Directed Funding Opportunity

To accelerate innovation and adoption of new biomanufacturing approaches that will foster growth of the bioeconomy, the DOE's Agile BioFoundry (ABF), www.agilebiofoundry.org, is overseeing a CRADA (Cooperative Research and Development Agreement) funding opportunity for participating national labs and industry partners, to utilize the ABF to develop novel microbial hosts and bioproducts or to develop new capabilities and approaches that will advance all aspects of the Design-Build-Test-Learn biomanufacturing cycle. To apply, teams will submit a proposal that identifies the technical challenges, approaches and impacts to the missions of the ABF.

The ABF anticipates a total of $5.7M to be made available to the National Labs to collaborate with industrial partners. Note that Federal funds shall support activities at the ABF National Labs only, and that project partners are required to provide cost share (including in-kind) of 20%.

Proposals may be submitted for two project levels:

- Seed projects (1 – 2 years in duration, awards <$500k)
- Full projects (2-3 years in duration, maximum award of $2M).

Please see the **special topics of interest** on page 3, indicating project areas of strategic value to the ABF consortium. Please also note that **project proposals not focused on those special topics are encouraged.**

Guidelines for Proposals

All submissions shall follow a similar template.

- For SEED projects, proposals should be **no more than 5 pages** in length,
- For FULL projects, proposals shall be **no more than 8 pages** in length.

Proposals should be emailed to: info@agilebiofoundry.org **no later than 5PM PDT March 31st, 2020**.

Each section of this template is aligned with specific review criteria for Agile BioFoundry directed CRADA-funded projects.

Required criteria for submissions include:

- Introduction (brief overview of project)
- Challenges
- Approaches
- Identification of risks and risk mitigation strategies
- Impacts and benefit to the ABF
- Appropriateness of government funding

- Key personnel
- Budget and timeline

To be considered, **submitting organizations must certify that they will adhere to the following:**

- Sign a Cooperative Research and Development Agreement (CRADA) that governs intellectual property and other terms, which can be downloaded here as an MS Word document: https://agilebiofoundry.org/work-with-us/. **Applicants are strongly encouraged to review this document prior to submitting a proposal. If your organization cannot sign up to the terms and conditions enclosed, it will not be possible to support your project.**
- Reporting: Commit to providing results during the project and for a period ~5 years after the project start date.
- Unique Lab Capabilities: Request assistance that is not reasonably available in the private sector. Projects are intended to make available the specialized expertise and equipment at the ABF national labs, not compete with the private sector.
- Cost Share: Commit to at least a 20% cost share, which can be in-kind. Examples: labor, travel, materials, equipment, organisms, enzymes, pathways, data or cash. **Federal funds may not be used as cost share.**
- Release of Information: Agree to allow non-proprietary information about your business and the success of the assistance to be featured in publicly available stories by DOE and the labs.

Review and Selection Process

Submissions will be reviewed and scored by a team of external reviewers, who are nominated and selected by the ABF and BETO according to their subject matter expertise and independence from proposal submissions, and will be drawn from academia, research institutions, and industry.

The review team shall score each of the applications according to the application criteria. The ABF shall then select from these submissions, according to reviewer recommendations, and prioritizing a strategic project portfolio and available resources that the ABF can bring to bear.

Post-Award

All projects will be subject to DOE reviews and reporting requests, a statement of the anticipated cost share and regular reports detailing how this requirement is being met, as well as the execution of all appropriate partnership documents required by DOE.

SPECIAL TOPICS OF INTEREST

1. **Culture heterogeneity and selection of desirable traits**

- Culture stability and heterogeneity across scales and over time: Even clonal isolates can demonstrate considerable physiological variability (asynchronous growth, viable/senescent cells) in the time course of a culture, which has impacts on titer, rate and yield (TRY). The ABF has the ability to grow cultures at different scales from 100 microliters to 1000 liters and omics testing capable of querying those culture conditions. In the bioreactors, ABF can perform prolonged biocatalysis after initial batch culturing to probe conditions that trigger heterogeneity. Hosts with issues that could benefit from such an examination, or innovative new ideas and methods to address these issues would be opposite facets of the issue that are both of interest.
- Selection of desirable traits from heterogeneous cultures: Traditional fermentation development utilizes mutagenesis and selection. Adaptive Laboratory Evolution (ALE) and related techniques are a more sophisticated manifestation of that approach. However, selection for increased product titer, for example, can be difficult as it confers no competitive advantage to the organism. The ABF has biosensor techniques that are advantageous in that regard and would welcome proposals to utilize them. The ABF would also welcome innovative ideas and methods to select for challenging but desirable attributes (including but not limited to TRY).

2. **AI-enhanced Biomanufacturing:**

- Machine Learning (ML) and Artificial Intelligence (AI) methods have become indispensable for many industries, yet their utility in synthetic biology is still being proven. A wealth of new applications tailored to biomanufacturing are under development – both 'in-house' by major industrial players and externally by firms specializing in these new approaches and at the ABF. One of the major challenges for adoption of AI is the requirement for large training datasets collected from well-designed laboratory experiments. A strength of datasets originating within the ABF is that they can include multi-omics analyses. Proposals are encouraged that leverage ML/AI approaches to improve DBTL cycle efficiency. Data needs can be derived from multi-omics analyses or through the use of HTP approaches for strain optimization and scaling. Expertise within the ABF in microfluidics and biosensor design can be used to accelerate and miniaturize experiments. These latter approaches will allow engineers to survey and characterize larger strain and process space and will be used to complement multi-omics analyses on strains with the best production performance in order to feed data-hungry AI approaches. Novel readout capabilities are required as experimental volumes are miniaturized. Here, expertise within the ABF in biosensor development can rapidly generate novel fluorescent assays for the detection of bioproduct concentrations, where massively parallel experiments (e.g., mutant library screening and factorial process development) can be conducted quickly. The results of these experiments can be used to identify those specific strains/conditions for which scaled demonstration of performance is warranted and/or initiate subsequent DBTL cycles – eventually enabling optimized performance at industrially relevant production scales. Opportunities exist to utilize ABF Learn resources to explore external datasets for optimization of production strains or scaled performance; conversely, proposals are welcome to use externally-developed methods and algorithms to analyze datasets collected within the ABF during its first three years of operation.

3. ABF Host Engineering and New Host Onboarding

- The ABF has onboarded several non-model host organisms, developing engineering tools and validating optimization of several bioproducts in them using the ABF Design, Build, Test, Learn infrastructure. These hosts include *Aspergillus niger* (An), *Aspergillus pseudoterreus* (Ap), *Corynebacterium glutamicum* (Cg), *Pseudomonas putida* (Pp), and *Rhodosporidium toruloides* (Rt). The ABF is seeking partners to use one or more of these organisms to develop new bioproducts or advance existing ones, including muconic acid (Pp and Cg), mono-, sesqui, and di-terpenes (Rt), fatty alcohols (Rt), itaconic and aconitic acid (An and Ap), 3-hydroxypropionic acid (An, Ap, and Rt), etc.

- In addition to the aforementioned hosts, the ABF is currently onboarding new host organisms compatible with a variety of different industrial applications. We are seeking partners interested in working with ABF to select, onboard, and develop new hosts, leveraging ABF infrastructure and expertise in method and tool development for non-model organisms.
