March of Dimes Funding Opportunities and Process

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Disclosure

I have nothing to disclose
The mission of the March of Dimes is to improve the health of babies by preventing birth defects, premature birth, and infant mortality
March of Dimes Research Foci

Polio    1938
Birth Defects  1960s
Prematurity    2003
MOD Research Grants

- Basil O’Connor Starter Awards (2 years)
- “General” Research Grants Investigator-Initiated (3 years)
- Transdisciplinary Centers for Prematurity Research (5-10 years)
- Chapter Grants: Education; Implementation
- Conference Support
Basil O’Connor Award

- “Starter” award
- Independent investigator; dedicated lab space
- Expectation that skills learned and data generated can be leveraged for future proposals
- Submitted 4-8 years after end of formal training (clinical fellowship or PhD)
  - Intervening K-award desirable or at least 4 years post doctoral fellowships
Cell Lineage & Differentiation Committee

- Cell lineage
- Embryonic differentiation
- Functional validation of discovered genes; characterization gene product
- Cellular effects of toxicants
- Cell division (meiosis, mitosis, repair)
- Intracellular trafficking and signaling
- Studies exclusively using non-mammalian organisms (C. elegans, Zebrafish, D. melanogaster)
Gene Discovery & Translation Committee

• Immediate or potential long-term translational (clinical) effects
• Mendelian disorders - Gene discovery
• Causes of chromosome abnormalities and cellular mechanisms
• Genome-wide or “Next Generation” sequencing methods and clinical application
• Natural history of children with birth defects or genetic disorders
Gene Discovery & Translation Committee

- Diagnostic tests to identify at-risk pregnancies or individuals
- Medical complications of pregnancy and their biological basis
- Neonatal sequelae of prematurity (retinopathy)
- Pilot projects to validate proof of principle of care interventions
- Epidemiological and registry linkage studies
Gene Discovery & Translation Committee

- Teratogen identification
- Mechanism of action of teratogens
- Pharmacogenetics and pharmacogenomics
- Mechanisms of action of infectious agents
- Microbiome and its role in perinatal disorders and early childhood disease
Processing Proposals

Letter of Intent (2 pages plus biosketch)

Triage Committee Senior Scientists

Invitation to Prepare Full Proposal (10 page research plan with detailed budget; 10% cap on indirect costs)

Review by Assigned Committee

+ Funded

Applicant provided succinct summary of strengths/weaknesses
Timeline

• Letter of Intent: March-April
• Triage for full proposal: June
• Committee reviews for ranking (October - April)
Transdisciplinary Research Centers

- Multiple Themes (4-5) per center
- Recruiting investigators not previously in field of preterm birth
- Communication among physician investigators, engineers, genomicists, and others
- Competence in latest technologies (genomics, imaging, bioinformatics)
Transdisciplinary Research Centers Themes

**March of Dimes Prematurity Research Center at Stanford University**
1. Microbiome and Preterm Birth
2. Placental Transcriptome
3. Data Coordination Center

**March of Dimes Prematurity Research Center Ohio Collaborative at Washington University in St. Louis**
1. Cervical Photoacoustic Endoscopy
2. 3-D Electromyometrial Imaging
3. Chrono-disruption and Preterm Birth

**March of Dimes Prematurity Research Center at The University of Pennsylvania**
1. Mitochondria and bioenergetics
2. Premature Cervical Remodeling
3. Placental Dysfunction

**March of Dimes Prematurity Research Center UChicago • Northwestern • Duke**
1. Gene Regulation in Pregnancy and PTB
2. Biological Responses to Maternal Stress
3. Models of Pregnancy

1. Genes Governing Gestational Length
2. Progesterone Signaling in Pregnancy Maintenance
3. Sociobiology of Racial Disparities in PTB

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What is the microbiome?

• Commensal microorganisms living within the human body

• Colonize all “exposed” tissues (oral, respiratory, digestive, skin, uro-genital)

• We have 10 times more organisms than we have human cells

What role do they play in preterm birth?
Microorganisms in the Reproductive Tract

• Could abnormal microbiome breakdown normal mucosal barrier and allow microbes or toxins into the cervix?

• Could a particular Community State Type (I, II, III, IV) of microorganisms provoke local/systemic inflammatory or inappropriate immune response?
Microorganisms in the Reproductive Tract

David Relman, MD
Professor of Microbiology and Immunology
Stanford University
Microorganisms in the Reproductive Tract

Gestational week of collection

Preterm

Term

CST IV
non-CST IV

CST= community state type
Uterine Contractions Using 3-D Electromyometrial Imaging

Alison Cahill, M.D. M.S.C.I.
Associate Professor, Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Washington University

Philip Cuculich, M.D.
Assistant Professor of Medicine, Cardiovascular Division, Washington University
Electrocardiographic Imaging to Identify Cardiac Pacemakers

Electrical Sensing + CT Imaging = Pacemaker Localization

Yoram Rudy, PhD. Washington University
Electromyometrical Imaging (EMMI) to identify Uterine Pacemakers

Electrical Sensing + MRI = Localization
Electromyometrial Imaging (EMMI) to identify Uterine Pacemakers

• What are the differences between productive contractions and non-productive contractions?

• Where are the locations of uterine pacemakers that signal contraction?
Genetics and Preterm Birth

- Heritability 30% (maternal only)
- Genes found in whole genome family linkage studies
  - FSHR (Finnish)
  - IGF1R (Finnish)
  - COL5A2 (Norwegian)
  - SERPINB2 (Mexican)

All protein-coding genes
What genes evolved to allow increased gestational length?

Are the most recently evolved genes also those that have undergone mutation and thus result in preterm birth?

Generate a data portal for the synthesis of “omics” and evolutionary genomic data for pregnancy-related tissues and phenotypes in many species

http://genestation.org
Most disease-associated variation is in ‘non-coding’ region (98.5% of genome)

① >90% of disease-associated variants reside in regions of the genome not coding for proteins (intronic; intergenic)

② These variants are likely to be involved in gene regulation

Data from NHGRI Catalog (Welter et al, 2014)
Regulation of Protein-Coding Genes

Genetics → Gene regulatory element (chromatin accessible) → Long range interactions → Transcription Factors

Environment → Histone modifications

Tissue specificity → DNA methylation and hydroxymethylation → mRNA, miRNA, lincRNA → RNA polymerase
March of Dimes Reproductive
ENCODE: ENCYclopedia Of DNA

- International collaboration launched by the NIH to learn where the gene regulatory elements are and how they regulate gene expression in specific cell types and in different species

- ENCODE has dramatically accelerated our understanding of how perturbations of gene expression contribute to much of the common disease burden in the population

But, data on reproductive organs and pregnancy were not sought with initial ENCODE
Regulatory Genes and Preterm Birth

- Does preterm birth (PTB) result from dysregulated gene expression in maternal and/or fetal tissues? Dysregulation could result from genetic variation or lifelong environmental exposures.

- Identify the regulatory elements that contribute to PTB, and thus also govern environmental ‘stressors’

- Could quantitative changes in regulatory genes provide biologic (molecular) explanation for persisting deleterious transgenerational effects of disparities in vulnerable populations?
Expected Results from Transdisciplinary Centers

Translate discoveries to treatment

• Identify biomarkers in maternal blood predictive of PTB
• Supplement or replace deficient gene product (protein)
• Upregulate or downregulate inappropriate fetal gene expression during pregnancy
• Impede action of premature signal to initiate labor
• Impede premature uterine pacemaker action
• Alter microbiome diversity
Thank you for your support of the March of Dimes and our mission

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