Applicant Information Webinar: Developmental Genotype-Tissue Expression (dGTEx)

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*Please note that this webinar will be recorded for internal NHGRI use only.*
Outline

• Background
• RFA Overview
  • Biospecimen Procurement Center
  • Laboratory, Data Analysis, Coordinating Center
• Key Dates
• Frequently asked questions
• Applicant questions
NIH Collaborations

Trans-NIH Initiative

• Co-leads
  • National Human Genome Research Institute (NHGRI)
  • National Institute of Child Health and Human Development (NICHD)

• Co-contributors
  • National Institute of Mental Health (NIMH)
  • National Institute of Neurological Disorders and Stroke (NINDS)
GTEx Accomplishments

- Established rapid autopsy program
- 965 donors (2010-2016)
- Surveyed gene expression in 53 tissues
- Provided new approach to map gene expression
- Decoded regulatory regions of genome

Over 2,000 consortium and non-consortium papers and 2nd most data access requests
Proposal: Developmental Genotype Tissue Expression (dGTEx)
Differences in Development

- Metabolism
- Endocrine function
- Immune function
- Drug response
- Exposure and susceptibility to environmental toxins
Goal: Establish resource database to study gene expression patterns across developmental stages.

- Fill key gaps in understanding gene expression in human development
- Provide insight on functional networks and pathways
- Understand how gene expression affects clinical factors (ex. drug response)
- Explore attitudes/concerns family decision makers, cultural differences, consent process
Objectives

Create an **atlas of tissue gene expression** on bulk tissues and single cells in pediatric populations.

Analyze **differences in gene expression**, regulation, and known eQTLs and sQTLs across developmental stages.

Create and make available **biobank of tissues and associated data** for further characterization.

Develop research projects on the **Ethical, Legal, and Social Implications** of post-mortem pediatric genomic research.
Study Design

- Early postnatal (0-2 yrs)
- Early childhood (2-8 yrs)
- Pre-pubertal (8-12.5 yrs)
- Post-pubertal (12.5-18 yrs)

Future assays
- Chromatin accessibility
- Histone modification
- DNA methylation

- Biospecimen collection (blood, bulk tissue)
- Assays (genomic, single cell)
- Special brain consideration
Tissue Procurement

- At a minimum, recruit 120 donors (at least 20-30 normal tissues per donor)
- Post-mortem tissues collected from neonates, young children, adolescents after acute event
- Collect as many tissues as possible similar to GTEx
- Prioritization of actual tissues collected determined by Steering Committee
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)
Program Formation and Governance

• Steering Committee
  • PIs from BPC, LDACC, NIH program staff
  • Oversees project goals and progress

• Community Advisory Board (CAB)
  • Convened by BPC investigators
  • Provide input on community concerns, strategies on outreach, education, and consent

• External Scientific Panel (ESP)
  • Convened by NIH
  • Provide scientific expert recommendations
Data Collection and Sharing

• Data Collection
  • Informed consent include language that biospecimens and derived data to be shared and deidentified

• Broad sharing and research results
  • Genomic and other relevant data shared with scientific community for research → AnVIL
  • Institutional certification designated as General Research Use
Biospecimen Procurement Center Award

Award
  • One award
  • Cooperative agreement U24 mechanism

Budget
  • Total cost $12.5M over the five-year budget period
  • Total cost range $1.4M - $3.6M depending on year
  • NICHD, NINDS, NIMH
Goal: Recruit 30+ donors from each age group

- Early post-natal (0-2 years)
- Early childhood (2-8 years)
- Pre-pubertal (8-12.5 years)
- Post-pubertal (12.5 – 18 years)
Administration and Data Management

- Oversight for BPC
- Manage entire biospecimen procurement project
Biospecimen Procurement Center

Biospecimen Collection

- Coordinate biospecimen procurement from numerous tissues and associated clinical data from donors
- Collaboration with multiple tissue source sites (TSS) will be required for meeting the procurement goals (e.g., organ donor organizations and medical examiners)
Biospecimen Procurement Center

Biospecimen Evaluation, Processing, and Transport

- Optimize tissue collection
- Provide standardized collection kits for biospecimen collection
- Pathological review of organ source
- Ship samples to LDACC
Ethical, Legal, Social Implications

- Attitudes and concerns of study participants (next of kin)
- Effectiveness of consent process
- Psychosocial impact of participation in study on families and healthcare staff
Project Overview

- Overall organizational structure and details of each component
- Experience in biospecimen procurement from post-mortem donors
- Plan for coordinating with LDACC
- Summarize collective team expertise and organizational strengths
Administration and Data Management

- Outline administrative structure
- Procedure for quality control
- Sample workflow management plan
- Policy for managing records
- Establish informatics system for sample tracking and data collection
BPC Research Strategy

Biospecimen Collection, Evaluation, Processing and Transport

- Coordination of expert clinical and technical personnel to acquire post-mortem tissues resulting in high-quality nucleic acids (DNA and RNA) and pathological evaluation
- Clinical data collection
- Suitable storage and shipment of obtained tissues, and transfer of associated clinical data
BPC Research Strategy

Ethical, Legal, and Social Implications

- Management plan how ELSI research will be integrated with tissue collection
- Strategy to approach families for consent and follow-up of research results
- Plans to identify and engage relevant communities and stakeholders
BPC Review Criteria

Scored Review Criteria

- **Significance**
  - Will the completion of the project result in a useful resource for the research community to drive the field forward?

- **Investigator(s)**
  - Are the PD(s)/PI(s), collaborators, and other researchers well suited for the project in terms of expertise and effort?

- **Innovation**
  - Are novel strategies employed to ensure success of the project?

- **Approach**
  - Is the conceptual design and overall operating plan adequate to procure and preserve tissue samples across developmental stages?

- **Environment**
  - Are the institutional support, equipment and other physical resources available for the successful completion of the project?
Laboratory, Data Analysis, Coordinating Center Award

Award

- One award
- Cooperative agreement U24 mechanism

Budget

- Total cost $14.25M over the five-year budget
- $1.5M - $3.5M Total cost
- In addition - $1.6M Total cost per year for brain sequencing and single cell analysis
Laboratory, Data Analysis, Coordinating Center

**Laboratory**
- Receive tissue aliquots from BPC
- Purify nucleic acids (DNA, RNA)
- Perform whole genome sequencing on blood, transcriptome sequencing on subset of bulk tissues and single-cell populations
- Biobanking for preservation of tissue aliquots
Data Analysis and Management

- Basic analyses
  - Genotyping and gene expression analysis at tissue and single-cell level
- Prepare datasets for public data release (AnVIL)
  - QA/QC
  - Harmonize metadata
  - Facilitate integration with GTEx data
Laboratory, Data Analysis, Coordinating Center

Coordinating Center

- Monitor study progress and lab performance
- Prepare general research reports
- Work with BPC to standardize data collection forms → link clinical and family information to tissue samples
- Manage project logistics
  - Organize working group calls
  - Organize 2 in-person SC meetings/yr and one remote SC meeting
  - Provide travel for ESP to attend SC meetings
Laboratory

• Develop protocols for high quality nucleic acids (DNA, RNA) for bulk tissue and single cell sequencing
  • Characterization of brain tissue
• Plan for preservation of tissue aliquots for further analyses
• Plan for genome (blood) and transcriptome sequencing (subset of tissues)
• Plan for single cell assays
• Plan to provide aliquots to research community
Data Analysis and Management

• Plan to prepare datasets for public release
• Develop plans for genotyping and gene expression
• Compare and integrate with original GTEx dataset
• Single cell analysis – contain meta data standards regarding technology, QC, cell location registration etc.
LDACC Research Strategy

Coordinating Center

• Monitor study progress, laboratory performance, preparation of statistical and other reports
• In coordination with BPC
  • Barcode-based identification with donor information
  • Report measures number of donors and tissues
  • Standardize data collection forms
LDACC Review Criteria

Scored Review Criteria

• Significance
  • Assess how proposed dGTEx data are interoperable with GTEx data?

• Investigator(s)
  • Will PD(s)/PI(s) dedicate sufficient time to meet needs of project?

• Innovation
  • Are data plans sufficiently innovative to meet the goals of the project?

• Approach
  • Will conceptual design and overall operating plan effectively investigate
    gene expression across developmental stages?
  • Is the approach to single cell sequencing and analysis robust?

• Environment
Timeline

Year 1

Development of protocols

BPC – assemble teams for procurement; ELSI research; set up CAB
LDACC – set up infrastructure to receive tissue samples
NIH – set up ESP

Years 2 - 4

Ramp up – tissue procurement, sequencing, ELSI research

BPC – recruit 120 donors; pathology review; send samples to LDACC
LDACC – WGS on blood, transcriptome seq on selected bulk tissues and single cells; gene expression analysis; deposit data in AnVIL; monitor study progress

Year 5

Ramp down

BPC – remaining recruitment
LDACC – sequencing and analysis
Publications, lessons learned
Funding Opportunities

Pediatric Biospecimen Procurement Center (BPC) Supporting the Developmental Gene Expression (dGTEX) Project (U24 Clinical Trial Not Allowed)

RFA-HD-21-008

Application Due Date(s): December 3, 2020
Expiration Date: December 4, 2020

Laboratory, Data Analysis, and Coordinating Center (LDACC) for the Developmental Genotype-Tissue Expression Project (U24 Clinical Trial Not Allowed)

RFA-HG-20-039

Application Due Date(s): November 13, 2020
Expiration Date: November 14, 2020

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

• Laboratory, Data Analysis, Coordinating Center RFA (HG-20-039)
  • Letters of Intent due October 13, 2020
  • Applications due November 13, 2020
  • Award – June 2021

• Biospecimen Procurement Center RFA (HD-20-008)
  • Letters of Intent due November 3, 2020
  • Applications due December 3, 2020
  • Award – June 2021
FAQs

• Is the Letter of Intent mandatory? No, this is optional
• Is this an open competition? Yes, anyone can apply
• How will LDACC work with AnVIL? - Data on gene expression and data analysis should be deposited in AnVIL on a timely and regular basis.
• Will there be RFAs for data analysis? FOAs likely in later years.
• Is ELSI study required? Yes
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Applicant Q&A

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