FINANCIAL ASSISTANCE
FUNDING OPPORTUNITY ANNOUNCEMENT

ADVANCED RESEARCH PROJECTS AGENCY – ENERGY (ARPA-E)
U.S. DEPARTMENT OF ENERGY

Energy and Carbon Optimized Synthesis for the Bioeconomy SBIR/STTR (ECOSynBio)

Announcement Type: Initial Announcement
Funding Opportunity No. DE-FOA-0002388
CFDA Number 81.135

Funding Opportunity Announcement (FOA) Issue Date:	September 10, 2020
First Deadline for Questions to ARPA-E-CO@hq.doe.gov:	5 PM ET, October 16, 2020
Submission Deadline for Concept Papers:	9:30 AM ET, October 26, 2020
Second Deadline for Questions to ARPA-E-CO@hq.doe.gov:	5 PM ET, TBD
Submission Deadline for Full Applications:	9:30 AM ET, TBD
Submission Deadline for Replies to Reviewer Comments:	5 PM ET, TBD
Expected Date for Selection Notifications:	TBD
Total Amount to Be Awarded	Approximately $25 million, subject to the availability of appropriated funds to be shared between FOAs DE-FOA-0002387 and DE-FOA-0002388.
Anticipated Awards	ARPA-E may issue one, multiple, or no awards under this FOA. Awards may vary between $256,580 and $3,677,642.

- For eligibility criteria, see Section III.A – III.D of the FOA.
- For cost share requirements under this FOA, see Section III.E of the FOA.
- To apply to this FOA, Applicants must register with and submit application materials through ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov/Registration.aspx). For detailed guidance on using ARPA-E eXCHANGE, see Section IV.H.1 of the FOA.
- Applicants are responsible for meeting each submission deadline. Applicants are strongly encouraged to submit their applications at least 48 hours in advance of the submission deadline.
- For detailed guidance on compliance and responsiveness criteria, see Sections III.F.1 through III.F.4 of the FOA.

Questions about this FOA? Check the Frequently Asked Questions available at http://arpa-e.energy.gov/faq. For questions that have not already been answered, email ARPA-E-CO@hq.doe.gov (with FOA name and number in subject line); see FOA Sec. VII.A. Problems with ARPA-E eXCHANGE? Email ExchangeHelp@hq.doe.gov (with FOA name and number in subject line).

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For an overview of the application process, see Section IV.A of the FOA.

For guidance regarding requisite application forms, see Section IV.B of the FOA.

For guidance regarding the content and form of Concept Papers, Full Applications, and Replies to Reviewer Comments, see Sections IV.C, IV.D, and IV.E of the FOA.

SUBMISSION	COMPONENTS	OPTIONAL/ MANDATORY	FOA SECTION	DEADLINE
Concept Paper	• Each Applicant must submit a Concept Paper in Adobe PDF format by the stated deadline. The Concept Paper must not exceed four (4) pages in length including graphics, figures, and/or tables and must include the following: (The Technical Performance Targets Table, provided in the Concept Paper Template, will not count as part of the four pages.) ○ Concept Summary ○ Innovation and Impact ○ Proposed Work ○ Team Organization and Capabilities ○ Technical Performance Targets Table (2 pages max)	Mandatory	IV.C	9:30 AM ET, October 26, 2020
Full Application	[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]	Mandatory	IV.D	9:30 AM ET, TBD
Reply to Reviewer Comments	[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]	Optional	IV.E	5 PM ET, TBD

I. FUNDING OPPORTUNITY DESCRIPTION

A. AGENCY OVERVIEW

The Advanced Research Projects Agency – Energy (ARPA-E), an organization within the Department of Energy (DOE), is chartered by Congress in the America COMPETES Act of 2007 (P.L. 110-69), as amended by the America COMPETES Reauthorization Act of 2010 (P.L. 111-358) to:

"(A) to enhance the economic and energy security of the United States through the development of energy technologies that result in—
  (i) reductions of imports of energy from foreign sources;
  (ii) reductions of energy-related emissions, including greenhouse gases; and
  (iii) improvement in the energy efficiency of all economic sectors; and
(B) to ensure that the United States maintains a technological lead in developing and deploying advanced energy technologies."

ARPA-E issues this Funding Opportunity Announcement (FOA) under the programmatic authorizing statute codified at 42 U.S.C. § 16538. The FOA and any awards made under this FOA are subject to 2 C.F.R. Part 200 as amended by 2 C.F.R. Part 910.

ARPA-E funds research on and the development of high-potential, high-impact energy technologies that are too early for private-sector investment. The agency focuses on technologies that can be meaningfully advanced with a modest investment over a defined period of time in order to catalyze the translation from scientific discovery to early-stage technology. For the latest news and information about ARPA-E, its programs and the research projects currently supported, see: http://arpa-e.energy.gov/.

ARPA-E funds transformational research. Existing energy technologies generally progress on established "learning curves" where refinements to a technology and the economies of scale that accrue as manufacturing and distribution to develop drive down the cost/performance metric in a gradual fashion. This continual improvement of a technology is important to its increased commercial deployment and is appropriately the focus of the private sector or the applied technology offices within DOE. By contrast, ARPA-E supports transformative research that has the potential to create fundamentally new learning curves. ARPA-E technology projects typically start with cost/performance estimates well above the level of an incumbent technology. Given the high risk inherent in these projects, many will fail to progress, but some may succeed in generating a new learning curve with a projected cost/performance metric that is significantly lower than that of the incumbent technology.

ARPA-E funds technology with the potential to be disruptive in the marketplace. The mere creation of a new learning curve does not ensure market penetration. Rather, the ultimate value of a technology is determined by the marketplace, and impactful technologies ultimately become disruptive – that is, they are widely adopted and displace existing technologies from the marketplace or create entirely new markets. ARPA-E understands that definitive proof of market disruption takes time, particularly for energy technologies. Therefore, ARPA-E funds the development of technologies that, if technically successful, have the clear disruptive potential, e.g., by demonstrating capability for manufacturing at competitive cost and deployment at scale.

ARPA-E funds applied research and development. The Office of Management and Budget defines "applied research" as an "original investigation undertaken in order to acquire new knowledge…directed primarily towards a specific practical aim or objective" and defines "experimental development" as "creative and systematic work, drawing on knowledge gained from research and practical experience, which is directed at producing new products or processes or improving existing products or processes."[1] Applicants interested in receiving financial assistance for basic research should contact the DOE's Office of Science (http://science.energy.gov/). Office of Science national scientific user facilities (http://science.energy.gov/user-facilities/) are open to all researchers, including ARPA-E Applicants and awardees. These facilities provide advanced tools of modern science including accelerators, colliders, supercomputers, light sources and neutron sources, as well as facilities for studying the nanoworld, the environment, and the atmosphere. Projects focused on early-stage R&D for the improvement of technology along defined roadmaps may be more appropriate for support through the DOE applied energy offices including: the Office of Energy Efficiency and Renewable Energy (http://www.eere.energy.gov/), the Office of Fossil Energy (http://fossil.energy.gov/), the Office of Nuclear Energy (http://www.energy.gov/ne/office-nuclear-energy), and the Office of Electricity Delivery and Energy Reliability (http://energy.gov/oe/office-electricity-delivery-and-energy-reliability).

B. SBIR/STTR PROGRAM OVERVIEW

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are Government-wide programs authorized under Section 9 of the Small Business Act (15 U.S.C. § 638). The objectives of the SBIR program are to (1) stimulate technological innovation in the private sector, (2) strengthen the role of Small Business Concerns in meeting Federal R&D needs, (3) increase private sector commercialization of innovations derived from Federal R&D activities, (4) foster and encourage participation by socially and economically disadvantaged and women-owned Small Business Concerns, and (5) improve the return on investment from Federally funded research and economic benefits to the Nation. The objective of the STTR program is to stimulate cooperative partnerships of ideas and technologies

[1] OMB Circular A-11 (https://www.whitehouse.gov/wp-content/uploads/2018/06/a11_web_toc.pdf), Section 84, pg. 3.

between Small Business Concerns and partnering Research Institutions through Federally funded R&D activities.[2]

ARPA-E administers a joint SBIR/STTR program in accordance with the Small Business Act and the SBIR and STTR Policy Directive issued by the U.S. Small Business Administration (SBA).[3] ARPA-E provides SBIR/STTR funding in three phases (Phase I, Phase II, and Phase IIS).

C. PROGRAM OVERVIEW

Carbon, as a major component of most fuels and materials, is the backbone of the modern global economy. Currently this requires reliance on fossilized carbon-based products which present sustainability, resource management, and greenhouse gas (GHG) exacerbated climate change challenges. Due to these challenges, there is the need for a global industrial transition towards sustainable production with greater circularity in carbon and natural resource flows. Specifically, new pathways to realize low-, zero-, or negative-carbon fuels, chemicals, and materials need to be established. The sustainable use of renewable biomass (aquatic and terrestrial) for energy, intermediate, and final products, termed the "bioeconomy", is one promising approach to pursue; and beyond offering a promising source of renewable carbon, biomass utilization has been shown to provide additional economic, environmental, social, and national security benefits as well[4].

A robust and sustainable bioeconomy can only be realized through the industrial-scale, carbon-neutral synthesis of fuels, chemicals, and materials. The rapid deployment of renewable power is driving down the cost and carbon intensity of electricity which presents the opportunity for a tradeoff: by using *more clean electricity* to power novel bioconversion platforms, *less* CO_2 will be produced. This will be made possible by engineering new biorefining systems capable of using electrically derived external reducing equivalents to improve the efficiency of biomass conversion and CO_2 utilization. In addition, externally sourced CO_2 itself may be used as a feedstock, enabling additional carbon neutral and even carbon-negative products. Successful new platforms will serve to maximize the utility of carbon resource inputs, minimize associated land use requirements, and mitigate lifecycle GHGs simultaneously.

This funding opportunity seeks submissions to establish new technologies to significantly improve the carbon efficiency of bioconversion platforms through the accommodation of external reducing equivalents. Proposed systems of interest include, but are not limited to: (1) carbon optimized fermentation strains that avoid CO_2 evolution, (2) engineered mixotrophic

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[2] Research Institutions include FFRDCs, nonprofit educational institutions, and other nonprofit research organizations owned and operated exclusively for scientific purposes. Eligible Research Institutions must maintain a place of business in the United States, operate primarily in the United States, or make a significant contribution to the U.S. economy through the payment of taxes or use of American products, materials, or labor.

[3] See 84 Fed. Reg. 12794 (Apr. 2, 2019).

[4] Golden JS *et al* 2015. "An economic impact analysis of the U.S. biobased products industry: a report to the Congress of the United States of America." *Industrial Biotechnology* 11:201-209.

consortia or systems that avoid CO_2 evolution, (3) biomass or gas fermentation with internal CO_2 utilization, (4) cell-free carbon optimized biocatalytic biomass conversion and/or CO_2 utilization, and (5) cross-cutting or other proposed carbon optimized bioconversion schemes. All systems will need to demonstrate the capacity to accommodate external reducing equivalents to optimize the carbon efficiency of the system as compared to traditional fermentation systems (i.e. the sum of the recoverable energy contents of the products is greater than the energy content of the biomass or primary carbon feedstock).

D. PROGRAM OBJECTIVES

In 2018, the U.S. bioeconomy generated 15 billion gallons of ethanol biofuel and 3.8 billion gallons of biomass-based diesel for use in the transportation sector, amounting to ~10% of domestic transportation energy demand[5]. Although this biofuel production represents a substantial capacity, the full potential of the U.S. bioeconomy could produce 50 billion gallons of fuel, as it has been estimated to be able to sustainably generate 1 billion tons of biomass or ~5 Quadrillion BTU of energy in the form of biofuels without impacting food production[6]. With new innovations throughout the bioeconomy supply chain being pursued through several ARPA-E programs such as ELECTROFUELS, PETRO, REMOTE, TERRA, ROOTS, SMARTFARM and OPEN programs, the path toward *carbon neutral* and even *carbon negative* biofuels and bioproducts is becoming possible.

In recent years, the rate of renewable wind and solar power deployment has grown exponentially[7], driving down both the cost and carbon intensity of U.S. power[8]. ARPA-E aims to establish new paradigms and develop critical new tools to leverage this inexpensive low carbon power to substantially improve the carbon benefits of the bioeconomy and its outputs.

Without carbon-optimized bioconversion platforms, synthetic pathways will continue to be built on carbon inefficient core technologies and natural systems. The current biosynthesis industry is highly lucrative for specialty niche products such as pharmaceuticals, fragrances, and/or flavors, but high-volume low-value products such as fuels, and commodity chemicals are still difficult to make profitable. One fundamental bottleneck is a stoichiometric waste of more than 1/3 of the feedstock carbon as CO_2 in the fermentation process. To fundamentally reconfigure the central metabolism of current industrial strains, and redesign carbon cycling and utilization in biorefinery systems for lower value higher volume products, a new platform must be developed that can demonstrate viability at scale. Through this program, ARPA-E intends to support the development of technologies that will improve the carbon conversion efficiency (CCE) of renewable feedstock to bioproduct pathways in order to enable a clear path

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[5] Department of Energy, Office of Energy Efficiency & Renewable Energy Alternative Fuels Data Center.
[6] Langholtz MH *et al* 2016 "Billion-ton report: Advancing domestic resources for a thriving bioeconomy, Vol 1: Economic availability of feedstock." Oak Ridge National Laboratory.
[7] Grim RG *et al* 2020 "Transforming the carbon economy: challenges and opportunities in the convergence of low-cost electricity and reductive CO_2 utilization" *Energy Environ Sci* 13:472-494.
[8] Rissman *et al* 2020 "Technologies and policies to decarbonize global industry: Review and assessment of mitigation drivers through 2070" *Appl Energ* 266:114848.

toward the expansion of biosynthetic products into industries where they have historically been unable to compete due to high production costs. In particular, ARPA-E intends to fund early stage, high risk research with the intent to enable the uptake of external reducing equivalents into industrially relevant microbial production strains, engineered bioprocesses, or cell-free biocatalytic synthesis platforms to eliminate or reverse the generation of CO_2 as a bioconversion byproduct. Realizing these bioconversion capabilities would allow for robust, highly selective, and maximally resource-efficient synthesis of renewable biofuels and biochemicals[9,10] capable of increasing biomass productivity by as much as 50% and gas phase carbon oxide utility by as much as 66% percent. Program success would enable the fundamental transformation of what was traditionally believed possible for biosynthesis and the bioeconomy as a whole.

1. BACKGROUND

State of the art fermentation pathways waste carbon

Ethanol biofuel, along with a growing number of other plant-based products, are almost exclusively produced via fermentation, the age-old technology that also produces wine, beer, and cheese. The majority of organisms currently involved in commercial fermentation spent millions of years adapting to environments in which energy is scarce, but carbon is abundant, resulting in the evolution of metabolic systems that prioritize energy efficiency over carbon utility. This means that current metabolic bioconversion pathways, upon which the current bioeconomy is built, are fundamentally ill-adapted for a future bioeconomy in which renewable energy is cheap and abundant, but carbon must be conserved because the cost of wasting it is high.

Current methods for ethanol production waste up to a third of the carbon in the feedstock as carbon dioxide (CO_2) in the fermentation step alone[11]. This loss confers additional greenhouse gas emissions and limits product yields, and wastes valuable carbon feedstock. The thermodynamic stability of CO_2 contributes to its emissions during fermentation. When carbohydrates are broken down via oxidative glycolysis—the mechanism for ethanol production via fermentation—they must be converted from six-carbon sugar molecules into two 2-carbon ethanol molecules, leaving two additional carbon atoms unaccounted for. In the presence of oxygen, the highly oxidized, stable nature of CO_2 makes it the most

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[9] Rollin JA *et al* 2018 "Biochemical production with purified cell-free systems" *Biochem Eng J* https://www.osti.gov/servlets/purl/1478729 .
[10] Claassens NJ *et al* 2019 "A critical comparison of cellular and cell-free bioproduction systems" *Curr Op Biotech* 60:221-29.
[11] Jones SW *et al* 2016 "CO_2 fixation by anaerobic non-photosynthetic mixotrophy for improved carbon conversion" *Nat Comm* 7:12800.

thermodynamically favorable compound for these two additional carbon atoms, resulting in the evolution of CO_2 as a waste product[12].

Fermentation is a small part of the bioproduction pathway, but it represents the critical chemical transformation from sugar to liquid fuel[13]. The fermentation to ethanol depends largely on the Embden–Meyerhoff–Parnas pathway, the most common glycolysis pathway[14]. In ordinary (oxidative) glycolysis, one molecule of glucose sugar is broken down into 2 molecules of ethanol, and 2 molecules of CO_2 are generated as a byproduct. The sugar is split and partially oxidized to pyruvate, a three-carbon molecule, and then decarboxylated to generate acetyl-coenzyme A (acetyl-CoA):

$$\text{Glucose} \rightarrow 2\text{ pyruvate} + 2\text{ NADH} + 2\text{ ATP}$$
$$\text{Pyruvate} + \text{NAD}^+ + \text{CoA-SH} \rightarrow \text{Acetyl-CoA} + \text{NADH} + CO_2$$

In sum:

$$\text{Glucose} \rightarrow 2\text{ Acetyl-CoA} + 2\ CO_2 + 4\text{ NADH} + 2\text{ ATP}$$

Acetyl-CoA is perhaps the most central molecule in metabolism: it is both the endpoint of catabolic pathways (those reactions breaking down complex molecules such as sugars) as well as the starting point of many anabolic pathways (those making more complex molecules like fatty acids). Thus, at the endpoint of glycolysis, the cells build up important stores of acetyl-CoA, reducing equivalent carrier cofactor nicotinamide adenine (phosphate) dinucleotide (NAD(P)H), and energy carrier adenosine triphosphate (ATP). Acetyl-CoA also is the ultimate source of carbon for fatty acids and many amino acids, so increasing its pool allows for more synthesis of these vital cellular molecules[15,16].

Though this is typically known as oxidative glycosylation, oxygen is not required for this reaction. Since the decarboxylation of pyruvate during glycolysis requires the loss of a carbon equivalent, the overall carbon yield during fermentation is limited to only two moles of two-carbon metabolites per mole of hexose, or 67% CCE. In the production of key biofuel ethanol, the ethanol serves as a key terminal electron acceptor in the absence of oxygen as cells accumulate NADH in the pyruvate steps above.

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_6O + 2\ CO_2$$
$$\text{Glucose} \rightarrow 2\text{ Ethanol} + 2\text{ Carbon Dioxide}$$

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[12] National Research Council (US) Chemical Sciences Roundtable 2001 *Carbon management: Implications for R&D in the chemical sciences and technology: A workshop report to the chemical sciences roundtable.* Washington DC: National Academies Press.
[13] Humbird D, *et al* 2011. "Process design and economics for biochemical conversion of lignocellulosic biomass to ethanol" Technical Report NREL/TP-5100-47764.
[14] Barnett JA 2003 "A history of research on yeasts 5: the fermentation pathway" *Yeast* 20:509-43.
[15] Shi and Tu 2015 "Acetyl-CoA and the regulation of metabolism: mechanisms and consequences" *Curr Op Cell Biol* 33:125-131.
[16] Lu *et al* 2019 "Constructing a synthetic pathway for acetylcoenzyme A from one-carbon through enzyme design" *Nat Comm* 10:1378.

The ability to prevent this loss of carbon as CO_2 would have a revolutionary effect on bioprocessing: the yield per unit input would increase by 50%. Because yeast also derive energy and reducing power from the glucose, additional reducing equivalents must be added to the system to conserve the carbon.

One notable recent example of a non-oxidative glycolysis (NOG) approach has shown great promise for conserving the carbon dioxide lost in the ordinary glycolysis reaction. This method, allowing for the stoichiometric splitting of 6-carbon (hexose), 5-carbon (pentose), and 3-carbon (triose) sugars without carbon loss has been designed, developed, and demonstrated *in silico*[17] and *in vivo* in *Escherichia coli*[18].

NOG pathways, or others not yet elucidated, could be engineered into industrially relevant strains such as *S. cerevisiae,* and those engineered strains could be optimized and evolved for desirable bioprocessing targets. Evidence from the literature suggests that *S. cerevisiae* may be amenable to modulation of and incorporation of non-native metabolic reactions to improve energy efficiency and reduce carbon loss for production of *n*-butanol[19] and isoprenoids[20]. In either case, large-scale, stable, semi-continuous NOG fermentation for stoichiometric sugar splitting with identified and demonstrated strategies for ensuring cyclic operation with real-time reducing equivalent accommodation represent an exciting option for increased CCE of renewable bioproducts.

Energy in the form of reducing equivalents limits the conservation of CO_2 in fermentation

A major limitation to improving the carbon efficiency of fermentation lies in the finite supply of reducing equivalents available for metabolic processes[21]. For example, it has been shown that *S. cerevisiae* cultures are limited in their ethanol production capacity by the availability of NAD(P)H[22,23]. There have been examples of microbes fixing carbon by taking in external

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[17] Bogorad IW *et al* 2013. "Synthetic non-oxidative glycolysis enables complete carbon conservation" *Nature* 502:693-697.
[18] Lin PP *et al* 2018 "Construction and evolution of an *E. coli* strain relying on nonoxidative glycolysis for sugar catabolism" *Proc Nat Acad Sci* 115:3538-3546.
[19] Schadeweg V and Boles E 2016 "n-Butanol production in *S. cerevisiae* is limited by the availability of coenzyme A and cytosolic acetyl-CoA" *Biotech Biofuel* 9:44.
[20] Meadows AL *et al* 2016 "Rewriting yeast central carbon metabolism for industrial isoprenoid production" *Nature* 537:694-697.
[21] Claassens NJ *et al* 2018 "Towards sustainable feedstocks: A guide to electron donors for microbial carbon fixation" *Curr Op Biotech* 50:195-205.
[22] Hou J *et al* 2010 "Metabolic impact of increased NADH availability in *S. cerevisiae*" *Appl Env Micr* 76:851-859.
[23] Henningsen BM *et al* 2015 "Increasing anaerobic acetate consumption and ethanol yields in *S. cerevisiae* with NADPH-specific alcohol dehydrogenase" *Appl Env Micr* 81:8101-17.

reducing equivalents[24] and making products of interest using energy from external sources[25], however, there has been limited effort focused on leveraging external reducing equivalents to avoid carbon loss in heterotrophic metabolism.

Heterotrophic organisms, like animals and many microbes, derive energy as reducing equivalents via feedstocks like glucose, but waste carbon in the process as CO_2. Autotrophic organisms, like plants and algae, take in CO_2 but require energy from light to enable the complex chemistry that builds up these feedstocks. Photosynthesis drives this process by building a pool of reducing equivalents across a membrane, essentially charging a battery that drives biosynthetic processes. Some chemoautotrophic bacteria have been described that can fix carbon dioxide by taking advantage of chemical imbalances in their environment[26]. Recently, it was reported that *E. coli* could be retooled to become autotrophic and use CO_2 as its sole carbon source[27]. Formate provides the critical reducing equivalents necessary for this carbon fixation. Similarly, an autotrophic route has been demonstrated in pharmaceutical workhorse *Pichia pastoris*[28], wherein CO_2 and methanol provide carbon and energy, respectively. This method takes advantage of that organism's native methanol-inducible metabolism.

While there have been examples of microbes fixing carbon by taking in external reducing equivalents[29] and making products of interest using energy from external sources[30], these have yet to be engineered into robust microbial platforms or systems of large-scale industrial relevance.

With additional reducing equivalents, it is possible to[31,32,33]:

- reduce or eliminate the amount of CO_2 produced by fermentation,
- uptake CO_2 as part of the fermentation process,
- increase total yields on a carbon feedstock basis by up to 50%, and
- substantially increase volumetric productivities beyond the state of art

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[24] Liu *et al* 2016 "Water splitting biosynthetic system with CO_2 reduction efficiencies exceeding photosynthesis" *Science* 352:1210-1213.
[25] Guo *et al* 2018 "Light-driven fine chemical production in yeast biohybrids" *Science* 362:813-816.
[26] Kelly DP and Wood AP 2006 "The Chemolithotrophic Prokaryotes" in The Prokaryotes. New York: Springer.
[27] Gleizer S *et al* 2019 "Conversion of *E. coli* to generate all biomass carbon from CO_2" *Cell* 179:1255-1263.
[28] Gassler T *et al* 2020 "The industrial yeast *Pichia pastoris* is converted from a heterotroph into an autotroph capable of growth on CO_2" *Nat Biotech* 38:210-216.
[29] Liu *et al* 2016 "Water splitting biosynthetic system with CO_2 reduction efficiencies exceeding photosynthesis" *Science* 352:1210-1213.
[30] Guo *et al* 2018 "Light-driven fine chemical production in yeast biohybrids" *Science* 362:813-816.
[31] Lin YH and Liu CG 2014. "Process design for very-high-gravity ethanol fermentation," *Energy Procedia* 61:2725-2728.
[32] Liu CG *et al* 2017. "Fermentation and Redox Potential," *Fermentation Processes*, Ch 2.
[33] Jones SW *et al* 2016, "CO_2 fixation by anaerobic non-photosynthetic mixotrophy for improved carbon conversion," *Nat Comm* 7:12800.

Delivery of reducing equivalents to biological systems is particularly challenging

The loss of carbon as CO_2 is a nearly unavoidable step, and it allows for a "pull" on the equilibrium of metabolism by Le Chatelier's principle. An additional challenge is that, unlike plants, which can harness light to drive these reactions, all available avenues for delivery of reducing equivalents to cellular systems require inputs of additional energy.

Heterologous delivery of reducing equivalents to these biological systems is challenging. The biologically relevant reducing equivalent cofactors (e.g. NAD(P)H, FAD(H_2), etc.), are expensive to synthesize and unstable in solution. While there are many potential candidate species that donate their electrons to biological cofactors like NAD(P)H, each option poses potential adoption challenges. Many are gases that are flammable and/or of low solubility, several are toxic to humans or the microbes doing the work, some require an engineered active transport into metabolic processes, and some are impractical because of low redox potential (Table 1)[34].

Table 1. Relevant properties for potential electron donors (adapted from Claassens NJ *et al* 2018)

Donor	Redox potential (mV)	Solubility	Cellular import	Microbial toxicity
Hydrogen (H_2)	-410	Low	Passive	Low
Carbon monoxide (CO)	-520	Low	Passive	Intermediate to high
Formate ($HCOO^-$)	-420	High	Passive	Intermediate to high
Methanol (CH_3OH)	-160 (to formic acid)	High	Passive / extracellular	Intermediate
Methane (CH_4)	+80 (to methanol)	Low	Passive	Low
Ammonia (NH_3)	+350	High	Passive / extracellular	Intermediate to high (NO_2^-)
Ferrous iron (Fe^{2+})	+770 (pH 2) -240 (pH 7)	Low to intermediate	Extracellular	Intermediate
Sulfur (S_0)	-210	Low	Extracellular	Low
Sulfide (S^{2-})	-270 (S^{2-} to S_0)	Low (S_0)	Passive / extracellular	High
Phosphite (HPO_3^{2-})	-650	High	Transport (ATP neutral)	Low
Cathodic electrons	--	--	Extracellular	Low

[34] Claassens NJ *et al* 2018 "Towards sustainable feedstocks: A guide to electron donors for microbial carbon fixation" *Curr Op Biotech* 50:195-205.

Any solution to the reducing equivalent delivery problem will need to address challenges at the interface between biological and non-biological systems: low solubility of gases[35,36], toxicity of a soluble mediator[37], and/or dimensional constraints in scaling surface chemistry[38].

In addition to the engineered autotrophy of *E. coli* and *P. pastoris*, there are organisms like *Clostridia*[39] and *Ralstonia*[40] that can perform some chemoautotrophic metabolism natively or with minimal engineering. However, these organisms are more recalcitrant to genetic manipulation, natively produce the bioplastic polyhydroxyalkanoate rather than a liquid fuel, and currently have low titers of desired fuel-like products[41,42]. These examples do not yet meet the goals of this program, as none were able to produce recoverable fuel or high volume low value biochemical product molecules at high titer, and all had slow growth and thus putative production rates; these examples are not yet relevant to large-scale biofuel or biochemical production.

ARPA-E is interested in solutions in which the reducing equivalent generation system is decoupled from its delivery to the bioconversion system. A potentially compelling use case of a decoupled system could be the use of biochemical reducing equivalents for electrical grid storage[43,44]. In fact, the ability to leverage grid power in such bioconversion systems is synonymous with the ability to leverage grid power in such bioconversion systems will be a critical piece of the bioeconomy of the future, and thus a stipulation of this Program will be that any proposed external energy carrier must be able to be regenerated electrochemically or produced electrocatalytically from H_2O, CO_2, or both.

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[35] Emerson DF and Stephanopolous G 2019 "Limitations in converting waste gases to fuels and chemicals" *Curr Op Biotech* 59:39-45.
[36] Liew FM *et al* 2016 "Gas Fermentation—A Flexible Platform for Commercial Scale Production of Low-Carbon-Fuels and Chemicals from Waste and Renewable Feedstocks" *Front Microbiol* 7: 694.
[37] Yishai O *et al* 2016 "The formate bio-economy" *Curr Op Chem Biol* 35:1-9.
[38] Liu *et al* 2016 "Water splitting biosynthetic system with CO_2 reduction efficiencies exceeding photosynthesis" *Science* 352:1210-1213.
[39] de Souza Pinto Lemgruber R *et al* 2019 "Systems-level engineering and characterisation of *C autoethanogenum* through heterologous production of poly-3-hydroxybutyrate (PHB)" *Metab Eng* 53:14-23.
[40] Müller J *et al* 2013 "Engineering of *R eutropha* H16 for autotrophic and heterotrophic production of methyl ketones" *Appl Env Microbiol* 79:4433-4439.
[41] Heffernan JK *et al* 2020 "Enhancing CO_2-valorization using *C autoethanogenum* for sustainable fuel and chemicals production" *bioRxiv* 2020.01.23.917666
[42] Grosseau *et al* 2014 "Isopropanol production with engineered *C necator* as bioproduction platform" *Appl Microbiol Biotechnol* 98:4277–4290.
[43] Grim RG *et al* 2020 "Transforming the carbon economy: challenges and opportunities in the convergence of low-cost electricity and reductive CO_2 utilization" *Energy Environ Sci* 13:472-494.
[44] Salimijazi F *et al* 2019 "Electrical energy storage with engineered biological systems" *J Biol Eng* 13:38.

Efficient delivery of reducing equivalents allows for carbon efficient fermentation

Beyond reducing or eliminating the CO_2 produced via fermentation, one additional goal of this Program is to support efforts exploring the potential to use CO_2 itself as an additional feedstock (or primary feedstock in gas fermentation submissions). Because the delivery of reducing equivalents is decoupled from the carbon source, processes capable of accommodating CO_2 could generate more products on a per-carbon basis than the sugar input to the system. With the addition of CO_2 and extraneous reducing equivalents, processes could reach yields *greater than 100%* on a sugar feedstock basis.

A similar concept has been proposed that uses a modified serine cycle to incorporate CO_2 and methanol into two carbon compounds[45], inspired in part through computationally designed carbon fixation pathways[46]. ARPA-E is also interested in pathways that could incorporate feedstocks of sugar, CO_2, and reducing equivalent donors to realize bioproduct synthesis that derives its carbon from *both* sugar and CO_2. This interest extends to gas fermentation systems as well, which are attractive due to inherent gas handling capacity which can make it easier to recycle and reuse CO_2 than sugar fermentation systems.

Available carbon-negative biomass feedstocks will be increased and improved by the agricultural tools and techniques resulting from other ARPA-E programs, including PETRO, TERRA, ROOTS, and SMARTFARM. The delivery of gaseous carbon and reducing equivalent feedstocks were improved by developments made under the ELECTROFUELS and REMOTE programs, and various projects from ARPA-E's OPEN solicitations. This program seeks to build on previous advances to realize more profitable and carbon efficient bioconversion platforms capable of servicing the growing demand for more sustainable technologies and pathways for a growing bioeconomy and burgeoning carbon markets.

Cell-free bioconversion and biocatalysis

Some of the biggest challenges in microbial bioprocessing involve the care and maintenance of the microbes themselves. The microbial biomass accumulation and maintenance is a sink of as much as 50% of the carbon and energy input[47], much of which could otherwise be embodied in the product of interest. Additionally, repeated fed-batch fermentation—the typical method for the generation of key products such as ethanol[48]—limits the production rate because of process downtime and the potential for contamination.

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[45] Yu and Liao 2018 "A modified serine cycle in *E coli* converts methanol and CO_2 to two-carbon compounds" *Nat Comm* 9:3992

[46] Bar-Even A *et al* 2010 "Design and analysis of synthetic carbon fixation pathways" *Proc Natl Acad Sci* 107, 8889–8894

[47] Häggström C *et al* 2014 "Integration of Ethanol Fermentation with Second Generation Biofuels Technologies" in *Biorefineries: Integrated Biochemical Processes for Liquid Biofuels* Elsevier p. 161-187.

[48] Seo HB *et al* 2009 "High-level production of ethanol during fed-batch ethanol fermentation with a controlled aeration rate and non-sterile glucose powder feeding of *S cerevisiae*" *Biotech Biopr Engr* 14:591.

A new approach which divorces key enzymes and metabolic pathways from living cells has the potential to transform the bioeconomy for more efficient, reproducible, and sustainable production[49]. By focusing only on the reactions that are part of the metabolic pathway from feedstock to product, several advantages can be realized, but significant challenges need to be overcome (Table 2). In particular, the advantages include more flexible and predictable production parameters, and far easier and economical product purification.

Two major approaches to generate such “cell-free” enzymatic systems are: (1) enzymes constituting the target metabolic pathway are expressed and purified separately, then combined in the reaction, and (2) enzymes are expressed together or in separate strains, and then the cells containing the enzymes are lysed in a single vessel for the reaction. Each approach has advantages and disadvantages: the first approach allows for greater control in the reaction, but costs would be higher as each enzyme is purified separately and cofactors need to be provided. The second approach takes advantage of the cofactors already present in the lysed cells, but these still need to be recharged in an undefined solution, and unwanted enzymes still present need to be removed. Hybrid approaches between the two are possible, e.g. purified enzymes or cofactors could be added to crude lysates.

Table 2. Potential advantages and challenges of cell-free biochemistry approach (adapted from Bowie *et al* 2020)

Potential advantages	Challenges
High yields and productivity: no other pathways to divert input biomass, higher enzyme concentrations, simpler product purification due to lack of membranes and fewer metabolites	**Enzyme production costs:** there are added costs required for enzyme preparation not needed in cell-based methods
Facile optimization: precise control over all system components including enzymes, cofactors, intermediates, kinetics, and purification	**Enzyme stability:** not all enzymes can be made sufficiently stable to function long term outside the cellular environment
Rapid design–build–test cycles: simplified problem diagnosis and implementation of fixes. More precise pathway optimization	**Enzyme inhibition, inactivation, or regulation by intermediates or products:** the absence of compartmentalization or repair pathways can make enzyme systems more prone to problematic metabolites
Great pathway design flexibility: do not need to feed processes to sustain living cells; Simplified computational modeling	**Cofactor costs:** there are additional costs for obtaining cofactors that would otherwise be naturally present in cell-based systems [ATP, NAD(P)H, etc.]
No need to account for cell toxicity that might inhibit production; Flexible reaction conditions: option to use diverse, even nonphysiological conditions	

[49] Bowie JU *et al* 2020 “Synthetic biochemistry: the bioinspired cell-free approach to commodity chemical production.” *Trends in Biotechnology* 38(7):766-768.

However, despite the potential for very high titers (e.g. 15 g/L sabinene[50], a monoterpene difficult to produce with whole cells), there has yet to be any commercial-scale demonstration of cell-free systems for small molecule bioproducts. The production and stability of the enzymes and cofactors remains a great challenge, as well as separating and regenerating the key energy-carrying cofactors from products of interest. Projects supported under previous ARPA-E program ELECTROFUELS addressed some of these challenges, but significant progress in the field has been made since the end of that program. Though there is potential for biofuel and bioproducts markets, significant parameters need to be de-risked before the technology can approach the scale of the existing fermentation industry.

For cell-free catalysis to become a viable and industrially relevant means of low-carbon and carbon-negative biofuels and bioproducts, some technical hurdles must be de-risked, including the economical generation of energy-bearing cofactors that provide reducing equivalents to drive the reactions forward, and long term stability of enzymes through immobilization and/or predictive mutagenesis

In summary, based on the opportunities specified above, ARPA-E seeks submissions to establish fermentation strains and/or bioconversion systems and platforms capable of:

- **(1) Accommodating necessary reducing equivalents in real-time**
- **(2) Enabling stoichiometric sugar splitting chemistries (system basis), enhanced carbon oxide utilization via gas fermentation, or cell-free biocatalytic biosynthesis without carbon loss, and**
- **(3) Generating fuels, fuel-relevant intermediates, or impactful chemicals *at or above* titers and production rates prescribed by a corresponding system-level and commercial scale techno-economic analysis (TEA) , which**
  - **a. Contain more embodied energy (specific energy (MJ/kg)) in the product than in the carbon feedstocks**
  - **b. Substantially decrease lifecycle GHG emissions for such products (as assessed by a corresponding life cycle analysis (LCA)), and**
  - **c. Are economically attractive at commercial scales (as assessed by a corresponding TEA).**

E. TECHNICAL CATEGORIES OF INTEREST

Previous ARPA-E and Department of Energy-funded research efforts under the ELECTROFUELS, PETRO, REMOTE, TERRA, ROOTS, SMARTFARM and OPEN programs focusing on advancing the bioeconomy have sought to increase efficiency and yields largely by targeting increased supply of carbonaceous feedstocks, innovative carbon delivery methods to fermentation systems, or

[50] Korman *et al* 2017 "A synthetic biochemistry platform for cell free production of monoterpenes from glucose." *Nature Communications* 8:15526.

bioconversion parameter control optimization. Here we focus on the carbon efficiency of the *fermentation or bioconversion process itself* by prescribing the accommodation of external reducing power to achieve greater carbon efficiency. That is, with the same quantity of sugar or primary carbon oxide feedstock, proposed systems supported under this Program will be expected to develop technologies to increase the yield of bioproduct on a carbon feedstock basis, while reducing or eliminating the CO_2 that is typically evolved.

Successful strategies will involve the economical delivery of external reducing equivalents to the microbial or cell-free platform. If carbon fixation or recycling systems are employed, this could also allow for CO_2 to become an additional feedstock, and more carbon would be embodied in the residual biomass and bioproducts than was contained in the primary biomass or primary carbon oxide feedstock.

Minimizing capital expenses (CAPEX) and operational expenses (OPEX) will be essential to allow economically competitive processes to be realized when combined with the expected yield and productivity increases that these novel platforms will enable. High-level technoeconomic (TEA) and life cycle analyses (LCA) considerations should be discussed by Applicants as part of the submission, with the expectation that all selected awardees perform continual improvements to the model and more detailed analyses as the processes become better established and closer to commercialization. These analyses should be performed to show feasibility using future projections and industrially relevant scales, and it is understood that various proposed approaches will inherently have different time horizons for transition to projected commercial markets as a function of the technical readiness of proposed approaches.

ARPA-E is interested in novel carbon optimized bioconversion pathway concepts. Concepts will not require proposed pathways and systems to conform to established biorefining norms, and thus will promote pathways with novel combinations of feedstocks, conversion platforms, and products. All proposed conversion platforms will be required to meet the global program metrics along with ambitious pathway-specific metrics depending on the use of particular strategies (discussed below) to achieve substantial advancement, and if possible, commercial viability within 3 years under assumed conditions for feedstock price, RE/electricity price, and effective carbon price. Successful projects will establish biotechnology platforms and biorelevant tools for a broad range of carbon optimized biosynthetic pathways. They will also demonstrate novel examples for fuel and fuel relevant intermediate synthesis from both biomass and waste carbon oxides.

ARPA-E has identified several major areas of technical interest that could be employed to engineer *carbon-optimized* systems that accommodate external energy to eliminate waste of carbon as CO_2 during bioconversion. Some approaches address whole-cell fermentation strategies, but technical areas of interest also include the targeted design of novel cell-free bioconversion and biocatalytic platforms or any combination of these strategies. Strategies of interest include, but are not limited to:

- ***Carbon optimized fermentation strain engineering***
  ARPA-E seeks submissions for the engineering of industrially relevant microorganisms that economically incorporate external reducing equivalents, increase yields, produce scale relevant bioproducts, and do not emit CO_2 as a byproduct of the fermentation. Since engineered strains produced in this category are expected to work with minimal modification to existing fermentation infrastructure, ARPA-E anticipates submissions with an emphasis on genetic manipulation of relevant microbes. For example, applications for engineering carbon-optimized metabolism in *Saccharomyces cerevisiae* or *Zymomonas mobilis* would take advantage of the large fermentation production capacity in the United States. Applications for engineering any other strain that can take advantage of the resources of the Agile BioFoundry[51] or similar consortia would also be desirable.

- ***Engineered systems or microbial consortia that utilize, recapture and/or recycle gaseous CO_2 into product***
  ARPA-E seeks applications for the engineering of integrated systems for carbon optimized bioconversion that either facilitate multi-trophic carbon flux and utilization i) among *multiple distinguished microbial cultures*, or ii) by *defined microbial cocultures*. Substantial effort is expected to allow such fermentation approaches to consistently accommodate external reducing power to optimize for carbon efficiency while achieving relevant scale for industrial use. Proposed research should focus on engineering systems that improve the stability of the microbial inoculum(s) over time, eliminate CO_2 emitted, most efficiently use and recycle reducing equivalents, and can demonstrate production economically on larger scales.

- ***Delivery of both primary carbon oxides feedstocks and reducing equivalents in the gas phase* (carbon utilization)**
  ARPA-E seeks applications proposing to engineer carbon optimized integrated systems using *gas fermentation*. The focus will be on engineering systems that maximize product yields, improve the mass transfer of carbon and hydrogen (or other reduced gases) from the gas to the liquid phases, eliminate CO_2 emitted (on a system basis), most efficiently use and recycle reducing equivalents, and can demonstrate production conditions that allow the process to operate economically on larger scales and with gas feedstock compositions that include increasing amounts of CO_2.

- ***Cell-free enzyme catalyzed bioconversion platforms***
  ARPA-E seeks applications for the engineering of integrated systems using *cell-free bioconversion platforms*. Submissions should focus on engineering systems that maximize yield, titer, and productivity of proposed fuel relevant or large volume bioproducts, increase the long-term stability of a production system, limit CO_2 emitted (on a system basis), maximize carbon flux to products, most efficiently use and recycle

[51] Agile BioFoundry: https://agilebiofoundry.org/

reducing equivalents, and demonstrate conditions that could allow production to proceed economically on larger scales.

- ***<u>Compelling strategies for carbon optimized bioconversion systems not otherwise described</u>***
  In addition to the potential strategies outlined above, ARPA-E seeks applications for incorporating carbonaceous feedstocks and external reducing equivalents to industrial bioproducts through compelling systems not specifically enumerated above. The focus will be on engineering systems that maximize yields (flux of feedstock carbon to products) of ethanol and other biofuel products, avoid CO_2 emitted (on a system basis), most efficiently use and recycle reducing equivalents, and can demonstrate production economically on larger scales.

F. TECHNICAL PERFORMANCE TARGETS

Because creative submissions for carbon-optimized bioconversion systems are encouraged, clearly delineated categories will not be defined. Instead overall "carbon-optimized" systems will be defined by global metrics, and additional requirements are specified for particular strategies, feedstocks, and products in order to drive ambitious outcomes. However, all outlined technical metrics beyond the specified mlobal metrics are flexible and can be uniquely defined and justified for proposed approaches using a system-level technoeconomic analysis (TEA).

ARPA-E requests submissions for engineered bioconversion platforms capable of maximizing primary carbon product yields by incorporating additional reducing equivalents and avoiding CO_2 evolution. Projects should be described in terms of:

- Modalities for delivering reducing equivalents from a source other than the primary feedstock (gas or soluble delivery)
- Estimated improvements in monthly yields over established state of the art
- Potential for competitiveness against state of the art when extrapolated to scale
- Life-cycle carbon intensity

Novel bioprocesses be considered under this FOA must meet the following specifications:

- Specific Energy yield ratio $U_{product}/U_{C\ feedstock}>1$. That is, the energy embodied in the bioproducts is greater than the energy embodied in the carbon feedstock. Further derivation of this ratio is provided in Appendix 1 to Section I of the FOA.
- Demonstrated incorporation of external reducing equivalents to allow for a boost in stoichiometric yield of products using the same mass of carbon feedstocks.
- Average productivity greater than 2 grams product per liter per hour over an entire batch process. This approaches current state-of-art ethanol production, but while incorporating this new carbon-optimized metabolism to improve overall yield.

Products, feedstocks, and other technical components of specific interest are listed in Appendix 2 to Section I of the FOA.

- Titer, on a volume-to-volume basis, greater than or equal to the same process that does not employ carbon-optimized bioconversion.

Bioconversion Improvements / Global Metrics (any proposed strategy or combination of strategies):

Key output yield: specific energy ratio[52]	$\frac{U_{product}}{U_{C\ feedstock}} > 1$
Avoided CO_2 evolution (system basis)	**100%**
External reducing equivalent accommodation	**Biologically relevant external reducing equivalent and/or energy carrier mechanism must be able to be regenerated electrochemically or produced electrocatalytically from H_2O, CO_2, or both**

Beyond the global metrics, which apply to all proposed systems, additional metrics will apply depending on which strategy or strategies are employed to engineer the *carbon optimized* capabilities. Additionally, there will be different allowances for, and metrics applied to, various proposed feedstocks and products. However, if outlined metrics should not apply, or if they constrain possibilities for proposed strategies to achieve the global metrics, alternate performance targets can be proposed and justified with a system-level TEA.

Carbon optimized fermentation for high-impact bioproducts synthesis

Production rate under carbon conserving metabolism[53]	**53 $kJ_{product}\ L_{broth}^{-1}\ h^{-1}$**
Target titer	**40 $g_{C\ in\ product}\ L^{-1}$**
Reducing equivalent source	**H_2 (g) or another source that can be justified by TEA**
Example strains	***S. cerevisiae, Z. mobilis*, or any other Agile BioFoundry strain or consortium**

[52] This ratio is derived via example in Appendix 1 to Section I of the FOA.
[53] This is the energy equivalent of 2.0 $g_{ethanol}\ L^{-1}h^{-1}$ but performers are encouraged to pursue products with a higher energy density.

Mixotrophic cultures and/or reactor systems

Production rate under recapture of CO_2 from gas	**40 $kJ_{product}$ L_{broth}^{-1} h^{-1}**
Strain engineering	**Demonstrate strain, pathway, and process engineering that simultaneously optimizes system kinetics and cellular metabolism**

Fermentation using gas phase:

C feedstock	**Delivery by gas: CO and CO_2, or CO_2**
Reducing equivalent feedstock	**H_2 delivered by gas**
Strain engineering	**Demonstrate strain, pathway, and process engineering approaches to optimize system kinetics and cellular metabolism**
Product exception	**Non-fuel, fuel relevant intermediate, or relevant chemical products must be produced for less than the cost of cellulosic sugar on a normalized carbon mass basis**
Production rate while running carbon-conserving or equivalent metabolism[54]	**40 $kJ_{product}$ L_{broth}^{-1} h^{-1}**

Cell-free enzyme catalyzed bioconversion platforms

Key output yield	**$g_{C\ product}\ g^{-1}_{C\ feedstock}$**
Key output yield: specific energy ratio	**$\frac{U_{product}}{U_{C\ feedstock}} > 1$**
Production rate while running carbon-conserving or equivalent metabolism	**40 $kJ_{product}$ L_{broth}^{-1} h^{-1}**

[54] This is the energy equivalent of 1.5 $g_{ethanol}$ h^{-1} but performers are encouraged to pursue products with a higher energy density.

Enzyme concentration	**Must be minimized for concurrent justification with TEA.**
Continuous, stable operation	**30 days**
Cofactor replenishment frequency	**< 10 % per week (mass basis). Greater replenishment frequencies must be justified with TEA.**
Feedstock exception	**In addition to biomass derived sugars, CO and CO_2, cell-free systems can propose platforms that use ethanol and/or carboxylic acids as feedstocks**

Compelling carbon optimized bioconversion systems not otherwise described

In addition to the categories above, ARPA-E seeks applications for incorporating carbonaceous feedstocks and external reducing equivalents to industrial bioproducts through compelling systems not specifically enumerated above that will still achieve the global metrics. The focus will be on engineering systems that maximize yields (flux of feedstock carbon to products) of ethanol and other biofuel products, avoid CO_2 emitted, most efficiently use and recycle reducing equivalents, and can demonstrate production economically on larger scales.

Each applicant must provide the information requested in the following Technical Performance Targets Table in their submission. The Technical Performance Targets Table provided in the Concept Paper Template, will not count as part of the four page limit of the Concept Paper and must not exceed 2 pages.

Technical Performance Targets Table

Item	Description
Feedstock	Define allowable carbonaceous feedstock(s) and the expected price range (in $ per kg). Projected price ranges are acceptable; ranges should cover the 90^{th} percentile of feedstock prices.
Reducing Equivalent	Define the reducing equivalent source(s) to be used and its role in the proposed stoichiometry.
Chemistry	Provide a balanced stoichiometric equation or set of equations accounting for all carbon feedstocks, reducing equivalent sources, and products.

Mass Balance	Use the above stoichiometry to predict mass balances for the proposed reactions. Specify mass flows in terms of the constituent sugars, gases, etc. match with the stoichiometry proposed[55]
Specific Energy Ratio	Using the derivation provided in the FOA, calculate $U_{product}/U_{C\ feedstock}$
Product	**Outputs:** List major outputs of the proposed process and the anticipated ratio. If a large product suite is anticipated, select the subset of products which would collectively contribute the majority (i.e. >80%) of revenue on the basis of product volume and/or value.
	Cost: Estimate the cost of production ($/kg) for each of the defined outputs and the capacity assumed to reach that cost.
	Price: Estimate the price ($/kg) and market size (MMT) for each of the defined outputs. Projected market sizes are acceptable, but must be sufficiently justified in terms of anticipated demand at the estimated $/kg price.
	Impact: As quantitatively as possible, estimate and justify the anticipated energy and/or emissions impact for each of the defined outputs.

G. TECHNOECONOMIC ANALYSIS REQUIREMENTS

Technoeconomic analyses (TEA) will be used to assess the technical and financial viability of the technology being proposed. Applicants will be required to submit requested feedstock, product, process, and mass and energy balance information to inform the development and continual update of system and technology specific TEAs as applicable for particular system designs. Submissions without the appropriate requested technical and economic data requested may be excluded from review under this FOA. In addition, certain provided information or data about proposed systems may be used as a basis for review and discussion during an initial verification post award, and may be used as the project's baseline.

Submissions should include details such as process information and data to support the technology readiness level of the overall process, the unit operations within the process, and the original application. Proposed technical metrics and milestones should be based on preliminary data and represent a meaningful baseline and set of targets.

[55] Note that "dry ton" is not useful for consideration here because at this stage of technology development the proposed bioconversion inputs need to be characterized by their constituent sugars, gases, etc. to tell if the stoichiometry proposed works in practice.

APPENDIX 1: Derivation of Specific Energy Ratio

For complete the carbon-optimized bioconversion processes desired in this program, the specific energy (U) of the desired salable products (sum) must be greater than the specific energy in the primary carbon feedstock. Natural heterotrophic systems use some of the carbon in the feedstock as energy to drive reactions, but the ECOSynBio program requires all feedstock carbon to be converted to product. This is only possible if the bioconversion can accommodate energy from a source other than the primary carbon feedstock, i.e. from an external reducing equivalent source for the proposed bioconversion chemistry. This specific energy ratio calculation is required to show that the proposed biochemistry accommodates external energy inputs into its products. This unique energy accommodation can be assessed by calculating the ratio of the specific energy of the salable products and the primary carbon feedstocks based on the stoichiometric masses of those products and feedstocks.

$$\frac{U_{product}}{U_{C\ feedstock}} = \frac{LHV_{product} * mass_{product}}{LHV_{C\ feedstock} * mass_{C\ feedstock}} > 1$$

It is helpful to examine an example comparing non-oxidative glycosylation for carbon-optimized generation of ethanol. Traditional fermentation has this stoichiometry:

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_6O + 2\ CO_2$$

Glucose → 2 Ethanol + 2 Carbon Dioxide

The specific useful energy (low heat value) of glucose is 15.50 MJ/kg and of ethanol is 26.95 MJ/kg (CRC). It follows from the stoichiometry that for 1 kg of ethanol, 1.96 kg of glucose is needed. No additional external reducing equivalents are provided. Thus, assuming perfect conversion of feedstock to product, almost 10% of the energy is lost in the process. Additionally, a third of the carbon is evolved as CO_2:

$$\frac{U_{ethanol}}{U_{glucose}} = \frac{26.95\ \text{MJ/kg} * 1\ \text{kg}}{15.50\ \text{MJ/kg} * 1.96\ \text{kg}} = \frac{26.95\ \text{MJ}}{30.31\ \text{MJ}} = 0.889 < 1$$

However, if we extend Lin et al 2018's example of non-oxidative glycosylation in *Escherichia coli*[56]to the generation of ethanol, the addition of external reducing equivalents as H_2 acts as a stoichiometry extender:

$$C_6H_{12}O_6 + H_2 \rightarrow 3\ C_2H_6O + 3\ H_2O$$

Glucose + Hydrogen → 3 Ethanol + 3 Water

[56] Lin PP *et al* 2018 "Construction and evolution of an *E. coli* strain relying on nonoxidative glycolysis for sugar catabolism" *Proc Nat Acad Sci* 115:3538-3546.

The specific energies of glucose and ethanol are the same, but the addition of H_2 allows for more ethanol to be produced per unit mass of glucose. It follows from the above stoichiometry that for 1 kg of ethanol, 1.30 kg of glucose and 0.0868 kg of H_2 are needed. In this case we see a notable boost in the amount of energy recoverable as fuel in the product.

$$\frac{U_{ethanol}}{U_{glucose}} = \frac{\text{26.95 MJ/kg * 1 kg}}{\text{15.50 MJ/kg * 1.30 kg}} = \frac{26.95\ \text{MJ}}{20.15\ \text{MJ}} = 1.337 > 1$$

The resources needed to refine raw corn or starch into feed glucose, or purify the ethanol from the mash, remain the same. Simply the energy yield per unit carbon feedstock is improved by about 50%. ARPA-E seeks applications that realize this stoichiometry-extending capability, with economical addition of external reducing equivalents.

Energy-relevant alternatives to the technical metrics outlined herein may be justified with techno-economic analysis (TEA), life-cycle analysis (LCA), and scalability analyses showing the capacity for the proposed system (including proposed feedstocks, conversion platform, and products) to produce fuels, fuel relevant intermediates, or other commodity chemicals at relevant scales.

APPENDIX 2: Technical components specifically of interest

Encouraged feedstocks	**Biomass-derived sugars (cellulose or starch), CO and CO_2, CO_2, or any combinations of such sugars and carbon oxides.**
Prohibited feedstocks	**CO as the sole carbon source, CH_4.**
Excepted feedstock	**Ethanol and/or carboxylic acids are allowable feedstocks for proposed cell-free systems assessed to produce encouraged products economically accounting for upstream costs and GHGs of the alternate feedstocks.**
Encouraged products	**Fuel or fuel-relevant intermediate; any target chemical or material of sufficient volume or potential volume to confer substantial GHG mitigation via a drop-in or functional replacement. Products with substantial GHG mitigation potential as assessed by sound life-cycle assessments are encouraged.**
Prohibited primary products	**Reduced 1-C products such as methane. High value products, e.g. fragrances, flavors, pharmaceuticals. Products that do not have a large potential for GHG reduction across the economy.**
Excepted products	**Ethanol is an allowable product for cell-free systems and gas fermentation systems. Ethanol is an allowable as a product from biomass derived sugar fermentation systems if cost parity to first generation corn ethanol production can be achieved.**
Reducing equivalent feedstocks	**Allowable reducing equivalent feedstocks must be able to be regenerated electrochemically or produced electrocatalytically from H_2O, CO_2, or both.**
Example strains for genetic engineering[57]	***Acinetobacter baylyi* *Aspergillus niger* *Aspergillus pseudoterreus* *Bacillus coagulans* *Clostridum autoethanogenum***

[57] Example strains have been aligned with strains included in the U.S. Department of Energy, Bioenegy Technologies Office's (BETO) Agile BioFoundry

	Clostridium carboxidivorans ***Clostridium ljungdahlii*** ***Clostridium tyrobutyricum*** ***Corynebacterium glutamicum*** ***Cupriavidus necator*** ***Pichia kudriavzevii*** ***Pichia pastoris*** ***Pseudomonas putida*** ***Rhodosporidium toruloides*** ***Saccharomyces cerevisiae*** ***Yarrowia lipolytica*** ***Zymomonus mobilis***

II. AWARD INFORMATION

A. AWARD OVERVIEW

ARPA-E expects to make approximately $25 million available for new awards, to be shared between FOAs DE-FOA-0002387 and DE-FOA-0002388, subject to the availability of appropriated funds. ARPA-E anticipates making approximately 8-12 awards under FOAs DE-FOA-0002387 and DE-FOA-0002388. ARPA-E may, at its discretion, issue one, multiple, or no awards.

ARPA-E will accept only new applications under this FOA. Applicants may not seek renewal or supplementation of their existing awards through this FOA.

ARPA-E plans to fully fund negotiated budgets at the time of award.

Applicants must apply for a Combined Phase I/II/IIS Award. Combined Phase I/II/IIS Awards are intended to develop transformational technologies with disruptive commercial potential. Such commercial potential may be evidenced by (1) the likelihood of follow-on funding by private or non-SBIR/STTR sources if the project is successful, or (2) the Small Business Concern's record of successfully commercializing technologies developed under prior SBIR/STTR awards. Phase IIS awards are a "sequential" (i.e., additional) Phase II award, intended to allow the continued development of promising energy technologies. Combined Phase I/II/IIS awards may be funded up to $3,677,642. Funding amounts will be consistent with the Phase I and Phase II limits posted on the SBA's website.[58]

ARPA-E reserves the right to select all or part of a proposed project (i.e. only Phase I, or only Phase I and Phase II). In the event that ARPA-E selects Phase I only or Phase I/II only, then the maximum award amount for a Phase I award is $256,580 and the maximum amount for a Phase I/II award is $1, 967,111.

The period of performance for funding agreements may not exceed 36 months for a Combined Phase I/II/IIS Award. ARPA-E expects the start date for funding agreements to be July 2021, or as negotiated.

B. RENEWAL AWARDS

At ARPA-E's sole discretion, awards resulting from this FOA may be renewed by adding one or more budget periods, extending the period of performance of the initial award, or issuing a new award. Renewal funding is contingent on: (1) availability of funds appropriated by Congress for

[58] For current SBIR Phase I and Phase II funding amounts, see https://www.sbir.gov/about/about-sbir. For current STTR Phase I and Phase II funding amounts, see https://www.sbir.gov/about/about-sttr. Phase IIS funding amounts are equal to Phase II funding amounts for both SBIR and STTR awards.

the purpose of this program; (2) substantial progress towards meeting the objectives of the approved application; (3) submittal of required reports; (4) compliance with the terms and conditions of the award; (5) ARPA-E approval of a renewal application; and (6) other factors identified by the Agency at the time it solicits a renewal application.

C. ARPA-E FUNDING AGREEMENTS

Through cooperative agreements, other transactions, and similar agreements, ARPA-E provides financial and other support to projects that have the potential to realize ARPA-E's statutory mission. ARPA-E does not use such agreements to acquire property or services for the direct benefit or use of the U.S. Government.

Congress directed ARPA-E to "establish and monitor project milestones, initiate research projects quickly, and just as quickly terminate or restructure projects if such milestones are not achieved."[59] Accordingly, ARPA-E has substantial involvement in the direction of every Cooperative Agreement, as described in Section II.C below.

Cooperative Agreements involve the provision of financial or other support to accomplish a public purpose of support or stimulation authorized by Federal statute. Under Cooperative Agreements, the Government and Prime Recipients share responsibility for the direction of projects.

Phase I will be made as a fixed-amount award. Phase II and Phase IIS of Combined Phase I/II/IIS awards will be made on a cost-reimbursement basis.

ARPA-E encourages Prime Recipients to review the Model Cooperative Agreement, which is available at https://arpa-e.energy.gov/?q=site-page/funding-agreements.

D. STATEMENT OF SUBSTANTIAL INVOLVEMENT

ARPA-E is substantially involved in the direction of projects from inception to completion. For the purposes of an ARPA-E project, substantial involvement means:

- Project Teams must adhere to ARPA-E's agency-specific and programmatic requirements.
- ARPA-E may intervene at any time in the conduct or performance of work under an award.
- ARPA-E does not limit its involvement to the administrative requirements of an award. Instead, ARPA-E has substantial involvement in the direction and redirection of the technical aspects of the project as a whole.
- ARPA-E may, at its sole discretion, modify or terminate projects that fail to achieve

[59] U.S. Congress, Conference Report to accompany the 21st Century Competitiveness Act of 2007, H. Rpt. 110-289 at 171-172 (Aug. 1, 2007).

predetermined Go/No Go decision points or technical milestones and deliverables.

- During award negotiations, ARPA-E Program Directors and Prime Recipients mutually establish an aggressive schedule of quantitative milestones and deliverables that must be met every quarter. In addition, ARPA-E will negotiate and establish "Go/No-Go" milestones for each project. If the Prime Recipient fails to achieve any of the "Go/No-Go" milestones or technical milestones and deliverables as determined by the ARPA-E Contracting Officer, ARPA-E may – at its discretion - renegotiate the statement of project objectives or schedule of technical milestones and deliverables for the project. In the alternative, ARPA-E may suspend or terminate the award in accordance with 2 C.F.R. §§ 200.338 and 200.339.
- ARPA-E may provide guidance and/or assistance to the Prime Recipient to accelerate the commercial deployment of ARPA-E-funded technologies. Guidance and assistance provided by ARPA-E may include coordination with other Government agencies and nonprofits[60] to provide mentoring and networking opportunities for Prime Recipients. ARPA-E may also organize and sponsor events to educate Prime Recipients about key barriers to the deployment of their ARPA-E-funded technologies. In addition, ARPA-E may establish collaborations with private and public entities to provide continued support for the development and deployment of ARPA-E-funded technologies.

[60] The term "nonprofit organization" or "nonprofit" is defined in Section IX.

III. ELIGIBILITY INFORMATION

A. ELIGIBLE APPLICANTS

1. SBIR ELIGIBILITY

SBA rules and guidelines govern eligibility to apply to this FOA. For information on program eligibility, please refer to SBA's "Guide to SBIR/ STTR Program Eligibility" available at http://sbir.gov/sites/default/files/elig_size_compliance_guide.pdf.

A Small Business Concern[61] may apply as a Standalone Applicant[62] or as the lead organization for a Project Team.[63] If applying as the lead organization, the Small Business Concern must perform at least 66.7% of the work in Phase I and at least 50% of the work in Phase II and Phase IIS, as measured by the Total Project Cost.[64]

For information on eligibility as a Small Business Concern, please refer to SBA's website (https://www.sba.gov/content/am-i-small-business-concern).

2. STTR ELIGIBILITY

SBA rules and guidelines govern eligibility to apply to this FOA. For information on program eligibility, please refer to SBA's "Guide to SBIR/ STTR Program Eligibility" available at http://sbir.gov/sites/default/files/elig_size_compliance_guide.pdf.

Only a Small Business Concern may apply as the lead organization for a Project Team. The Small Business Concern must perform at least 40% of the work in Phase I, Phase II, and/or Phase IIS, as measured by the Total Project Cost. A single Research Institution must perform at least 30% of the work in Phase I, Phase II, and/or Phase IIS, as measured by the Total Project

[61] A Small Business Concern is a for-profit entity that: (1) maintains a place of business located in the United States; (2) operates primarily within the United States or makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor; (3) is an individual proprietorship, partnership, corporation, limited liability company, joint venture, association, trust, or cooperative; and (4) meets the size eligibility requirements set forth in 13 C.F.R. § 121.702. Where the entity is formed as a joint venture, there can be no more than 49% participation by foreign business entities in the joint venture.

[62] A "Standalone Applicant" is an Applicant that applies for funding on its own, not as part of a Project Team.

[63] The term "Project Team" is used to mean any entity with multiple players working collaboratively and could encompass anything from an existing organization to an ad hoc teaming arrangement. A Project Team consists of the Prime Recipient, Subrecipients, and others performing any of the research and development work under an ARPA-E funding agreement, whether or not costs of performing the research and development work are being reimbursed under any agreement.

[64] The Total Project Cost is the sum of the Prime Recipient share and the Federal Government share of total allowable costs. The Federal Government share generally includes costs incurred by GOGOs, FFRDCs, and GOCOs.

Cost. Please refer to Section III.B.1 of the FOA for guidance on Research Institutions' participation in STTR projects.

For information on eligibility as a Small Business Concern, please refer to SBA's website (https://www.sba.gov/content/am-i-small-business-concern).

3. JOINT SBIR AND STTR ELIGIBILITY

An Applicant that meets both the SBIR and STTR eligibility criteria above may request both SBIR and STTR funding if:

- The Small Business Concern is partnered with a Research Institution;
- The Small Business Concern performs at least 66.7% of the work in Phase I and at least 50% of the work in Phase II and/or Phase IIS (as applicable), as measured by the Total Project Cost;
- The partnering Research Institution performs 30-33.3% of the work in Phase I and 30-50% of the work in Phase II and/or Phase IIS (as applicable), as measured by the Total Project Cost; and
- The Principal Investigator (PI) is employed by the Small Business Concern. If the PI is employed by the Research Institution, submissions will be considered only under the STTR program.

B. ELIGIBLE SUBRECIPIENTS

1. RESEARCH INSTITUTIONS

A Research Institution[65] may apply only as a member of a Project Team (i.e., as a Subrecipient to a Small Business Concern). In STTR projects, a single Research Institution must perform at least 30%, but no more than 60%, of the work under the award in Phase I, Phase II, and/or Phase IIS (as applicable), as measured by the Total Project Cost.

2. OTHER PROJECT TEAM MEMBERS

The following entities are eligible to apply for SBIR/STTR funding as a member of a Project Team (i.e., as a Subrecipient to a Small Business Concern):

- For-profit entities, including Small Business Concerns

[65] Research Institutions include FFRDCs, nonprofit educational institutions, and other nonprofit research organizations owned and operated exclusively for scientific purposes. Eligible Research Institutions must maintain a place of business in the United States, operate primarily in the United States, or make a significant contribution to the U.S. economy through the payment of taxes or use of American products, materials, or labor.

- Nonprofits other than Research Institutions[66]
- Government-Owned, Government Operated laboratories (GOGOs)
- State, local, and tribal government entities
- Foreign entities[67]

In SBIR projects, Project Team members other than the lead organization, including but not limited to Research Institutions, may collectively perform no more than 33.3% of the work under the award in Phase I and no more than 50% of the work under the award in Phase II and/or Phase IIS. This includes efforts performed by Research Institutions.

In STTR projects, Project Team members (other than the lead organization and the partnering Research Institution) may collectively perform no more than 30% of work under the award in Phase I, Phase II, and/or Phase IIS.

C. ELIGIBLE PRINCIPAL INVESTIGATORS

1. SBIR

For the duration of the award, the PI for the proposed project (or, if multiple PIs, at least one PI) must be employed by, and perform more than 50% of his or her work for, the Prime Recipient. The Contracting Officer may waive this requirement or approve the substitution of the PI after consultation with the ARPA-E SBIR/STTR Program Director.

For projects with multiple PIs, at least one PI must meet the primary employment requirement. That PI will serve as the contact PI for the Project Team.

2. STTR

For the duration of the award, the PI for the proposed project (or, if multiple PIs, at least one PI) must be employed by, and perform more than 50% his or her work for, the Prime Recipient or the partnering Research Institution. The Contracting Officer may waive this requirement or approve the substitution of the PI after consultation with the ARPA-E SBIR/STTR Program Director.

For projects with multiple PIs, at least one PI must meet the primary employment requirement. That PI will serve as the contact PI for the Project Team.

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[66]Nonprofit organizations described in section 501(c)(4) of the Internal Revenue Code of 1986 that engaged in lobbying activities after December 31, 1995 are not eligible to apply for funding as a Subrecipient.
[67] All work by foreign entities must be performed by subsidiaries or affiliates incorporated in the United States (see Section IV.G.6 of the FOA). However, the Applicant may request a waiver of this requirement in the Business Assurances & Disclosures Form submitted with the Full Application.

D. Eligibility of Prior SBIR and STTR Awardees: SBA Benchmarks on Progress Towards Commercialization

Applicants awarded multiple prior SBIR or STTR awards must meet DOE's benchmark requirements for progress towards commercialization before ARPA-E may issue a new Phase I award. For purposes of this requirement, Applicants are assessed using their prior Phase I and Phase II SBIR and STTR awards across all SBIR agencies. If an awardee fails to meet either of the benchmarks, that awardee is not eligible for an SBIR or STTR Phase I award and any Phase II award for a period of one year from the time of the determination.

ARPA-E applies two benchmark rates addressing an Applicant's progress towards commercialization: (1) the DOE Phase II Transition Rate Benchmark and (2) the SBA Commercialization Rate Benchmark:

- The DOE Phase II Transition Rate Benchmark sets the minimum required number of Phase II awards the Applicant must have received for a given number of Phase I awards received during the specified period. **This Transition Rate Benchmark applies only to Phase I Applicants that have received more than 20 Phase I awards during the last five (5) year period, excluding the most recently completed fiscal year**. DOE's Phase II Transition Rate Benchmark requires that 25% of all Phase I awards received over the past five years transition to Phase II awards.

  The SBIR/STTR Phase II transition rates and commercialization rates are calculated using the data in the SBA's TechNet database. For the purpose of these benchmark requirements, awardee firms are assessed once a year, on June 1st, using their prior SBIR and STTR awards across all agencies. SBA makes this tabulation of awardee transition rates and commercialization rates available to all federal agencies. ARPA-E uses this tabulation to determine which companies do not meet the DOE benchmark rates and are, therefore, ineligible to receive new Phase I awards.

- The Commercialization Rate Benchmark sets the minimum Phase III[68] commercialization results that an Applicant must have achieved from work it performed under prior Phase II awards (i.e. this measures an Applicant's progress from Phase II or Phase IIS to Phase III awards). **This benchmark requirement applies only to Applicants that have received more than 15 Phase II awards during the last 10 fiscal years, excluding the two most recently completed fiscal years.**

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[68] Phase III refers to work that derives from, extends or completes an effort made under prior SBIR/STTR funding agreements, but is funded by sources other than the SBIR/STTR Program. Phase III work is typically oriented towards commercialization of SBIR/STTR research or technology. For more information please refer to the Small Business Administration's "Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Program Program Policy Directive" at https://www.sbir.gov/sites/default/files/SBIR-STTR_Policy_Directive_2019.pdf.

The current Commercialization Benchmark requirement, agreed upon and established by all 11 SBIR agencies, is that the Applicants must have received, to date, an average of at least $100,000 of sales and/or investments per Phase II award received, or have received a number of patents resulting from the relevant SBIR/STTR work equal to or greater than 15% of the number of Phase II awards received during the period.

- On June 1 of each year, SBIR/STTR awardees registered on SBIR.gov are assessed to determine if they meet the Phase II Transition Rate Benchmark requirement. (At this time, SBA is not identifying companies that fail to meet the Commercialization Rate Benchmark requirement). Companies that fail to meet the Phase II Transition Rate Benchmark as of June 1 of a given year will not be eligible to apply to an SBIR/STTR FOA for the following year. For example, if SBA determined on June 1, 2017 that a small business failed to meet the Phase II Transition Rate Benchmark requirement, that small business would not be eligible to apply to an ARPA-E SBIR/STTR FOA from June 1, 2017 to May 31, 2018.

E. COST SHARING[69]

Cost sharing is not required for this FOA.

F. OTHER

1. COMPLIANT CRITERIA

Concept Papers are deemed compliant if:

- The Applicant meets the eligibility requirements in Section III.A of the FOA;
- The Concept Paper complies with the content and form requirements in Section IV.C of the FOA; and
- The Applicant entered all required information, successfully uploaded all required documents, and clicked the "Submit" button in ARPA-E eXCHANGE by the deadline stated in the FOA.

Concept Papers found to be noncompliant may not be merit reviewed or considered for award. ARPA-E may not review or consider noncompliant Concept Papers, including Concept Papers submitted through other means, Concept Papers submitted after the applicable deadline, and incomplete Concept Papers. A Concept Paper is incomplete if it does not include required information. ARPA-E will not extend the submission deadline for Applicants that fail to submit required information and documents due to server/connection congestion.

[69] Please refer to Section VI.B.3-4 of the FOA for guidance on cost share payments and reporting.

Full Applications are deemed compliant if:

- The Applicant submitted a compliant and responsive Concept Paper;
- The Applicant meets the eligibility requirements in Section III.A of the FOA;
- The Full Application complies with the content and form requirements in Section IV.D of the FOA; and
- The Applicant entered all required information, successfully uploaded all required documents, and clicked the "Submit" button in ARPA-E eXCHANGE by the deadline stated in the FOA.

Full Applications found to be noncompliant may not be merit reviewed or considered for award. ARPA-E may not review or consider noncompliant Full Applications, including Full Applications submitted through other means, Full Applications submitted after the applicable deadline, and incomplete Full Applications. A Full Application is incomplete if it does not include required information and documents, such as Forms SF-424 and SF-424A. ARPA-E will not extend the submission deadline for Applicants that fail to submit required information and documents due to server/connection congestion.

Replies to Reviewer Comments are deemed compliant if:

- The Applicant successfully uploads its response to ARPA-E eXCHANGE by the deadline stated in the FOA; and
- The Replies to Reviewer Comments comply with the content and form requirements of Section IV.E of the FOA.

ARPA-E will not review or consider noncompliant Replies to Reviewer Comments, including Replies submitted through other means and Replies submitted after the applicable deadline. ARPA-E will not extend the submission deadline for Applicants that fail to submit required information due to server/connection congestion. ARPA-E will review and consider each compliant and responsive Full Application, even if no Reply is submitted or if the Reply is found to be noncompliant.

2. RESPONSIVENESS CRITERIA

ARPA-E performs a preliminary technical review of Concept Papers and Full Applications. The following types of submissions may be deemed nonresponsive and may not be reviewed or considered:

- Submissions that fall outside the technical parameters specified in this FOA.
- Submissions that have been submitted in response to currently issued ARPA-E FOAs.
- Submissions that are not scientifically distinct from applications submitted in response to currently issued ARPA-E FOAs.

- Submissions for basic research aimed solely at discovery and/or fundamental knowledge generation.
- Submissions for large-scale demonstration projects of existing technologies.
- Submissions for proposed technologies that represent incremental improvements to existing technologies.
- Submissions for proposed technologies that are not based on sound scientific principles (e.g., violates a law of thermodynamics).
- Submissions for proposed technologies that are not transformational, as described in Section I.A of the FOA.
- Submissions for proposed technologies that do not have the potential to become disruptive in nature, as described in Section I.A of the FOA. Technologies must be scalable such that they could be disruptive with sufficient technical progress.
- Submissions that are not distinct in scientific approach or objective from activities currently supported by or actively under consideration for funding by any other office within Department of Energy.
- Submissions that are not distinct in scientific approach or objective from activities currently supported by or actively under consideration for funding by other government agencies or the private sector.
- Submissions that do not propose a R&D plan that allows ARPA-E to evaluate the submission under the applicable merit review criteria provided in Section V.A of the FOA.
- Submissions that do not propose a Combined Phase I/II/IIS Award, as described in Section II.A of the FOA.

3. Submissions Specifically not of Interest

Submissions that propose the following will be deemed nonresponsive and will not be merit reviewed or considered:

- Proposed processes lacking at least one biological conversion step consisting of a whole-cell fermentation, and/or a multi-step cell-free biosynthesis catalyzed by two or more distinct enzymes (i.e. processes consisting of only chemical, thermochemical, and/or electrocatalytic steps without being coupled with a biological conversion pathway are ineligible).
- Use of methane as a feedstock, or carbon monoxide as a primary feedstock.
- Prohibited primary products: Reduced 1-C products such as methane.
- Prohibited primary products: High value products, e.g. fragrances, flavors, pharmaceuticals.
- Prohibited primary products: Products that do not have a large potential for GHG reduction across the economy.

Applicants are encouraged to consult Appendix 2 of Section I of this FOA (Funding Opportunity Description) for additional guidance regarding of topics within scope of interest.

4. LIMITATION ON NUMBER OF SUBMISSIONS

ARPA-E is not limiting the number of submissions from Applicants. Applicants may submit more than one application to this FOA, provided that each application is scientifically distinct.

However, small businesses that qualify as a "Small Business Concern" may apply to only one of the two ARPA-E ECOSynBIO FOAs: ARPA-E FOA DE-FOA-0002388 (SBIR/STTR), Energy and Carbon Optimized Synthesis for the Bioeconomy SBIR/STTR (ECOSynBIO SBIR/STTR), or ARPA-E FOA DE-FOA-0002387, Energy and Carbon Optimized Synthesis for the Bioeconomy (ECOSynBio). Small businesses that qualify as "Small Business Concerns" are strongly encouraged to apply under the former (SBIR/STTR FOA). To determine eligibility as a "Small Business Concern" under DE-FOA-0002388, please review the eligibility requirements in Sections III.A – III.D above.

IV. APPLICATION AND SUBMISSION INFORMATION

A. APPLICATION PROCESS OVERVIEW

1. REGISTRATION IN SBA COMPANY REGISTRY

The first step in applying to this FOA is registering in the U.S. Small Business Administration (SBA) Company Registry (http://sbir.gov/registration). Upon completing registration, Applicants will receive a unique small business Control ID and Registration Certificate in Adobe PDF format, which may be used at any participating SBIR and STTR agencies. Applicants that have previously registered in the SBA Company Registry need not register again.

Applicants that are sole proprietors and do not have an Employer Identification Number may use social security numbers for purposes of registering in the SBA Company Registry. Applicants that do not possess a Dun and Bradstreet Data Universal Numbering System (DUNS) number may also use their social security number in the SBA Company Registry.

Applicants must submit their Registration Certificate in ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov) as part of their Full Application (see Section IV.D.5 of the FOA).

2. REGISTRATION IN ARPA-E eXCHANGE

The first step in applying to this FOA is registration in ARPA-E eXCHANGE, ARPA-E's online application portal. For detailed guidance on using ARPA-E eXCHANGE, please refer to Section IV.H.1 of the FOA and the "ARPA-E eXCHANGE User Guide" (https://arpa-e-foa.energy.gov/Manuals.aspx).

3. CONCEPT PAPERS

Applicants must submit a Concept Paper by the deadline stated in the FOA. Section IV.C of the FOA provides instructions on submitting a Concept Paper.

ARPA-E performs a preliminary review of Concept Papers to determine whether they are compliant and responsive, as described in Section III.F of the FOA. Concept Papers found to be noncompliant or nonresponsive may not be merit reviewed or considered for award. ARPA-E makes an independent assessment of each compliant and responsive Concept Paper based on the criteria and program policy factors in Sections V.A.1 and V.B.1 of the FOA.

ARPA-E will encourage a subset of Applicants to submit Full Applications. Other Applicants will be discouraged from submitting a Full Application in order to save them the time and expense of preparing an application submission that is unlikely to be selected for award negotiations. By discouraging the submission of a Full Application, ARPA-E intends to convey its lack of programmatic interest in the proposed project. Such assessments do not necessarily reflect judgments on the merits of the proposed project. Unsuccessful Applicants should continue to submit innovative ideas and concepts to future FOAs.

4. FULL APPLICATIONS

Applicants must submit a Full Application by the deadline stated in the FOA. Applicants will have approximately 45 days from receipt of the Encourage/Discourage notification to prepare and submit a Full Application. Section IV.D of the FOA provides instructions on submitting a Full Application.

ARPA-E performs a preliminary review of Full Applications to determine whether they are compliant and responsive, as described in Section III.F of the FOA. Full Applications found to be noncompliant or nonresponsive may not be merit reviewed or considered for award. ARPA-E makes an independent assessment of each compliant and responsive Full Application based on the criteria and program policy factors in Sections V.A and V.B of the FOA.

5. REPLY TO REVIEWER COMMENTS

Once ARPA-E has completed its review of Full Applications, reviewer comments on compliant and responsive Full Applications are made available to Applicants via ARPA-E eXCHANGE. Applicants may submit an optional Reply to Reviewer Comments, which must be submitted by the deadline stated in the FOA. Section IV.E of the FOA provides instructions on submitting a Reply to Reviewer Comments.

ARPA-E performs a preliminary review of Replies to determine whether they are compliant, as described in Section III.F.1 of the FOA. ARPA-E will review and consider compliant Replies only. ARPA-E will review and consider each compliant and responsive Full Application, even if no Reply is submitted or if the Reply is found to be non-compliant.

6. PRE-SELECTION CLARIFICATIONS AND "DOWN-SELECT" PROCESS

Once ARPA-E completes its review of Full Applications and Replies to Reviewer Comments, it may, at the Contracting Officer's discretion, conduct a pre-selection clarification process and/or perform a "down-select" of Full Applications. Through the pre-selection clarification process or down-select process, ARPA-E may obtain additional information from select Applicants through pre-selection meetings, webinars, videoconferences, conference calls, written correspondence, or site visits that can be used to make a final selection determination. ARPA-E will not reimburse Applicants for travel and other expenses relating to pre-selection meetings or site visits, nor will these costs be eligible for reimbursement as pre-award costs.

ARPA-E may select applications for award negotiations and make awards without pre-selection meetings and site visits. Participation in a pre-selection meeting or site visit with ARPA-E does not signify that Applicants have been selected for award negotiations.

7. Selection for Award Negotiations

ARPA-E carefully considers all of the information obtained through the application process and makes an independent assessment of each compliant and responsive Full Application based on the criteria and program policy factors in Sections V.A.2 and V.B.1 of the FOA. The Selection Official may select all or part of a Full Application for award negotiations. The Selection Official may also postpone a final selection determination on one or more Full Applications until a later date, subject to availability of funds and other factors. ARPA-E will enter into award negotiations only with selected Applicants.

Applicants are promptly notified of ARPA-E's selection determination. ARPA-E may stagger its selection determinations. As a result, some Applicants may receive their notification letter in advance of other Applicants. Please refer to Section VI.A of the FOA for guidance on award notifications.

B. Application Forms

Required forms for Full Applications are available on ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov), including the SF-424 and Budget Justification Workbook/SF-424A. A sample Summary Slide is available on ARPA-E eXCHANGE. Applicants may use the templates available on ARPA-E eXCHANGE, including the template for the Concept Paper, the template for the Technical Volume of the Full Application, the template for the Summary Slide, the template for the Summary for Public Release, the template for the Reply to Reviewer Comments, and the template for the Business Assurances & Disclosures Form. A sample response to the Business Assurances & Disclosures Form is available on ARPA-E eXCHANGE.

C. Content and Form of Concept Papers

The Concept Paper is mandatory (i.e. in order to submit a Full Application, a compliant and responsive Concept Paper must have been submitted) and must conform to the following formatting requirements:

- The Concept Paper must not exceed four (4) pages in length including graphics, figures, and/or tables (except the Technical Performance Targets Table, provided in the Concept Paper Template, which will not count as part of the 4 pages and must not exceed 2 pages.
- The Concept Paper must be submitted in Adobe PDF format.
- The Concept Paper must be written in English.

- All pages must be formatted to fit on 8-1/2 by 11 inch paper with margins not less than one inch on every side. Single space all text and use Times New Roman typeface, a black font color, and a font size of 12 point or larger (except in figures and tables).
- The ARPA-E assigned Control Number, the Lead Organization Name, and the Principal Investigator's Last Name must be prominently displayed on the upper right corner of the header of every page. Page numbers must be included in the footer of every page.
- The first paragraph must include the Lead Organization's Name and Location, Principal Investigator's Name, Technical Category, Proposed Funding Requested (Federal and Cost Share), and Project Duration.

Concept Papers found to be noncompliant or nonresponsive may not be merit reviewed or considered for award (see Section III.F of the FOA).

Each Concept Paper must be limited to a single concept or technology. Unrelated concepts and technologies must not be consolidated into a single Concept Paper.

A fillable Concept Paper template is available on ARPA-E eXCHANGE at https://arpa-e-foa.energy.gov.

Concept Papers must conform to the content requirements described below. If Applicants exceed the maximum page length indicated above, ARPA-E will review only the authorized number of pages and disregard any additional pages.

1. Concept Paper

a. Concept Summary

- Describe the proposed concept with minimal jargon, and explain how it addresses the Program Objectives of the FOA.

b. Innovation and Impact

- Clearly identify the problem to be solved with the proposed technology concept.
- Describe how the proposed effort represents an innovative and potentially transformational solution to the technical challenges posed by the FOA.
- Explain the concept's potential to be disruptive compared to existing or emerging technologies.
- To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies and to the

Technical Performance Targets in Section I.F of the FOA for the appropriate Technology Category in Section I.E of the FOA.

c. PROPOSED WORK

- Describe the final deliverable(s) for the project and the overall technical approach used to achieve project objectives.
- Discuss alternative approaches considered, if any, and why the proposed approach is most appropriate for the project objectives.
- Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Provide specific examples of supporting data and/or appropriate citations to the scientific and technical literature.
- Describe why the proposed effort is a significant technical challenge and the key technical risks to the project. Does the approach require one or more entirely new technical developments to succeed? How will technical risk be mitigated?
- Identify techno-economic challenges to be overcome for the proposed technology to be commercially relevant.

d. TEAM ORGANIZATION AND CAPABILITIES

- Indicate the roles and responsibilities of the organizations and key personnel that comprise the Project Team.
- Provide the name, position, and institution of each key team member and describe in 1-2 sentences the skills and experience that he/she brings to the team.
- Identify key capabilities provided by the organizations comprising the Project Team and how those key capabilities will be used in the proposed effort.
- Identify (if applicable) previous collaborative efforts among team members relevant to the proposed effort.

e. TECHNICAL PERFORMANCE TARGETS TABLE

In addition to the requirements stated in the FOA, please include this table in the Concept Paper. The Technical Performance Targets Table, will not count as part of the four page limit of the Concept Paper and must not exceed 2 pages.

Item	**Description**
Feedstock	Define allowable carbonaceous feedstock(s) and the expected price range (in $ per kg). Projected price ranges are acceptable; ranges should cover the 90th percentile of feedstock prices.

Reducing Equivalent	Define the reducing equivalent source(s) to be used and its role in the proposed stoichiometry.
Chemistry	Provide a balanced stoichiometric equation or set of equations accounting for all carbon feedstocks, reducing equivalent sources, and products.
Mass Balance	Use the above stoichiometry to predict mass balances for the proposed reactions. Specify mass flows in terms of the constituent sugars, gases, etc. match with the stoichiometry proposed[70]
Specific Energy Ratio	Using the derivation provided in the FOA, calculate $U_{product}/U_{C\ feedstock}$
Product	**Outputs:** List major outputs of the proposed process and the anticipated ratio. If a large product suite is anticipated, select the subset of products which would collectively contribute the majority (i.e. >80%) of revenue on the basis of product volume and/or value.
	Cost: Estimate the cost of production ($/kg) for each of the defined outputs and the capacity assumed to reach that cost.
	Price: Estimate the price ($/kg) and market size (MMT) for each of the defined outputs. Projected market sizes are acceptable, but must be sufficiently justified in terms of anticipated demand at the estimated $/kg price.
	Impact: As quantitatively as possible, estimate and justify the anticipated energy and/or emissions impact for each of the defined outputs.

D. Content and Form of Full Applications

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

E. Content and Form of Replies to Reviewer Comments

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

F. Intergovernmental Review

This program is not subject to Executive Order 12372 (Intergovernmental Review of Federal Programs).

[70] Note that "dry ton" is not useful for consideration here because at this stage of technology development the proposed bioconversion inputs need to be characterized by their constituent sugars, gases, etc. to tell if the stoichiometry proposed works in practice.

G. FUNDING RESTRICTIONS

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

H. OTHER SUBMISSION REQUIREMENTS

1. USE OF ARPA-E eXCHANGE

To apply to this FOA, Applicants must register with ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov/Registration.aspx). Concept Papers, Full Applications, and Replies to Reviewer Comments must be submitted through ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov/login.aspx). ARPA-E will not review or consider applications submitted through other means (e.g., fax, hand delivery, email, postal mail). For detailed guidance on using ARPA-E eXCHANGE, please refer to the "ARPA-E eXCHANGE Applicant Guide" (https://arpa-e-foa.energy.gov/Manuals.aspx).

Upon creating an application submission in ARPA-E eXCHANGE, Applicants will be assigned a Control Number. If the Applicant creates more than one application submission, a different Control Number will be assigned for each application.

Once logged in to ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov/login.aspx), Applicants may access their submissions by clicking the "My Submissions" link in the navigation on the left side of the page. Every application that the Applicant has submitted to ARPA-E and the corresponding Control Number is displayed on that page. If the Applicant submits more than one application to a particular FOA, a different Control Number is shown for each application.

Applicants are responsible for meeting each submission deadline in ARPA-E eXCHANGE. **Applicants are strongly encouraged to submit their applications at least 48 hours in advance of the submission deadline.** Under normal conditions (i.e., at least 48 hours in advance of the submission deadline), Applicants should allow at least 1 hour to submit a Concept Paper, or Full Application. In addition, Applicants should allow at least 15 minutes to submit a Reply to Reviewer Comments. Once the application is submitted in ARPA-E eXCHANGE, Applicants may revise or update their application until the expiration of the applicable deadline.

Applicants should not wait until the last minute to begin the submission process. During the final hours before the submission deadline, Applicants may experience server/connection congestion that prevents them from completing the necessary steps in ARPA-E eXCHANGE to submit their applications. **ARPA-E will not extend the submission deadline for Applicants that fail to submit required information and documents due to server/connection congestion.**

ARPA-E may not review or consider incomplete applications and applications received after the deadline stated in the FOA. Such applications may be deemed noncompliant (see Section III.F.1 of the FOA). The following errors could cause an application to be deemed "incomplete" and thus noncompliant:

- Failing to comply with the form and content requirements in Section IV of the FOA;
- Failing to enter required information in ARPA-E eXCHANGE;
- Failing to upload required document(s) to ARPA-E eXCHANGE;
- Failing to click the "Submit" button in ARPA-E eXCHANGE by the deadline stated in the FOA;
- Uploading the wrong document(s) or application(s) to ARPA-E eXCHANGE; and
- Uploading the same document twice, but labeling it as different documents. (In the latter scenario, the Applicant failed to submit a required document.)

ARPA-E urges Applicants to carefully review their applications and to allow sufficient time for the submission of required information and documents.

V. APPLICATION REVIEW INFORMATION

A. CRITERIA

ARPA-E performs a preliminary review of Concept Papers and Full Applications to determine whether they are compliant and responsive (see Section III.F of the FOA). ARPA-E also performs a preliminary review of Replies to Reviewer Comments to determine whether they are compliant.

ARPA-E considers a mix of quantitative and qualitative criteria in determining whether to encourage the submission of a Full Application and whether to select a Full Application for award negotiations.

1. CRITERIA FOR CONCEPT PAPERS

(1) Impact of the Proposed Technology Relative to FOA Targets (50%) - This criterion involves consideration of the following:

- The potential for a transformational and disruptive (not incremental) advancement compared to existing or emerging technologies;
- Achievement of the technical performance targets defined in Section I.F of the FOA for the appropriate technology Category in Section I.E of the FOA;
- Identification of techno-economic challenges that must be overcome for the proposed technology to be commercially relevant; and
- Demonstration of awareness of competing commercial and emerging technologies and identifies how the proposed concept/technology provides significant improvement over existing solutions.

(2) *Overall Scientific and Technical Merit* (50%) - This criterion involves consideration of the following:

- The feasibility of the proposed work, as justified by appropriate background, theory, simulation, modeling, experimental data, or other sound scientific and engineering practices;
- Sufficiency of technical approach to accomplish the proposed R&D objectives, including why the proposed concept is more appropriate than alternative approaches and how technical risk will be mitigated;
- Clearly defined project outcomes and final deliverables; and
- The demonstrated capabilities of the individuals performing the project, the key capabilities of the organizations comprising the Project Team, the roles and responsibilities of each organization and (if applicable) previous collaborations among team members supporting the proposed project.

Submissions will not be evaluated against each other since they are not submitted in accordance with a common work statement. The above criteria will be weighted as follows:

Impact of the Proposed Technology Relative to FOA Targets	50%
Overall Scientific and Technical Merit	50%

2. Criteria for Full Applications

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

3. Criteria for Replies to Reviewer Comments

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

B. Review and Selection Process

1. Program Policy Factors

In addition to the above criteria, ARPA-E may consider the following program policy factors in determining which Concept Papers to encourage to submit a Full Application and which Full Applications to select for award negotiations:

I. **ARPA-E Portfolio Balance**. Project balances ARPA-E portfolio in one or more of the following areas:
   a. Diversity of technical personnel in the proposed Project Team;
   b. Technological diversity;
   c. Organizational diversity;

d. Geographic diversity;
e. Technical or commercialization risk; or
f. Stage of technology development.

II. **Relevance to ARPA-E Mission Advancement.** Project contributes to one or more of ARPA-E's key statutory goals:
   a. Reduction of U.S. dependence on foreign energy sources;
   b. Stimulation of domestic manufacturing/U.S. Manufacturing Plan;
   c. Reduction of energy-related emissions;
   d. Increase in U.S. energy efficiency;
   e. Enhancement of U.S. economic and energy security; or
   f. Promotion of U.S. advanced energy technologies competitiveness.

III. **Synergy of Public and Private Efforts**.
   a. Avoids duplication and overlap with other publicly or privately funded projects;
   b. Promotes increased coordination with nongovernmental entities for demonstration of technologies and research applications to facilitate technology transfer; or
   c. Increases unique research collaborations.

IV. **Low likelihood of other sources of funding.** High technical and/or financial uncertainty that results in the non-availability of other public, private or internal funding or resources to support the project.

V. **High Project Impact Relative to Project Cost.**

VI. **Qualified Opportunity Zone (QOZ).** Whether the entity is located in an urban and economically distressed area including a Qualified Opportunity Zone (QOZ) or the proposed project will occur in a QOZ or otherwise advance the goals of QOZ. The goals include spurring economic development and job creation in distressed communities throughout the United States. For a list or map of QOZs go to: https://www.cdfifund.gov/Pages/Opportunity-Zones.aspx.

2. ARPA-E REVIEWERS

By submitting an application to ARPA-E, Applicants consent to ARPA-E's use of Federal employees, contractors, and experts from educational institutions, nonprofits, industry, and governmental and intergovernmental entities as reviewers. ARPA-E selects reviewers based on their knowledge and understanding of the relevant field and application, their experience and skills, and their ability to provide constructive feedback on applications.

ARPA-E requires all reviewers to complete a Conflict-of-Interest Certification and Nondisclosure Agreement through which they disclose their knowledge of any actual or apparent conflicts and agree to safeguard confidential information contained in Concept Papers, Full Applications, and Replies to Reviewer Comments. In addition, ARPA-E trains its reviewers in proper evaluation techniques and procedures.

Applicants are not permitted to nominate reviewers for their applications. Applicants may contact the Contracting Officer by email (ARPA-E-CO@hq.doe.gov) if they have knowledge of a potential conflict of interest or a reasonable belief that a potential conflict exists.

3. ARPA-E Support Contractor

ARPA-E utilizes contractors to assist with the evaluation of applications and project management. To avoid actual and apparent conflicts of interest, ARPA-E prohibits its support contractors from submitting or participating in the preparation of applications to ARPA-E.

By submitting an application to ARPA-E, Applicants represent that they are not performing support contractor services for ARPA-E in any capacity and did not obtain the assistance of ARPA-E's support contractor to prepare the application. ARPA-E will not consider any applications that are submitted by or prepared with the assistance of its support contractors.

C. Anticipated Announcement and Award Dates

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

VI. AWARD ADMINISTRATION INFORMATION

A. AWARD NOTICES

1. REJECTED SUBMISSIONS

Noncompliant and nonresponsive Concept Papers and Full Applications are rejected by the Contracting Officer and are not merit reviewed or considered for award. The Contracting Officer sends a notification letter by email to the technical and administrative points of contact designated by the Applicant in ARPA-E eXCHANGE. The notification letter states the basis upon which the Concept Paper or Full Application was rejected.

2. CONCEPT PAPER NOTIFICATIONS

ARPA-E promptly notifies Applicants of its determination to encourage or discourage the submission of a Full Application. ARPA-E sends a notification letter by email to the technical and administrative points of contact designated by the Applicant in ARPA-E eXCHANGE. ARPA-E provides feedback in the notification letter in order to guide further development of the proposed technology.

Applicants may submit a Full Application even if they receive a notification discouraging them from doing so. By discouraging the submission of a Full Application, ARPA-E intends to convey its lack of programmatic interest in the proposed project. Such assessments do not necessarily reflect judgments on the merits of the proposed project. The purpose of the Concept Paper phase is to save Applicants the considerable time and expense of preparing a Full Application that is unlikely to be selected for award negotiations.

A notification letter encouraging the submission of a Full Application does not authorize the Applicant to commence performance of the project. Please refer to Section IV.G of the FOA for guidance on pre-award costs.

3. FULL APPLICATION NOTIFICATIONS

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

B. ADMINISTRATIVE AND NATIONAL POLICY REQUIREMENTS

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

C. REPORTING

[TO BE INSERTED BY FOA MODIFICATION IN DECEMBER 2020]

VII. Agency Contacts

A. Communications with ARPA-E

Upon the issuance of a FOA, only the Contracting Officer may communicate with Applicants. ARPA-E personnel and our support contractors are prohibited from communicating (in writing or otherwise) with Applicants regarding the FOA. This "quiet period" remains in effect until ARPA-E's public announcement of its project selections.

During the "quiet period," Applicants are required to submit all questions regarding this FOA to ARPA-E-CO@hq.doe.gov. Questions and Answers (Q&As) about ARPA-E and the FOA are available at http://arpa-e.energy.gov/faq. For questions that have not already been answered, please send an email with the FOA name and number in the subject line to ARPA-E-CO@hq.doe.gov. Due to the volume of questions received, ARPA-E will only answer pertinent questions that have not yet been answered and posted at the above link.

- ARPA-E will post responses on a weekly basis to any questions that are received that have not already been addressed at the link above. ARPA-E may re-phrase questions or consolidate similar questions for administrative purposes.
- ARPA-E will cease to accept questions approximately 10 business days in advance of each submission deadline. Responses to questions received before the cutoff will be posted approximately one business day in advance of the submission deadline. ARPA-E may re-phrase questions or consolidate similar questions for administrative purposes.
- Responses are published in a document specific to this FOA under "CURRENT FUNDING OPPORTUNITIES – FAQS" on ARPA-E's website (http://arpa-e.energy.gov/faq).

Applicants may submit questions regarding ARPA-E eXCHANGE, ARPA-E's online application portal, to ExchangeHelp@hq.doe.gov. ARPA-E will promptly respond to emails that raise legitimate, technical issues with ARPA-E eXCHANGE. ARPA-E will refer any questions regarding the FOA to ARPA-E-CO@hq.doe.gov.

ARPA-E will not accept or respond to communications received by other means (e.g., fax, telephone, mail, hand delivery). Emails sent to other email addresses will be disregarded.

During the "quiet period," only the Contracting Officer may authorize communications between ARPA-E personnel and Applicants. The Contracting Officer may communicate with Applicants as necessary and appropriate. As described in Section IV.A of the FOA, the Contracting Officer may arrange pre-selection meetings and/or site visits during the "quiet period."

B. Debriefings

ARPA-E does not offer or provide debriefings. ARPA-E provides Applicants with a notification encouraging or discouraging the submission of a Full Application based on ARPA-E's assessment of the Concept Paper. In addition, ARPA-E provides Applicants with reviewer comments on Full Applications before the submission deadline for Replies to Reviewer Comments.

VIII. OTHER INFORMATION

A. TITLE TO SUBJECT INVENTIONS

Ownership of subject inventions is governed pursuant to the authorities listed below. Typically, either by operation of law or under the authority of a patent waiver, Prime Recipients and Subrecipients may elect to retain title to their subject inventions under ARPA-E funding agreements.

- Domestic Small Businesses, Educational Institutions, and Nonprofits: Under the Bayh-Dole Act (35 U.S.C. § 200 et seq.), domestic small businesses, educational institutions, and nonprofits may elect to retain title to their subject inventions. If Prime Recipients/Subrecipients elect to retain title, they must file a patent application in a timely fashion, generally one year from election of title, though: a) extensions can be granted, and b) earlier filing is required for certain situations ("statutory bars," governed by 35 U.S.C. § 102) involving publication, sale, or public use of the subject invention.
- All other parties: The Federal Non-Nuclear Energy Research and Development Act of 1974, 42. U.S.C. 5908, provides that the Government obtains title to new inventions unless a waiver is granted (*see below)*.
- Class Waiver: Under 42 U.S.C. § 5908, title to subject inventions vests in the U.S. Government and large businesses and foreign entities do not have the automatic right to elect to retain title to subject inventions. However, ARPA-E typically issues "class patent waivers" under which large businesses and foreign entities that meet certain stated requirements, such as cost sharing of at least 20%, may elect to retain title to their subject inventions. If a large business or foreign entity elects to retain title to its subject invention, it must file a patent application in a timely fashion. If the class waiver does not apply, a party may request a waiver in accordance with 10 C.F.R. §784.
- GOGOs are subject to the requirements of 37 C.F.R. Part 501.
- Determination of Exceptional Circumstances (DEC): DOE has determined that exceptional circumstances exist that warrant the modification of the standard patent rights clause for small businesses and non-profit awardees under Bayh-Dole to maximize the manufacture of technologies supported by ARPA-E awards in the United States. The DEC, including a right of appeal, is dated September 9, 2013 and is available at the following link: http://energy.gov/gc/downloads/determination-exceptional-circumstances-under-bayh-dole-act-energy-efficiency-renewable. Please see Section IV.D and VI.B for more information on U.S. Manufacturing Requirements.

B. GOVERNMENT RIGHTS IN SUBJECT INVENTIONS

Where Prime Recipients and Subrecipients retain title to subject inventions, the U.S. Government retains certain rights.

1. Government Use License

The U.S. Government retains a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world. This license extends to contractors doing work on behalf of the Government.

2. March-In Rights

The U.S. Government retains march-in rights with respect to all subject inventions. Through "march-in rights," the Government may require a Prime Recipient or Subrecipient who has elected to retain title to a subject invention (or their assignees or exclusive licensees), to grant a license for use of the invention. In addition, the Government may grant licenses for use of the subject invention when Prime Recipients, Subrecipients, or their assignees and exclusive licensees refuse to do so.

The U.S. Government may exercise its march-in rights if it determines that such action is necessary under any of the four following conditions:

- The owner or licensee has not taken or is not expected to take effective steps to achieve practical application of the invention within a reasonable time;
- The owner or licensee has not taken action to alleviate health or safety needs in a reasonably satisfactory manner;
- The owner has not met public use requirements specified by Federal statutes in a reasonably satisfactory manner; or
- The U.S. Manufacturing requirement has not been met.

C. Rights in Technical Data

Data rights differ based on whether data is first produced under an award or instead was developed at private expense outside the award.

- Background or "Limited Rights Data": The U.S. Government will not normally require delivery of technical data developed solely at private expense prior to issuance of an award, except as necessary to monitor technical progress and evaluate the potential of proposed technologies to reach specific technical and cost metrics.
- Generated Data: Pursuant to special statutory authority for SBIR/STTR awards, data generated under ARPA-E SBIR/STTR awards may be protected from public disclosure for twenty years from the date of award in accordance with provisions that will be set forth in the award. In addition, invention disclosures may be protected from public disclosure for a reasonable time in order to allow for filing a patent application.

D. PROTECTED PERSONALLY IDENTIFIABLE INFORMATION

Applicants may not include any Protected Personally Identifiable Information (Protected PII) in their submissions to ARPA-E. Protected PII is defined as data that, if compromised, could cause harm to an individual such as identity theft. Listed below are examples of Protected PII that Applicants must not include in their submissions.

- Social Security Numbers in any form;
- Place of Birth associated with an individual;
- Date of Birth associated with an individual;
- Mother's maiden name associated with an individual;
- Biometric record associated with an individual;
- Fingerprint;
- Iris scan;
- DNA;
- Medical history information associated with an individual;
- Medical conditions, including history of disease;
- Metric information, e.g. weight, height, blood pressure;
- Criminal history associated with an individual;
- Ratings;
- Disciplinary actions;
- Performance elements and standards (or work expectations) are PII when they are so intertwined with performance appraisals that their disclosure would reveal an individual's performance appraisal;
- Financial information associated with an individual;
- Credit card numbers;
- Bank account numbers; and
- Security clearance history or related information (not including actual clearances held).

E. FOAS AND FOA MODIFICATIONS

FOAs are posted on ARPA-E eXCHANGE (https://arpa-e-foa.energy.gov/), Grants.gov (http://www.grants.gov/), and FedConnect (https://www.fedconnect.net/FedConnect/). Any modifications to the FOA are also posted to these websites. You can receive an e-mail when a modification is posted by registering with FedConnect as an interested party for this FOA. It is recommended that you register as soon as possible after release of the FOA to ensure that you receive timely notice of any modifications or other announcements. More information is available at https://www.fedconnect.net.

F. Obligation of Public Funds

The Contracting Officer is the only individual who can make awards on behalf of ARPA-E or obligate ARPA-E to the expenditure of public funds. A commitment or obligation by any individual other than the Contracting Officer, either explicit or implied, is invalid.

ARPA-E awards may not be transferred, assigned, or assumed without the prior written consent of a Contracting Officer.

G. Requirement for Full And Complete Disclosure

Applicants are required to make a full and complete disclosure of the information requested in the Business Assurances & Disclosures Form. Disclosure of the requested information is mandatory. Any failure to make a full and complete disclosure of the requested information may result in:

- The rejection of a Concept Paper, Full Application, and/or Reply to Reviewer Comments;
- The termination of award negotiations;
- The modification, suspension, and/or termination of a funding agreement;
- The initiation of debarment proceedings, debarment, and/or a declaration of ineligibility for receipt of Federal contracts, subcontracts, and financial assistance and benefits; and
- Civil and/or criminal penalties.

H. Retention of Submissions

ARPA-E expects to retain copies of all Concept Papers, Full Applications, Replies to Reviewer Comments, and other submissions. No submissions will be returned. By applying to ARPA-E for funding, Applicants consent to ARPA-E's retention of their submissions.

I. Marking of Confidential Information

ARPA-E will use data and other information contained in Concept Papers, Full Applications, and Replies to Reviewer Comments strictly for evaluation purposes.

Concept Papers, Full Applications, Replies to Reviewer Comments, and other submissions containing confidential, proprietary, or privileged information should be marked on the cover page with the following:

Notice of Restriction on Disclosure and Use of Data:

This document contains trade secrets or commercial or financial information that is privileged or confidential and exempt from public disclosure and is submitted only for the purposes of internal agency review of this Application. The Government may not use or disclose any information herein without permission.

The header and footer of every page that contains confidential, proprietary, or privileged information must be marked as follows: "Contains Confidential, Proprietary, or Privileged Information Exempt from Public Disclosure."

J. ADDITIONAL NOTICES

- This FOA is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR or STTR funding agreement, the terms of the funding agreement are controlling.
- Before award of an SBIR or STTR funding agreement, ARPA-E may request the selectee to submit certain organizational, management, personnel, and financial information to assure responsibility of the Prime Recipient. In addition, selectees will be required to make certain legal commitments at the time of execution of funding agreements resulting from this FOA. ARPA-E encourages Prime Recipients to review the Model Cooperative Agreement for SBIR/STTR Awards, which is available at https://arpa-e.energy.gov/?q=site-page/funding-agreements.
- ARPA-E will not pay a fee or profit on Cooperative Agreements resulting from this FOA to recipients or subrecipients.
- Actual or suspected fraud, waste, or abuse may be reported to the DOE Office of Inspector General (OIG) at 1-800-541-1625.

K. COMPLIANCE AUDIT REQUIREMENT

A prime recipient organized as a for-profit entity expending $750,000 or more of DOE funds in the entity's fiscal year (including funds expended as a Subrecipient) must have an annual compliance audit performed at the completion of its fiscal year. For additional information, refer to Subpart F of: (i) 2 C.F.R. Part 200, and (ii) 2 C.F.R. Part 910.

If an educational institution, non-profit organization, or state/local government is either a Prime Recipient or a Subrecipient, and has expended $750,000 or more of Federal funds in the entity's fiscal year, the entity must have an annual compliance audit performed at the completion of its fiscal year. For additional information refer to Subpart F of 2 C.F.R. Part 200.

IX. GLOSSARY

Applicant: The entity that submits the application to ARPA-E. In the case of a Project Team, the Applicant is the lead organization listed on the application.

Application: The entire submission received by ARPA-E, including the Concept Paper, Full Application, and Reply to Reviewer Comments.

ARPA-E: is the Advanced Research Projects Agency – Energy, an agency of the U.S. Department of Energy.

Cost Sharing: is the portion of project costs not paid by Federal funds (unless otherwise authorized by Federal statue). Refer to 2 C.F.R. § 200.29.

Deliverable: A deliverable is the quantifiable goods or services that will be provided upon the successful completion of a project task or sub-task.

DOE: U.S. Department of Energy.

DOE/NNSA: U.S. Department of Energy/National Nuclear Security Administration

FFRDCs: Federally Funded Research and Development Centers.

FOA: Funding Opportunity Announcement.

GOCOs: U.S. Government Owned, Contractor Operated laboratories.

GOGOs: U.S. Government Owned, Government Operated laboratories.

Milestone: A milestone is the tangible, observable measurement that will be provided upon the successful completion of a project task or sub-task.

Nonprofit Organizations (or *nonprofits*): Has the meaning set forth at 2 C.F.R. § 200.70.

Prime Recipient: The signatory to the funding agreement with ARPA-E.

PI: Principal Investigator.

Project Team: A Project Team consists of the Prime Recipient, Subrecipients, and others performing any of the research and development work under an ARPA-E funding agreement, whether or not costs of performing the research and development work are being reimbursed under any agreement.

SBA: U.S. Small Business Administration.

SBIR: Small Business Innovation Research Program.

Small Business Concern: A for-profit entity that: (1) maintains a place of business located in the United States; (2) operates primarily within the United States or makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor; (3) is an individual proprietorship, partnership, corporation, limited liability company, joint venture, association, trust, or cooperative; and (4) meets the size eligibility requirements set forth in 13 C.F.R. § 121.702. Where the entity is formed as a joint venture, there can be no more than 49% participation by foreign business entities in the joint venture.

Standalone Applicant: An Applicant that applies for funding on its own, not as part of a Project Team.

STTR: Small Business Technology Transfer Program.

Subject Invention: Any invention conceived or first actually reduced to practice under an ARPA-E funding agreement.

Task: A task is an operation or segment of the work plan that requires both effort and resources. Each task (or sub-task) is connected to the overall objective of the project, via the achievement of a milestone or a deliverable.

Total Project Cost: The sum of the Prime Recipient share and the Federal Government share of total allowable costs. The Federal Government share generally includes costs incurred by GOGOs, FFRDCs, and GOCOs.