

## Accelerating Discovery for Non-Hormonal Contraceptives: A Grand Challenge

*“That’s the idea behind Grand Challenges - to focus bright scientists on the problems of the poorest, take some risks, and deliver results.” Bill Gates*

*“Family planning and access to contraception - including information, supplies, and services - is an issue that I am passionate about, and it has become one of my personal priorities at the foundation.*

*I believe it’s one of the most urgent issues of our time.” Melinda Gates*

### Background

Family planning is one of the most cost-effective ways to reduce maternal, infant and child mortality and contributes to the empowerment of women and families, as well as the expansion of opportunities for economic development. In recent decades, there have been tremendous improvements in the reproductive health of women in low resource settings. Global efforts have substantially accelerated progress toward the goal of reaching 120 million additional users of contraception by 2020 in the world’s poorest countries, an achievement well worth celebrating. Nonetheless, it is estimated that over 214 million women in developing countries have an unmet need for modern contraception.

While current contraceptive methods for women include exceptionally safe and effective options, not all methods are suitable for or acceptable to all women at all stages of their reproductive lives, and concerns about undesirable side effects remain a significant barrier to greater uptake and continued use of existing methods. As a result, women who desire to avoid pregnancy often find themselves without viable options that meet their needs. In particular, changes in uterine bleeding patterns are associated with use of hormonal contraceptive methods and copper intrauterine devices and, combined with access challenges and social or religious norms related to contraceptive use or menstrual bleeding, contribute to high discontinuation rates for these methods (up to 40% in the first year of use). While the concept of developing a non-hormonal pharmaceutical contraceptive with an improved tolerability profile as a suitable alternative has been promoted through research efforts and publications, a focused discovery effort has not been systematically pursued.

### Objectives

The Bill & Melinda Gates Foundation is committed to a long-term vision of expanding contraceptive options for the most vulnerable women in low-resource settings through development of new methods that better align with women’s preferences. Contraceptive product innovation will be required to achieve this goal. Specifically, the emphasis for this work is on developing **safe and effective non-hormonal contraceptive agents with both improved overall tolerability and a side effect profile differentiated from hormonal methods**. This emphasis is based on an understanding that overall tolerability of and side effects from hormonal methods present real and meaningful barriers to women realizing their reproductive intentions.

This vision demands establishment of a strong research foundation upon which to build a robust pipeline of product candidates, recognizing that the attrition rate of products in preclinical and clinical development will likely be substantial due to the high bar for safety and efficacy. In order to establish a set of critical reproductive biology and early stage discovery capabilities, in-source novel ideas from other areas of science, and improve the knowledge base needed to support such an effort, the foundation is launching the “Accelerating Discovery for Non-Hormonal Contraceptives” Grand Challenge in 2020. The goal of this Grand Challenge is to identify new approaches and concepts directed at the characterization of novel contraceptive drug targets, the identification of active contraceptive compounds useful for target validation and proof-of-principle studies, and the development of novel and impactful research tools with the potential to revolutionize the field of contraceptive R&D.

The ultimate outcome driving the foundation’s investment in this area is the discovery new drug candidates that i) provide safe and effective contraception, ii) do not rely on systemic administration of reproductive steroid hormones or act through perturbation of sex steroid pathways, and iii) are suitable and appropriate for deployment in a low resource setting. The focus of this Grand Challenge is on broadly enhancing the research ecosystem for contraceptive discovery and advancing novel and bold ideas that can accelerate drug discovery in this field. We do not expect that novel contraceptive product candidates ready for entry into preclinical development will be identified in this early stage of funding. We anticipate, however, that projects funded through this Grand Challenge will identify new drug discovery approaches and technologies that have yet to be effectively applied to contraceptive R&D. We expect to engage a broad range of expertise across disciplines in a collaborative and coordinated research program. It is anticipated, but not guaranteed, that success in these efforts would justify additional investment in a broader drug discovery effort by the Bill & Melinda Gates Foundation, with the goal of developing innovative non-hormonal contraceptive methods to better serve the needs of women.

## **Approach**

As approaches to discovery of new drugs for other indications have become increasingly sophisticated, these advances have not been applied to field of contraceptives. As a result, critical technical barriers continue to hamper progress and limit our ability to effectively identify novel contraceptive agents. These barriers include, but are not limited to:

- The inability to appropriately replicate in the laboratory a number of complex multi-cellular reproductive processes for the purposes of compound screening (e.g. ovulation);
- Poor understanding of contraceptive drug targets associated with key fertility pathways, and a lack of validated and scalable approaches to validate and assay potential targets;
- Lack of appropriate medium- to high-throughput phenotypic screening methodologies for identifying compounds capable of exerting a specific and potent contraceptive effect;
- Lack of appropriate in vitro and in vivo preclinical assays and biomarkers to assess i) the efficacy of agents targeting novel contraceptive mechanisms and ii) the potential side effects of novel agents.

It is our belief that these challenges can be addressed, and that doing so will create substantial new opportunities for contraceptive drug discovery. We seek to leverage advances in other areas of reproductive biology, both basic and applied, and emerging technologies in drug discovery to establish a suite of capabilities that can support a robust drug discovery program. It is not our intention to establish fully integrated end-to-end drug discovery capabilities with individual institutions through this program,

but rather to fund a network of researchers, with each bringing a unique approach, and facilitate interactions between partners to maximize impact. Applicants should keep this in mind when articulating a project plan and focus on the key strengths that their expertise, approach, and technology can provide. Proposals should be aligned with one or more of the funding focus areas outlined below.

**We are looking for proposals that:**

- Engage scientists across a variety of disciplines, including those new to the field of contraceptive R&D;
- Demonstrate innovative thinking by applying or incorporating concepts, methods or technologies not currently being used for contraceptive discovery;
- Present concepts and strategies that are “off the beaten track,” significantly radical in conception, and daring in premise;

**We will NOT consider funding for:**

- Proposals focused on development of male contraceptives, including work on sperm-based approaches that could only feasibly be applied as vaginal methods;
- Proposals targeting the endometrium for the prevention on embryo implantation;
- Proposals on novel drug delivery systems for contraception;
- Discovery of adjunct or complementary molecules intended for co-delivery with hormonal contraceptive regimens;
- Basic studies of human reproductive biology without a clear connection to enabling non-hormonal contraceptive discovery;
- Pre-clinical or clinical development of advanced leads and candidates;
- Social science, marketing, or acceptability studies related to contraceptive use and uptake

Awardees through this Grand Challenge may have the opportunity to access other Gates Foundation-funded resources, technology platforms, and grantee networks to help support their projects, facilitated by their Gates Foundation Program Officer. Applicants should, as completely as possible, describe what the proposed project will deliver within the scope of the application and the potential path forward, even if that encompasses activities that are beyond the scope of the current funding opportunity. Applicants invited to submit full proposals following LOI review (see the Review Process as detailed in the Rules and Guidelines) should expect to include critical milestones and relevant go/no-go decisions for the proposed project.

**Funding Focus Areas:**

**1. Biological Assay Development**

Many aspects of female reproduction remain challenging to replicate or model in a tractable, physiologically relevant, and highly reproducible fashion, but such tools and models will be fundamentally important to identifying and profiling contraceptive drug targets and contraceptive compounds. A better toolset of in vitro assays is needed that can recapitulate **oocyte and follicle development, follicle selection, follicular rupture/ovulation, corpus luteum formation, cumulus-oocyte complex dynamics, and fertilization, including peri-fertilization events**. New models should focus on assay tractability as well as establishing physiological relevance and

modeling closely relevant features of the in vivo environment. Applicants seeking to develop such systems should clearly describe the planned approach and how this would improve upon existing methods. Including approaches to validate with human samples or human genetics/genomic information would be viewed favorably. Proposals should include a discussion on how assays will be standardized, validated, and scaled, including where possible the use of genetic or chemical probes as positive controls to demonstrate biologically relevant outcomes following assay perturbation.

## **2. Drug Target Identification and Validation**

In the past two decades, target-based drug discovery approaches have become increasingly sophisticated and powerful, but further and complementary approaches are needed to sustain a pipeline of potential drug targets and enhance our understanding of target biology. Emphasis will be placed on unbiased approaches to identify potential contraceptive drug targets. These may include (but are not limited to):

- a. RNAi- or CRISPR-based methods utilizing a robust and relevant biological assay,
- b. chemical genomics or proteomics linking probe compound activity to specific drug targets or pathways,
- c. analyses of human infertility as a pathway to identify relevant drug targets, or
- d. artificial intelligence-enabled approaches to target identification.

Target characterization and validation efforts should focus on the determination of whether any particular gene that is critical for a reproductive process is vulnerable to inhibition by a small molecule inhibitor (using, for example, tunable knockdown or inducible degradation techniques), can likely be safely modulated by such an inhibitor (including assessment of roles in somatic tissue and activity of closely related homologs), and is likely to provide the desired contraceptive effect at realistic levels of inhibition (as opposed to complete loss-of-function). Applicants should clearly describe the critical assays, methods, or approaches they are proposing to underpin this work, and describe how such approaches will yield compelling and relevant data that could be used to support entry of identified targets into target-based drug discovery activities.

## **3. Chemical genomics, probe generation, pilot screening**

The availability of active compounds that interfere with key steps in fertility would open up many avenues for further biological exploration and target validation, but methods for screening small compound libraries for chemical probe discovery are currently limited. Applications will be considered that propose small pilot-scale screening in complex systems for the purposes of identifying active compounds interfering with key reproductive functions. Applicants must detail how screening systems will be developed, tested, and validated in a format suitable for testing compounds, and should detail the type and source of chemical libraries that would be utilized. Biologically-informed hypotheses may be proposed to select mechanism- or target class-focused libraries as a starting point. We will not consider applications for screening of a single proposed target, but mechanism-focused approaches that interrogate multiple targets involved in a key reproductive process would be considered. Applicants must then describe an approach to deduce the specific targets of compounds identified in cell-based screens and demonstrate concordance between target-based activity and functional activity in validated in vitro systems.

#### 4. Contraceptive Antibodies

While the cost and practicality of antibody-based therapeutics has historically been a challenge, particularly for application in a low resource setting, new advances in antibody half-life extension and cost-effective production open up the possibility that antibodies may be a more tractable option in the future, particularly if used in an “on demand” contraceptive modality. Moreover, this may allow consideration of targets that would otherwise not be amenable to small molecule inhibitors and may provide an enhanced safety window. Applications focused on contraceptive antibodies should clearly articulate the data supporting the validation of the proposed antigen target, the methods to be used for antibody identification, and the assays to be used relevant to determination of antibody function.

(Note: the foundation is not accepting applications based on contraceptive immunization as an intervention modality, though such approaches could be applied experimentally for target validation.)

#### 5. Translational Science/Preclinical Evaluation Tools

In addition to target and hit discovery activities, downstream aspects of drug and product development require early consideration to ensure the appropriate tools and data are in place once advanced leads and candidates are identified. We would consider funding for projects aimed at the following issues:

- a. Identifying **candidate biomarkers of efficacy** for non-hormonal contraceptive mechanisms-of-action, including biochemical or imaging markers, that can be applied to preclinical in vivo models and, ideally, that could be applicable for validation in human clinical studies.
- b. Improving our understanding and prediction of **reproductive tract and reproductive tissue pharmacokinetics** to assist in building PK/PD models and enable early dose selection and safety risk evaluation.
- c. Improved and tractable **in vivo models** for contraceptive efficacy that overcome limitations of existing rodent and primate models.
- d. Innovative methods for early assessment of **safety, toxicity, and side effect risk**, with particular emphasis on the potential for endocrine disruption and bleeding side effects.

There are clear thematic overlaps in the focus areas described above, and we would be happy to receive proposals that are directed at multiple focus areas, so long as the application demonstrates strength in all related areas of proposed work.

#### Award

This Grand Challenges request for proposals intends to fund individual awards of up to USD \$2 million and for up to 3 years, based on the scope of the proposed project. The proposed budget must realistically reflect the technical work and project deliverables within a 3-year timeframe; in some cases, a smaller budget may be justified to establish initial proof-of-concept. Budgets and scope may be negotiated with applicants as part of the review process to ensure the foundation’s ability to fund a robust and balanced portfolio with existing available budget (see the Review Process as detailed in the Rules and Guidelines).

Successful award recipients may have the opportunity to apply for additional funding at the end of the grant period, based on technical success, portfolio fit, and continued strategic alignment with the foundation's priorities. We reserve the right to determine eligibility for subsequent funding for this call based on these criteria.