Family Health

Grand Challenges in Global Health

Preventing Preterm Birth Initiative

A Systems Biology Approach to Pregnancy and Prematurity

Sponsored in partnership by:

Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), an initiative of Seattle Children's,

and

Bill & Melinda Gates Foundation

Table of Contents

1 INTRODUCTION

Challenge Statement

To discover and characterize the biological processes responsible for maintaining normal pregnancy and those which when perturbed, lead to adverse outcomes such as preterm labor and birth. Studies will strive to understand the biological mechanisms which control pregnancy and will identify underlying mechanisms responsible for adverse outcomes, utilizing data and specimens collected from pregnant women over the course of gestation that are analyzed by high dimensional systems biology techniques. The intent of these experiments is to ultimately exploit their findings for development of biomarkers, and new prevention and treatment strategies that will address the burden of preterm birth around the globe.

The goal of this RFP is to solicit applications utilizing one or more high-throughput systems biology approaches in a pilot study using data and biologic samples collected prospectively throughout the course of gestation for 50 women with spontaneous term delivery and 25 women with early spontaneous preterm birth ($\leq$34 weeks gestation).

State of the field

"Few biological processes as central to the survival of a species as parturition are so incompletely understood" – Romero et al. 2002

This concise, yet powerful statement is unfortunately equally as true today as when it was first published more than a decade ago. Accumulating evidence suggests that poor maternal and fetal health set in motion an irreversible trajectory with serious negative consequences for health in infancy, childhood, and adulthood. At present, research to guide the discovery and development of pregnancy and perinatal interventions is hampered by a lack of collaborative, global efforts that engage scientists from a range of scientific and technological disciplines. As a consequence, there are few broadly applicable preventative and therapeutic solutions for major adverse pregnancy outcomes such as preterm birth. Preterm birth is now the leading cause of neonatal death, and the second leading cause of childhood death globally.

Understanding the pathways leading to both normal and abnormal pregnancy outcomes has been hampered by the traditional scientific approach of "reductionism" – the study of small, simple tractable units within complex systems. High-throughput systems biology, or "-omics" biology (including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and metagenomics) affords an opportunity for in-depth study across the continuum of both healthy pregnancy and pregnancies resulting in adverse outcomes such as preterm birth. Systems biology has been widely adapted and utilized to characterize a wide range of disease states, but has been poorly utilized in reproductive biology and pregnancy; more than 90,000 articles have been published utilizing systems biology, and yet fewer than 2,000 related to reproductive biology and pregnancy.

Therefore, there is an urgent need for a broad range of scientific studies utilizing systems biology to illuminate the root causes, underlying molecular pathways and potential targets for future interventions to improve pregnancy, fetal, and newborn outcomes. Furthermore, such studies must be integrated and coordinated to reflect the dynamic processes that result in a continuum of maternal, fetal, and neonatal health outcomes, especially in the context of populations where adverse outcomes are prevalent.

2 KEY DATES

Open Date	October 1, 2014
Letter of Intent Due Date	December 1, 2014
Full Application invitation	January 15, 2015
Application Due Date	March 16, 2015
Scientific Merit/ Executive Committee Review	May 1, 2015
Earliest Start Date	June 15, 2015

3 PROGRAM GOALS

Newly developed research tools and platforms in high-throughput systems biology and computational biology provide a unique opportunity to advance the knowledge gaps in pregnancy and perinatal health to elucidate healthy pregnancy biology and how its perturbations lead to adverse outcomes.

Request for Proposals

The present Request for Proposals (RFP) is the third call for proposals of the Preventing Preterm Birth initiative. The present Request for Proposals (RFP) is meant to catalyze additional research into longitudinal determinants of both healthy and abnormal pregnancy, ***with emphasis on preterm birth***, by funding pilot studies to assess the feasibility of applying multi-omics high-throughput systems biology. It is anticipated that this approach will facilitate an understanding of normal gestational biology, will lead to biomarker discovery to identify pregnancies at risk for adverse outcomes, and begin to identify key targets for new prevention modalities for preterm labor and birth. Requests from investigators new to the field of reproductive sciences are welcome.

The primary goals of this RFP are to:

1. Identify existing prospective cohorts of pregnant women with well-characterized clinical phenotypes and biologic samples collected throughout the course of gestation that are suitable for multi-platform systems biology analysis.

2. Perform pilot studies to assess the feasibility and reproducibility of a multi-platform systems biologic approach using a limited number of samples from pregnancies that result in term and spontaneous preterm deliveries at $\leq$ 34 weeks of gestation.

3. Complete pilot studies within two years that will provide evidence to guide development of expanded studies that will promote identification and testing of new diagnostics, and will potentially lead to products or interventions to prevent preterm labor and birth. *Support for clinical trials will not be provided in the context of this RFP*

These primary goals are in support of a broader plan to bring new investigators, novel technologies, and global attention to the field of maternal, neonatal, and child health through the application of systems biology and computational analysis to pregnancy. Ultimately, we envision the establishment of collaborative networks in high-burden settings. We expect these collaborations to lead to refinement of cohort studies and offer open, broad-based sharing of specimens, research approaches, protocols, and data essential to discovery and intervention studies.

Studies funded through this initiative are intended to identify existing prospective cohorts of pregnant patients with appropriate biologic samples collected throughout the course of gestation and to characterize normal and abnormal pregnancies by a systems biology approach, with a special emphasis on spontaneous preterm birth.

Note:

Information on the first awards of the Preventing Preterm Birth initiative can be found at: www.gapps.org/healthybirth

4 PROJECT OBJECTIVES:

Assess methods to explore gestational origins and biological mechanisms that support normal pregnancy and perturbations that contribute to preterm birth, using well-characterized specimens collected throughout the course of pregnancy and by utilizing a broad range of high-throughput systems biology approaches from a variety of biologic samples.

Note: This feasibility study will require biologic samples from 50 patients with uncomplicated term pregnancies and 25 patients with spontaneous preterm birth less than or equal to 34 weeks of

gestation. Exclusion criteria include multiple gestations, congenital malformations, and other severe fetal and maternal medical complications.

Characteristics of successful proposals

The overarching **goal** is to assess the feasibility and reproducibility of multi-platform systems biologic approaches to characterize normal and abnormal pregnancy in a limited series of pilot projects.

Successful proposals

Successful proposals should address investigational approaches to identify biomarkers, pathways, or mechanisms directed towards prevention or early diagnosis of disease, as opposed to treatment of established disease. The studies proposed should be relevant to large at-risk populations within affected low- and middle-income countries, enhancing the potential for translational solutions.

Successful proposals may include one or more of the following components, or Aims:

1. *Aim 1.* Identification of a prospective cohort of pregnant women with at minimum blood, urine, stool, and vaginal samples collected at a minimum of two time points during gestation and at delivery. Fetal cord blood and placenta should be collected at delivery.
    a. The cohort should be sufficiently scaled to provide at least 25 patients with spontaneous preterm birth at ≤ 34 weeks gestation and 50 patients with spontaneous term delivery.
    b. Biologic samples must include detailed phenotypic characterization of patients including medical, environmental exposures, and obstetrical history and complications.
    c. Samples may be distributed to other investigators funded by this RFP for "omics" analysis
    d. Data sharing should comply with established formats and protocols to insure system compatability.

2. *Aim 2*. Utilization of high-throughput platforms for analysis of samples obtained from patients enrolled in #1, above. These analyses may include one or more of the following and utilize one or more biologic fluids:
        i. Genomics, transcriptomics, and micro-RNA
        ii. Proteomics
        iii. Metabolomics
        iv. Lipidomics
        v. Metagenomics

3. *Aim 3*. Computational analysis of meta-data from multiple platforms (both within and across platforms) above to identify pathways and biomarkers. This may be performed by an independent subcontractor or service, or may be included in individual proposals above.

Proposals we will not consider for funding:

We will not consider proposals from sites that do not have demonstrated experience in enrolling and following women throughout the course of gestation and in collaboration with other investigators (Aim 1), proposals that fail to demonstrate proficiency in high-throughput platforms (Aim 2) or computational analysis across platforms (Aim 3), and proposals that fail to demonstrate willingness and ability to participate in sharing results, data, and other forms of collaboration with other PPB investigators.

Specifically, we will not accept proposals that:

1. Propose clinical trials or specific interventions
2. Do not participate in data sharing agreements
3. Do not have demonstrated expertise in cohort development, systems biology, or computational biology
4. Proposals that do not include studies of data and samples on enrollees with spontaneous preterm birth.

5 PROGRAM STRUCTURE

5.1 Participants

We expect to fund a diverse group of investigators with skills and innovative approaches who will ultimately work together to interrogate hypotheses using state-of-the-art model systems. Collaboration and cooperation among Research Investigators will be required with preference for cross-disciplinary studies and computational biology that could provide the most detailed interrogation of hypotheses, validation, and interventions appropriate to low-resource settings.

5.2 Program Phases

These pilot projects will be funded for a total of 2 years, based on project scope and progress, and separated into two phases:

1. *Identification of or development of a prospective pregnancy cohort*. During this phase, either existing cohorts or newly developed prospective cohorts will be identified that can provide for the collection of maternal blood, urine, and vaginal secretions from at least 2 time-points in the second and third trimester of pregnancy, and collection of biologic samples, including cord blood and placenta at the time of delivery. ***For this pilot project RFP, it is anticipated that 50***

patients with normal singleton gestation and term delivery and 25 patients with singleton spontaneous preterm birth < 34 weeks of gestation will be required. Phase 1 would most likely take up to the first one year of the project period.

2. *Analysis of samples from multiple biological sources obtained from Aim 1 across multiple systems biology platforms*. The goal of Aims 2 & 3 is to characterize, by multiple platforms, longitudinal samples obtained from Aim 1. Investigators will be required to share data.

Specific milestones proposed in Phase 1 will need to be completed at 12 months into the program as evidence of progress towards the initiative. Progress will be evaluated by the Executive Committee of the Preventing Preterm Birth Initiative.

5.2.1 Collaboration and Harmonization of Activities

The aim of this initiative is to create a consortium of individually-funded projects that will benefit from information sharing activities among its members. The collaborative nature of sharing experimental methods, data, and resources is intended to increase the efficiency of the overall effort to discover novel interventions for those that need them most in low-resource settings. The specific terms of the collaborative activities will be negotiated prior to the grant award.

1. **Data Sharing:** Data generated through the PPB studies will be shared with the broader scientific community in accordance with the Bill & Melinda Gates Foundation's Global Health Data Access Principles (http://www.gatesfoundation.org/global-health/Documents/data-access-principles.pdf). A data sharing plan will be developed that is equitable, ethical and efficient, and will include:
    a. a data sharing and publication policy
    b. data use agreement
    c. PPB manuscript citation
    d. acknowledgement of the core PPB investigators.

6 RULES AND GUIDELINES

6.1 Program Direction

To oversee program management, an Executive Committee will be formed with representation from GAPPS, the Bill and Melinda Gates Foundation, and outside advisors from the scientific and global health community. The PPB Executive Committee, in consultation with a review panel of independent, external experts, will oversee the review and selection of specific projects from among the solicited proposals to insure that funded proposals are consistent with the overall objectives of the PPB. In

collaboration with research investigators, the Executive Committee will also develop key indicators of success and critical milestones for each project.

Assuming proposals of sufficient scientific merit, the level of funding requested should be commensurate with the type and scope of the research proposed to assure completion of the goals in the initiative time frame. This competition is expected to fund up to 8 projects. **It is anticipated that the total budget for each project including institutional, indirect costs, will not exceed $500,000 US dollars for the two year funding period.**

6.2 Application Instructions & Review Process

This RFP will utilize an online application process:

Step 1:

Download the Letter of Inquiry (LOI) instructions and LOI application form from www.gapps.org/healthybirth

Step 2:

Submission of a letter of inquiry (LOI) to GAPPS by December 1st, 2014. There is a five (5) page limit on the LOI which includes a general questions face page. Instructions for the completion of the LOI may be found at www.gapps.org/healthybirth.

Applicant organizations submitting an LOI must fully meet the eligibility criteria listed on page 10 of this RFP. Elements included in the LOI must include:

1. Project Purpose and Background
2. Project Framework
3. General Approach
4. Major Assumptions
5. Proposed Budget
6. Organization Experience and Collaborative Partnerships
7. Certification

Letters of inquiry must be submitted electronically, using the forms, instructions, and process described at: www.gapps.org/healthybirth. Each LOI must include in the header of the narrative pages the text "GCGH Preventing Preterm Birth." Multiple LOIs from the same institution or organization are permitted. Those applicants who are eligible and have projects of further interest will be contacted directly and will be invited to submit a full proposal. GAPPS will not provide individual critiques of LOIs not selected to submit full proposals.

Even at the LOI step, however, it is important to read carefully the full guidelines for applicants given below to make certain that the applicant organization is fully capable of complying with all the requirements and terms of award.

Submission of Full Proposal:

If the LOI is successful, the applicant will be invited to submit a full proposal, not to exceed 12 pages. Instructions on the preparation of full proposals will be provided to selected applicants. Final selection will be based upon an evaluation of:

- Scientific and technical excellence
- Execution plan
- Translational potential for high-burden settings in low- and middle-income countries.

The **evaluation criteria** that will be used to make a final selection of proposals for funding are as follows:

Significance. Is the approach likely to add to knowledge about normal gestational biology, and pathways and biomarkers associated with preterm birth? Do the assays, technologies, and systems for analysis proposed have broad applicability?

Approach. Are the conceptual framework, design, methods, and analyses innovative, adequately developed, and appropriate to the aims of the proposal? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is the likelihood of successful project completion high within the funding period? Are the proposed timelines and interim milestones appropriate, feasible, and technically sound?

Organizational and Investigator Capability. Is the research and development team appropriately trained, experienced, and positioned to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other proposed researchers? Is there strong evidence of substantive organizational capability and commitment? Is there experience in development of partnerships, multi-investigator project experience? Are collaborative arrangements in place? Is there evidence of an infrastructure for adoption of standard operating procedures, data collection, transfer, and sharing?

Environment. Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments, including partnerships with industry or employ useful, collaborative arrangements? Is there adequate evidence of institutional support?

Translational Feasibility. Is there potential for advancing scientific findings into pre-clinical development? Is there reasonable gain in knowledge at a reasonable cost?

6.2.1 Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies, or other recognized institutions that can successfully execute the activities in their respective topic areas. Grantees awarded projects will be required to actively collaborate with members of this research consortium.

6.2.2 Allowable Costs

Grant funds may be used for the following costs for a total cost of $500,000 (including indirect costs): personnel, necessary travel, supplies, contracted services, sub-grants, and consultants. Partial or full support for equipment may be requested subject to the circumstances described below. Please provide budget estimates according to these categories.

- Equipment: Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether GAPPS will permit purchase of equipment with a depreciable life that is greater than the grant period being requested. In such cases, leasing would be preferable.
- Indirect costs: GAPPS provides a limited amount of indirect costs, if any, based on the nature of the applicant organization. Indirect costs must be included within the proposed total budget.

6.2.3 Privacy Notice

To help the governing Executive Committee and GAPPS staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to GAPPS (collectively, "Submission Materials") will become the property of GAPPS and may be subject to confidential, external review by independent subject matter experts and potential co-funders in addition to analysis by GAPPS and the Bill & Melinda Gates Foundation. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, GAPPS recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission, and whether more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, GAPPS and the Foundation may publicly disclose all information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

6.2.4 Warranty

By providing any Submission Materials, the sender warrants GAPPS, Seattle Children's, and the Bill & Melinda Gates Foundation that they have the right to provide the information submitted.

Applicants with questions concerning the contents of their Submission Materials may contact GAPPS at gappsgrants@seattlechildrens.org

6.2.5 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products for use in low- and middle-income countries, the successful development of these products may require involvement and support of the private sector, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. Intellectual property rights and the management of intellectual property rights may play an important role in achieving the goals of this program. GAPPS' Global Access Strategy will guide our approach to intellectual property, and we urge all applicants, even at the Letter of inquiry stage, to consider their willingness to submit a full proposal in compliance with the GAPPS Global Access Strategy, the guiding principles of which are as follows:

- Appropriate solutions to global health challenges are made accessible to people most in need, particularly in the developing world. Accessibility relates to price, supply, and availability.

- Knowledge gained through discovery is broadly, and as promptly as possible, distributed to the global scientific community.

Grantees will be required to develop and sign a Global Access Agreement with GAPPS in line with the guiding principles. For further information, please refer to GAPPS' intellectual property policy at www.gapps.org/healthybirth.

6.2.6 Additional administrative requirements

While this document provides an overview of the PPB initiative rules and regulations, additional requirements may be added at the time that full proposals are requested from eligible investigators.

7 RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, GAPPS will require that for each venue in which any part of the project is conducted (either by your organization or a sub-grantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. GAPPS will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

7.1 Research Involving Human Subjects.

Research supported by this award must comply with the International Conference on Harmonization (ICH) guidelines. You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site and submitted to GAPPS for review.

7.2 Clinical Trials

We do not expect any projects in this research program to conduct clinical trials.

7.3 Coverage for all Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a sub-grantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

7.4 Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; including management of data confidentiality; research involving animals; research using substances or organisms classified as Select Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

7.5 Institutional Review Board (IRB) Approval

You agree to obtain the review and approval of all final protocols by the appropriate IRBs and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to GAPPS if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

7.6 Provision of Care for Human Subjects Research

In keeping with "Good Clinical Practice" standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should be similarly developed, approved and implemented with notice to the employees.