	**END OF WORKSHOP**	

Index of Speaker Abstracts

Evan Hadley, National Institute on Aging
Workshop Background and Goals

This workshop's goals are to explore in differing ways might be learned from comparing primate species with differing life spans that could help in finding interventions that could enhance human longevity and health span. It will first review human translational longevity studies, and then the complementary role to such studies that comparisons of species with differing life spans can provide. This will be followed by considerations of possible unique contributions that comparisons of primate species with differing life spans can make to human longevity studies, particularly regarding factors in primate evolution that may have influenced longevity. This will be followed by discussions about research opportunities and resources for engagement and collaboration on this topic among the fields represented at the workshop.

The workshop's foci reflect the following perspectives:

Comparisons of humans who survive to differing ages have been an important tool in efforts to identify factors contributing to increased life span and health span. These studies have identified genetic and phenotypic factors associated with increased likelihood of survival to very advanced age. Omics and chemoinformatics analyses based on such data are beginning to be used to identify mechanistic targets for interventions that could extend healthy longevity, and drugs or other interventions that could engage these targets.

As a strategy for identifying strategies to increase life span, interindividual human comparisons have some limitations that can be addressed by complementary use of data from comparisons of species of differing life spans. Such complementary contributions of interspecies comparisons include

- A greater range of interspecies variation in longevity compared to variation among humans, providing potentially stronger signals to detect mechanisms influencing life span.
- Potential to identify factors whose variation across species contributes to differences in species lifespans, but which do not vary much among humans. Such factors nevertheless might be alterable by interventions in humans to produce favorable effects on life span or health span.
- Ability to assess relationships of factors in development and other early life history traits to longevity. The wide range of lifespans across species, coupled with the narrower lifespan variation *within* many species, provides a considerable choice of largely nonoverlapping species survival curves, across which relationships of early-life factors to species life span can be assessed, even in the absence of longitudinal individual survival data. Analogous studies in young humans are constrained by the paucity of longitudinal data on relationships of early-life factors to late-life outcomes and considerable logistical challenges to obtaining such data.

- Some translational longevity studies have begun to integrate human and comparative species data on multiple phyla including primates, particularly regarding the possibility of longevity-influencing mechanisms that are shared across phyla. There could be value in further exploring the potential contribution of comparisons of humans and other primates relating to considerations such as the following:
- Nonhuman primates' phylogenetic proximity to humans may reduce some comparative analytic problems, e.g., homolog and paralog identification and establishment of reference genomes
- Primates have a very wide range of species life spans including some of the longest terrestrial mammal life spans, allowing analyses to assess whether differing mechanisms influence longevity of short-lived vs. long-lived primate species.
- There may be primate-specific mechanisms that contribute to evolution of differencing life spans. Primate-unique evolutionary changes in features such as brain anatomy, locomotion, behavior, life histories, and social organization may involve mechanisms that also influence species life spans.
- The presence of diverse wild and captive primate populations provides unique opportunities to assess gene-environmental interactions that could influence evolution of primate longevity.
- Evolutionary changes in factors related to increased primate species longevity may have differing favorable or unfavorable ("tradeoff") effects on risk or progression of individual aging-related conditions such as cardiovascular diseases and cognitive deficits.

Notably, primates provide an opportunity for a variety of types of comparisons that could help to determine similarities and differences between factors responsible for longer life spans of hominids compared to other primate families, and factors responsible for longer life span of humans compared to other hominids.
Thus, there are potentially valuable contributions from fields such as physical anthropology, primatology, and evolutionary biology to research on these issues, and from increased interaction of these fields with ongoing human and comparative biology research to identify factors contributing to increased human longevity, and potential interventions to modulate these factors. Such interactions might be enhanced by the development of new biological and informational resources pertinent to these topics. In addition, developing effective interdisciplinary collaborations on these translational issues could benefit from planning and infrastructure development. NIA provides a variety of support mechanisms (in addition to research project grants) for such activities.

Susan C. Alberts, Duke University
The biodemographic pace and shape of aging in human and nonhuman primates: implications for the rate of aging

A decades-long trend toward increasing life expectancy and greater lifespan equality in human populations raises the possibility that we can slow the rate of aging. But the rate of ageing is closely correlated with other traits and may be highly constrained or even relatively fixed within species, according to the 'invariant rate of ageing' hypothesis. To gain insight into biological constraints on ageing, we use an unprecedented collection of datasets from 39 human and nonhuman primate populations, representing 7 genera distributed across the order Primates. We show that the highly regular linear relationship between life expectancy and lifespan equality reported in humans is recapitulated in other primate genera. We next demonstrate that variation in the rate of ageing within genera is orders of magnitude smaller than variation in pre-adult and age-independent mortality. Thus, within primate genera, longer life expectancies are not associated with a lower rate of ageing, but with fewer early deaths. We also demonstrate that changes in the rate of ageing, but not other ageing parameters, can produce striking, species-atypical changes in mortality patterns. Our results support the invariant rate of ageing hypothesis, suggesting biological constraints on how much we can slow the human rate of ageing.

Steven N. Austad, University of Alabama at Birmingham
Primate Aging Studies: Considerations for selecting species of exceptional interest

As the closest phylogenetic relatives of humans, other primate species with their combination of long pre-reproductive lives, prolonged offspring care, complex social lives, and exceptional longevity relative to their body size, are particularly relevant for understanding the intricacies of human aging. Yet there are some intricacies in selecting species for special focus to give maximum insight into human aging biology. Of primary significance is the longevity of the species in question and accurately characterizing it, particularly in relation to other species. In brief, it is time to re-think the use of a single captive longevity record with which to characterize a species, which is the most common practice in comparative biology. There are multiple reasons for abandoning this practice, which I will discuss with examples, but a key future direction that emerges from those reasons is that engaging professional demographers with both zoo and field biologists with expertise in the species of interest will be critical for developing alternatives that better characterize a species longevity. Second, among the reasons to re-think longevity records as a way of characterizing species longevity is that it does not allow characterization of sex differences in aging and longevity, which are virtually ubiquitous and unusually striking in humans. Current information indicates that primate species are highly variable in the nature of sex differences in aging and longevity. This offers an opportunity to target species with both female and male longevity advantages in order to better understand mechanisms of sex differences in aging. Again, future directions would include engaging field biologists and zoo

biologists with one another in characterizing and investigating sex differences. One potentially informative avenue of investigation would be focusing on reproductive, as contrasted with actuarial, aging. Finally, captive husbandry, including characterizing diet and appropriate social environment, on a species-by-species basis, should be re-evaluated for all species in which captive studies are warranted. Finally, for reasons mentioned above and others, incorporation of field studies into any large aging studies of nonhuman primate species should be considered. Even for species in which captive populations are sparse or nonexistent, field studies might be informative, especially as non- or minimally invasive molecular tools continue to be developed.

Courtney Babbitt, University of Massachusetts Amherst
Evolutionary genetic changes in hominoids influencing multiple functions, behavioral plasticity, and responses to environmental factors

A defining characteristic of primates is a significantly larger brain relative to body size, for which humans exhibit the greatest amount of difference. Part of the engine for this at the cellular level is that humans have evolved an especially metabolically demanding brain, utilizing over 20% of total glucose metabolism while chimpanzees, their closest living relatives, use less than 10%. Metabolism in the brain is critical for neurological function, as it provides cellular energy and critical biomolecules necessary for the complex cellular network characteristic of the brain. Two main types of cells in the brain are neurons and astrocytes; astrocytes support neurological function by provisioning metabolites to neurons for energy. Yet, there is a clear gap in our knowledge of how astrocyte function has changed over human and primate evolutionary history. Additionally, many studies of comparative primate gene expression in the brain rely on human-chimpanzee comparisons. Our preliminary data suggests that chimpanzees have extensive changes in brain gene expression as compared to other non-human primates. Therefore, there is a need to investigate these questions in a broader phylogenetic context to understand what changes are uniquely human.

To investigate cell-type specific interspecies differences in brain gene expression, we conducted RNA-Seq on neural progenitor cells (NPCs), neurons, and astrocytes generated from induced pluripotent stem cells (iPSCs) from humans and chimpanzees. Interspecies differential expression (DE) analyses revealed that twice as many genes exhibit DE in astrocytes (12.2% of all genes expressed) than neurons (5.8%). Pathway enrichment analyses determined that astrocytes, rather than neurons, diverged in expression of glucose and lactate transmembrane transport, as well as pyruvate processing and oxidative phosphorylation. These findings suggest that astrocytes may have contributed significantly to the evolution of greater brain glucose metabolism with proximity to humans. Evolved differences in metabolic investment may be the basis for a number of primate-specific phenotypes, including those that are unique to humans, (e.g. slow reproduction and long lifespan). Our results provide insight into the metabolic changes that were necessary to support evolution of the human brain. We have demonstrated a significant interspecies divergence in aerobic glycolytic gene

expression in astrocytes, suggesting that this traditionally understudied glial cell type likely contributes to the tissue-level shifts in gene expression and that astrocytes play an important role in the evolution of the metabolically expensive human brain. This study also highlights the need for non-human primate stem cell resources. Standardized iPSC lines and techniques could allow for more phylogenetically-award data collection; highlighting results that are human or primate specific and allowing us to test how different cell lineages have evolved in human health and disease.

Robert Barton, Durham University
Brains and life history evolution

Brain size variation in mammals correlates with life histories: larger-brained species have longer gestations, mature later and have increased lifespans. Two general classes of hypothesis to explain this pattern make different predictions. The cognitive buffer hypothesis posits that large-brained species have a survival advantage, because their superior cognitive abilities enable them to respond flexibly to environmental challenges. On the other hand, developmental costs hypotheses suggest that larger brains simply take longer to grow, and this slows down life histories. Analysis of variation in brain size and allocation of brain growth to pre- and post-natal development supports the idea of developmental costs. Neonate brain size increases with gestation length, and postnatal brain growth increases with the duration of lactation. Increased postnatal brain growth is associated with significantly later age at first reproduction, explaining the well-known correlation between adult brain size and postnatal life histories. Once the effect of maternal investment duration is taken into account, adult brain size is uncorrelated with juvenile period, age at first reproduction and adult lifespan, suggesting that the association between brain size and life histories primarily reflects the developmental costs rather than the cognitive benefits of large brains I enhancing longevity. We further tested the developmental costs hypothesis by examining the life history correlates of brain regions with different developmental trajectories. While neocortical growth is allocated primarily to pre-natal development, the cerebellum exhibits relatively substantial post-natal growth. Consistent with developmental costs, neocortical expansion is related primarily to extended gestation while cerebellar expansion to extended post-natal development, particularly the juvenile period. Contrary to the cognitive buffer hypothesis, adult lifespan explains relatively little variance in the whole brain or neocortex volume once pre-adult life-history phases are accounted for. Only the cerebellum shows a relationship with lifespan after accounting for developmental periods. Together, these results imply a major role of maternal investment and offspring development in brain evolution, and imply that environmental input during post-natal maturation may be particularly crucial for the development of cerebellar function. They also suggest that relatively extended post-natal maturation times provide a developmental mechanism for the marked expansion of the cerebellum in the apes, including humans.

One implication of these findings is that there are quite intricate relationships between brains, development and life histories. Different brain regions may differ in their vulnerability to environmental disruption depending on when such disruptions occur in the life course. Similarly, some brain regions and neural functions may be more vulnerable than others to ageing. We still know very little about these kinds of effects. More comparative work on neural development and degeneration and their links to lifespan would be of value in this regard.

Annette Baudisch, University of Southern Denmark
The pace and shape of aging: comparative measures motivated by evolutionary demographic theory

What determines how aging and lifespan differ among human and non-human populations? One aspect that is central to answering this question are the measures that we use to characterize aging patterns. Do traditional measures, such as the initial mortality rate and the rate of aging, provide us with information on all aspects of aging that are relevant? Here I argue that, though traditional measures of aging are fine measures, they mainly pertain to one dimension of aging – the "pace of aging". Evolutionary demographic theory reveals, however, that measures should capture not one, but (at least) two dimensions of aging – the "pace" and the "shape" of aging. Studies that distinguish between the pace and shape dimensions of aging have been revealing major new regularities of aging and longevity over evolutionary and historical time. These suggest that future comparative studies of aging should capture both dimensions, the pace as well as the shape of aging. Last not least, the dimensions of pace and shape do not only pertain to mortality, but also to fertility. Measures of the pace and shape of reproductive aging readily derive from recently developed lifetable relationships for fertility, which mirror the classic relationships for mortality. Hence, data permitted, future biodemographic studies of aging should capture the pace and shape of mortality and fertility to cover the (currently known) major dimensions of aging.

Alan A. Cohen, University of Sherbrooke
Rates of age-related physiologic dysregulation across primate species

Lab has developed and validated multi-biomarker metrics of the aging process, mostly in humans. Specifically, homeostatic dysregulation (HD) is quantified as the statistical distance of standard clinical biomarkers and measures how far an individual is from a homeostatic norm. High dysregulation scores are associated with a wide variety of health outcomes. Integrated albunemia (IA) is a process that integrates anemia, low albumin levels, low calcium levels, and inflammation, and predicts mortality and frailty but not chronic disease. Both metrics are derived from a complex systems model of aging which suggests that key aspects of the aging process may emerge at higher organizational levels than the individual molecules and pathways that are often studied. The lab validated the phylogenetic stability of these metrics across primates

using humans and 11 species from the internet Primate Aging Database (iPAD). Specifically, assessed whether each metric increased with age or predicted mortality in each sex of each species. Assessed the stability of the metrics to variations in the component biomarkers and to calibration based on other species. Concluded that HD generally increases with age in all species and predicts mortality in most for which there were sufficient data. IA also appears to increase with age; data are inconclusive with respect to mortality. HD can be cross-calibrated across species, but with substantial loss of signal as phylogenetic distance increases. IA, in contrast, is quite well conserved across species with no apparent phylogenetic signal.

Both HD and IA can be easily monitored longitudinally in studies of primates and used as informative measures of the biological aging process. The necessary biomarker data generally are already routinely collected in most primate colonies as a result of veterinary follow-up, and the algorithms are easy to implement. The resulting time series are more detailed than what is available in most human cohort studies, and more regular than in most human clinical data. They are thus likely to be among the most accessible measures of the impacts of healthspan interventions in primates. Beyond this application, these results show the potential of integrative approaches to biomarkers that could be applied to time-varying -omics data. Use of primates as translational models implies inferences about the stability of biological processes across phylogenetic distance, and our results show contrasting examples of phylogenetically stable and phylogenetically decaying biological processes. Viewing future findings in this light could help assess the relevance for human health.

Melissa Emery Thompson, University of New Mexico
Relationships of primate species variation in reproductive strategies to aging and lifespan

Across mammals, there is a well-recognized inverse relationship between reproductive rate and lifespan, demonstrative of a tradeoff between life history investments in reproduction and survival. This tradeoff is central to evolutionary theories of aging, where it is understood that genes which promote reproductive success early in life will be selected for despite negative effects they may have on long-term survival (William's antagonistic pleiotropy model). Furthermore, Kirkwood's 'disposable soma' theory argues that organisms will prioritize energetic investment in reproduction at the expense of repair and defense mechanisms that would promote long-term survival.

While the proximate tradeoffs between reproductive and somatic investment are undeniable, studies of humans have not yielded clear evidence that individual differences in reproductive effort account for significant differences in survival or health status, even in resource-limiting conditions. Methodological challenges are often raised to explain inconsistent findings. However, the alternative explanation is that human survival is highly buffered against the costs of reproduction. Humans exhibit unusually risk-averse reproductive strategies involving both physiological adaptations

and the social context of reproduction. The roots of these adaptations can be revealed by examining how reproductive adaptations have evolved across primates.

Life history traits, including lifespan and birth rates, are strongly dependent on body size. Nevertheless, primate lifespans are longer, and reproductive rates lower, than expected for mammals of their size. This suggests that primates as a group show evidence of shifting priority towards survival. However, life history correlations in the hominids, the group that includes humans and other great apes, are inconsistent with other primates. The evolution of hominids involved a shift toward a more conservative reproductive rate than would be predicted by either lifespan or body mass. To reverse this trend, humans do something that other closely-related primates do not do by weaning offspring before they are nutritionally self-sufficient and caring for multiple dependents. Thus, the combination of costly offspring and rapid reproductive rates makes it a particular paradox that humans can so effectively manage the survival costs of reproduction.

Here, I highlight shifts in reproductive strategies across primates that are important for understanding how humans manage the costs of reproduction. There is a transition from seasonal, "income"-based breeding strategies in smaller primates towards strategies in larger primates where fecundity is calibrated to maternal condition. Birth spacing mechanisms in the hominids also differ from other primates and mammals in ways that prioritize maternal health, even at the expense of offspring development. Thus, in humans' close relatives, the chimpanzees, we find few impacts of reproduction on maternal health, even in the absence of cooperative caregiving.

These patterns suggest that in humans and closest ape relatives, female reproductive effort is carefully calibrated to the individual's ability to accommodate and recover from its costs. This apparent reversal of the expected tradeoff between survival and reproduction may be a necessity to accommodate the high costs of infant care in the hominids, wherein variance in lifespan contributes disproportionately to fitness. While broadly adaptive, these mechanisms may also be poorly matched to modern environments, pointing to important needs to study interactions between reproductive health and longevity across diverse populations. One concern is that mechanisms that evolved to constrain reproduction under conditions of resource scarcity may promote unhealthy rates of reproduction in populations experiencing rapid nutritional transitions. Additionally, human reproductive adaptations evolved under conditions of cooperative caregiving and social support which may be less reliable in some modern ecologies. Thus, research priorities should include investigations into how social and ecological factors shape maternal health across the lifespan.

Despite decades of research with wild primates, cross-species examinations are hindered by a remarkable scarcity of data on longevity for most species, and few species are represented by demographic information on more than a single population. Additionally, where reliable mortality data exist, they are often used as the only

available proxies for health or aging, despite considerable interspecific variation in sources of mortality. This owes in part to the difficult of maintaining core research funding to support objectives such as demographic study, as opposed to short-term funding for narrow research questions. Thus, key priorities for research investments are (a) general support mechanisms to shore up investments in important research populations that can provide essential data on life course biology; (b) investments in pathobiology and health monitoring programs to resolve links between proximate health insults, aging, and mortality; (c) support for advanced demographic analysis, particularly innovative methods to resolve common data issues in field demography (e.g., age uncertainties, mortality selection, censoring for migration); (d) development and continued support for collaborative networks (e.g., the Primate Life Histories Working Group) that provide standardized protocols for demographic data analysis and conduct novel cross-species comparisons.

Luigi Ferrucci, National Institute on Aging
Longitudinal Studies

Studies are focused on changes in biology, phenotypes and function that occur across the life course and are often approached by comparing cross-sectionally "individuals" of different age, and less often by measuring certain characteristics multiple times in the same individual over an extended life period. Generally, cross-sectional studies can be performed relatively quickly on large populations but are vulnerable to biases such as the difficulty to distinguish the effect of different age and exposure to different environmental conditions. An historical example is the study that compared adults who were in utero during the Dutch Hunger Winter to controls born in other years. There was a clear and significant effect of the intrauterine environment on outcomes in later life, with higher likelihood of a metabolic syndrome phenotypes. Another limitation of cross-sectional studies is the selective attrition or loss to follow-up with those individuals who are healthier than others in the population. These healthier individuals tend to disappear from the observation because of selecting mortality or higher non-participation. Because of informative censoring, the effect of aging on specific parameters related to health tend to be underestimated in cross-sectional studies compared to longitudinal studies. For example, the estimated decline of aerobic capacity from longitudinal studies is steeper than what has been previously estimated in cross-sectional studies. Studies aimed at estimating composite measures of aging using "omics" are hampered by a cross sectional design in many ways. For example, some of the specific biomarkers used to estimate the "pace" of aging may already be altered during early life. For example, the few longitudinal studies that measured methylation have found that many of the CpGs included in the weighted calculation of many epigenetic clocks shows little to no differences in longitudinal studies. Expanding longitudinal studies in humans as well as in model organisms is critical to understand mechanisms by which the aging process affect the decline of physical and cognitive function with aging.

Caleb Finch, University of Southern California
Genomics of human evolution in relation to the exposome

Human lifespans are 20 years longer than great apes due to our unique post reproductive phase. Human life history evolved with delayed reproduction and brain development, integrated with unique social systems for multigenerational support and resource sharing that enable our two-fold more frequent pregnancies. Genomic changes can be mapped in the evolution of the human exposome as we encountered novel environmental inflammogens and pathogens. Some genetic innovations serve immunity, brain development, and brain aging, illustrated by two gene systems, CD33 and ApoE. CD33 encodes a receptor for sialoglycan ligands of bacterial pathogens with isoform variants that impact reproduction and Alzheimer (AD) pathogenesis. ApoE isoforms influence blood cholesterol and the risk of cardiovascular disease (CVD) and AD. ApoE4, the ancestral allele, increases blood cholesterol, CVD and AD, relative to ApoE3 which evolved about 0.25 mya. ApoE3 also increases synapse density during development in brain regions vulnerable to ischemia and AD. The maintenance of ApoE4 in all human populations may be associated with increased resistance to infections. The apoE gene is within a highly conserved cluster of interactive genes that mediate reproduction, metabolism, and immunity. The CD33 and ApoE gene systems demonstrate the integrative evolution of reproduction, immunity, and brain in enabling human longevity.
Finch & Yassine, *Front Aging* Neurosci 2020; Schwartz *PNAS* 2016; Landig *Evol. Appl.*, 2019 Trumble & Finch *Q Rev Biol* 2019; Hooper *Proc Roy Soc B* 2015.

Lucía F. Franchini, Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (INGEBI), Consejo de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina
Non-coding genetic regions of accelerated human evolutionary change; relationships of human specific traits to alterations in development

It has been proposed that the phenotypic differences in cognitive abilities among modern and archaic humans and with our closest living relatives, the chimpanzees, are largely due to changes in the regulation of genes involved in the development and function of the brain. To investigate this hypothesis, in our lab we study noncoding conserved regions that underwent accelerated evolution in the human lineage and have been named Human Accelerated Regions (HARs). These sequences have been identified using several bioinformatics approaches and constitute a rich dataset to investigate the impact of human specific evolution on gene regulatory function. We have mapped HARs in the human genome and found that they are not distributed randomly but they accumulate in particular genes and genomic territories. We have identified the gene *Neuronal PAS Domain Protein 3* (*NPAS3*) as the one that accumulates the largest number of HAR in its transcriptional unit. We consider the transcriptional unit as the genomic region contained between the transcription start to the transcription end and including introns. *NPAS3* encodes a transcription factor of the bHLH-PAS family that is widely expressed in the

developing nervous system of vertebrates, and its dysfunction has been associated with the etiology of schizophrenia and bipolar disorder in humans. Thus *NPAS3* is an ideal candidate to study human-specific gene regulation, evolution and function. We have functionally characterized the 14 NPAS3-HARs as regulatory regions through a transgenic zebrafish enhancer assay comparing the function of the human and the chimpanzee version of each sequence. Through this approach we have identified at least three HARs that lost or gained function in the human lineage. We have particularly focused on HAR202, since its human version displays a loss of function compared to the chimpanzee version of the sequence. Moreover, we found a lack of reporter EGFP expression in the brains of fishes carrying the *Homo sapiens* version of HAR202, while the rest of vertebrate orthologs tested (chimpanzee, macaque, mouse, chicken and zebrafish) showed strong expression in this organ. Remarkably, we also found that the HAR202 *Homo neanderthalensis* ortholog sequence, displaying just one substitution compared to the *H. sapiens*, showed also strong expression in the brain. We also observed this modern human-specific loss of activity in mouse transgenic reporter assays, comparing human and neanderthal HAR202 enhancer activity. Our results suggest that the HAR202 element lost its enhancer function constituting one of the few examples of a HAR that displays functional evolution in the brain as a result of the fast molecular evolution process undergone in the *H. sapiens* lineage.

Furthermore, investigating other gene regions that accumulate exceptionally high numbers of HARs, we found that the topologically associating domain (TAD) determined using developing human cerebral cortex containing the *FOXP2* locus includes two clusters of 12 HARs, placing the locus occupied by *FOXP2* (forkhead box P2) among the top regions showing fast acceleration rates in non-coding regions in the human genome. FOXP2/foxp2 encodes a transcription factor that is highly conserved among vertebrates and that is widely expressed in the nervous system and other organs and tissues throughout development and in adults. FOXP2 has been linked to the ability of spoken language in humans since it was discovered that mutations affecting this gene in a large family impacted directly on the acquisition of speech. Moreover, this gene has been associated to the evolution of language in humans because evolutionary studies found that human FOXP2 displays two amino acid changes compared to our closest living relatives chimpanzees, gorillas and rhesus macaques and it has been suggested that this gene underwent positive selection in the human lineage. Using in vivo enhancer assays in zebrafish, we found that at least five *FOXP2*-HARs behave as transcriptional enhancers throughout different developmental stages. Moreover, we uncovered two *FOXP2*-HARs showing reporter expression gain of function in the nervous system when compared with the chimpanzee ortholog sequences. In addition, we found that these *FOXP2*-HARs direct the expression of the reporter gene EGFP to foxP2 expressing regions and cells. Our results indicate that regulatory sequences in the *FOXP2* locus underwent a human-specific evolutionary process suggesting that the transcriptional machinery controlling this gene could have also evolved differentially in the human lineage. In summary, we found several HARs linked to *NPAS3* and *FOXP2* displaying functional changes in

comparative studies. These HARs constitute a basement for more complex analysis in mammalian models to identify the phenotypic impact they could have had in the human brain. What is the importance of our work? First, understanding our species origins and also shedding light on the genetic mechanisms underlying morphological evolution through the evolution of gene regulation. Additionally, since the genes involved in human brain evolution that we study are also involved in human specific mental diseases such as bipolar disorder, schizophrenia, autism, etc, we expect that our studies will help to better know these genes function and thus to illuminate our understanding of complex mental diseases.

Vadim Gladyshev, Brigham and Women's Hospital, Harvard Medical School
Molecular and metabolic signatures of longevity from cross-species comparisons; correlations of species life span with other life history traits

Much of the current research on longevity focuses on the aging process within a single species. Many molecular players, pharmacological interventions and dietary approaches have been found to modestly extend lifespan in model organisms. However, natural lifespan varies much more significantly across species. Within mammals alone, maximum lifespan differs more than 100-fold, but the underlying regulatory mechanisms remain poorly understood. Recent comparative studies are beginning to shed light on the molecular signatures associated with exceptional longevity. These include genome sequencing of naked mole rat, microbat, blind mole rat, bowhead whale, beaver and other species with exceptional longevity, and comparative analyses of gene expression, metabolites, lipids and ions across multiple mammalian species. Together, these studies point towards several putative strategies for regulation of lifespan and other life history traits, as well as pathways and metabolites associated with longevity variation. In particular, longevity may be achieved by both lineage-specific adaptations and common mechanisms that apply across the species. These findings also provide direct insights into how nature reversibly adjusts lifespan and other traits during adaptive radiation of lineages. Primates occupy a particular place in these analyses, as these organisms are longer lived than comparatively sized mammals, and human longevity is further extended within primates. Analysis of cross-species molecular signatures and within-species lifespan extension strategies, and understanding how these apply to primates, should improve our understanding of mechanisms of longevity control and lead to novel effective longevity interventions.

Manu Goyal, Washington University School of Medicine, St. Louis, MO
Costs of Human Brain Neoteny

There is now increasing evidence that the human brain exhibits neoteny relative to other mammals. Brain neoteny--defined here as the expansion and prolongation of juvenile and developmental traits in the brain--is likely associated with several advantages to brain function, and might be one of the defining characteristics of the

human species. It is striking then that the degree of brain neoteny seen in humans has not yet evolved in other primate species. What limits the evolution of brain neoteny? Here we raise several possible theories of what these evolutionary constraints and trade-offs might have been and how they might have been overcome by the human species.

In part due to a higher encephalization quotient, the adult human brain is relatively more metabolically expensive than in other primates, but the developing human brain is particularly expensive. This increased expense is further exacerbated by prolongation of the developmental period extending into adulthood, which significantly increases the total caloric and nutrient burden required to sustain optimal human brain maturation. We discuss the potential implications of this requirement, including physiologic, symbiotic, and societal adaptations that might have occurred as a result. A key point is that ensuring neotenous brain maturation likely requires profound changes at multiple levels that might well have driven several aspects of human evolution.

We will then turn to the physiologic processes presumably underlying brain neoteny that might also impact (both positively and negatively) the risk of aging-related cognitive decline and neurodegenerative diseases. We will discuss studies on brain amyloid pathology, brain resilience and early versus late life effects of *ApoE* allelic variants as potential examples of such trade-offs. Moreover, we propose that brain neoteny should theoretically be associated with increased complexity in the genetic, molecular, anatomic and metabolic processes governing human brain function, with potential implications relevant to the risk of developmental, aging-related and mental illnesses.

As a theoretical proposal, it is clear that more evidence will be needed to test the hypotheses presented here. We will end by discussing directions for future research aimed at gathering this evidence and identifying opportunities that maintain the positive aspects of human brain neoteny and/or mitigate its negative consequences. Key aspects of this proposed research include 1) development and refinement of methods to measure neotenous processes in the human/primate brain *in vivo*, 2) identifying sources of inter- and intra-species variability in brain neoteny, and 3) measuring its positive and negative consequences upon aging-related illnesses. Longitudinal cohort studies in humans will be critical to these efforts. As the effects of neteony likely span several decades, studies in shorter lifespan primates will also be needed, and might provide a platform to trial interventions targeted at improving the cognitive healthspan of humans.

M. Lon Lammey, Charles River Laboratories
Cardiovascular Disease in Captive Chimpanzees (Pan troglodytes)

The primary disease process that affects Great Apes, particularly captive chimpanzees is cardiovascular disease. The Alamogordo Primate Facility (APF) has focused on

providing quality animal care and welfare to over 250 captive chimpanzees during the past 17 years. All animals undergo annual physical exams that included electrocardiograms and serial blood pressures. Since 2003, complete cardiac evaluations have been performed regularly on the animals by a board-certified veterinary cardiologist. Histologic examination of the hearts has revealed various amounts of myocardial fibrosis, which appears to lead to arrhythmias. For the majority of the animals that have died in APF, sudden cardiac death has been the primary diagnosis. Most of the animals diagnosed with cardiac disease are male, although some females have been noted to have the disease as well. More data is needed to identify the possible causes of myocardial fibrosis and sudden cardiac death in captive chimpanzees.

J. Pedro de Magalhaes, University of Liverpool
Genes and pathways related to evolution of primate species longevity; developmental factors influencing primate species longevity

Given the extraordinary diversity of life on earth, it is not surprising to observe that some species exhibit an exceptionally quick degeneration while others appear not to age at all. In primates, the ageing phenotype is remarkably similar, though the pace of ageing can be extremely variable. Many traits have been analyzed for correlations with species longevity and our AnAge database of ageing and longevity in animals (http://genomics.senescence.info/species/) is one powerful tool for such comparative approaches. Moreover, recent advances in genome sequencing allow genome-wide cross-species comparisons which open new avenues for unraveling the genetic basis of species differences in ageing. In this talk, I will discuss novel comparative genomics methods to identify genomic features and specific genes and pathways associated with the evolution of longevity. Furthermore, I will discuss our experiences in *de novo* genome sequencing of long-lived species using next-generation sequencing platforms. The molecular and genetic basis of species differences in ageing remains a major mystery but one that if solved would provide important insights about the roots of the ageing process and human age-related diseases.

Amanda D. Melin, University of Calgary
Variation in lifespans and pace of aging among monkeys in the Americas (Platyrrhini), and capuchins in a comparative context.

Studies of nonhuman primate longevity, aging processes, and age-related diseases provide important comparative context for understanding human aging. To date, most information comes from a few species of catarrhine primates (monkeys and apes in Africa and Asia) as well as select lemurs. In addition, captive studies are far more represented in available literature, as data from wild primates are difficult to obtain. Data on the lifespans in presented as well as and pace of aging in a diverse radiation of monkeys in the Americas (the platyrrhines), which occupy a wide range of ecological

niches, body sizes, and life histories. Intriguingly, the range of lifespans in these monkeys is extensive and surpasses the range seen in catarrhine monkeys. The study of this diverse group of primates offers many opportunities to study molecular, social, and environmental factors affecting longevity and aging processes in relatively poorly known but highly relevant species. In particular, capuchin monkeys are a fascinating taxon, living more than 50 years despite having a body mass similar to a domestic cat. Discussion of capuchins in a comparative context, highlighting genes under positive selection that might contribute to their derived longevity. Additionally, discussion on developments in methods for non-invasive tissue and biological material sampling that hold promise for investigating hallmarks of aging in wild primate populations. Developing and refining techniques for population-level sampling of wild animals – especially when combined with established, leading methodologies – will open up new study systems and questions. Overall, by expanding the comparative study of aging processing to include diverse platyrrhine species, including exceptionally long-lived species, we stand to improve comparative frameworks for understanding variation in primate species lifespans, discover new molecular signatures of longevity, innovate new ways to study relevant species in situ, and create new opportunities to discover factors impacting human aging.

Rich Miller, University of Michigan
Multi-Cladal Cellular Biogerontology: Clues for Basic and Translational Aging Research

Nature is much better at making very old mammals than we are. The very best interventions (low calorie diets, drugs like acarbose and rapamycin and 17-alpha-estradiol, mutations like GHRKO and Snell/Ames dwarfs) can extend lifespan of mice and dogs by as much as 40%, but evolutionary pressures can create long-lived species from shorter-lived ancestors, with longevity effects of 5-fold to 10-fold within closely related clades of warm-blooded vertebrates. Comparison of cellular, biochemical, physiological and genomic traits across species capitalizes on these many, parallel, natural experiments and has begun to reveal points of leverage to which pharmacological ingenuity can now be applied.

Today's miniscule talk will focus on two case studies that support three key concepts.

Concept 1: surprisingly, cultures of fibroblasts often retain species-specific properties, even after propagation, that distinguish long-lived from short-lived species. These suggest clues to how evolution molds lifespan and aging rate.

Concept 2: if the same association between trait and species lifespan is seen in multiple independent clades (example: rodents, primates, birds, Laurasiatherian mammals), it is unlikely to be just coincidental. Such a finding suggests that it is not possible to make a long-lived vertebrate without modifying the trait in question.

Concept 3: in some (but not all) cases, the trait discovered by cross-species comparative approach is also modified, in mice, by diets or drugs or genes that extend healthy lifespan.

Case Study 1 (Pickering, PMID 25070662): Cells were exposed to an oxidative stress (hydrogen peroxide) for one hr, and then tested for protein carbonyl, an index of oxidative damage to proteins. Cells from short-lived species, as expected, showed an increase in carbonyls. Cells from species with the longest lifespan, however, showed a paradoxical decrease in protein carbonyl after exposure to peroxide. This suggests that cells from long-lived species sense oxidative stresses and quickly turn on a pathway that actively removes damaged proteins. The same phenomenon was seen in rodents, primates, and Laurasiatherian mammals. Learning the basis for this unexpected defense pathway, and how to turn it on, deserves experimental attention.

Case Study 2 (Pickering, PMID 28474396): A survey, across species of primates, birds, and rodents, showed elevation, in longer lived species, of thioredoxin reductase (TXNRD), an enzyme that limits oxidative damage to proteins. Of the three isoforms of TXNRD, only one, the mitochondrial enzyme TXNRD2, was elevated, with changes noted at mRNA and protein level among primate species. Analysis of public mRNA databases showed association of species lifespan with high levels of TXNRD2 mRNA in all tested tissues. Tissues of Snell dwarf mice, a mutant that lives about 35% longer than littermate controls, also had elevated TXNRD2 mRNA. At least one drug that extends lifespan of male mice (NDGA) also elevates TXNRD2 mRNA. Flies with elevated mitochondrial TXNRD show longer lifespan, too. Evolution of long-lived species seems to require increased TXNRD function in mitochondria, and studies of drugs, or engineered constructs, that elevate TXNRD2 in mice are now well justified.

Time constraints preclude presentation of data on Case Studies 3 – 7, that would have dealt with cross-species associations between lifespan and proteasome structure, cellular resistance to lethal stresses, stress kinase activation kinetics, miRNAs that regulate Sirt1 via p53, and plasma membrane permeability to the toxic heavy metal Cd. Systematic analysis of proteomic, transcriptomic, and metabolomic data in groups of 20 – 150 species will shortly add many new, testable ideas about cellular traits that co-segregate with species lifespan, some of which may prove amenable to alteration in mice or in people.

Herman Pontzer, Duke University
Primate Species Bioenergetic Differences in Relation to Brain and Life History

Among the placental mammals, primates are remarkable for their slow rates of growth, reproduction, and aging. Humans in particular have longer childhoods and greater longevity than any other primate. In this talk I examine potential links between metabolic rate (energy expended per day) and the slow life histories of humans and other primates. Over a century ago, Max Rubner proposed a "rate of living" hypothesis

to explain differences in species' lifespans, suggesting that cells have a finite lifetime capacity for energy expenditure and that species which burn their energy faster must die earlier. The rate of living hypothesis has since been soundly refuted, but the apparent connections between metabolic rate and longevity remain. In laboratory studies, calorie restriction reduces metabolic rate and extends lifespan in many species, including nonhuman primates, with suggestive evidence of similar effects in humans. Among species, primates' slow life history and remarkable longevity is consistent with their slow metabolic rates. Nonetheless, humans have both faster metabolic rates and greater longevity than other apes, indicating that metabolic rate alone does not determine lifespan. I examine evidence for related mechanisms, such as the production of oxidative stress, for linking metabolic rates to longevity and explaining how species such as humans can evolve both faster metabolic rates and longer lifespans.

Nicholas Schork, Translational Genomics Research Institute (TGen)
Integrative Approaches to Identify Candidate Targets and Drugs Using Human and Nonhuman Data

Longevity is complex and multifactorial phenotype. The fact that both genetic and environmental factors interact to determine an individual's longevity – including factors that impact disease processes and not necessarily sought-after basic mechanisms of aging – can obscure the contribution of any one factor to more comprehensive and systematic characterizations of the determinants of longevity. Despite this fact, many studies exploring the determinants of variation in longevity that considered within (intra-) vs. across (inter-) species variation have begun to identify individual longevity-associated genes and genetic variants. Integrating or reconciling the results of studies of longevity in human and non-human species using broader systems-level analysis methods is necessary, and is beginning to receive attention, but will require sensitivity to a number of facts and phenomena going forward. Of these, two are more pronounced. First, differences in gene structure and content are more pronounced across species than within-species, complicating direct comparisons of, e.g., the effect of specific nucleotide substitutions on longevity. Second, the functional elements and processes involved in the regulation of genes have likely undergone substantial 'rewiring' as species diverged over an evolutionary timescale. The practical consequences of this rewiring when trying to generalize, e.g., a lifespan-altering genetic variant effect or the effect of an induced perturbation or manipulation observed in a non-human species to the human species are largely unknown. Ultimately, research focused on barriers to the generalizability of the results of longevity studies from one species to another, and how phenomena observed in studies of one species can inform the interpretation of observations in another species, must emphasize and consider these phenomena. In addition, a number of additional themes will likely emerge as more systematic perspectives of the results of genetic and genomic studies of human and non-human longevity are put together:

- Genetic variation impacting a phenotype *within* a species (i.e., intra-species variation) can reveal possibly conserved, pathway-specific genes, while studies of

variation *across* species (i.e., studies of inter-species variation) do not suggest those genes are associated with the phenotype, and vice-versa.

- Longevity has a polygenic component, and the variants defining individual polygenic load affect a wide variety of genes and regulatory elements.
- The multigenic basis of longevity suggests that there may be a large number of potential drug targets for further consideration, but the degree and context to which these genes contribute to longevity and hence provide evidence of their candidacy and consideration as drug targets needs exploration.
- Gene loss – or 'gene erosion' events (i.e., loss of components of genes that may change gene function or those genes' contribution to the activity of a larger network of genes) – occurring during the evolutionary divergence of species that are associated with the lifespans of those species could reveal targets for inhibitors that may enhance longevity.
- Common phenotypes that are associated with longevity and that could be studied longitudinally, like blood-based clinical chemistries among others, *should* be studied more comprehensively since they could reveal mechanisms through which conserved or nonconserved genes and genetic variants impact longevity.
- There is a need to better characterize both regulatory networks within species, as well as the potential 'rewiring' of those networks across species that has occurred over evolution as this will help put into context the potential that a gene has as a target for longevity-enhancing drug development.

Paola Sebastiani, Tufts Medical Center

Genetics and Omics Approaches in Studies of Extreme Human Longevity

Over the last decade, several studies have provided evidence that many centenarians and their offspring delay or escape aging-related diseases such as cardiovascular and Alzheimer's disease. More than 90% of people living to 100 are functionally independent at the mean age of 92 years and thus markedly delay disability (1-3). While a variety of studies of centenarians have provided evidence for the compression of morbidity and disability (4), the genetic, molecular and environmental determinants of this phenomenon remain elusive and the identification of the modifiable factors that allow centenarians to live long and healthy lives is still an open problem (5).

The heritability of age at death, that is the portion of the variability of the age at death that can be attributed to shared genetic environment, is limited (6). However, extreme human longevity is not aging, and the evidence that extreme human longevity is heritable is solid: extreme longevity clusters in families (7), and siblings of centenarians have a much better chance of living to extreme old ages compared to their generation (8-10).

Genome-wide association studies (GWAS) of centenarians have identified genetic variants that associate with extreme human longevity (11-14) (5, 15), including the well replicated association of *APOE* (16), *FOXO3 (17)*, and *CDKN2A/CDKN2B* (18, 19). Most

of the GWASs of extreme human longevity have focused on common genetic variants that can be measured using SNP arrays. Whole genome sequence studies of centenarians are still in their early phase and limited in sample size (20-22). Several large studies of healthy agers and centenarians such as the Long Life Family Study (23) are gearing up for whole genome sequencing and it is reasonable to expect that the next few years will bring novel finding about the genetics of extreme human longevity.

In parallel to genetics, which discovers unmodifiable risk factors, genomics studies are showing that healthy agers and centenarians carry specific molecular profiles that include biomarkers of biological aging and longevity (19, 24-27). Some of these biomarkers can be relate to genetic variants of extreme longevity, for example *APOE* alleles (28), or *CDKN2B* (19) and initial results suggest that the effect of some genetic variants of extreme human longevity may delay molecular aging.

Larger studies will be needed to connect genetics to molecular profiles of longevity and identify targets for health aging therapeutics. NIH funded studies including the Long Life Family Study, the Longevity Consortium and the Integrative Longevity Omics will generate multi-omics profiles of thousands of centenarians and their offspring in the next few years and create a unique resource to discover the biological mechanism of human longevity.

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Chet C. Sherwood, George Washington University
Human neurobiology in comparative perspective

Human neurobiology can be understood through the lens of evolution by tracing shared and derived traits in comparison to our close relatives, the primates. Such an approach can shed light on aspects of human brain structure that have coevolved with our species' large brain size, relatively slow development, and extended lifespan, as well as those features that are invariant with allometric scaling. In this presentation, I will review comparative studies of various aspects of primate brain structure that help to place humans in evolutionary context. Features of human neurobiology that have changed relative to other primates include prolonged myelination of the cerebral cortex in development, volumetric enlargement of certain neocortical and cerebellar regions, and increased cortical and striatal innervation by specific neurotransmitter systems. To some extent, these evolutionary modifications are correlated with human brain enlargement. In contrast, other aspects of human cortical microstructure are relatively conserved and invariant with respect to brain size variation across primates, including the distribution of GABAergic interneurons and synaptic densities. Taken together, these findings help to demonstrate the dynamics of human brain evolution that interact with developmental timing and lifespan, leading to the distinctive profile of our species' vulnerability to neuropsychiatric and neurodegenerative diseases.

In my opinion, future comparative primate biology research would benefit from investment in the following public resources: 1) The generation of comparative maps of tissue-specific gene expression, regulation, and histological structure from a wide range of primate species (modeled after the current GTEx resources). This would provide insight into the functional evolution and developmental biology underlying changes in a range of organ systems. Studies would be able to examine co-evolution and functional trade-offs in various biological systems based on multiple lines of evidence from anatomy, gene expression, cell biology, behavior, and more. Additionally, comprehensive datasets from a broad array of primates would allow for rigorous tests for rates of evolution in the human lineage to pinpoint episodes of exceptional acceleration, enable studies that uncover developmental mechanisms of human

specializations, and provide ground-truth of human-specific cellular, molecular, and anatomical phenotypes for new experimental tools such stem cell models and organoids. 2) Coordination and standardization of biobanking of samples from diverse primate species across a range of ages from National Primate Research Centers, zoos, and sanctuaries. This is especially important for tissues from chimpanzees and other great apes as an essential comparative basis for understanding what is distinctive about human health and disease through the lifespan.

Lary Walker, Emory University
The exceptional vulnerability of humans to Alzheimer's disease: A comparative primate perspective

The defining process in the pathogenesis of Alzheimer's disease (AD) is the misfolding and aggregation in the brain of Aβ (a protein fragment that forms Aβ- ['senile'] plaques) and tau (the protein that forms neurofibrillary tangles). Genetic, pathologic and biomarker evidence favors an initiating role of Aβ in the cascade of events leading to Alzheimer's disease, but the ensuing emergence of tauopathy is necessary for the development of dementia. In addition, inflammation, oxidative stress, and many other changes are present in the Alzheimeric brain, probably in response to the insult caused by the proliferation of abnormal proteinaceous assemblies. All nonhuman primate species studied to date express Aβ and tau that are similar to the proteins in humans, and they manifest copious Aβ plaques as they age. However, the full clinicopathologic phenotype of Alzheimer's disease, including neurofibrillary tangles and dementia, has not yet been identified in a nonhuman species. The reasons for the resistance of monkeys and apes to Alzheimer's are not yet known. Research suggests that the crucial link between Aβ aggregation and tauopathy is somehow disengaged in aged monkeys, but other possible causes are variation in the misfolding or modification of Aβ and/or tau, differences in environmental or biological factors, and in the intricate response of the brain to proteopathic stress. Understanding why species that are biologically close to humans resist Alzheimer´s disease, even in the presence of abundant Aβ, could reveal new molecular objectives for preventing or treating Alzheimer's disease, as well as general strategies for lengthening the health span in aging humans.
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Yong Zhang, Institute of Zoology (IOZ), Chinese Academy of Sciences (CAS)
Evolution of primate-specific, hominoid-specific, and human-specific genes and relationships to phenotypes

Numerous mechanisms (*e.g.*, duplication) underlie a flux of lineage- or species-specific new genes, which shape phenotypic evolution. Mounting efforts including our own studied the origination process and biological function of new genes in various species especially in humans. First, we found that tandem duplication together with transposon (retrotransposons and DNA transposons) mediated duplication mechanisms generate

new genes or new gene structures in human genome. In spite of the different nature of these mechanisms, they often generate incomplete duplications and induce exon shuffling. Second, we found that new genes tend to be involved in fast-evolving processes including spermatogenesis, immune response, mother-fetus interaction or brain development. Different from this general picture, *HBBP1*, which appears to be an unexpressed pseudogene in non-human primates, confers human-specific essentiality in a seemingly conserved process, *i.e.*, erythropoiesis. Finally, despite the significance of primate- or human-specific genes for phenotypic evolution, these genes tend to be uncharacterized partially due to lack of a new-gene-focused database. We thus have been maintaining and updating a database for human genome (GenTree, http://gentree.ioz.ac.cn), which facilitate users to evaluate when and how a gene arises and what type of function it may have.

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