EBRC Engineering Biology Research Consortium

Response to DOE Request for Information on Identifying Basic Research Challenges to Accelerate U.S. Biotechnology Leadership

The Engineering Biology Research Consortium (EBRC) is a nonprofit that brings together researchers and industry leaders to advance the field of engineering biology to address national and global needs. EBRC's members include experts from over 100 universities and research institutes, alongside leaders from more than 30 companies, philanthropies, and other organizations. Working closely with partners across the engineering biology ecosystem, EBRC focuses on four key areas: Research Roadmapping, Policy & International Engagement, Education, and Security.

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Category A: Fundamental Science & Biodesign Goals

1. Most Significant Near-Term Scientific Bottlenecks

Existing biological data must be converted into datasets that are sufficiently representative, contextualized, consistent, interoperable, and connected to function for predictive modeling. Data gaps include insufficient coverage of diverse biological conditions and outcomes, including negative results. Additionally, inconsistent experimental standards and limited scalable measurements of biochemical functions and phenotypes constrain which biological functions models can reliably predict. Datasets used for predictive modeling and machine learning must connect genotype, molecular structure, and multilayered regulatory networks across organisms, environmental conditions, and scales (organismal and mass) with biochemical function, phenotype, and relevant dynamic kinetics to enable models to identify relationships that generalize across experiments and beyond steady-state assumptions. Minimum contextual information, common representations, and standards are needed to structure, annotate, and link biological data across research environments, including conditions associated with negative outcomes. Experimentally-tractable systems, including cell-free systems, synthetic cells, engineered hosts, and defined microbial communities, should be used to determine where predictions generalize. Finally, models must demonstrate that they can guide new biological designs, not simply reproduce known relationships, and be validated experimentally. These priorities build on EBRC's *Engineering Biology* and *Microbiome Engineering* roadmaps, which emphasize data integration, modeling, automation, and community-level engineering.

2. Key Missing Capabilities to Scale Biodesign Principles

Predictive biosystems design calls for integrating mechanistic, kinetic, and physics-based models and approaches to connect molecular interactions to cellular, organismal, and system-level behavior. This requires transfer learning frameworks that use robust uncertainty quantification to weigh previous models against new data when generalizing across contexts and scales. Experimental tools to engineer and characterize non-model organisms and extremophiles are needed to expand beyond established chassis and ensure systems capture biological variability and identify truly generalizable design principles. Additionally, automated DBTL systems and biofoundries must pivot from maximizing throughput to executing high-information experiments that generate standardized and interoperable data, systematically test predictive model boundaries, and inform subsequent designs. Finally, biosystems design

must incorporate deployment and production constraints early across the full spectrum of biomanufacturing systems, including cell-free, microbial, unicellular, multicellular, and plant platforms. As partially highlighted in EBRC's *Engineering Biology & Materials Science* roadmap, models must account for performance under realistic manufacturing conditions, including productivity, stability, product quality and recovery, downstream separation and purification, and process sustainability.

Category B: High-Priority Biotechnology Applications

3. High-Potential Targets for Industrial Breakthroughs and Public Benefit

Targets for industrial breakthroughs center on programmable biomolecular systems and bioenergy feedstocks. For proteins and enzymes, the frontier must advance beyond discovery toward engineering dynamic conformational ensembles, allosterically regulated biocatalysts, and multi-enzyme cascades that are optimized for non-natural chemistry and difficult chemical transformations. Priority material applications include structural proteins, adhesives, fibers, and self-assembling polymers with tunable mechanical or thermal properties. For application as biosystems, priority target areas must include bioenergy crops, perennial biomass, and plant and bacterial systems engineered to function as industrial feedstocks and for environmental resilience and modulation applications. Connecting genotype, biological mechanism, phenotype, and environmental response will enable deliberate engineering of biosystems and feedstocks optimized for bioprocessing, stability, and stress resilience. These priorities build on EBRC's *Engineering Biology* and *Engineering Biology for Climate & Sustainability* roadmaps, advancing plant-microbe interactions and sustainable feedstocks to drive a scalable biomanufacturing economy.

Category C: Partnerships and Collaboration

4. Public-Private Partnerships, Cross-Agency Cooperation, & Translation

Translating biosystems design requires public-private partnerships (PPP) that connect foundational academic discovery, national laboratory scale and infrastructure, and industry deployment targets. Existing models (e.g., BioMADE, BioFabUSA, NIIMBL) offer translational lessons, but next-generation PPP mechanisms must be simplified and expanded to address under-prioritized domains, including gas fermentation, agricultural crop-microbiosystems, and complex microbial communities. Leveraging Genesis Mission activities, DOE national laboratories should provide shared, closed-loop testbeds connecting advanced computational model-driven design with automated build characterization and functional validation at scales that individual academic labs and companies cannot maintain. Federal investments must establish interoperable biological data, measurement, and metadata standards across sectors. DOE must deepen integration with academia to strengthen workforce development and knowledge transfer, while preserving academia's foundational research role and leveraging DOE's scale. This should include joint appointments, user sabbaticals, and inclusion of national lab capabilities in academic curricula and training programs. Finally, DOE should partner with experts, including nonprofit organizations, to incorporate ethical R&D practices, governance, public dialogue, and bioliteracy as essential prerequisites to guide technology development and ensure safe and socially responsible industrial deployment.