Novel Interventions Targeting Placental and Gut Inflammation to Improve Fetal Growth

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.

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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.

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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:

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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;	• Mechanistic validation of candidate activity; • Biomarker-linked evidence of efficacy in relevant models; • Advancement decision package suitable for early

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Focus Area	Description	Primary Deliverables
for use of placental and or gut applications.	• 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.	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

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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 within the duration of the track.
- 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**

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- 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 pathways modified by oxidative stress

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2. 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.
3. Organoid or trophoblast stem cell systems, including co-culture models with immune cells or microbiome-derived metabolites to study mechanistic interactions.
4. Models of environmental enteropathy or chronic low-grade inflammation relevant to global south settings, including preclinical models of infection and protein/calorie deficiency.
5. Chemically induced colitis/barrier injury models (e.g., DSS, Indomethacin).
6. Maternal undernutrition or micronutrient deficiency models where inflammatory or oxidative stress mechanisms are explicitly interrogated.
7. Ex vivo perfused human placental cotyledon systems to assess nutrient transport, vascular reactivity, or oxidative stress responses in real time.
8. 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.
9. Advanced multi-omic integration platforms, including transcriptomic, metabolomic, proteomic, redox profiling, and microbiome datasets, particularly when paired with functional perturbation approaches.
10. 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.
11. 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.

Initiative: Grand Challenges

Challenge Topic: Inflammation

Date Opens: May 17, 2026, 9:00 am PDT

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- Improving Fetal Growth - Frequently Asked Questions (FAQs)

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