Applicant Information Webinar: Non-Human Primate Developmental Genotype-Tissue Expression (NHP dGTEx)

RFA-HG-21-026

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National Human Genome Research Institute

The **Forefront** of **Genomics**

NIH Collaboration

National Human Genome Research Institute (NHGRI)

- Simona Volpi (GTEx), Jyoti Dayal (dGTEx), Allie Osgood (moderator), Laurie Findley (moderator), Jerryl Somani (IT), and William Maye (IT)

National Institute of Mental Health (NIMH)

- Tara Dutka and Alexander Arguello

Office of Research Infrastructure Programs (ORIP)

- Sige Zou and Sheri Hild

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- Tuba Fehr, John Ilkes (dGTEx), Bettina Buhring, and Melissa Parisi

Applicant Information Webinar: Developmental Genotype Tissue Expression (dGTEx)

Welcome!

- Check your audio and video to confirm that you can hear and see the meeting.
- To ask a question at any time, use the Q&A function located at the bottom of your screen.
- After the presentations, to ask questions verbally, use the raise hand function and moderators will call on you.
- Should you experience any technical problems, please contact Allie Osgood at allie.osgood@nih.gov.

Please note that this webinar will be recorded

Outline

- Background
- RFA Overview
- Frequently asked questions
- Applicant questions

Purpose of NHP dGTEx

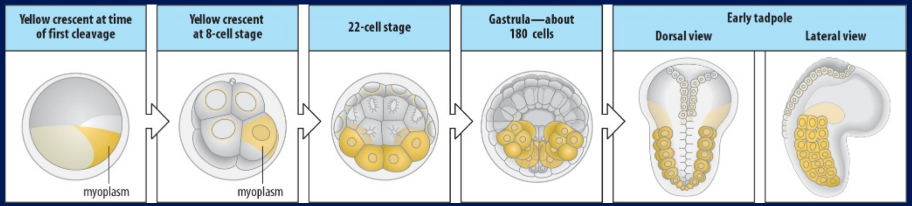
Study gene expression patterns in multiple reference tissues across developmental stages in NHPs and compare them to human gene expression patterns

- Determine common developmental networks and pathways
- Identify developmental patterns that are primate- or human-specific
- Establish datasets and samples for comparative developmental genomics
- Inform model selection for functional and developmental studies

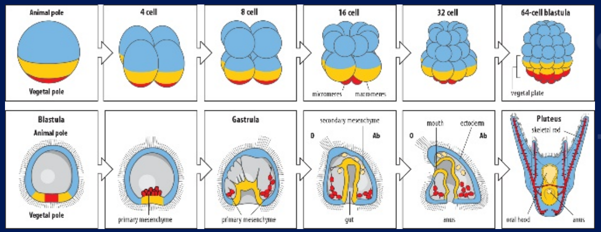
Genotype-Tissue Expression Projects

- GTEx – Common Fund program (complete)
  - 838 postmortem adults, 49 tissues; DNA and RNA seq
  - Tissue-specific gene expression profiles, eQTLs, highly used resource
- dGTEx – NHGRI, NICHD, NIMH, NINDS (beginning)
  - 120 postmortem infants and children, 30+ tissues; DNA and bulk and scRNA seq
  - Developmentally regulated tissue-specific expression
  - Impact of variation on development
- NHP dGTEx – NHGRI, NIMH, ORIP (NICHD)
  - Experimentally tractable laboratory animals
  - Allow for prenatal as well as postnatal stages
  - Build on developmental knowledge from model and other organisms

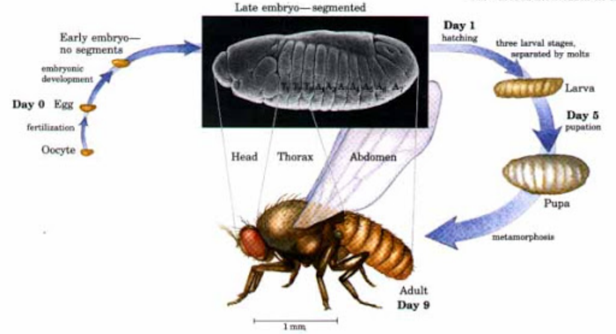
Developmental genomics in model systems



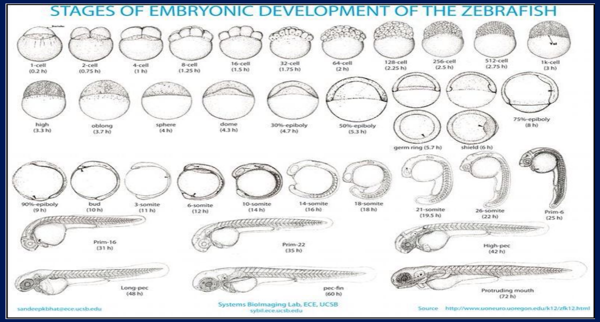
WORM



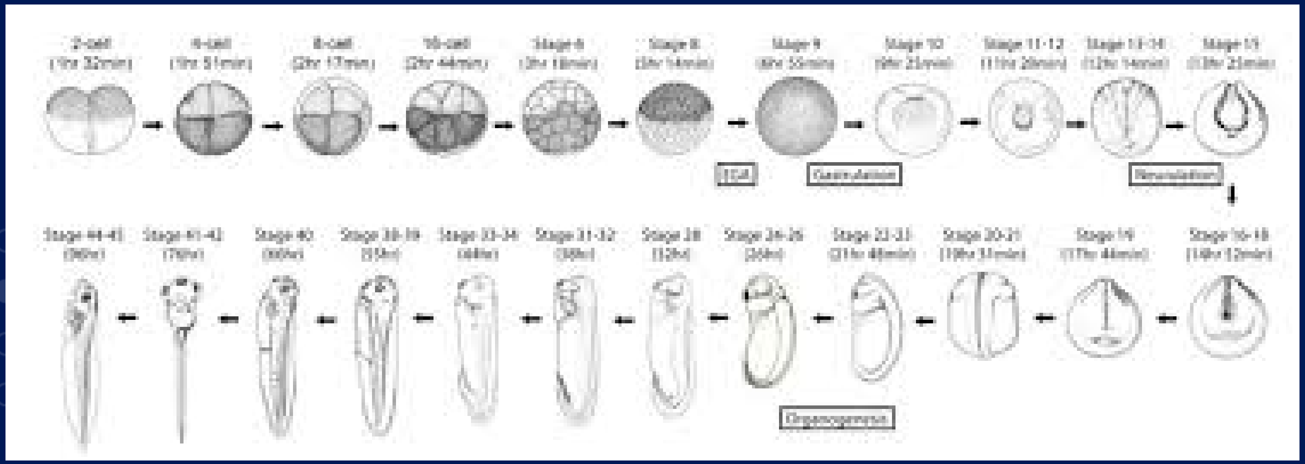
SEA URCHIN



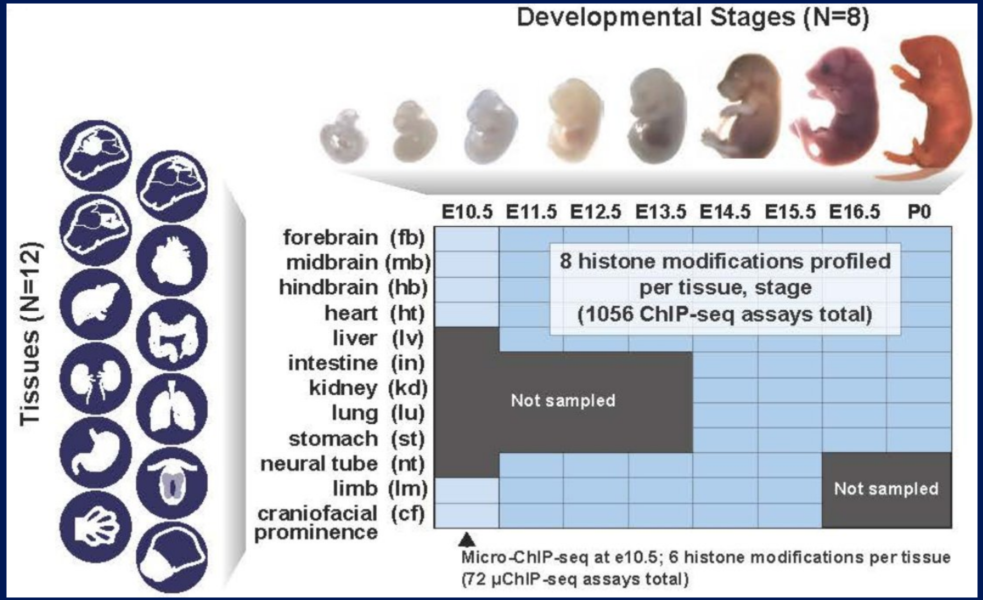
FRUIT FLY



ZEBRAFISH



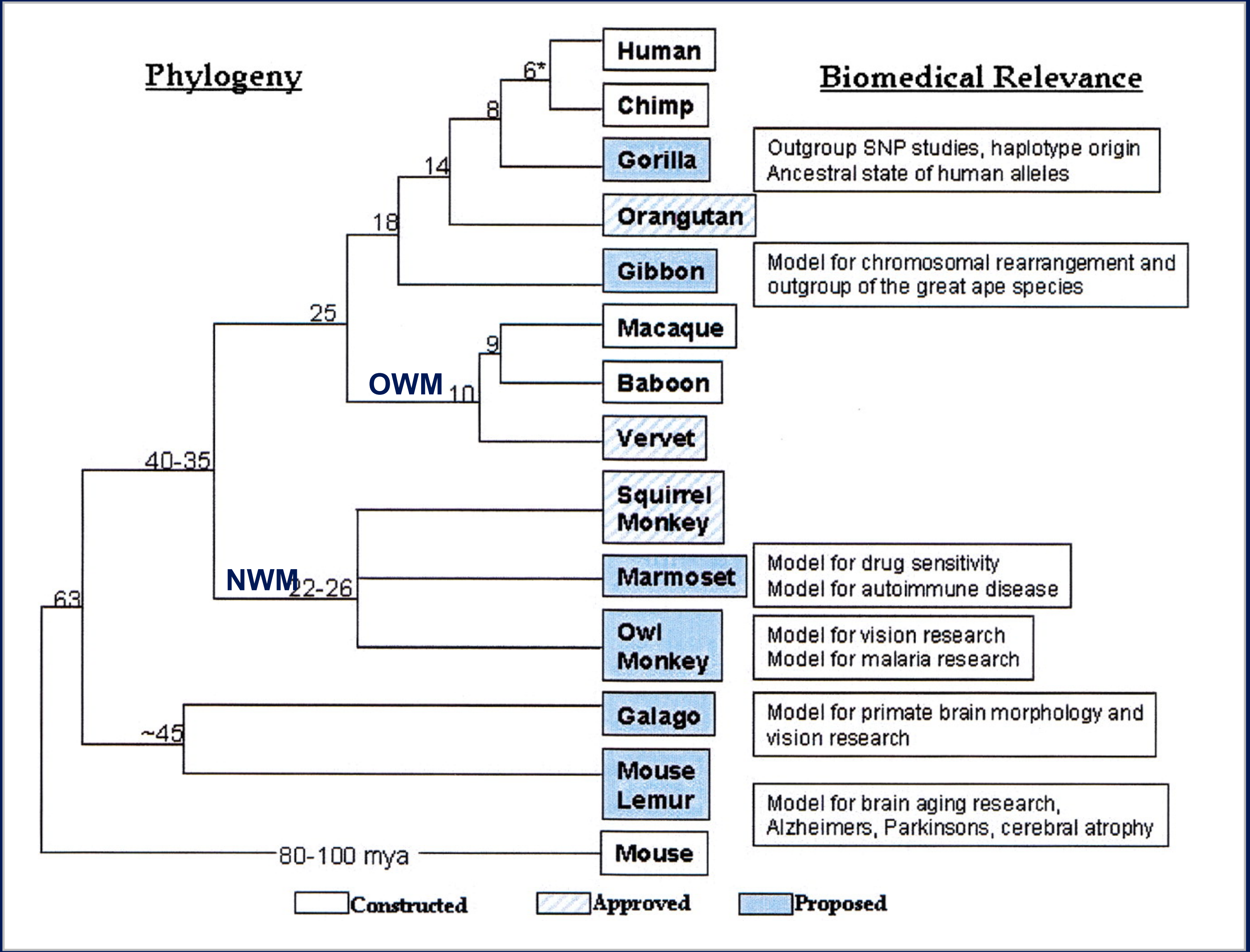
FROG



MOUSE

NHP advantages

- Close relatives
- Similar development
- Genomic diversity
- Biomedical models
- Comparative genomics



Biomedical Applications and Studies of Molecular Evolution: A Proposal for a Primate Genomic Library Resource. Evan E. Eichler and Pieter J. DeJong

NHP dGTEx basics

1-2 NHP Centers

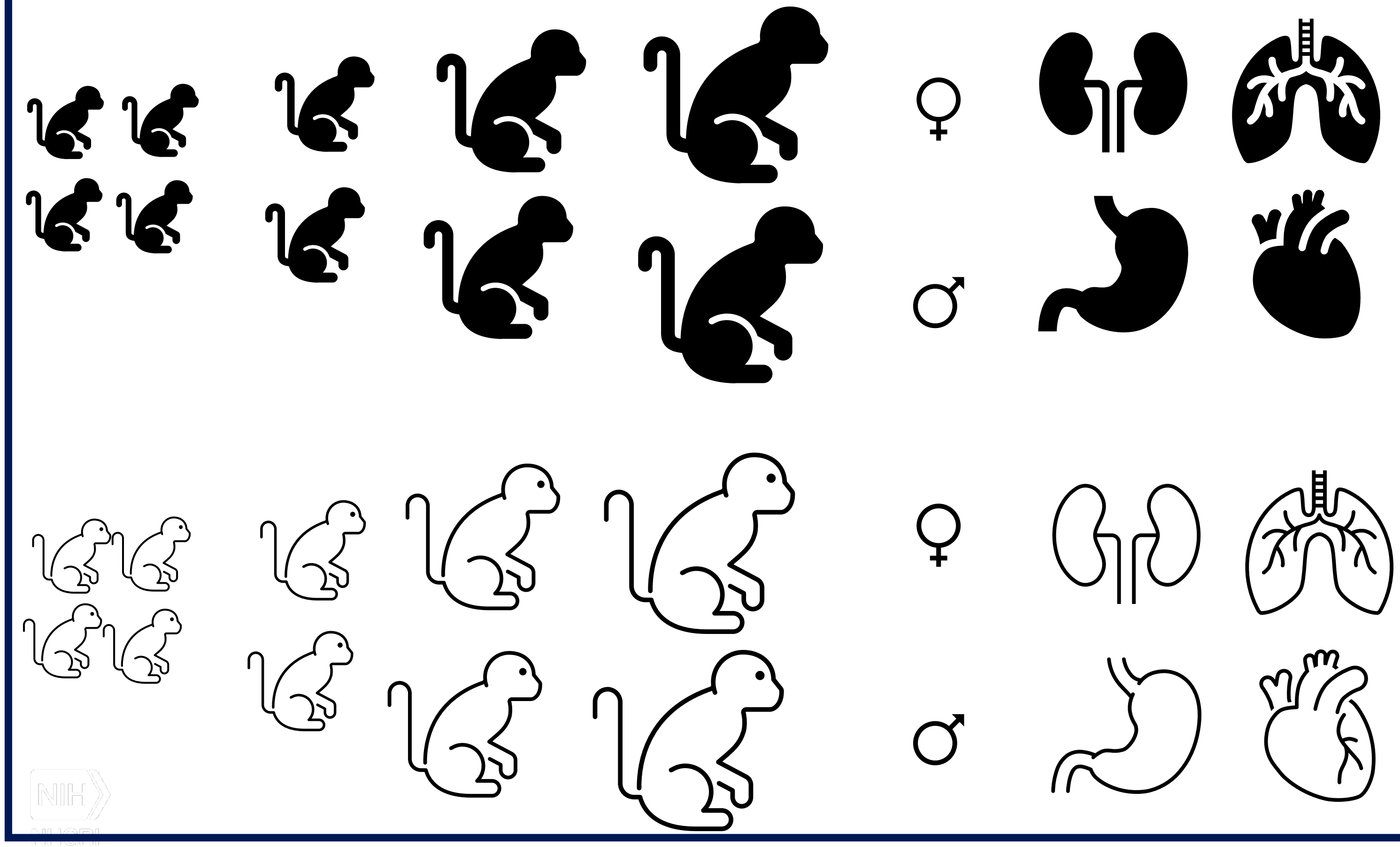
$17.5M Over 5 years ($3.5M/year)

- Expression data
  - Multiple developmental stages, tissues, species
  - May propose additional assays – single cell encouraged
- Make data available and useable to the community
- Use opportunistic and banked samples where possible

NHP dGTEx Centers

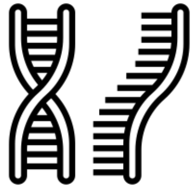
Provide Samples:

2 species (Old World and New World) X 6 stages (prenatal and postnatal) X 12 animals (male and female) X 30 tissues

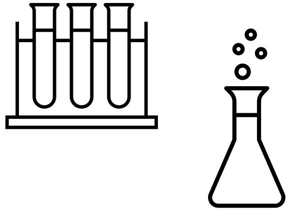


Generate Data:

WGS for each animal, RNAseq for each tissue

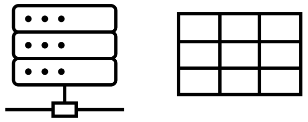


Other assays TBD

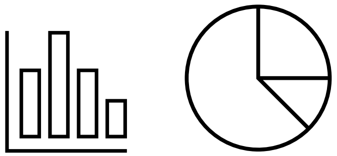


Manage Data:

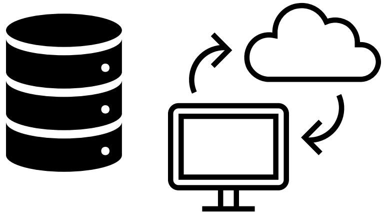
QC



Basic analyses



Submission to appropriate resources



RFA-HG-21-026 PURPOSE:

1. Create a tissue resource of multiple reference tissues across developmental stages in non-human primates (NHPs)
2. Perform transcriptome sequencing and other genomic analysis of single-cell and bulk tissues;
3. Analyze gene expression patterns in NHPs and compare them to human gene expression patterns
4. Make the tissue samples and data available and usable for the research community

non-responsive applications:

- Projects that do not have a plan to leverage evolutionary distance (e.g. by using Old and New World primates)
- Projects that do not propose comparative genomics approaches that will help to validate and interpret the data generated in the human dGTEx project
- Proposed work that does not have clear plans to make the NHP tissue resource and data available and usable to the community

Research plan:

- *A high-level strategy for generating useful data for the community that complements and builds on human dGTEx and other developmental genomic resources in order to effectively investigate gene expression across developmental stages*
- *A description of the overall structure of the project including management and reporting structures.*
- *A description and justification of the overall study design.*
- *A plan for the provision of high-quality blood and tissue samples for DNA and RNA sequencing, as well as the maintenance of appropriate sample storage, tracking, and safeguards to preserve samples for future additional assays and analyses.*
- *A plan for genomic data generation.*
- *A plan for data analysis, data management and generation of data for the broader research community.*
- *An overall view of how NHP dGTEx will be compatible with additional US and international efforts that provide developmental expression data to the community, as well as with other NHP genomic resources.*
- *Plans for community outreach and engagement.*

Significance:

- How will the scientific knowledge gained address research gaps in our understanding of development?
- Is the plan for providing a useful and useable community resource adequate?
- Will this project enable comparative genomics analyses that improve our understanding of primate-specific, and human-specific expression profiles throughout development?

Investigator(s)

- Does the PD(s)/PI(s) have prior experience working as part of a large collaborative research project that involves multiple investigators at different institutions, developing consensus approaches to address particular research-related topics, or other collaborative activities to meet individual study and collaborative goals?
- Will the PD(s)/PI(s) dedicate sufficient time to meet the needs of NHP dGTEx?

Innovation

- Are data sharing and analysis plans sufficiently innovative to meet the goals of the project?
- As new technologies become available, is the research team poised to leverage and implement them to do further research analyses?
- Are there effective and innovative plans for outreach to the community?

Approach (slide 1)

- will the conceptual design and overall operating plan effectively use comparative genomics approaches to investigate gene expression across developmental stages?
- Do applicants describe an adequate approach for incorporating relevant information from the human dGTEx project into their final strategy?
- Do the applicants describe an overall structure for the project to operate as a cohesive whole?
- Are the proposed species, animals, developmental stages, tissue types, and assays well justified?
- Is there a plan to maximize the benefits of these samples, including establishing and maintaining a sustainable tissue resource for these samples?

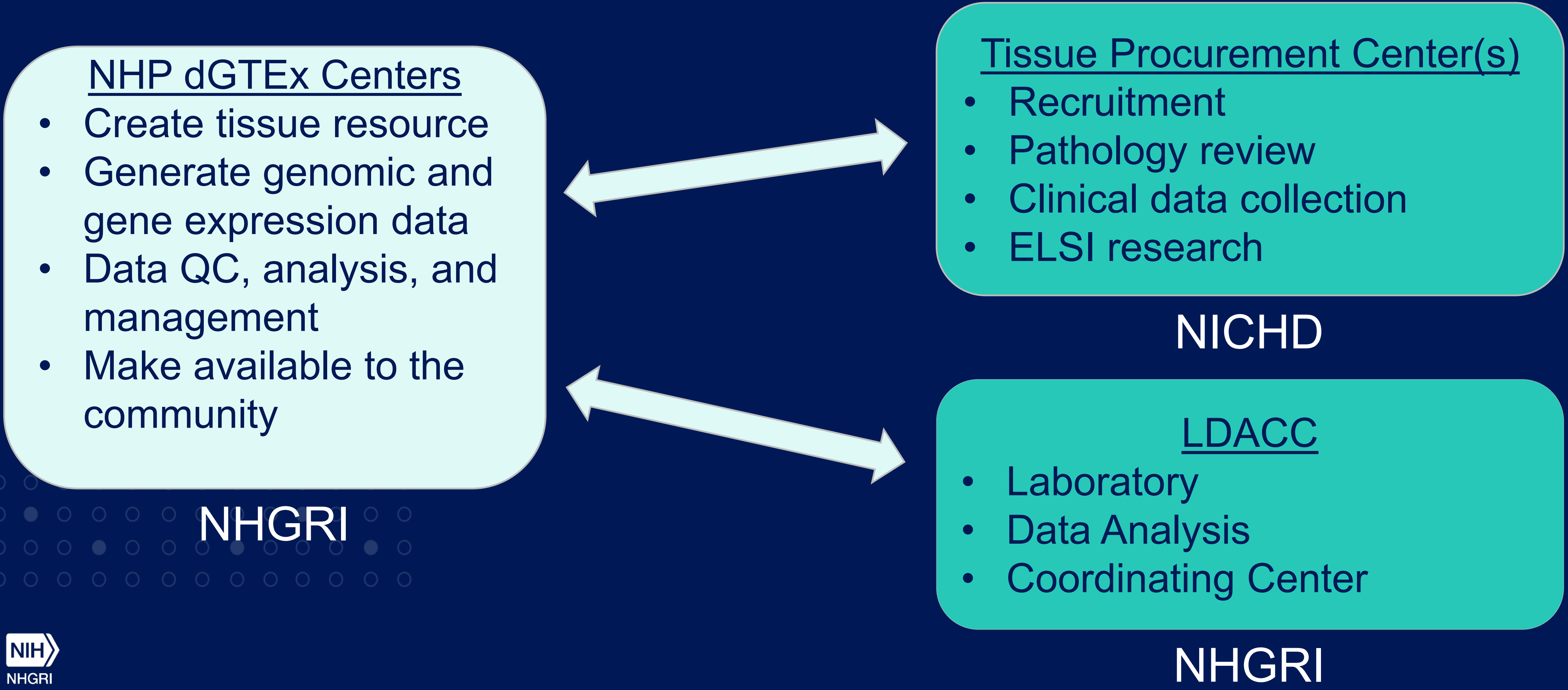
Approach (slide 2)

- Do the applicants have plans that will yield high quality nucleic acid (DNA and RNA) sequencing data?
- Are other genomic assays appropriate and well justified?
- Have investigators presented an adequate plan for QC and analysis that will enable the objective of having data available and useable to the research community?
- Does the data management plan include approaches that will facilitate the interoperability of the resultant datasets with data from other initiatives?
- Does the operating plan provide opportunity for collaboration, integration, and interaction with other appropriate resources?
- Are there adequate plans for engaging the user community early and throughout the production of the resource?

Environment

- Are the resources, equipment, and infrastructure available and in place (or readily obtainable) to allow for quick ramp-up?
- Are the bioinformatics infrastructure and capabilities and computational resources in place (or readily obtainable) and adequate to support the project?

Ensure Interoperability with dGTEx



NHP dGTEx Centers

- Create tissue resource
- Generate genomic and gene expression data
- Data QC, analysis, and management
- Make available to the community

NHGRI

Tissue Procurement Center(s)

- Recruitment
- Pathology review
- Clinical data collection
- ELSI research

NICHD

LDACC

- Laboratory
- Data Analysis
- Coordinating Center

NHGRI

Special Consideration - Brain

- Tissue Procurement
  - Expert evaluation, precise dissection using a coordinate system or equivalent, and optimal preservation of brain tissue for single-cell data generation (optimally, PMI < 8hrs)

- Sequencing and analysis
  - Special expertise for processing tissue and generating and analyzing single-cell (~10 subregions) expression data
  - Standards compatible with Brain Initiative Cell Census Network (BICCN)

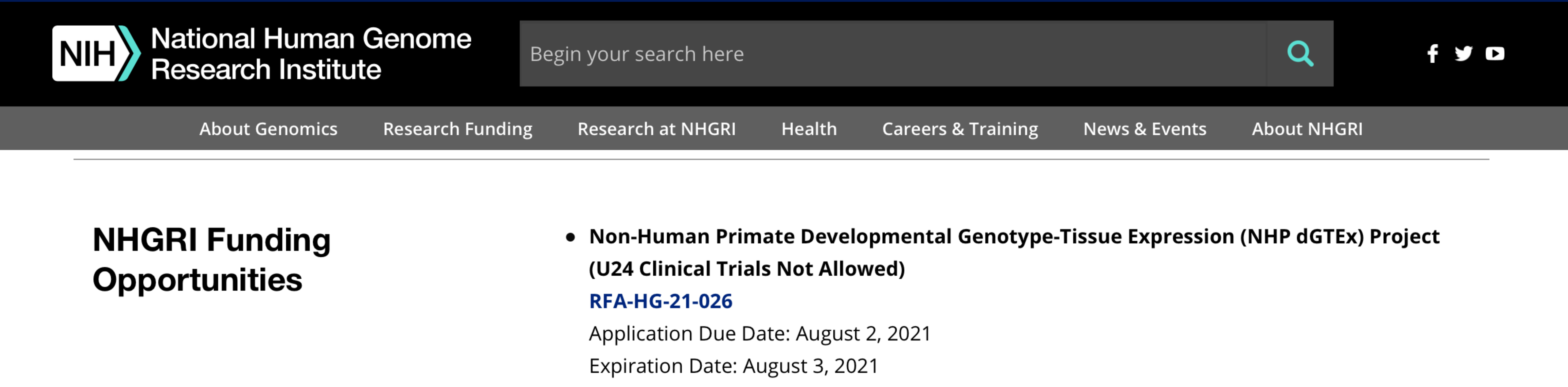
Considerations of balance

- Multidimensional data
  - Developmental stages, individuals, tissues, assays, species
- Providing data and samples
  - New vs. existing resources

FAQs

- Is the Letter of Intent mandatory? No, this is optional
- Is this an open competition? Yes, anyone can apply
- Will there be RFAs for data analysis? Probably
- Can there be a research component? Yes, if it is proof of principal for utility of the data and does not add significant cost; resource is the primary goal
- Is $3.5M/year direct costs or total costs? Total
- Can we submit applications that request more? It is allowed
- How many applications will be funded? 1 or 2

Resources



NHGRI Funding Opportunities

- **Non-Human Primate Developmental Genotype-Tissue Expression (NHP dGTEx) Project (U24 Clinical Trials Not Allowed)**
  RFA-HG-21-026
  Application Due Date: August 2, 2021
  Expiration Date: August 3, 2021

URL: https://www.genome.gov/Funded-Programs-Projects/Developmental-Genotype-Tissue-Expression

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NHP dGTEx Centers

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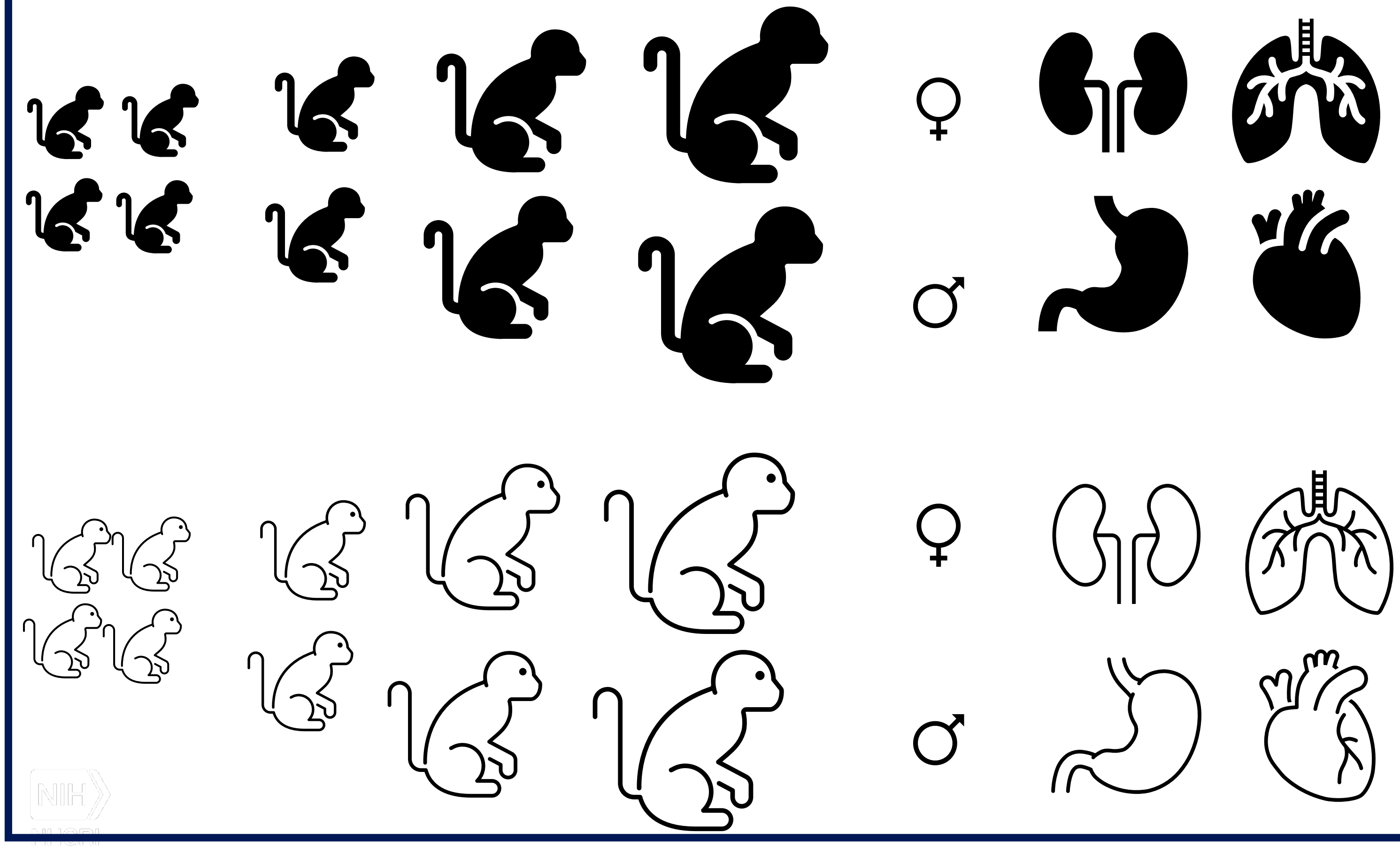

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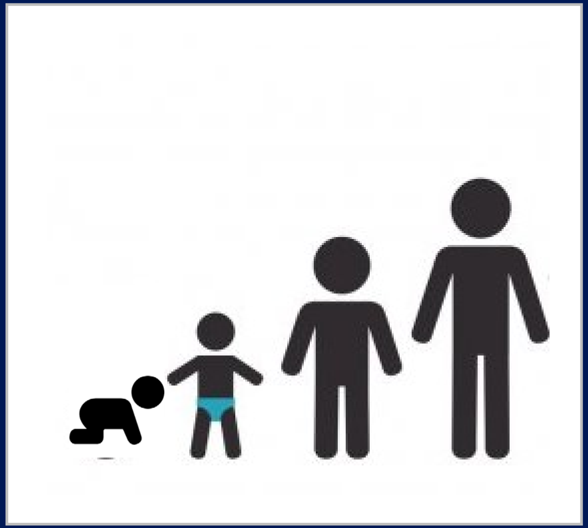
Background-dGTEx Study Design



- Early post natal (0-2 yrs)
- Childhood (2-8 yrs)
- Pre-pubertal (8-12.5 yrs)
- Post-pubertal (12.5-18 yrs)

- Sequencing (WGS, RNA)
- Biospecimen collection (blood, bulk tissue and single cell)

- Chromatin accessibility
- Histone modification
- DNA methylation