Novel Interventions Targeting Placental and Gut Inflammation to Improve Fetal Growth

Grand Challenges

Request for Proposals

Applications due no later than April 28 2026, 11:30 a.m. U.S. Pacific Time

Before applying, applicants should familiarize themselves with the supporting documents for this Grand Challenge request for proposals (RFP), including the terms and conditions of the Gates Foundation, the Rules and Guidelines, Application Instructions, and Frequently Asked Questions.

If you are planning to apply to this RFP, we will be hosting a dedicated webinar on March 23, from 8:30-9:30 AM Pacific Time. This session will provide a comprehensive overview of the RFP details and an opportunity to have your questions answered. To participate in the webinar, please register and submit your questions in advance. If you cannot attend live, the webinar will be recorded and available on this challenge page after the session.

This is a call for transformative innovation. We seek solutions that can accelerate identification and early validation of interventions (novel or repurposed), including drug-based, biologic, dietary, and microbiome-informed approaches, that modulate inflammatory and or oxidative stress processes in the placenta-maternal gut axis, with the potential to improve fetal growth outcomes. We encourage applicants to pair ambitious ideas with a feasible plan to generate decision-grade evidence within the award duration.

Background

Fetal Growth Restriction (FGR), also known as intrauterine growth restriction (IUGR), is a major contributor to stillbirth, neonatal mortality, and lifelong morbidity. Globally, an estimated 23.4 million infants are born growth-restricted each year (95% UI: 20.1-25.5M where 60-70% of small-for-gestational-age births occur in sub-Saharan Africa (SSA) and South Asia, where prevalence estimates range from 15-25% of all pregnancies. In these settings, FGR contributes substantially to preterm birth, small for gestational age, still birth, impaired immune and metabolic development, and increased risk of non-communicable diseases across the life course.

Despite advances in biological understanding, there are currently no scalable, effective therapeutic interventions that directly prevent or reverse fetal growth restriction, with clinical management largely focused on monitoring and timing of delivery.

Placental dysfunction is a central driver of FGR, often characterized by impaired vascularization, altered nutrient transport, and dysregulated immune signaling. A growing body of experimental, clinical, and epidemiologic evidence suggests that inflammatory processes may contribute to placental dysfunction and impaired fetal growth, although causal pathways are not yet fully defined. Altered placental immune signaling, endothelial activation, and dysregulated cytokine profiles have been observed in pregnancies affected by FGR.

In parallel, emerging research points to a potential role for maternal gut health and systemic inflammation, including changes in gut permeability, microbial composition, and immune activation, thereby modulating metabolism, reducing nutrient uptake and assimilation, placental function and fetal growth and development. Furthermore, while oxidative stress is a well-characterized component of chronic inflammation and mucosal injury in the gut, specific research directly linking oxidative stress in the gut to these untoward pregnancy outcomes is limited. Together, these findings on the impact of gut inflammation on systemic inflammation raise the possibility that maternal gut-placenta inflammatory axes could represent modifiable contributors to fetal growth restriction, but critical gaps remain in mechanistic understanding, target validation, and translational relevance, particularly in the global south.

This Grand Challenge seeks to catalyze novel, scalable interventions - including but not limited to drug-based approaches - that target maternal gut-placenta inflammatory axes and oxidative stress during pregnancy with the potential to improve fetal growth outcomes in global south contexts.

The Challenge

Although definitive causal mechanisms connecting maternal inflammation and FGR are not fully established, clinical, epidemiologic, and laboratory evidence suggests that gut-placenta inflammatory axes could influence metabolism and therefore impact placental function and fetal growth outcomes. This Grand Challenge includes three funding tracks designed to accelerate mechanistic discovery, candidate advancement, and early validation of interventions targeting maternal gut-placenta inflammatory axes and oxidative stress to improve fetal growth outcomes.

- **Track 1: Mechanism and Target Discovery** - Supports identification and mechanistic validation of inflammatory and or oxidative stress pathways relevant to placental or maternal gut biology, culminating in nomination of at least one actionable intervention target.
- **Track 2: Candidate Validation and Translational Advancement** – Supports rigorous preclinical and translational validation of a defined intervention candidate (novel or repurposed), generating biomarker-linked evidence sufficient to justify progression to early clinical testing.
- **Track 3: Early Clinical Proof-of-Concept (POC)** - Supports small, well-designed early human studies to demonstrate biological activity, target engagement, safety, and feasibility of a candidate with prior preclinical validation.

Mechanistic Readiness Expectations

Given the time and budget constraints of this call, proposals should begin from a plausible mechanistic hypothesis grounded in existing evidence and should prioritize testing within established experimental platforms (e.g., validated in vitro/ex vivo systems, organoids, or established animal models) and or well-characterized human datasets/biobanks that enable mechanistic inference. Proposals are expected to:

- Specify the hypothesized pathway(s) linking inflammation and or oxidative stress to gut and placental function, their interaction and how they may impact fetal growth;
- Justify why the chosen approaches can interrogate those pathway(s) within the award period; and

- Define quantitative success criteria (biomarkers, functional readouts, or fetal growth proxies) and go/no-go thresholds for advancing the candidate or target to the next stage of development, relevant to each track.

We are looking for projects that are ambitious in approach and feasible within the time and budget parameters below. We consider the following to be out of scope for this challenge:

- Purely observational studies without an intervention component.
- Interventions requiring highly specialized infrastructure that are unlikely to be scalable in the global south.
- Nutritional interventions that do not directly address inflammatory or oxidative stress mechanisms.

Focus Areas

Applicants may propose work in one the following tracks:

Focus Area	Description	Primary Deliverables
Track 1: Mechanism and Target Discovery Supports mechanistic investigation and target nomination, not advancement of a finalized intervention candidate.	Projects under this track should begin with a clearly articulated biological question or pathway hypothesis related to maternal gut-placenta inflammatory or oxidative stress axes. Applicants may use human cohorts, biobanks, multi-omic analyses, AI-enabled prioritization approaches, and or established experimental systems to: • Define a clear mechanistic hypothesis linking inflammatory and or oxidative stress biology to placental function and fetal growth; • Generate experimental validation of at least one prioritized target or pathway; • Nominate at least one actionable intervention strategy (e.g., druggable target, repurposable compound class, biologic, microbiome-directed approach, bioactive proteins, lipids or fibers).	• A validated mechanistic pathway; • A prioritized and justified intervention target; • Quantitative biomarkers and pre-specified advancement criteria; • A clear next-step development plan.
Track 2: Candidate Validation and Translational Advancement Supports advancement of a defined intervention candidate that is specified at the time of application.	Projects under this track must begin with a named candidate (novel or repurposed) and a clear mechanistic rationale. Activities may include rigorous preclinical and translational validation using established experimental systems and or well-characterized human specimens or datasets to: • Demonstrate biological activity linked to modulation of inflammatory and or oxidative stress pathways; • Show quantitative improvements in placental and or gut function, inflammatory/immune biomarkers, oxidative stress markers, nutrient transfer, or fetal growth proxies; • Generate a translational data package sufficient to justify early human evaluation.	• Mechanistic validation of candidate activity; • Biomarker-linked evidence of efficacy in relevant models; • Advancement decision package suitable for early clinical evaluation.
Track 3: Early Clinical Proof-of-Concept (POC) Supports advancement of repurposed candidate	Projects in this track should generate early human evidence of biological activity, safety, feasibility, and biomarker modulation for advanced or repurposed candidates targeting placental and or gut inflammatory or oxidative stress pathways.	• Evidence of target engagement or biomarker modulation; • Safety and feasibility data;

Focus Area	Description	Primary Deliverables
for use of placental and or gut applications.	Eligibility for this track requires: • Strong preclinical or translational data supporting biological plausibility; • Preliminary safety data sufficient to justify early human evaluation (where applicable); • A clearly defined pharmacodynamic or biomarker-based primary endpoint. Projects may include: • Small early human studies focused on safety and biological activity; • Dose-finding or biomarker modulation studies; • Feasibility studies in populations relevant to global south settings. Large-scale efficacy trials are out of scope.	• Defined criteria for progression to larger clinical studies.

Key Requirements and considerations

- If the proposal includes early discovery effort, including exploring potential for repurposing drugs, bioactive molecules or nutritional interventions such as resistant starches or complementary diets, they must be completed within the time for this RFP. Consider including screening or mechanistic efforts linking the intervention activity to improvements in one or more of the following:
    - Placental or gut structure or function
    - Nutrient transfer
    - Inflammatory or immune biomarkers relevant to FGR
    - Indicators of fetal growth
    - Indicators of placental or gut oxidative stress
- Novel small molecules, biologics, host-directed therapies, targeted nutritional approaches that include bioactive proteins, metabolites or ingredients, or microbiome-informed approaches targeting:
    - Placental dysfunction or immune dysregulation may be impacted by gut-placental axis.
    - Maternal gut inflammation and its downstream systemic (including placental) effects
- If the proposal includes use of candidate intervention in preclinical/translational or clinical effort,
    - The proposal should articulate the biological rationale connecting the targeted intervention to placental or gut inflammatory processes with relevance to fetal growth.
    - The proposal must include identification and preliminary validation of biomarkers linking intervention effects to placental biology or fetal growth proxies.
    - The proposal should include information regarding or plans to demonstrate the potential for scalability and deployment in global south contexts, including considerations of manufacturability, safety, delivery and cost.

- If the proposal includes a clinical component, it must also include completed or proposed translational validation (i.e., in physiologically relevant in vitro, ex vivo, organoid, or animal models; or in early human studies if appropriate) that establishes biological activity and signals related to inflammation and or oxidative stress modulation.
- Projects must include quantitative milestones and pre-specified go/no-go decision points.

What we are looking for:

Successful proposals will demonstrate:

- Strong scientific rationale grounded in existing evidence linking gut or placental inflammation, oxidative stress and pregnancy outcomes.
- A novel or significantly advanced approach to intervention identification or early validation.
- A feasible strategy with measurable timelines and deliverables over 18 months.
- A clear plan to generate preliminary data sufficient to support future decisions on investment and development.
- Engagement of multidisciplinary expertise (e.g., immunology, obstetrics, pharmacology, translational biology).

The proposal should articulate how findings will inform **future development pathways**, including next steps for efficacy testing or implementation research.

Funding Level and Duration

Option	***Scope***	***Target (summary)***	***Funding***	***Duration***
Track 1	**Mechanism and Target Discovery**	Validated inflammatory and or oxidative stress pathway linked to placental or maternal gut biology; ≥1 prioritized, actionable target nominated; defined biomarker framework; quantitative go/no-go criteria for advancement	Up to **US$400,000**	Up to **18 months**
Track 2	**Candidate Validation and Translational Advancement**	Defined intervention candidate (novel or repurposed); biomarker-linked biological activity demonstrated in established models; mechanistic validation; advancement-ready translational data package; scalability considerations addressed	Up to **US$750,000**	Up to **24 months**
Track 3	**Early Clinical Proof-of-Concept (POC)**	Early human evidence of target engagement and or biomarker modulation; safety and feasibility data; defined progression criteria for Phase II or larger efficacy evaluation	Up to **US$1,000,000**	Up to **30 months**

Budgets should be commensurate with proposed work and justified in the context of deliverables. Indirect costs should not exceed standard institutional policy thresholds (e.g., 10-15% if applicable).

We will not fund proposals that:

- Include commercial nutritional supplements already available on the market that lack evidence of mechanistic impact on the pathophysiology of placental or gut axis inflammation and or infection.
- Propose the use of antibiotics or antimicrobials in ways that carry meaningful risk of contributing to antimicrobial resistance (AMR).
- Involve drugs, biologics, or bioactive compounds with known contraindications during pregnancy or lactation.

Eligibility

This Grand Challenge is open to global applicants including non-profit organizations, for-profit companies, academic, research institutions, international organizations and consortia.

Collaboration with global south institutions and local investigators is strongly encouraged to ensure relevance and respect local context.

Individuals and organizations classified as individuals for U.S. tax purposes are not eligible to receive an award from the foundation as part of this initiative.

Definitions and Notes

- Placental and gut inflammation are defined broadly to include immunologic, cytokine, immune cell, and microbial-related pathways that could plausibly influence placental health and fetal development.
- Early human studies, where proposed, should include appropriate ethical oversight, power calculations and justification.
- Placental and gut oxidative stress is defined broadly to include excessive generation of reactive oxygen and nitrogen species and or impaired antioxidant defenses within placental tissues and the maternal gastrointestinal tract that may disrupt normal cellular, immune, metabolic, or vascular function during pregnancy. This includes, but is not limited to:
    - Mitochondrial dysfunction and altered redox balance
    - Oxidative damage to lipids, proteins, and nucleic acids
    - Inflammatory signaling cascades amplified by oxidative stress
    - Endothelial or epithelial barrier dysfunction
    - Crosstalk between oxidative stress and immune activation, including how it may impact enteropathogen prevalence and colonization
    - Interactions between oxidative stress, microbial products, and host responses in the maternal gut
    - Downstream effects on placental perfusion, nutrient transport, and fetal growth
- Definition of placental or enteric oxidative stress encompasses both localized and systemic oxidative stress pathways that may influence placental function and pregnancy outcomes, without presupposing specific causal mechanisms.

Examples of potential preclinical models for testing may include, but are not limited to:

I) Genetic or transgenic models targeting inflammatory mediators, oxidative stress regulators (e.g., redox enzymes, NRF2-axis components), endothelial signaling pathways, or nutrient transporters relevant to placental function.
II) Placenta-on-a-chip, gut-on-a-chip, or multi-organ micro physiological systems enabling interrogation of gut-placenta crosstalk, endothelial activation, nutrient transfer, and inflammatory signaling under controlled conditions.
III) Organoid or trophoblast stem cell systems, including co-culture models with immune cells or microbiome-derived metabolites to study mechanistic interactions.
IV) Models of environmental enteropathy or chronic low-grade inflammation relevant to global south settings, including preclinical models of infection and protein/calorie deficiency.
V) Chemically induced colitis/barrier injury models (e.g., DSS, Indomethacin).
VI) Maternal undernutrition or micronutrient deficiency models where inflammatory or oxidative stress mechanisms are explicitly interrogated.
VII) Ex vivo perfused human placental cotyledon systems to assess nutrient transport, vascular reactivity, or oxidative stress responses in real time.
VIII) Human cohort-based translational platforms, including longitudinal pregnancy cohorts, well-characterized biobanks, or linked maternal-placental-cord blood datasets enabling biomarker validation and mechanistic inference.
IX) Advanced multi-omic integration platforms, including transcriptomic, metabolomic, proteomic, redox profiling, and microbiome datasets, particularly when paired with functional perturbation approaches.
X) Imaging-based platforms (e.g., Doppler ultrasound, advanced placental MRI methods in translational settings) that allow quantitative assessment of placental perfusion or function as intermediate readouts.
XI) In vitro endothelial or epithelial barrier assays or organoid systems evaluating tight junction integrity, mucus production, secretion of enhancers or activators of barrier function (i.e., GLP2), immune activation, oxidative stress responses, and translocation of microbial products.

Applicants are not limited to these examples but must clearly justify model selection based on biological relevance to gut–placenta inflammatory or oxidative stress pathways, feasibility within the award period, and the ability to generate quantitative, decision-grade data aligned with proposed advancement milestones.