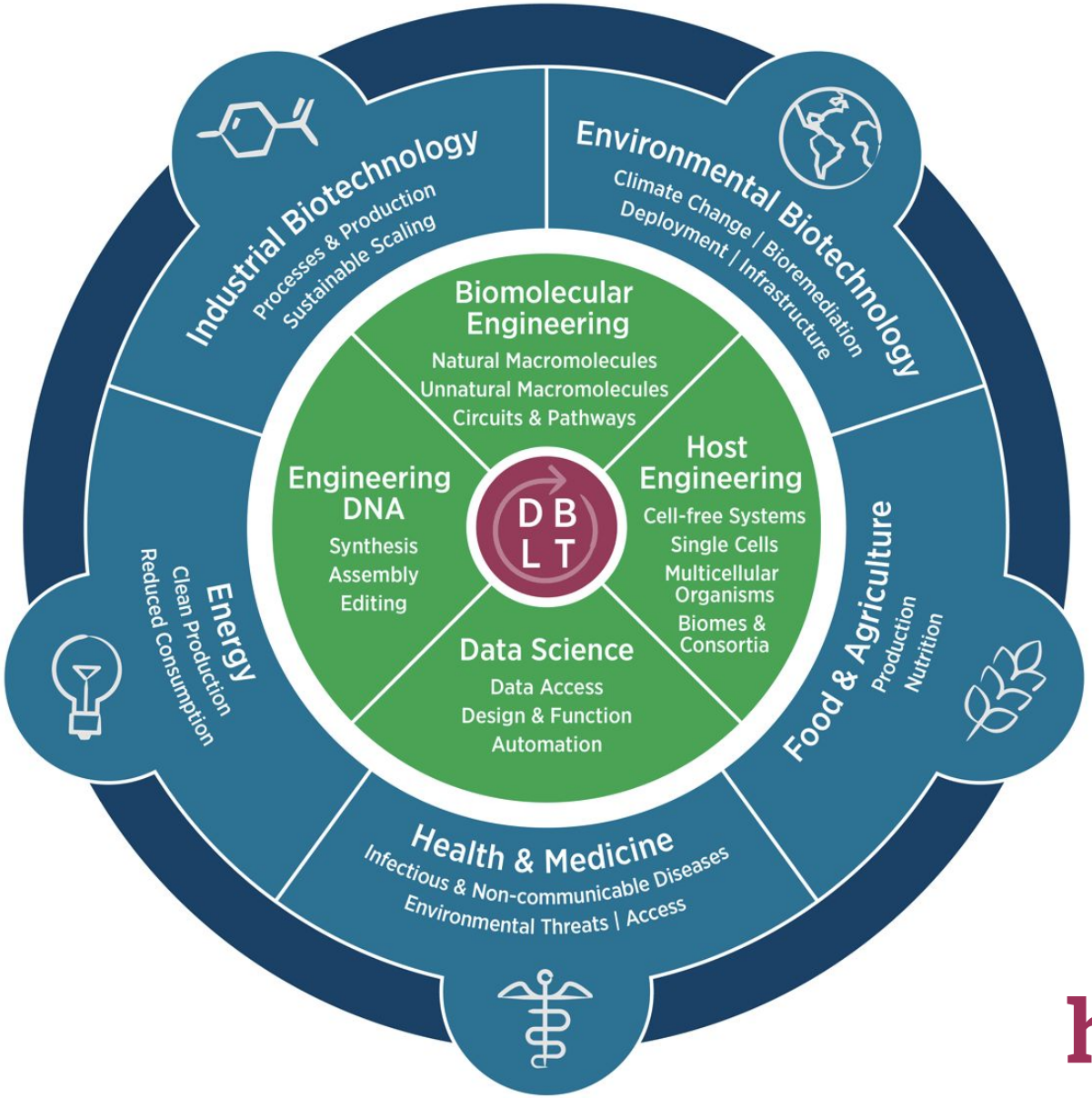

Engineering Biology

A Research Roadmap for the Next-Generation Bioeconomy

Technical Themes	Application Sectors
Engineering DNA	Industrial Biotechnology
Biomolecular Engineering	Health & Medicine
Host Engineering	Food & Agriculture
Data Science	Environmental Biotechnology
	Energy

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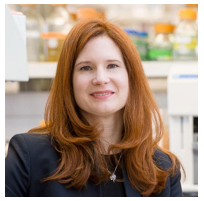

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A Matrixed Approach

Technical Themes

Sectors	Engineering DNA	Biomolecular Engineering	Host Engineering	Data Science
Industrial Biotechnology				
Health & Medicine				
Food & Agriculture				
Environmental Biotechnology				
Energy				

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The next four slides in the presentation are representations of roadmap elements in each of the four Technical Themes. The contents of the slides has been selected for optimal display during presentations and represents a very small snapshot of each theme.

Please indicate to your audience that the information presented on the following slides is **for representation only and not inclusive of the goal and breakthrough capability displayed**.

GENE EDITING, SYNTHESIS, AND ASSEMBLY

Goal	Breakthough Capability	Milestone

Precision genome editing at multiple sites simultaneously with no off-target effects.

2 Years	5 Years	10 Years	20 Years
Ability to reliably create any precise, defined edit(s) (single nucleotide polymorphisms or gene replacement) with no unintended editing in any organism, with edits ranging from a single base change to insertion of entire pathways.			
Ability to generate any defined single base pair change in model organisms.	High efficiency editing (> 90%) across the genome with no off-target activity.	High-efficiency gene insertion or deletion of moderately large changes (< 10 kb) via homologous recombination.	Precise, parallel editing or regulatory modifications (10 to 1000 modifications) across model and non-model organisms, including plants and animals.
Precise, predictable, and tunable control of gene expression for many genes inside diverse cells and organisms across different timescales.			
Achieve long-lasting gene repression and activation.	Ability to regulate expression in non-model organisms.	Technologies to monitor and manipulate genetic and epigenetic mechanisms controlling tissue-wide and organism-wide expression levels over time.	Ability to precisely regulate gene expression in whole-body organisms, with single-cell resolution using dynamic or static control.
Ability to reproducibly deliver editing cargo efficiently and specifically to a given target cells or tissues, and control dosage and timing of the editing machinery.			
Improve editors to function without sequence requirements with activity comparable to 2019 state-of-the-art capabilities.	Routine use of editors without detectable off-target effects.	Enhance specificity of delivery modalities for high efficiency (>90% efficient) editing of cells in a defined tissue.	Quantitative, specific, and multiplexed editing of any site, in any cell, in any organism.

BIOMOLECULE, PATHWAY, AND CIRCUIT ENGINEERING

Goal	Breakthough Capability	Milestone

Holistic, integrated design of multi-part genetic systems (i.e., circuits and pathways).

Ability to rationally engineer sensor suites, genetic circuits, metabolic pathways, signaling cascades, and cell differentiation pathways.

2 Years	5 Years	10 Years	20 Years
Reliable engineering of genetic circuits with more than 10 regulators for sophisticated computations.	Reliable engineering of novel, many-enzyme pathways utilizing combinations of bioprospected enzymes with well-characterized kinetics.	Reliable expression of redesigned synthases to produce secondary metabolites.	Simultaneous, tunable, timed expression of many transcription factors controlling mammalian cell state.
	Five-time improvement and expansion of inducers/promoters for model organisms that respond to environmental inputs and any intracellular metabolite.	Computational design of protein-ligand and RNA-ligand interfaces suitable for engineering protein-based or RNA-based sensors.	
	Utilize machine-learning approaches to use the vast amount of uncurated literature results within pathway design.		

HOST AND CONSORTIA ENGINEERING

Goal	Breakthough Capability	Milestone

On-demand production of single-cell hosts capable of natural and non-natural biochemistry.

Routine domestication of non-model organisms through DNA delivery and genetic modification.

2 Years	5 Years	10 Years	20 Years
Catalog and assay current methodologies and tools for carrying out DNA delivery in microbial/mammalian systems and plant systems.	Development of well-characterized and robust insertion sites in plant genomes.	Develop high-throughput, targeted editing and rapid-genome-evolution tools that couple genetic changes to phenotypic changes.	Routine genetic manipulation of any non-model host in less than one week from first isolation.
Develop high-throughput methods that can be done in parallel for DNA delivery (using standard methods) into non-model hosts.	Develop high-throughput, genome-wide editing tools for non-model organisms.		
Establish a suite of gene-editing tools for the rapid insertion and/or deletion of genetic elements in diverse primary mammalian cells.	Establish robust temporal and/or spatial control of gene expression in mammalian cells.	Develop universal approaches to transforming any plant.	
Characterize basic DNA parts for expression strength in non-model organisms.	Develop broad-host-range vectors for a variety of model and non-model organisms.		

DATA INTEGRATION, MODELING, AND AUTOMATION

Goal	Breakthough Capability	Milestone

Establish functional prediction through biological engineering design at the biomolecular, cellular, and consortium scale.

Fully-automated molecular design from integrated, large-scale design data frameworks.

2 Years	5 Years	10 Years	20 Years
Structure- and comparative analysis-based libraries for automated directed evolution, with feedback of large-scale results to algorithms.	Automated designs for integrated manufacturing to enable more successful, iterated workflows. Large-scale design data generation to inform next-generation algorithms for molecular design.	Use of large-scale design data in integrated frameworks.	Design and integration of thousands of critical catalytic activities into proteins for a set of model hosts and creation of standard tools for allosteric control of these activities.

Scalable, data-driven host design for complex environments that enable high-level production of natural biomolecules.

2 Years	5 Years	10 Years	20 Years
Ability to make and screen multiple host mutations for epistasis mapping and synthetic interactions, making large-scale host optimization possible. Better data on physiology and fitness in deployment environments suitable for informing design.	Thematic design rules for host system engineering inferred from data. Tools to acquire and transfer data to a novel host to inform both genetic-domestication and prediction and determination of function. Novel design tools to support host design for more complex, natural (non-laboratory) environments.	Data-driven domestication of any new host for new activities in any environment and scale.	

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