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Genomics:GTL

Systems Biology for Energy and Environment

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U.S. Department of Energy
Office of Science
Office of Biological and Environmental Research

Genomics:GTL Awardee Workshop VI

Feb. 11, 2008

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Genomicsgtl.energy.gov

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Mission-Inspired Science

Just as DOE's mission to understand health impacts of energy inspired the Human Genome Project, GTL is a systems approach to understanding biology, built on genomics and inspired by DOE missions in Energy, Climate, and Environment.

- **Develop biofuels as a major secure national energy resource.**
- **Understand relationships between climate change and earth's ocean and terrestrial ecosystems and assess options for carbon sequestration in these systems.**
- **Develop biological solutions for intractable environmental problems.**

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Mission Challenges for Biology

Biofuels

Gain knowledge and tools for using microbes and plants to build a national biofuel capability to

- Develop sustainable energy crops.
- Develop biotechnologies for producing advanced biofuels.

Cleanup

Understand microbial and plant impacts on subsurface contaminant fate to

- Develop better assessment tools.
- Design improved bioremediation methodologies.

Climate Stabilization

Determine ocean and terrestrial ecosystem contributions to the global carbon cycle to

- Improve projections of climate change and its impacts.
- Create carbon-biosequestration strategies.

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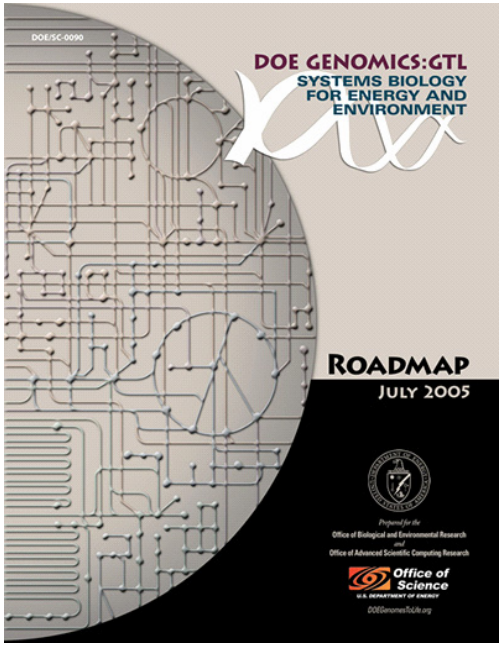
The Genomics: GTL Roadmap



- systems biology plan to accelerate the scientific discovery needed to support the development of practical applications for DOE energy and environmental missions
- Issued in July 2005
- Science goals and objectives still important
- Exists as a living document
- New developments required updating the GTL Strategic Plan!

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National Academy Review

"The use of systems and synthetic biology approaches in the Genomics: GTL program to address some of the most pressing issues in microbial genomics relevant to DOE's mission in energy security, environmental remediation, and carbon cycling and sequestration is not only appropriate but necessary…….

Systems biology research is needed to develop models for predicting the behavior of complex biological systems, to engineer microorganisms for bioremediation and energy-related needs, and to understand carbon cycling……

Systems biology research on plants and microorganisms is not likely to be conducted on a large scale without DOE's visionary thinking……

The concept of infrastructure for research and technology development offers a logical and even necessary pathway for achieving DOE's research goals…."

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GTL Core Science Goals at All Scales

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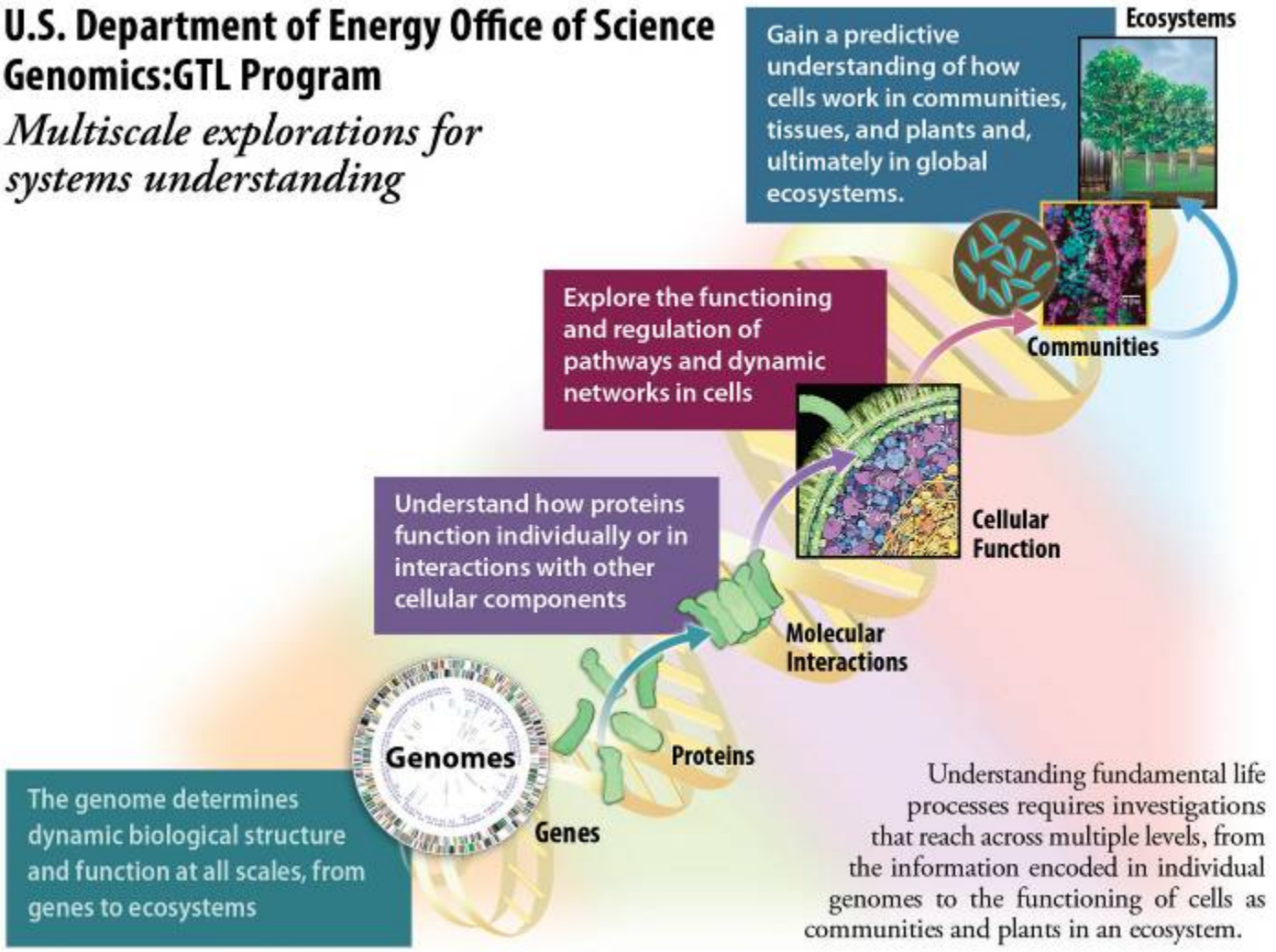
Genomics:GTL Program
Multiscale explorations for systems understanding



Understanding fundamental life processes requires investigations that reach across multiple levels, from the information encoded in individual genomes to the functioning of cells as communities and plants in an ecosystem.

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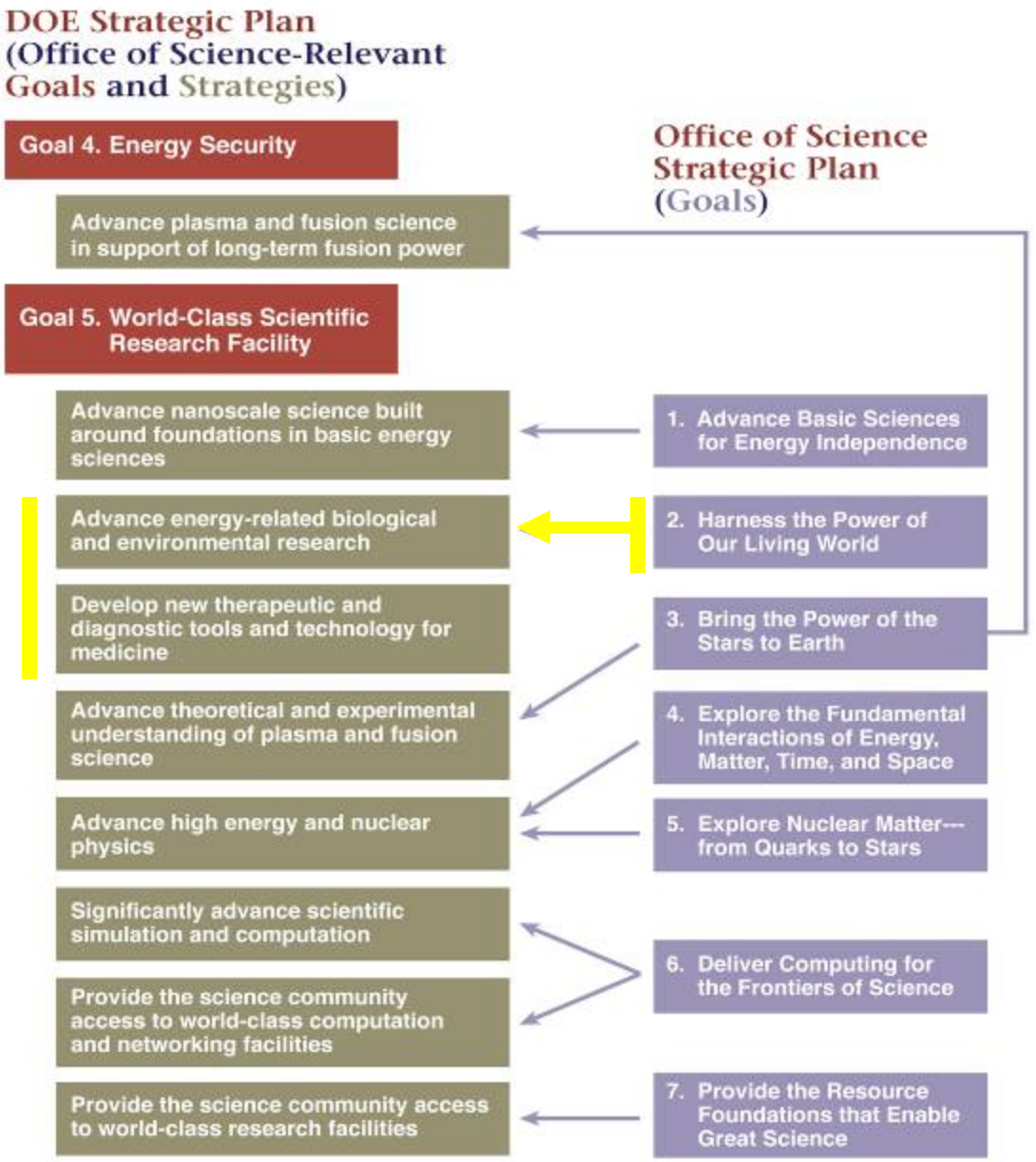
Science at Scales

- ***Molecular:*** Focusing on genes, proteins, multicomponent protein complexes, and other biomolecules that provide structure and perform the cell's functions -- to understand how the genome determines dynamic biological structure and function at all scales from genes to ecosystems, and to understand how proteins function individually or in interactions with other cellular components.

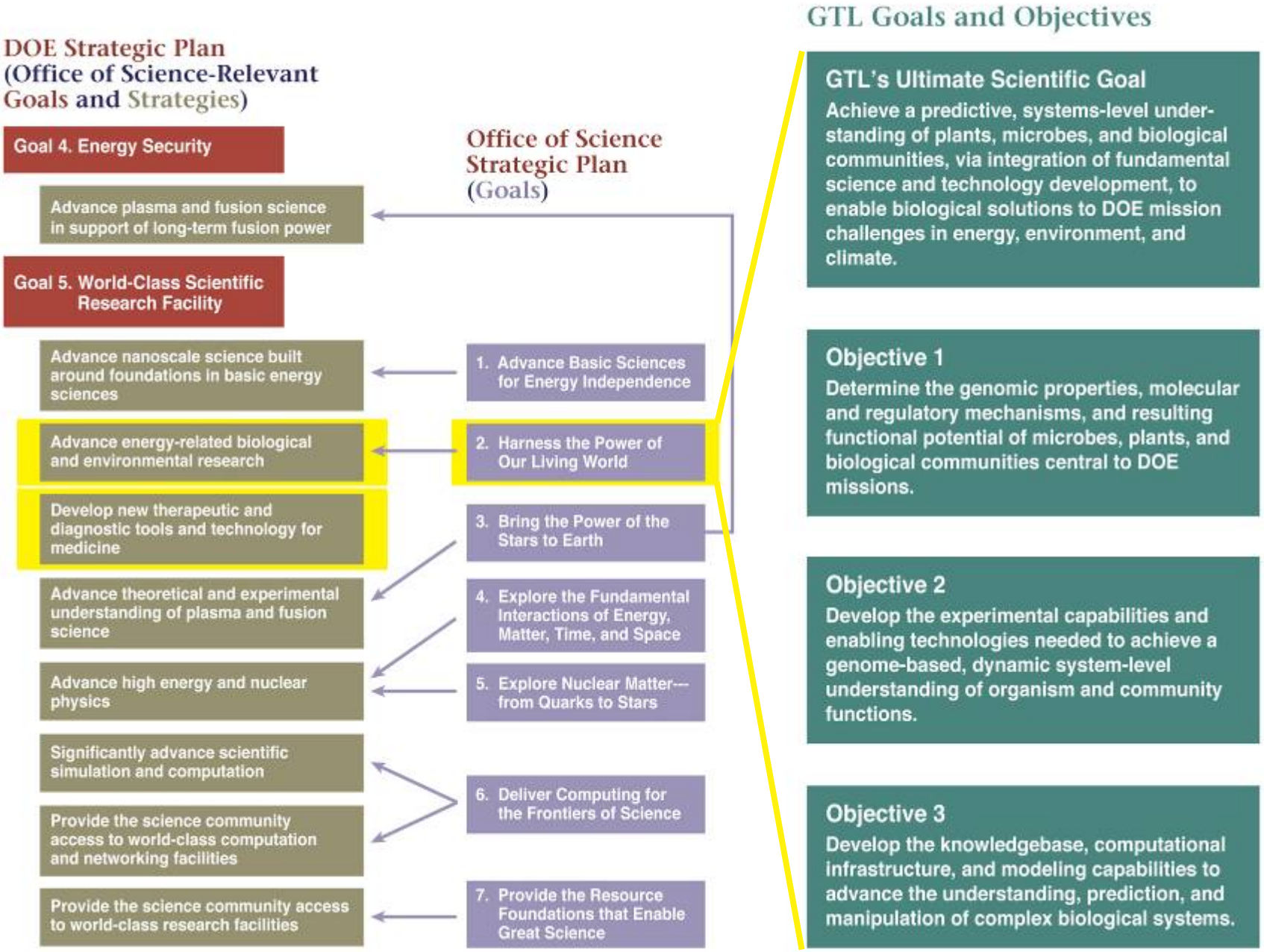
- ***Whole cell:*** Investigating how dynamic molecular processes, networks, and subsystems are controlled and coordinated to enable such complex cellular processes as growth and metabolism in cells.

- ***Microbial community and higher organisms:*** Exploring how diverse cellular systems interact to carry out coordinated complex processes and both respond to and alter their environments – how cells work in communities, tissues, and plants, and ultimately in global ecosystems.

GTL Goals, Objectives Link to Higher DOE Goals



GTL Goals, Objectives Link to Higher DOE Goals



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GTL Goal and Objectives

GTL's Ultimate Scientific Goal

Achieve a predictive, systems-level understanding of plants, microbes, and biological communities, via integration of fundamental science and technology development, to enable biological solutions to DOE mission challenges in energy, environment, and climate.

- ***Objective 1***

  Determine the genomic properties, molecular and regulatory mechanisms, and resulting functional potential of microbes, plants, and biological communities central to DOE missions.

- ***Objective 2***

  Develop the experimental capabilities and enabling technologies needed to achieve a genome-based, dynamic systems-level understanding of organism and community functions.

- ***Objective 3***

  Develop the knowledgebase, computational infrastructure, and modeling capabilities to advance the understanding, prediction, and manipulation of complex biological systems.

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GTL Approach

- A genomics-based systems biology perspective and associated methods
- A focus on mission systems and problems
- Relies on collaborative and other integrative approaches
- Establishes and utilizes user facilities, integrated capabilities, and centers
- Employs creative management approaches for achieving results.

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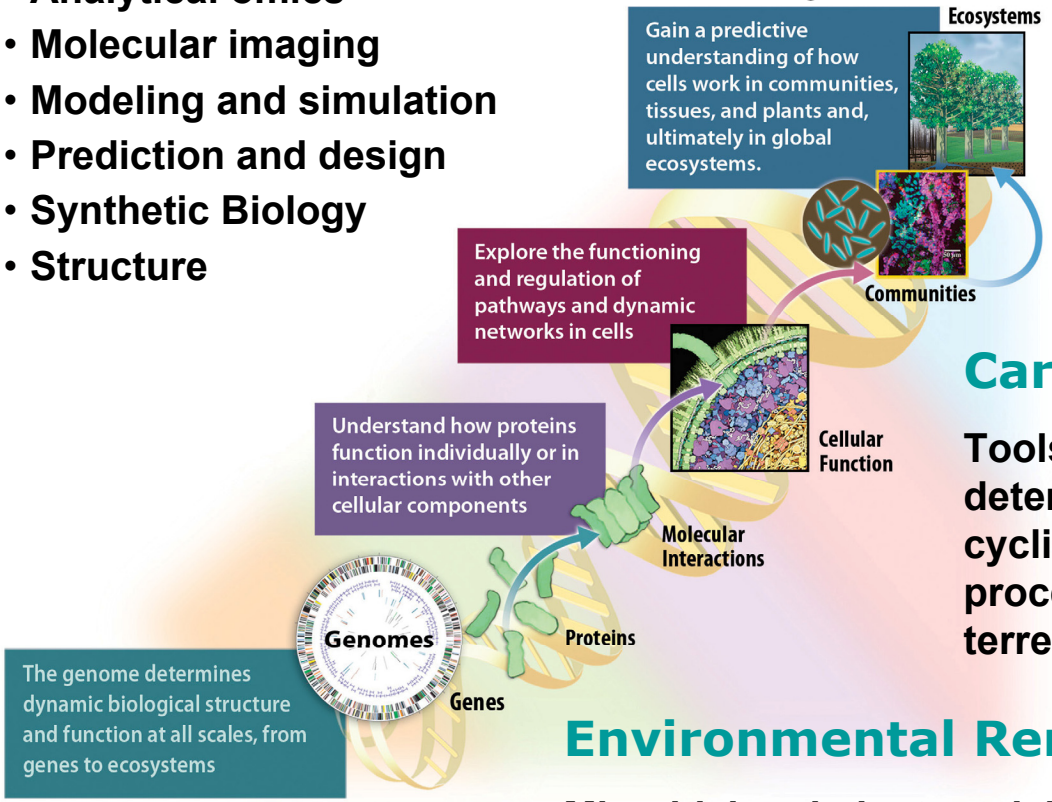
Genomics:GTL — A Mission-Inspired Fundamental Research Approach

GTL Systems Biology and Technology Development	Core Science Goals	Mission Grand Challenges for Biology

- Microbe-, plant-, meta-genomics
- Analytical omics
- Molecular imaging
- Modeling and simulation
- Prediction and design
- Synthetic Biology
- Structure



Energy

Tools and concepts for designing and engineering bioenergy plant and microbial systems, including the mechanistic bases.

Carbon Cycle

Tools and concepts to determine the carbon-cycling and sequestration processes of ocean and terrestrial ecosystems.

Environmental Remediation

Microbial and plant modeling and experiments to predict and control contaminant fate and transport.

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Technology Endpoints

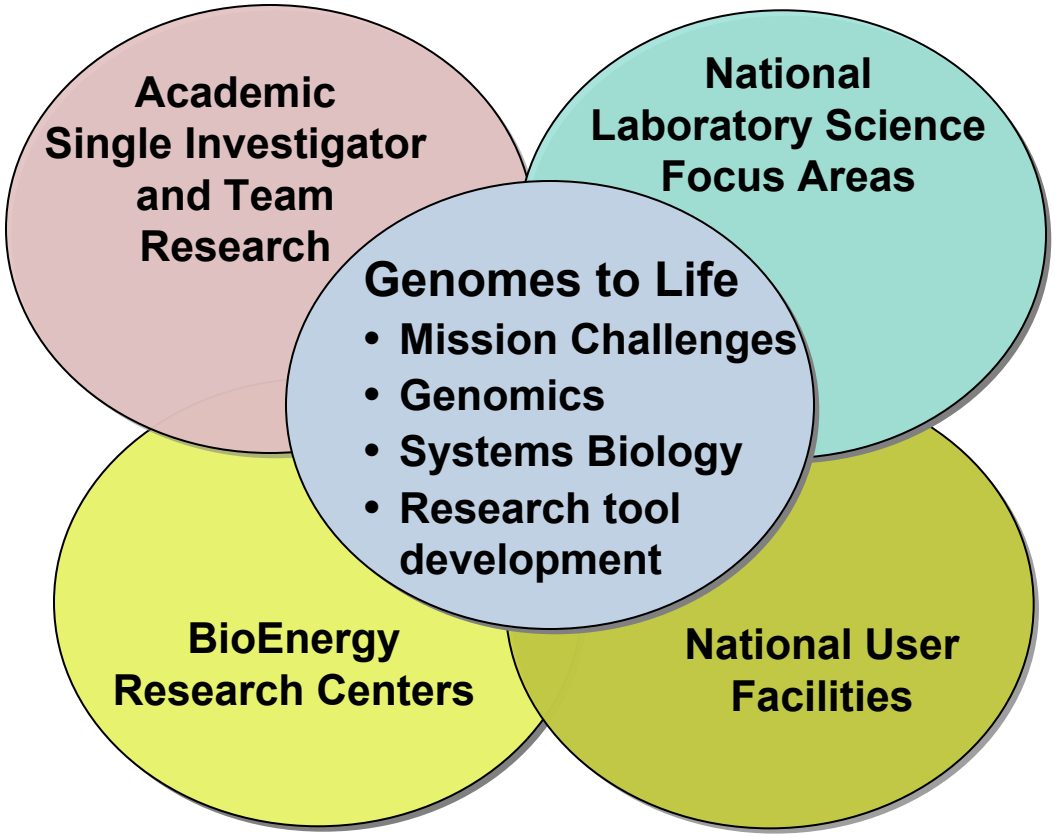
Payoffs for the Nation

Viable Biofuels Technologies

Earth Systems Modeling and Biosequestration Strategies

Improved Strategies for Bioremediation

The GTL Research Enterprise



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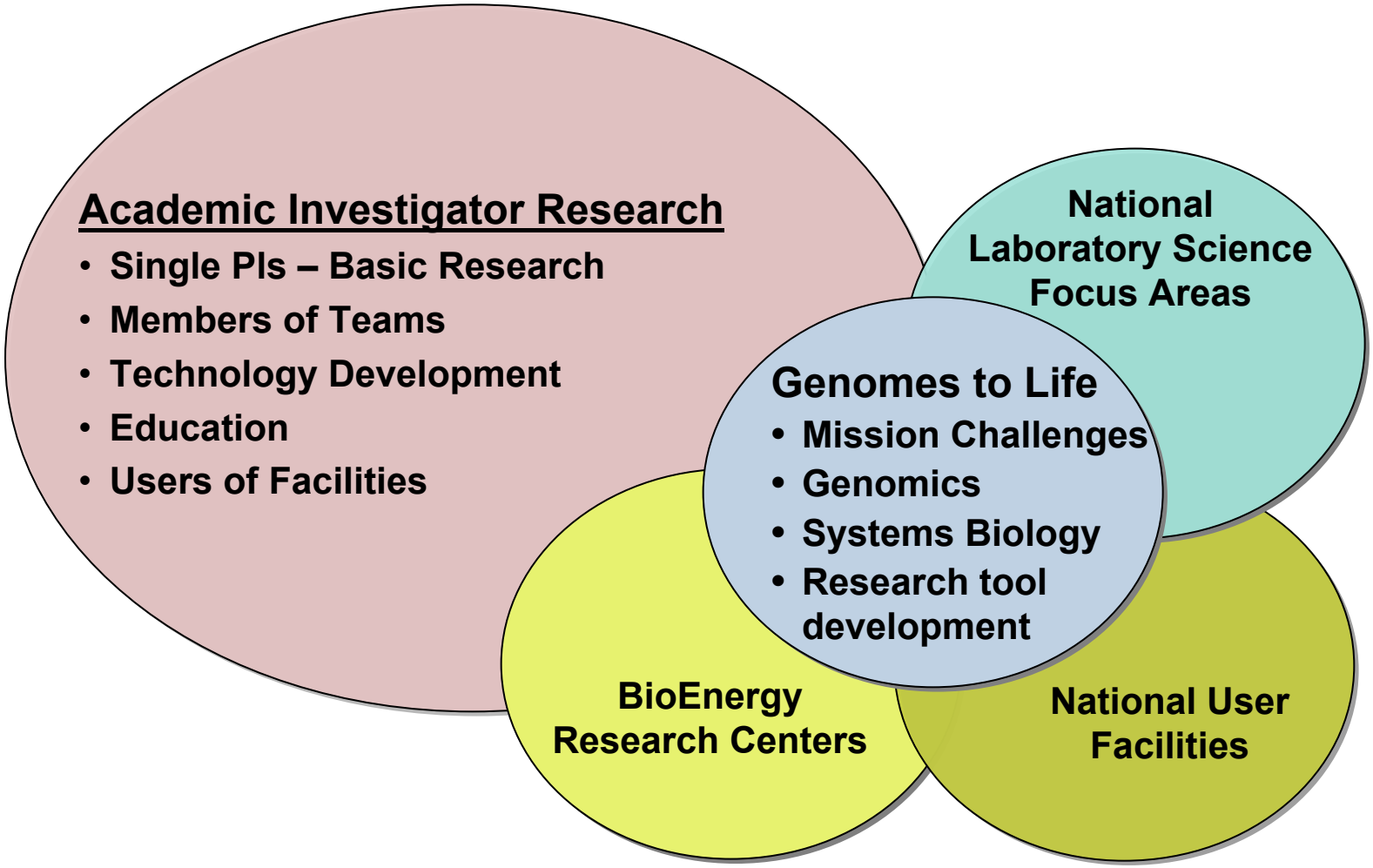
The GTL Research Enterprise



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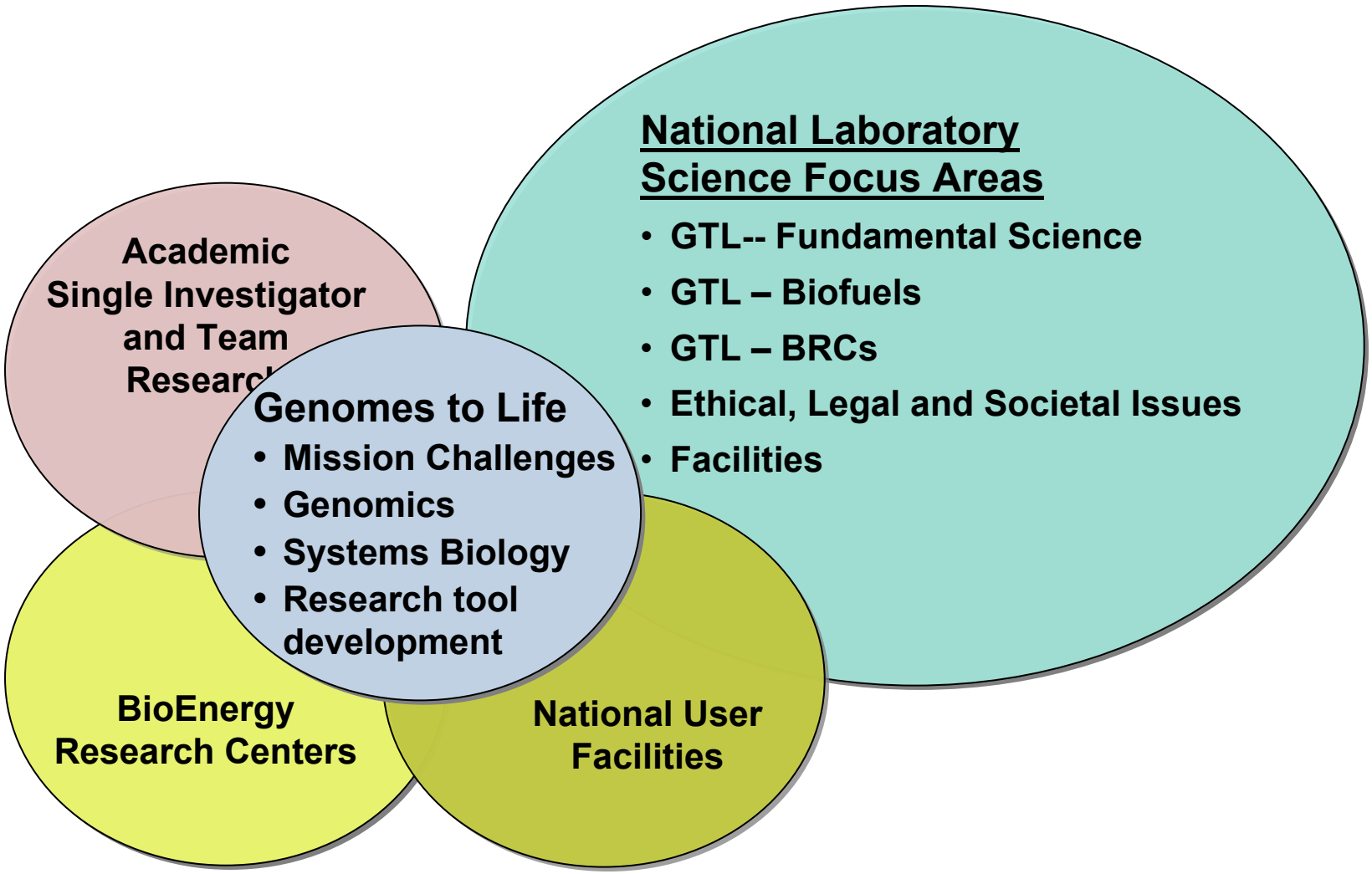
The GTL Research Enterprise



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National Laboratory Science Focus Areas

DOE National Laboratories

- **Unique resources for fundamental, merit-reviewed research and technology innovation and as sites for national scientific user facilities.**
- **Centers of Excellence for BER research and technology development.**
  - **Take advantage of, exploit, and highlight the broad and unique national laboratory scientific and administrative environment**

Examples

- **Use of novel instrumentation or combinations of instrumentation.**
- **Integration of research across disciplines or scientific challenges in a specific focus area.**
- **Flexibility to rapidly test or address new hypotheses or discoveries, significant roadblocks, or emerging scientific or technical challenges.**

Research and technology development at the National Laboratories should play a leading, unique, integrating and complementary role, not a competing role, in BER's broad portfolio that includes scientific investments at universities, in the private sector, and at National Laboratories.

Prospective SFAs

- **GTL-- Fundamental Science**
- **GTL – Biofuels**
- **GTL – Bioenergy Research Centers**
- **Ethical, Legal and Societal Issues**
- **Facilities**

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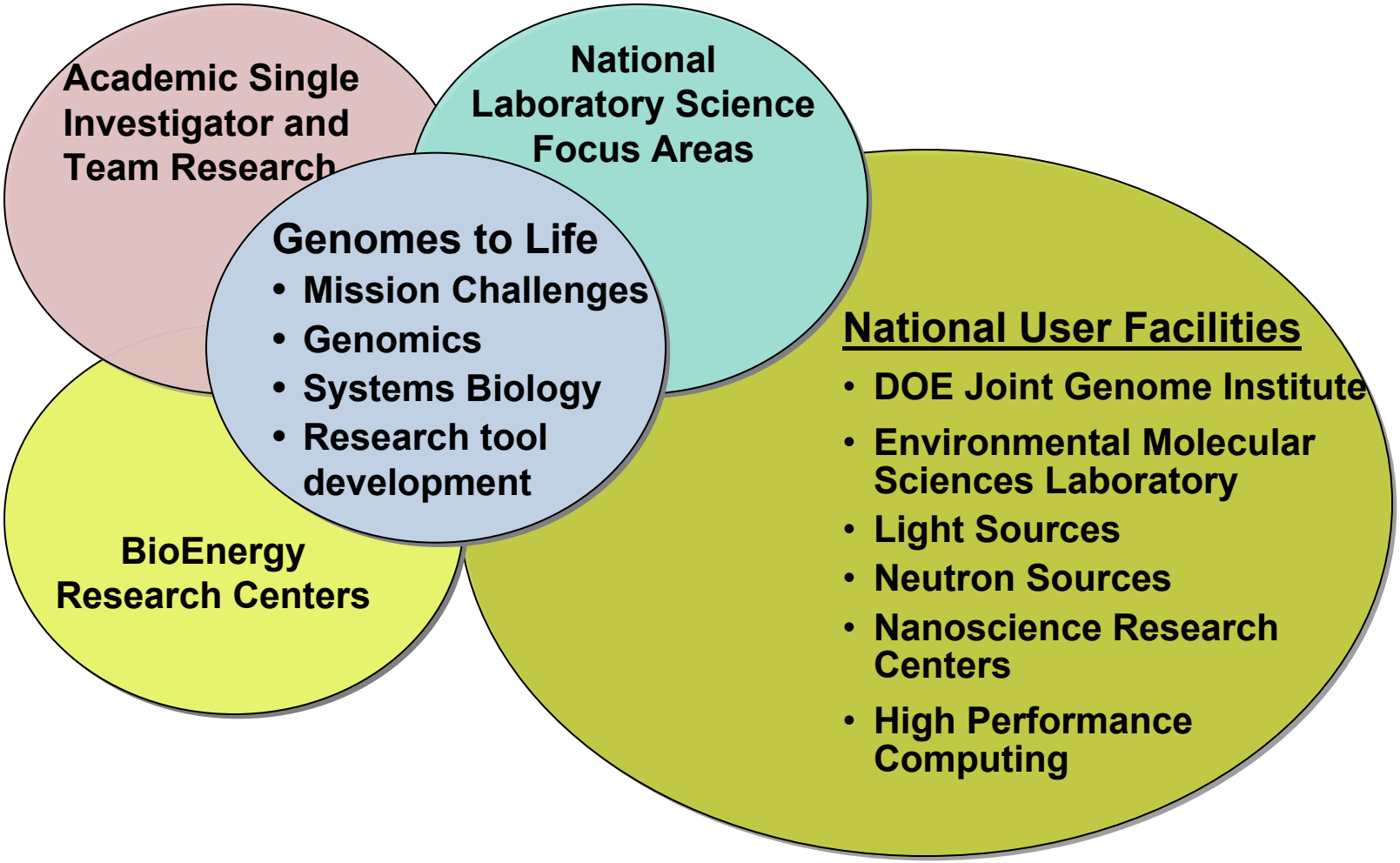

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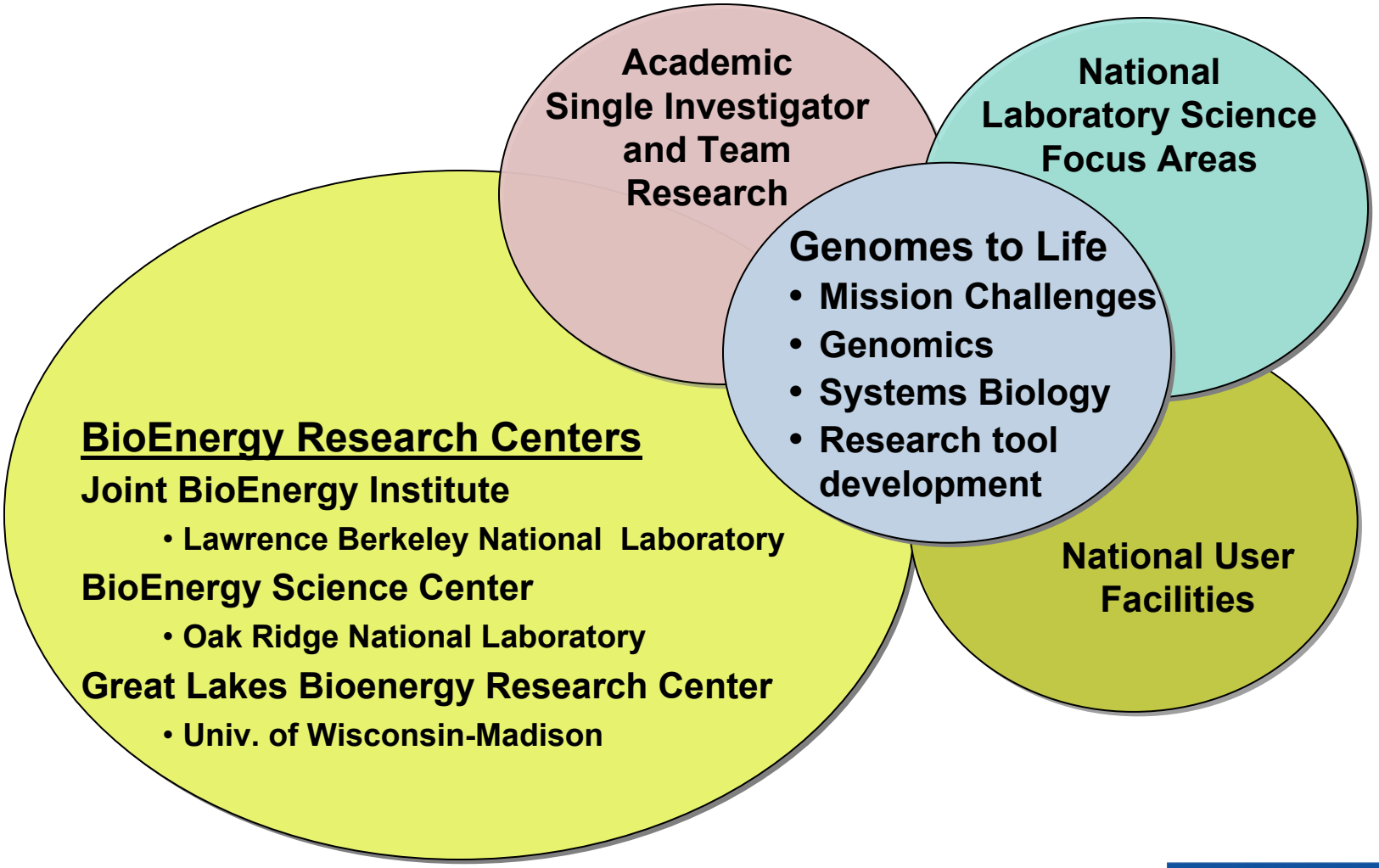
The GTL Research Enterprise



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GTL Science Hallmarks

- Mission-inspired fundamental science
- Global, genome-derived principles of microbial, plant, and community functions
- Development of enabling experimental technologies and capabilities to provide comprehensive data
- Modeling and simulation tools for predictive understanding across multiple scales of biological organization
- Building a GTL Knowledgebase facilitating data and information sharing for modeling and comparative analyses

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GTL Operational Hallmarks

- Maintains a strategically-managed research portfolio to respond to emerging national priorities and mission needs
- Selects research based on scientific merit and peer-review
- Supports research conducted by individual investigators, collaborative teams, and research centers at DOE national laboratories, academic institutions, and industry
- Leverages capabilities and resources across BER programs and scientific user facilities
- Encourages communication across the scientific community through the annual GTL program meeting, workshops, symposia, and exhibits at national meetings
- Fosters an atmosphere of open access to data and information
- Coordinates with other DOE programs and other federal agencies

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Biomass to Biofuels Workshop Plan 2006

GTL-led workshop created foundation for science to break barriers to cellulosic ethanol production on an industrial scale

DOE OBER GTL- & DOE Energy Efficiency and Renewable Energy - Sponsored workshop

Workshop research strategies influenced

- GTL Bioenergy Research Centers FOA
- Individual GTL investigator projects in bioenergy
- BP Center call for proposals
- Biofuels research agendas internationally
- Commercial planning including Venture Capital
- >6000 distribution

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Copies available at:
http://genomicsgtl.energy.gov/biofuels/b2bworkshop.shtml

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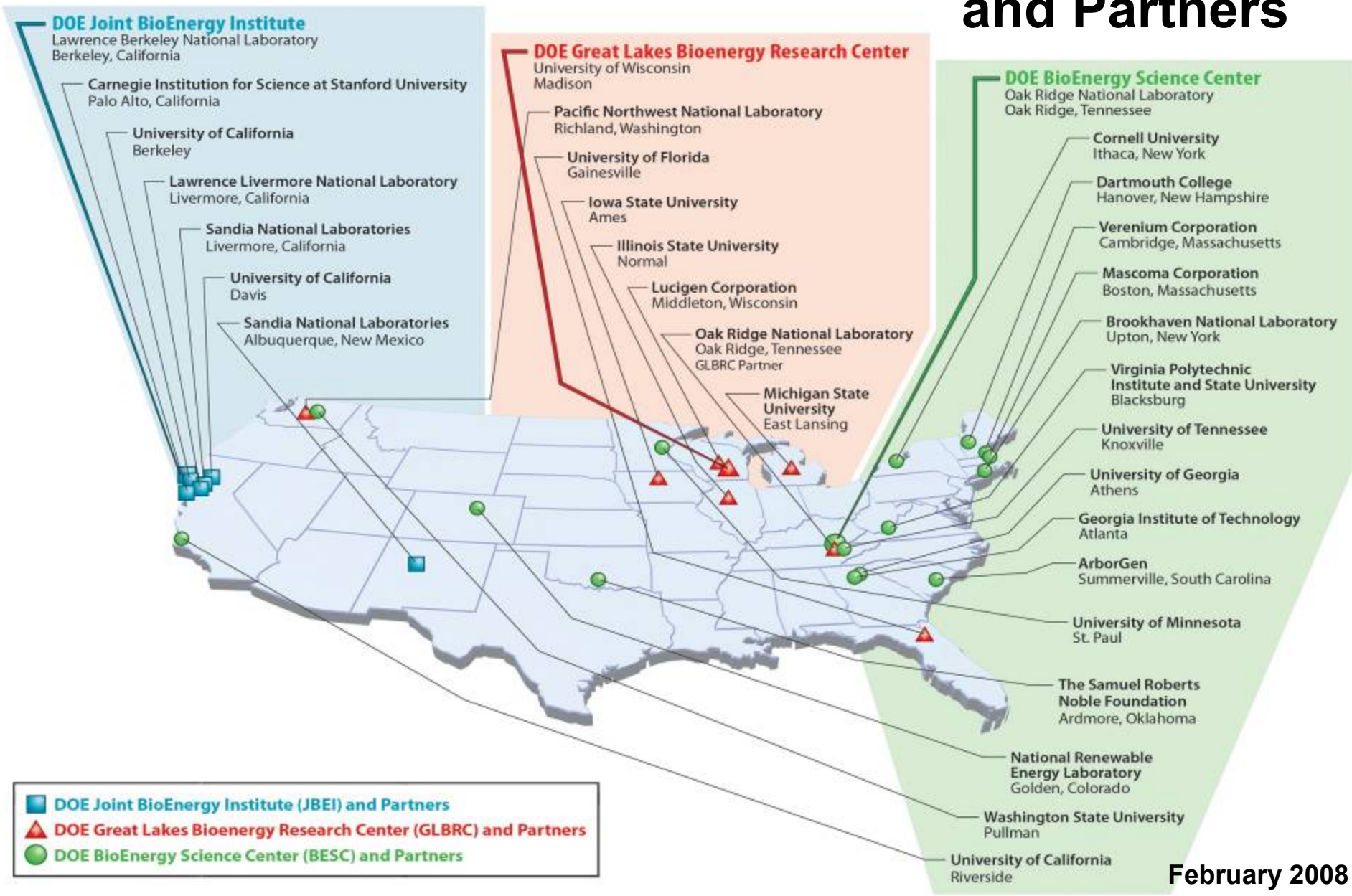
DOE Bioenergy Research Centers and Partners



February 2008

DOE Bioenergy Research Center Strategies at a Glance

Grand Challenge: Development of Next-Generation Bioenergy Crops

- **BESC** – Decrease or eliminate harsh chemical pretreatments by engineering plant cell walls in poplar and switchgrass to be less recalcitrant; simultaneously increase total biomass produced per acre.
- **GLBRC** – Engineer "model" plants and potential energy crops to produce new forms of lignin and more starches and oils, which are more easily processed into fuels.
- **JBEI** – Enhance lignin degradation in "model" plants by changing cross-links between lignin and other cell-wall components and translate these genetic developments to switchgrass.

Grand Challenge: Discovery and Design of Enzymes and Microbes with Novel Biomass-Degrading Capabilities

- **BESC** – Screen natural thermal springs to identify enzymes and microbes that effectively break down biomass at high temperatures; understand and engineer cellulosomes—multifunctional enzyme complexes for degrading cellulose.
- **GLBRC** – Identify combinations of enzymes and pretreatments needed to digest specific biomass types; express biomass-degrading enzymes in the stems and leaves of corn and other plants.
- **JBEI** – Improve performance and stability of enzymes harvested from the rainforest floor and other environments; engineer, through directed evolution, highly efficient cellulase enzymes.

Grand Challenge: Discovery and Design of Microbes that Transform Fuel Production from Biomass

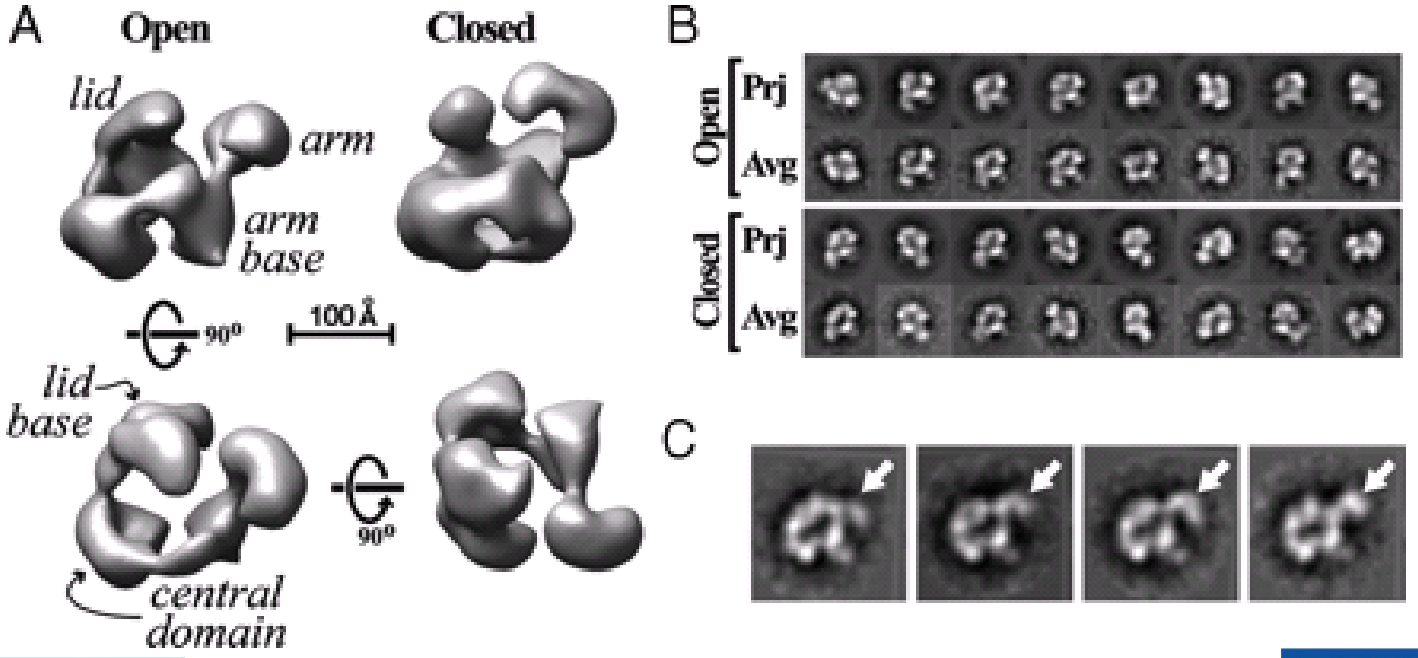
- **BESC** – Reduce the total number of cellulosic ethanol production steps by engineering a cellulose-degrading microbe to produce ethanol more efficiently.
- **GLBRC** – Reduce the total number of cellulosic ethanol production steps by engineering an efficient ethanol-producing microbe to degrade cellulose.
- **JBEI** – Connect diverse biological parts and pathways to create entirely new organisms that produce fuels other than ethanol; engineer organisms to produce and withstand high concentrations of biofuels; derive useful chemical products from lignin degradation.

Center information accurate as of Jan 2008

Structural Studies
Getting the Picture

Orthogonal Tilt Reconstruction

- Simplifies, improves generation of reliable CryoEM initial molecular models
- Complementary 2D images at 90°-- Providing critical missing views
- Removes distortion reconstructions of molecules -- detect and characterize conformational flexibility



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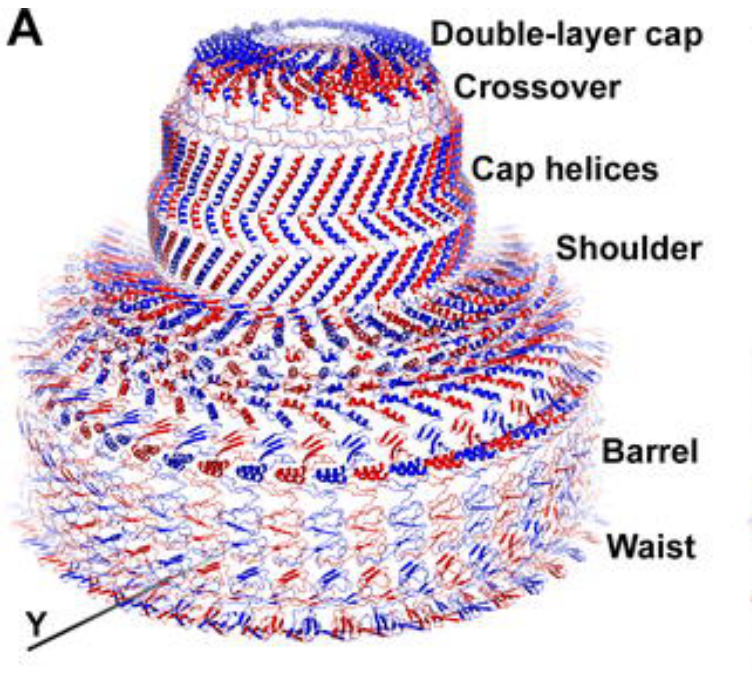
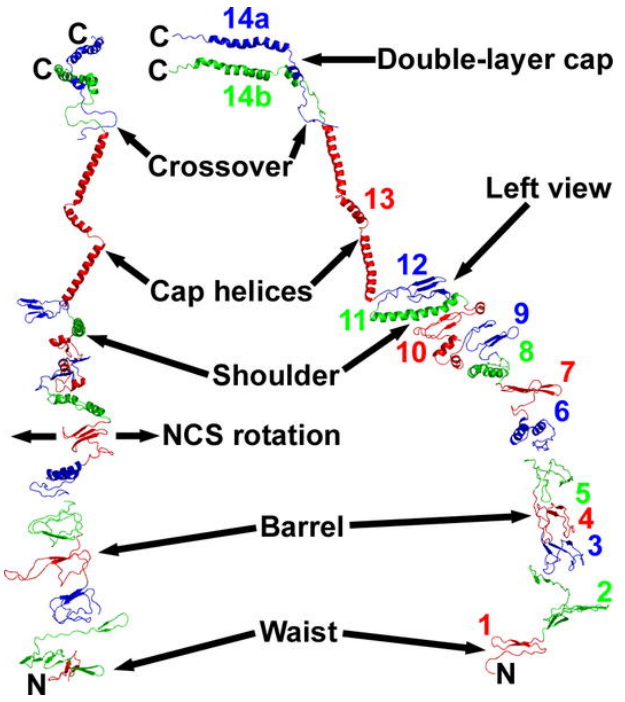
The Major Vault Protein



The external structure of the top half of the multiprotein complex



The structures of the protein domains that assemble into the complex

The complete structure and the structures of the components were determined using electron microscopy, x-ray crystallography, nuclear magnetic resonance spectrometry or computational modeling
The senior author, David Eisenberg, is Director of the UCLA-DOE Institute for Genomics and Proteomics

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Anderson, Kickhoefer, Sievers, Rome, and Eisenberg,
"Draft Crystal Structure of the Vault Shell at 9-Å Resolution"
PLoS Biology 5(11): e318 (2007)

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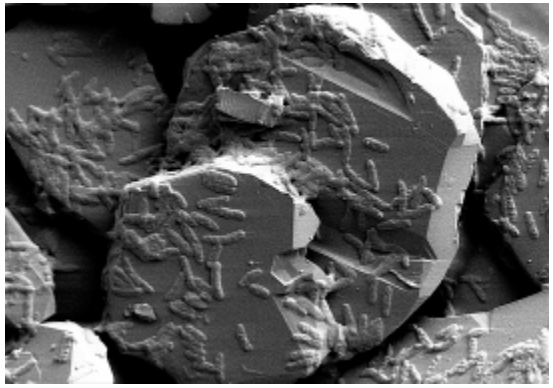
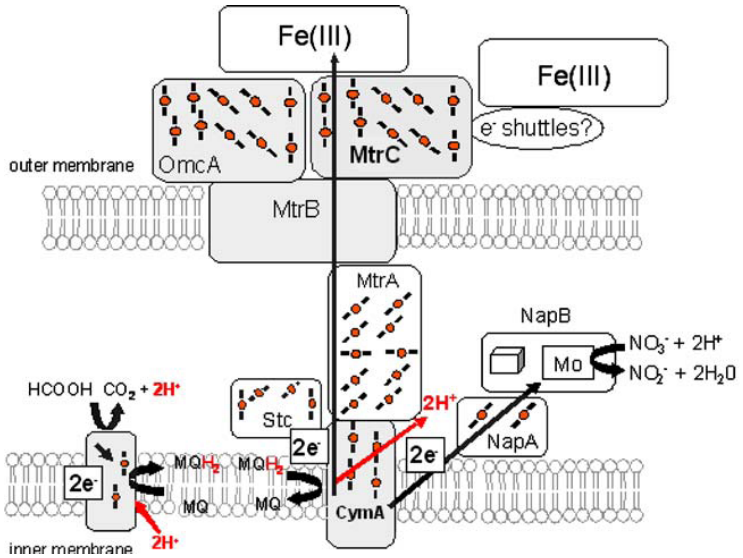
Extracellular Electron Transfer
Solid State Respiration





- **Bacteria such as *Geobacter* and *Shewanella* are able to transfer electrons to solid phase mineral substrates outside of the cell**
- **The genomes of these organisms encode an array of multi-heme cytochromes, some of which are translocated to the cell envelope where they can transfer electrons directly to mineral or electrode surfaces**
- **These proteins are novel components of "molecular wires" that facilitate electron transfer from the cell membrane to the exterior environment**
- **Electron transfer between microbial cells and metals is a fundamental process that controls energy exchange throughout the geosphere and can be an important control on radionuclide contaminant migration**

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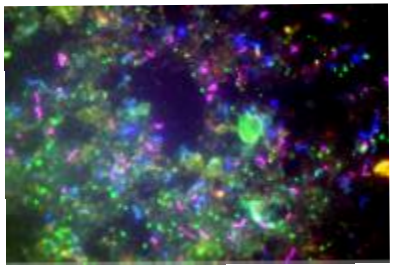
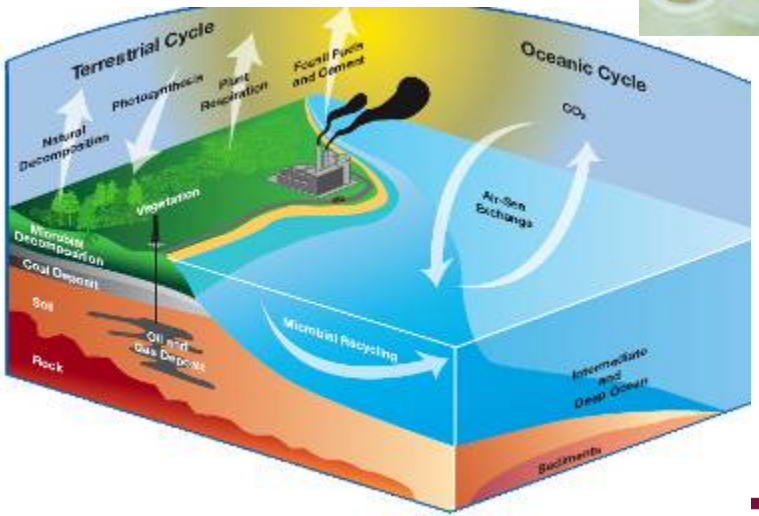
JGI – DOE Mission Targets

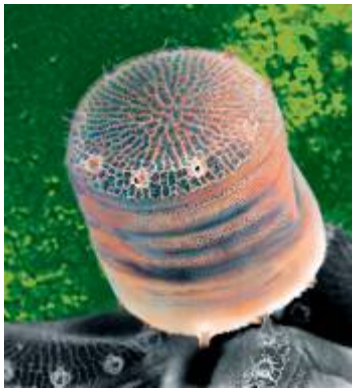
Bioenergy

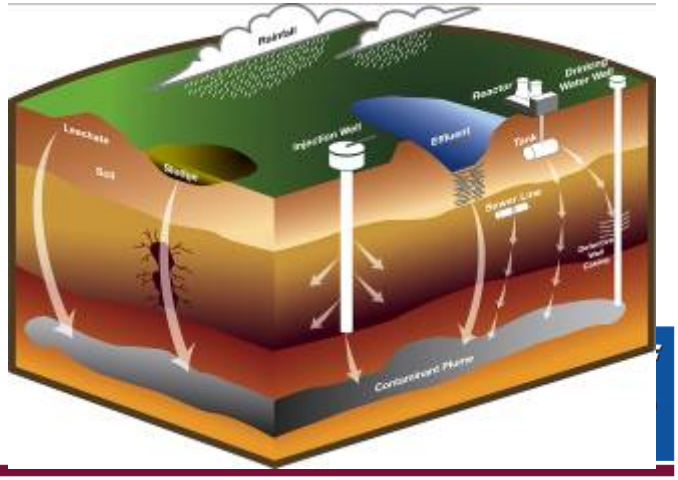


Carbon Cycling



Bioremediation





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The Joint Genome Institute A DOE User Facility

- **Expanding capacity to sequence and analyze the genomes and metagenomes of a growing collection of organisms and communities**
  - **A first step toward whole biological systems understanding required for biological applications to DOE missions of critical national needs**
  - **State of the art capabilities, expert staff in an array of computing and biological research disciplines, workshops, and annotation jamborees are unique, value-added features critical to the broad biological user community and DOE mission science.**

Organisms and microbial consortia sequenced or in progress include

- **Microbes relevant to bioremediation approaches**
- **Microbial communities responsible for creating acid mine drainage**
- **Microbes performing critical processes in Earth's carbon cycle including photosynthesis, carbon fixation, and respiration**
- **Plants as potential biomass crops for bioenergy**
- **Microbes and microbial consortia using novel enzymes to process biomass to bioethanol and other fuels**

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Metamethods

Metagenomics and Metaproteomics

Genomic and molecular characterization of complex environmental communities has revolutionized Microbial Ecology

- **> 99% of microbes resist lab culture techniques**
- **Genomic metamethods are revealing the genes underlying critical interactions in complex communities**
  - **Stunning genetic diversity (millions of unique genes) discovered in marine and terrestrial metagenomics and metaproteomics studies**
  - **New mechanisms for survival and adaptation by massive genetic exchange and creation of new families of proteins within communities.**

These methods and discoveries have fundamental and practical value

- **Opening a new era of scientific discovery resulting in entirely new**
  - **Industrial applications including biofuels**
  - **Understanding of planetary biogeochemical cycles important for climate change and bioenergy crop sustainability**
  - **Understanding of microbial and plant capabilities important to remediation**

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Life at the Limits
Mining Acid Mine Drainage

- **Dense microbial communities thriving in the presence of extremely low pH and high concentrations of toxic metals**
- **Metagenomics & Metaproteomics reveal that bacteria survive and adapt in this environment via exchange of large sections of their genomic DNA, resulting in the modular creation of new proteins**
- **Metamethods open a new era in microbial ecology and provide new paths to bioremediation and industrial processing.**

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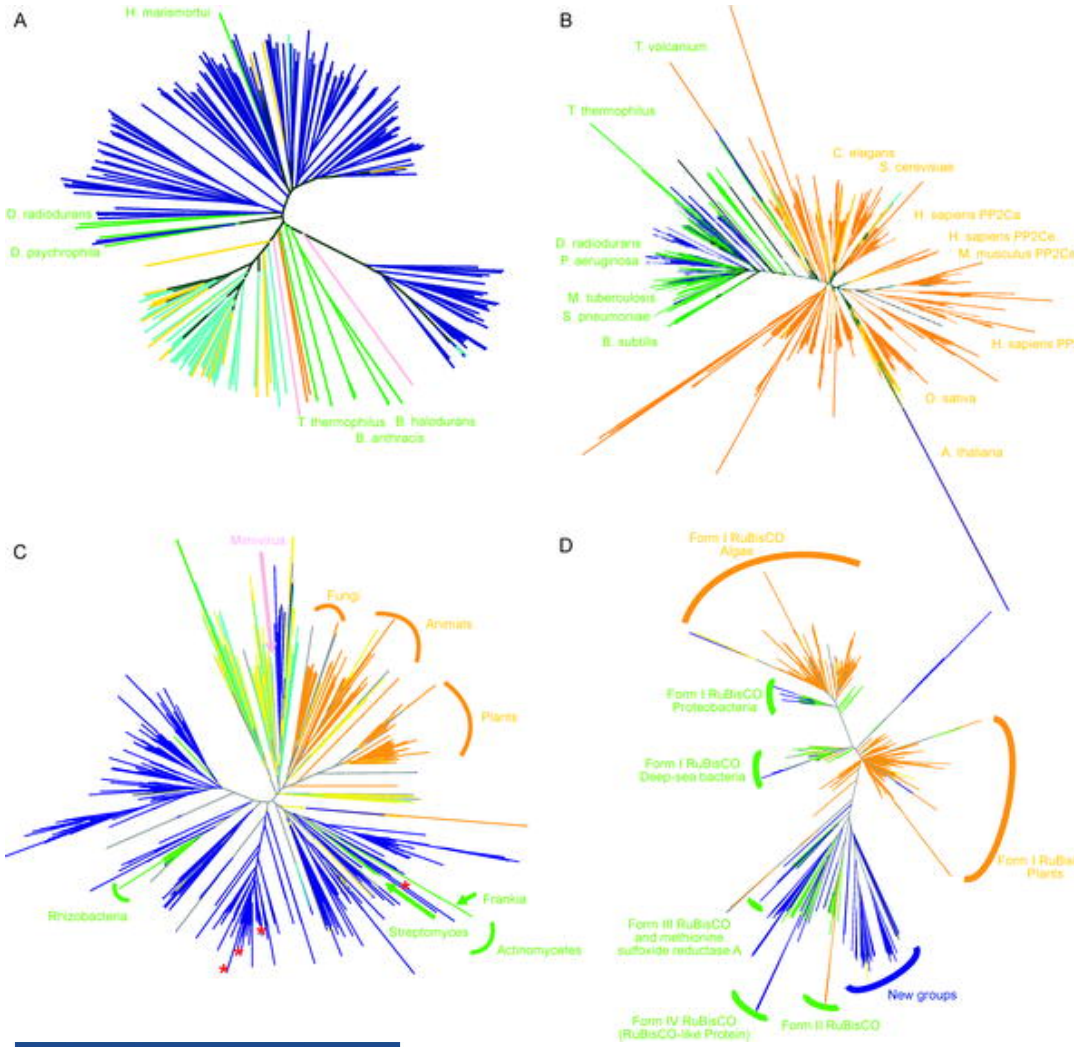
Global Ocean Survey (GOS)
A Sea of Proteins



Metagenomics of diverse marine environments across the globe

6.3 billion base pairs

Spurring development of powerful new computational tools to predict protein function and genetic adaptation from sequence

Astonishingly high number of novel proteins – a new era in protein function discovery and industrial innovation.

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GTL Grand Challenges

BER history of high-risk mission-inspired multidisciplinary science

- **The Human Genome Project is an example**
- **Genomics enables systems explorations for solutions to complex mission problems**

Characteristics of a Grand Challenge

- **Hard problem**
- **Solvable problem**
- **Significant impact**

- **GTL grand challenges will be identified through community input and workshops**
- **Proof of principle, high-risk pilot activities will be initiated**
- **Solicitations will be issued for research strategies to build upon successful pilot projects**
- **GTL data sharing and Knowledgebase will be critical for establishing productive research partnerships**

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Environmental Restoration

Grand Challenge examples

- Microbial and plant modeling and experiments to predict and control contaminant fate and transport.
- Systems biology methods to understand, predict, and control the behavior of geochemically driven microbial communities.

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Carbon Cycling and Biosequestration

Understanding biological contributions to the global carbon cycle is critical to advancing climate change research. GTL research can contribute by:

- **Examining biological carbon sources and sinks in terrestrial and ocean systems that fix, transform, or reemit CO_2**
- **Facilitating connection of data across multiple scales of complexity: organism, community, ecosystem**
- **Improving integration of experimental approaches and modeling efforts**
- **Providing fundamental knowledge that will inform potential mitigation strategies**

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DOE-OBER workshop

Carbon Cycling and Biosequestration

Washington DC, March 4-6, 2008

Workshop Purpose

- Identify research needs and opportunities for understanding biological carbon cycling and biosequestration
- Provide an assessment of where the science and technology now stand and where barriers to progress might exist
- Describe the directions for fundamental research that can be pursued to meet these goals.
  - Terrestrial Plant Productivity & Carbon Biosequestration
  - Biological Cycling of Carbon in Terrestrial Environments
  - Biological Cycling of Carbon in Ocean Environments
  - Effects of Climate Change on Carbon Cycling & Biosequestration
  - Cross-cutting science

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Data Management Policies and Workshop

- **DOE mission science requires GTL to address complex problems**
  - **A systems approach involving many different disciplines**
  - **Cycles of theory, computational modeling, and experimentation**
  - **Models of the collective interactions in a system; requires global approaches**
  - **High-throughput quantitative techniques**
    - **Genomics + omics = data to build and validate models**
  - **Requires integration and availability of heterogeneous data and information.**
  - **Success of GTL is dependent on data and information integration and sharing policies, practices and processes.**
  - **Develop and implement a GTL Systems Biology Network/ Knowledgebase**
    - **Standards, ontologies, and databases**
    - **Curation and archiving of data**

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