William R. Wiley EMSL
Environmental Molecular Sciences Laboratory

EMSL Scientific Grand Challenges: Case Studies in Collaborative User Research

David W. Koppenaal
Chief Technology Officer
Environmental Molecular Sciences Laboratory

NUFO 2008

EMSL Grand Challenges- Background & Perspective

- EMSL Mission and Capabilities
- The EMSL scientific Grand Challenge challenge
- Development of the Scientific Grand Challenge concept
- Scientific Grand Challenge Model & Implementation
  - BioGeochemistry Grand Challenge
  - Membrane Biology Grand Challenge
- Development of the Membrane Biology Scientific Grand Challenge
  - Solicitation, review, and selection
  - Launching the Membrane Biology Scientific Grand Challenge
  - Timeline
  - Review & Evaluation Process
- Measuring success
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EMSL Mission

William R. Wiley's Vision:
An innovative multipurpose user facility providing *"synergism between the physical, mathematical, and life sciences."*

EMSL, ***a national scientific user facility*** at the Pacific Northwest National Laboratory, provides integrated experimental and computational resources for discovery and technological innovation in the environmental molecular sciences to support the needs of DOE and the nation.

Providing Extraordinary Tools & Scientific Staff

- **Signature EMSL Capabilities**
  - Aerosol and cluster characterization
  - Molecular science computing
  - Interfacial & nanoscale synthesis and characterization
  - Molecular Spectroscopy & Imaging
  - High Field Magnetic Resonance Spectrometry
  - High Performance Mass Spectrometry for Global Proteomics
- **Support**
  - Computing and networking services
  - Instrument development laboratory
  - User services

Aerosol & Cluster Characterization

Molecular Science Computing

Interfacial & Nanoscale Synthesis & Characterization

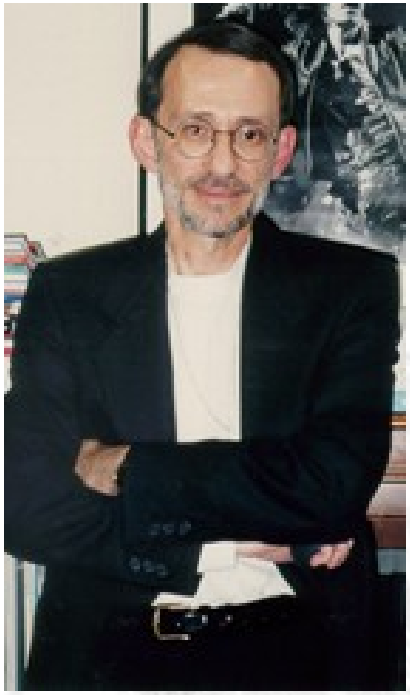
High Field Magnetic Resonance

High Performance Mass Spectrometry

Spectroscopy & Imaging

The Scientific Grand Challenge *Challenge*

- Spring 2002: In response to an EMSL review, then-DOE Office of Biological and Environmental Research (BER) Director Dr. Ari Patrinos challenged EMSL management to develop integrated, team-based approaches to ***solving large, grand challenge problems in biology***.



Grand Challenge - Drivers for EMSL

- Increase the scientific impact of EMSL
- Increase the use and user base of EMSL
- Demonstrate a new model for EMSL use and engagement
- Develop and employ new capabilities in EMSL

Development of the Scientific Grand Challenge Concept

- PNNL worked with BER to formalize the GC concept
  - BER made GC efforts part of PNNL's contractual requirements:

    1.1.2 The Contractor will i***ncrease the scientific impact of the EMSL user program*** within the environmental and biology research community. Specific measures of success are:

    1.1.2.1 ***Development and implementation within the EMSL user program of two scientific grand challenges*** in the area of subsurface fate & transport and biology. The increased scientific impact of the user program by one of these grand challenges will be ***verified and validated by a subcommittee of BERAC*** which will provide a recommendation to BER regarding the successful completion of this measure.

Scientific Grand Challenge Model

- Two different Scientific Grand Challenges with two different approaches:
  - Biogeochemistry/Subsurface Transport
    - Conceptual vetting with BER/ERSD
    - Internally led by PNNL with external collaborators
    - 3-year effort
  - Biology
    - Conceptual vetting by independent group
    - Formal solicitation and review process
    - Externally led with PNNL as collaborators
    - 3-5 year effort

Biogeochemistry Grand Challenge

"Electron Transfer at the Microbe-Mineral Interface"

Jim Fredrickson and John Zachara
Pacific Northwest National Laboratory
Tom DiChristina – Georgia Tech
Kevin Rosso – PNNL/EMSL

DOE-BER
May 9, 2006

Task Leaders

Disciplines: Biophysics, Biochemistry, Microbiology, Biogeochemistry, Surface Science, Mineral Physics

Alex Beliaev, PNNL
Terry Beveridge, Univ. of Guelph
Mike Bowman, PNNL
Gordon Brown, Stanford Univ.
***Tom DiChristina**, Georgia Tech.*
Tim Droubay, PNNL
Michel Dupuis, PNNL
Carrick Eggleston, Univ. of Wyoming
Scott Fendorf, Stanford Univ.
Gill Geesey, Montana State Univ.
Mike Hochella, Virginia Tech.

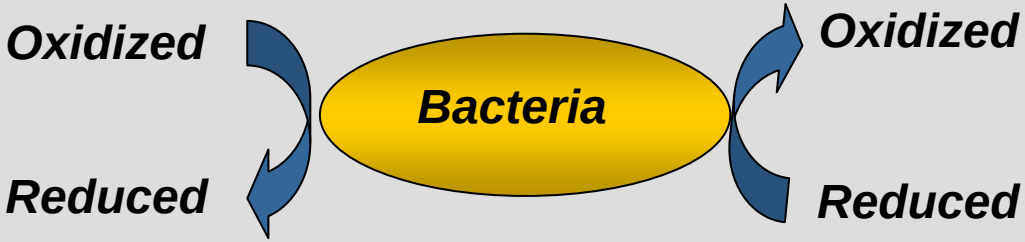
Mike Kennedy, PNNL
Brian Lower, PNNL
Ken Nealson, Univ. of S. California
David Richardson, Univ. of East Anglia
Kevin Rosso, PNNL
Daad Saffarini, Univ. of Wisconsin
Liang Shi, PNNL
Alfred Spormann, Stanford Univ.

Funding ~ EMSL/DOE-OBER and PNNL-LDRD

Poorly Explored Terrain: The Mineral-Microbe Interface

- Microorganisms influence their environment through energy and materials transfer across a complex biologic-solvent-solid interface
- The interfacial region is dynamic with chemistry and structure determined by interplay and response

Bacterial mediation of geochemical reaction



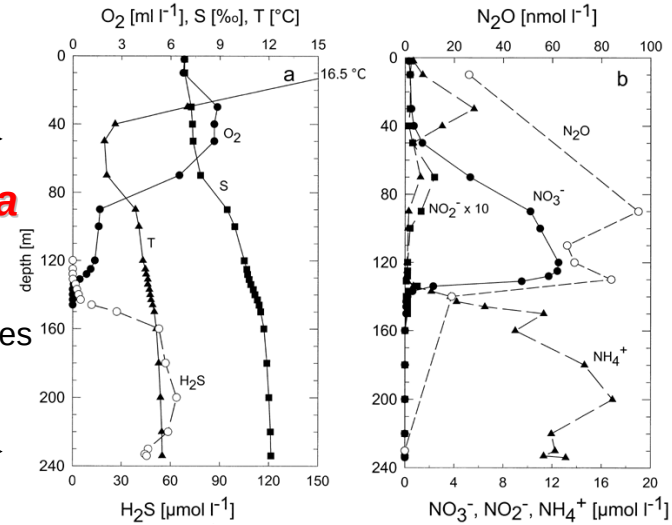
- *Microorganisms mediate kinetically inhibited, but thermodynamically favorable reactions*
- *ΔE for metabolism and growth*

Why *Shewanella*?

- Facultative aerobic Gram-negative, γ-*Proteobacteria*, easily cultivated
- MR-1 genome has been sequenced, ~5.0 MB
- Tractable genetics
- Respiratory versatile organism
  - ~ 40 *c*-type cytochromes, 8 decaheme *c*-type cytochromes, 3 are OM lipoproteins
- Reduces metals & radionuclides
- Widely distributed
  - Soil, sediment, water column
- A "gradient" organism, member of anoxic communities, biofilms
- 16 additional strains being sequenced by DOE's Joint Genome Institute

Gotland Deep, Central Baltic Sea

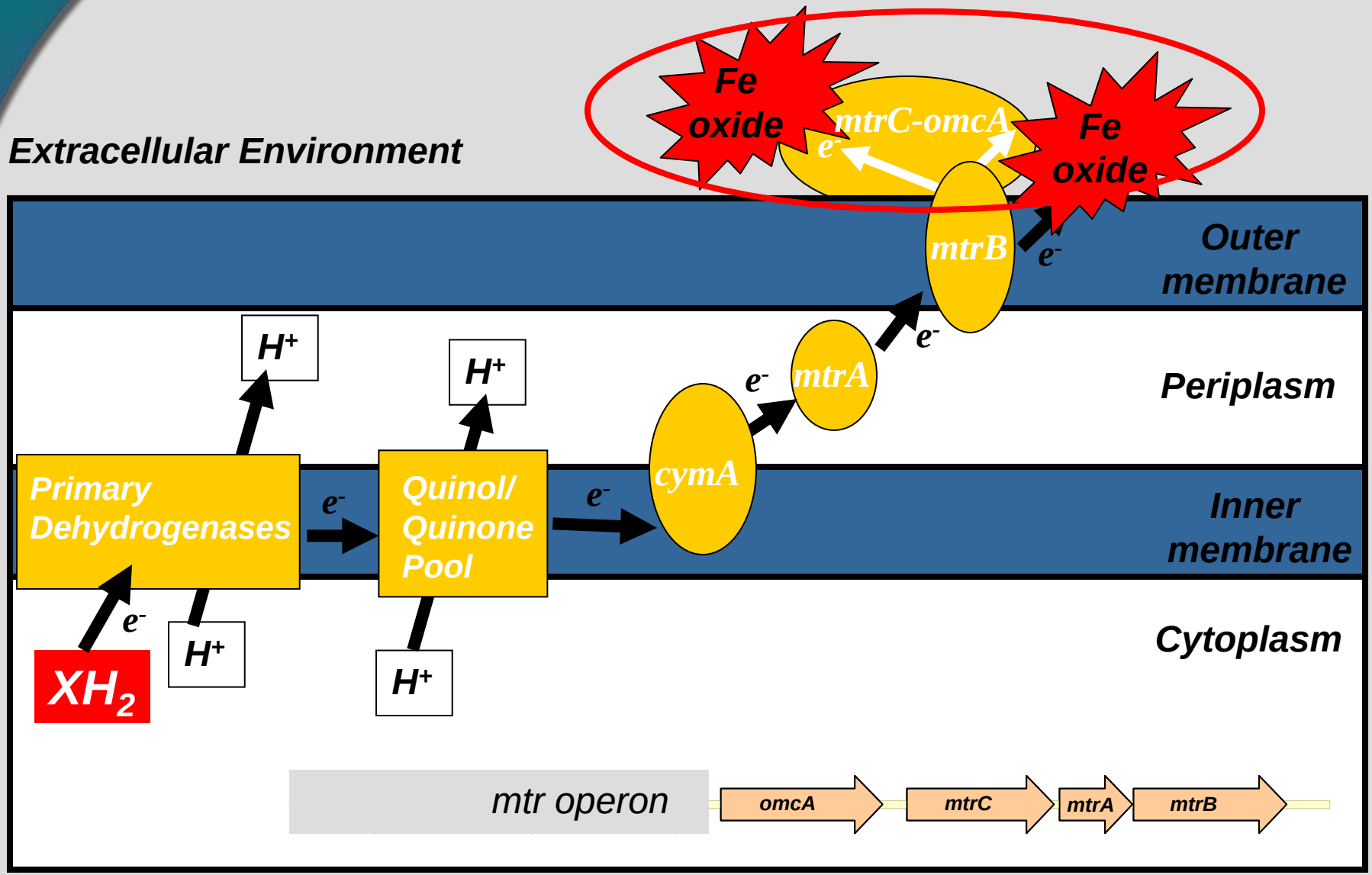
Shewanella baltica dominated recovered isolates (77%)



(From Brettar, Moore, Höefle, 2001 *Microbial Ecology*)

- *Marine/high salt environments*
- *Organic-rich*
- *Cosmopolitan*

Current Conceptual Model for Electron Transfer to Extracellular Substrates: Shewanella



Development of the Membrane Biology Scientific Grand Challenge

- External steering committee formed to develop candidate biology scientific research areas
  - Composed of Marv Cassman, Len Spicer, Steve Wiley, Mina Bissell, Mike Knotek, and Bill Rogers (then-EMSL Director)
  - Met in June 2003 in San Francisco
  - Recommendations
    - Focus on membrane biology and membrane protein dynamics and interactions
    - Advice on solicitation, review, and selection process

Solicitation, Review, and Selection

- In 2004, solicitations for research concepts were placed in *Science* and *ASM News*
- Fourteen proposals were received and reviewed by internal and external panels
- Five were deemed outstanding
- Winning proposal: Himadri Pakrasi, Washington University in St. Louis

A Scientific Grand Challenge in Membrane Biology

Call for Concept Papers

The William R. Wiley Environmental Molecular Sciences Laboratory (EMSL), a multiprogram national scientific user facility located at the Pacific Northwest National Laboratory (PNNL) in Richland, Washington, is seeking concept papers for a Scientific Grand Challenge in the area of membrane biology. Membrane processes are critical to solving highly complex problems related to energy production, carbon sequestration, bioremediation—all mission areas of the U.S. Department of Energy (DOE)—and other problems of national interest in energy and environmental science. The solutions to these problems require an approach that not only involves multidisciplinary teams of experts in the scientific area of choice, but that also require access to a range of cutting-edge instrumentation and computational resources not available at a single institution. This Scientific Grand Challenge will build interdisciplinary "team science" in biology while using multiple capabilities at EMSL to achieve a systems-level understanding of membrane processes.

Background

EMSL houses researchers who perform molecular studies focused on solving the major environmental challenges facing DOE and the nation. The facility contains a broad spectrum of world-class scientific resources that integrate theory, modeling, and simulation with experimentation and enable novel approaches for solving such difficult challenges.

In Fiscal Year 2004, EMSL is implementing a set of Scientific Grand Challenges to address important scientific questions using a collaborative approach. These Scientific Grand Challenges—each expected to last three to five years in duration— will have a set of well-defined goals that must lead to enduring scientific impact and may involve additional capability development. They will focus on critical milestones in the advancement or use of science, will be user driven, will take advantage of the full spectrum of resources and technical expertise available at EMSL, and will support DOE mission areas.

Successful concept papers submitted for EMSL's Scientific Grand Challenges will pose scientific questions that cannot readily be addressed without access for substantial periods of time to the full range of scientific instrumentation, computational resources, and research teams located at EMSL. In addition to the capabilities of the EMSL, these Scientific Grand Challenges will require teaming of scientists from multiple disciplines and use of specialized instrumentation at the participants' home institutions, and possibly use of capabilities located at other DOE user facilities (e.g., Joint Genome Institute, synchrotron light sources). The concept papers must clearly identify a scientific leader who will be responsible for the overall management of the proposed work and who is able to attract some of the best research scientists in the applicable research area.

Research Area of the Call for Concept Papers

One research area of interest to EMSL's Scientific Grand Challenges—addressed by this Call for Concept Papers—is biological membrane processes in cells (e.g., energy transduction, metal/ion regulation and transport, photosynthesis, signal transduction, cellular membrane architecture, dynamics of membrane proteins, and regulation of conformation states of proteins). Understanding membrane processes requires a systems-level analysis of fundamental cellular processes including the genetics, biochemistry, and biophysics of such processes, the characterization of which are particularly well suited to the capabilities of EMSL. Accomplishment of this Scientific Grand Challenge will elucidate how these membrane processes fit into the overall cellular physiology and ecology.

EMSL Signature Characteristics and Capabilities

EMSL's signature characteristics include

- integrated theory, modeling, and simulation with experimentation
- multidisciplinary teams and collaborative modes of operation to solve major scientific problems
- research teams responsible for developing extraordinary tools and methodologies
- scientists who design experimental strategies and operate state-of-the-art instruments
- education and training in the use of sophisticated instrumentation and computational systems and approaches
- a cyber infrastructure that facilitates productive remote interactions
- the charter to deliver capability in a transparent manner and to facilitate user outreach.

EMSL also boasts unparalleled resources and infrastructure in high-performance computing and informatics, nuclear magnetic resonance spectroscopy, multimodal optical spectroscopies, and imaging technologies, as well as advanced mass spectrometry capability for global proteomics—all of which are essential to progress in the study of membrane biology. Supporting these technologies are world-class researchers from PNNL, including chemists, biologists, physicists, and software engineers, as well as instrument designers and builders.

Process for Submitting Concept Papers

EMSL requests submission of a concept paper outlining the Scientific Grand Challenge goal, approach, technical requirements, and expected scientific and technical outcomes. Interested parties should become familiar with EMSL and its capabilities (http://www.emsl.pnl.gov/). Concept papers of no more than five pages must be postmarked by **May 14, 2004**, to the address below. An external review committee will select concepts for further development based upon scientific merit and potential for sustained scientific impact, appropriateness of EMSL resources for investigation of the challenge, and alignment with DOE mission needs in biology. EMSL will then host a workshop(s) for the successful concept team(s) to develop a scientific plan, strategy, and resource requirements for the Scientific Grand Challenge, and this information will be used for final selection of the challenge to be implemented. EMSL staff will provide assistance to the successful team in implementing their Scientific Grand Challenge. To submit concept papers or obtain further information, contact:

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Director, William R. Wiley Environmental Molecular Sciences Laboratory
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jw.rogers@pnl.gov

Membrane Biology Grand Challenge Team

Washington University in St. Louis

Himadri Pakrasi
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Teruo Ogawa

Pacific Northwest National Laboratory
Operated by Battelle for the U.S. Department of Energy

Office of Science

Battelle

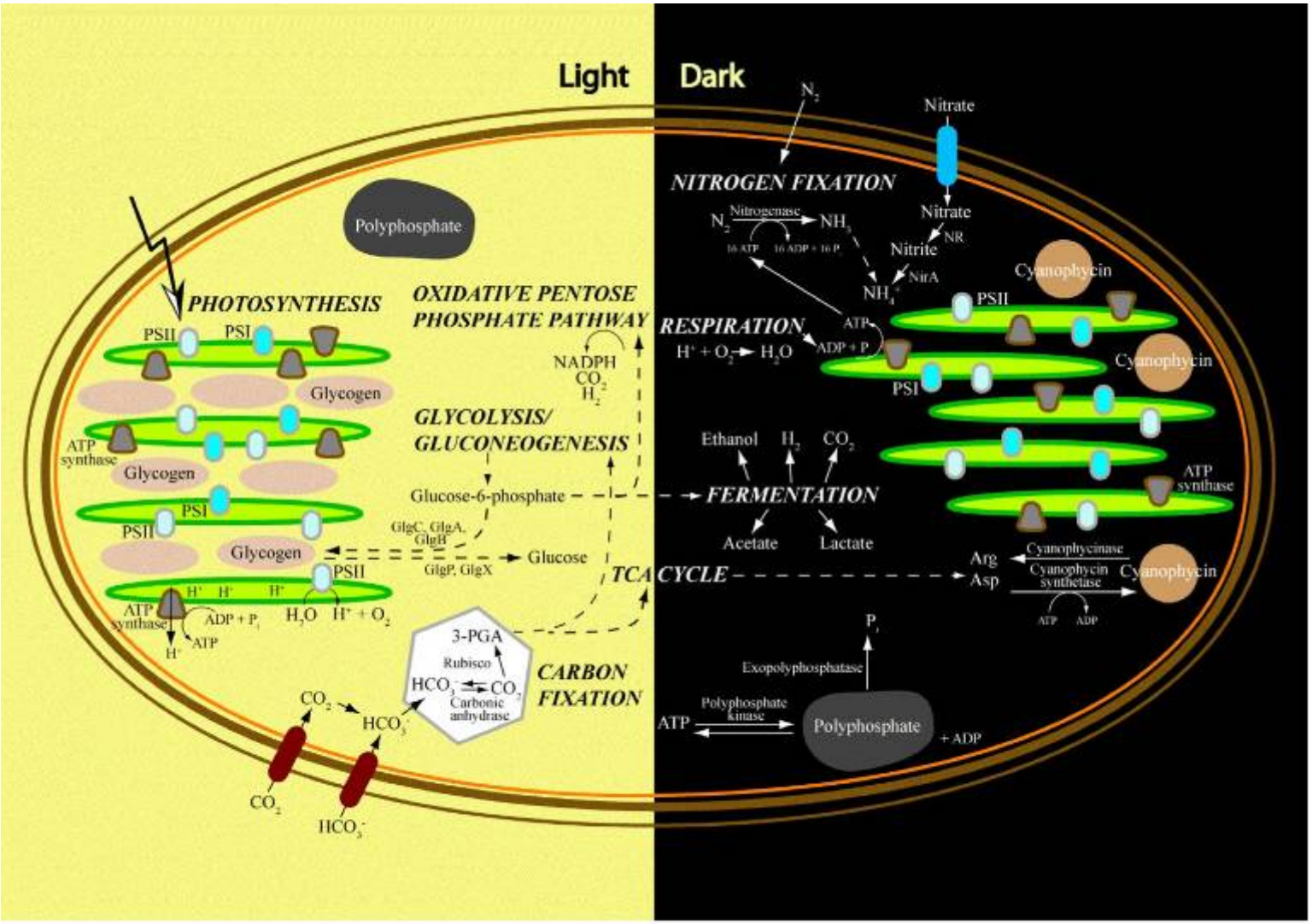
Office of Science
U.S. DEPARTMENT OF ENERGY

//mbgc.emsl.pnl.gov

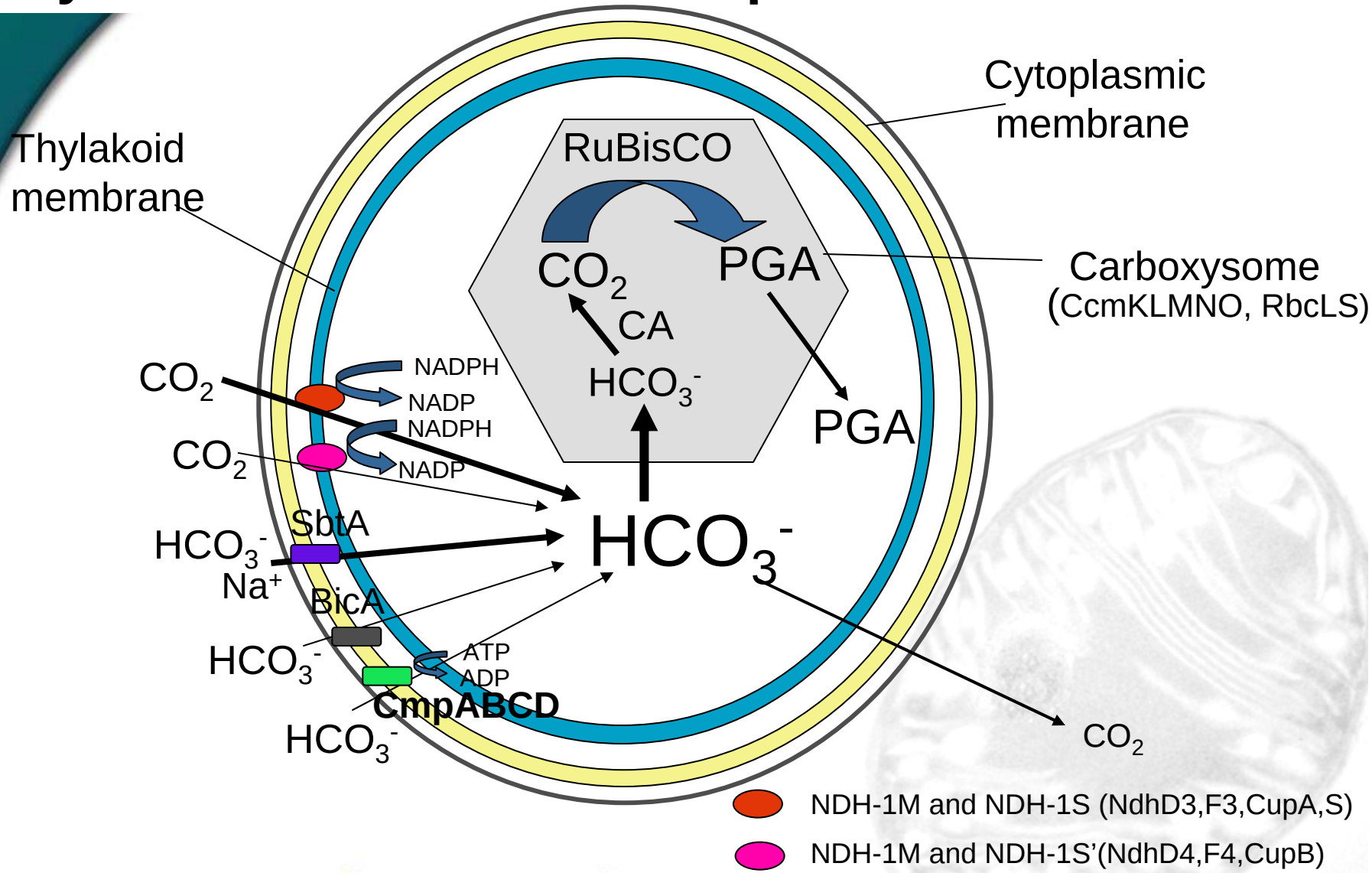
Cyanothece sp. ATCC 51142

- Unicellular cyanobacterium
- Capable of oxygenic photosynthesis and N_2 fixation
- Photosynthesis produces O_2, but N_2ase is oxygen sensitive
- Robust Circadian Rhythm: Photosynthesis at daytime, N_2-fixation at night

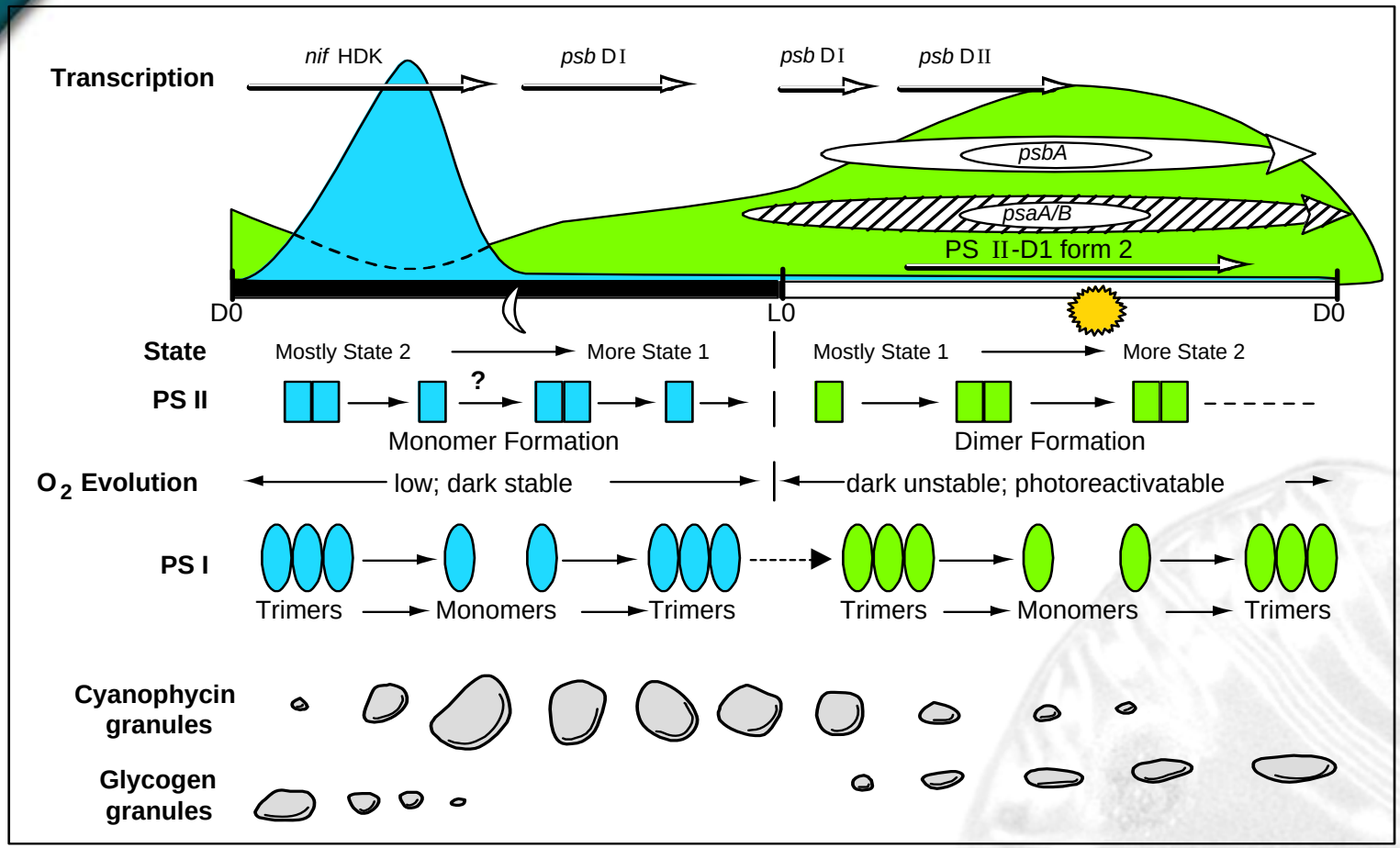
A Genome Level View of Rhythms in *Cyanothece* Metabolism



Cyanobacterial Carbon Sequestration Processes



Metabolic Rhythms in *Cyanothece* 51142



This summary illustrates the diurnal patterns of N_2-fixation in the dark and photosynthesis in light

Launching the Membrane Biology Scientific Grand Challenge

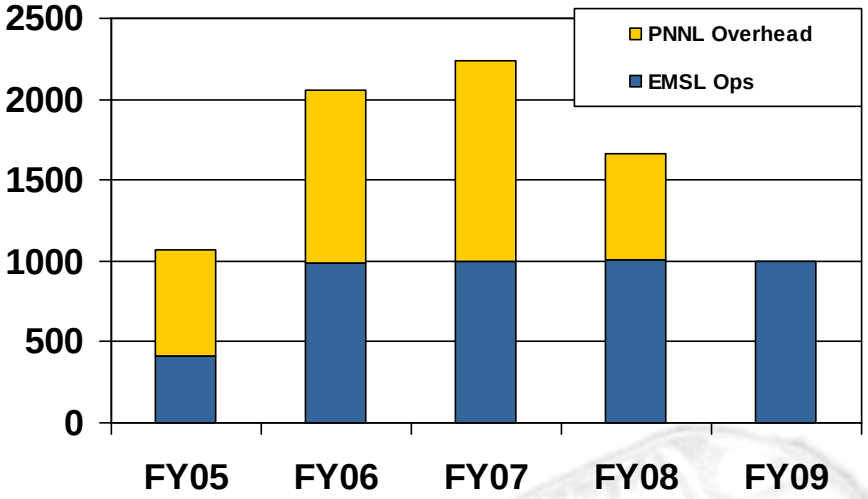
- Scoping workshop in December 2004
  - Team bonding
  - Identified EMSL, external capabilities
  - Refined scientific scope
  - Worked through funding and contractual mechanisms
  - Set aggressive working schedule.

Membrane Biology Scientific Grand Challenge Timeline

- Steering Committee Meeting: June 30, 2003
- First advertisement for call in *Science*: April 2, 2004 (May 11 deadline)
- Second advertisement for call in *AMS*: May 2004 (June 14 deadline)
- Concept papers sent to external reviewers: June 29, 2004
- Concept papers sent to internal reviewers: July 8, 2004
- Internal review scores to external reviewers: July 13, 2004
- Deadline for external review: July 23, 2004
- Final receipt of external reviews: August 11, 2004
- Review of scores: August 20, 2004
- Notification to team members: August 30, 2004
- Notification to selected proposal team: August 31, 2004
- Project scoping workshop at EMSL: December 2004
- Project funding (project start): April/May 2005
- Advisory committee review at EMSL: November 2005
- Project workshop at Washington University in St. Louis: April 2007
- Advisory committee review/project workshop at EMSL: August 2007
- Project Report September 2007
- BERAC Subcommittee Review, November 2007
- Formal BER/SC Evaluation Results, January 2008
- Phase I project ends April 2008

Scientific Grand Challenge Funding Profile

- Funding roughly 50% EMSL/50% PNNL overhead (e.g., LDRD, PDM)
- PNNL overhead funding ends in Fiscal Year 2008
- Capital funding also provided (EMSL - $1.6M, PNNL - $235K)
  - Cryo-transmission electron microscope
  - LTQ Orbitrap mass spectrometer (~ 50% funded by PNNL)
  - Three bioreactors
  - LTQ linear ion trap mass spectrometer.



Funding for Membrane Biology Grand Challenge

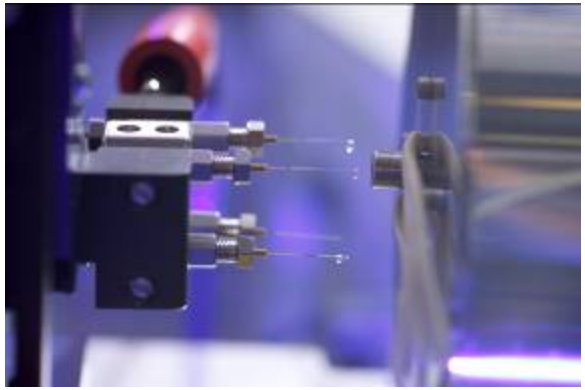
MBGC - $6.6M over 3 years
GtL - $20M over 4 years

Membrane Biology Scientific Grand Challenge Advisory Committee

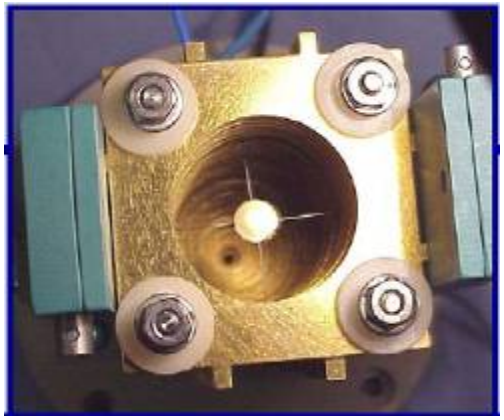
- Dr. Jack Johnson, Chair, Scripps Institute
- Professor Mark Ellisman, University of California, San Diego
- Dr. James Fredrickson, PNNL
- Dr. Gary Siuzdak, Scripps Institute
- Professor James Liao, University of California, Los Angeles

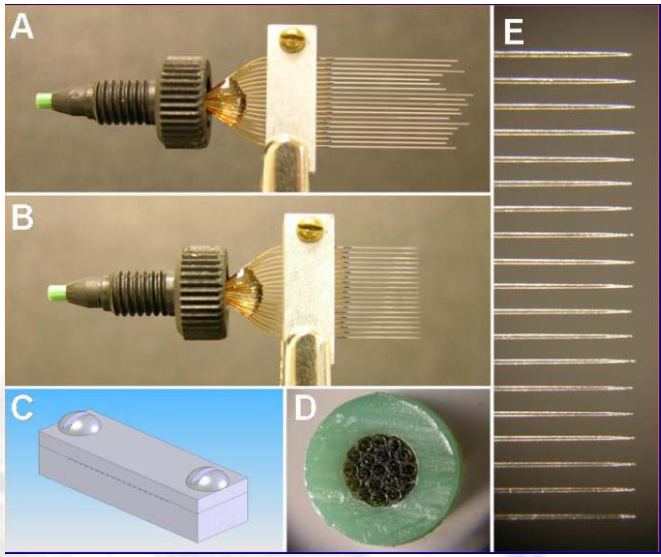
Unique technology at PNNL/EMSL to Power Proteome Characterization

- Increased throughput
  - Suite of cutting edge MS instrumentation
  - All automated for 24/7 analyses
  - All configured for 4 LC column analysis (no column washing down-time)

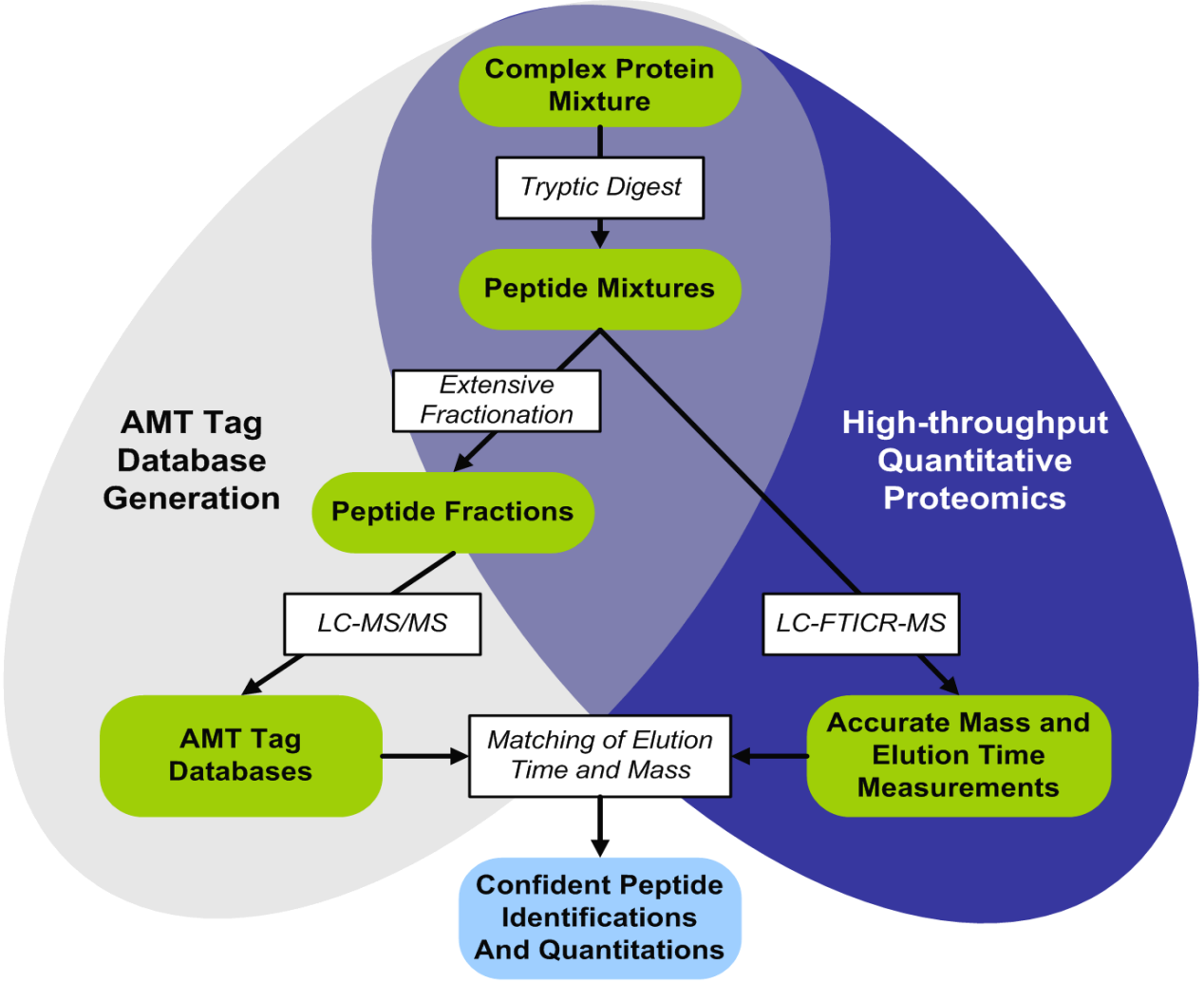


- Increased sensitivity
  - Implementation of small diameter capillary column LC separations, (75 µm standard)
  - Development of electrospray multi-emitter array
  - Utilization of additional pre-MS peptide separation to achieve increased dynamic range of detection.
  - Implementation of Ion funnel interfaces.



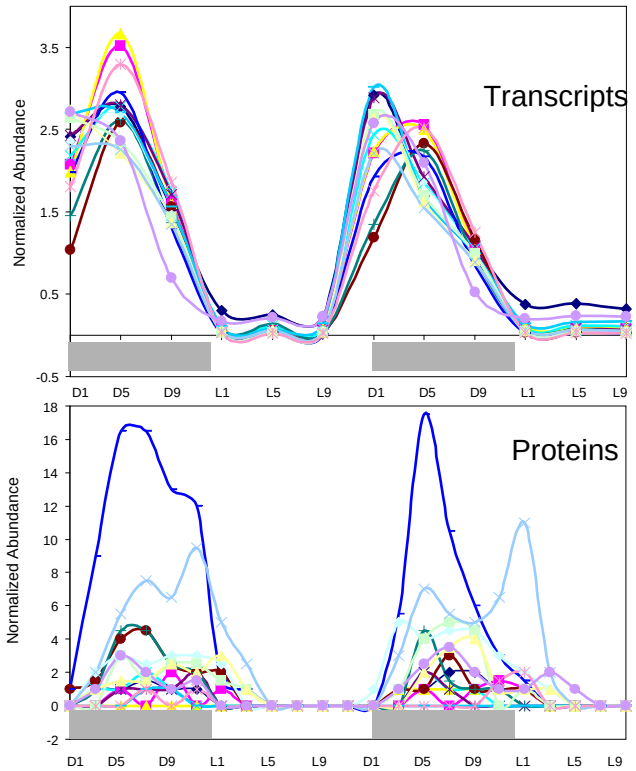


Global Proteomic Analysis Strategy



Cyanothece Protein Cycling Results

- Measurements taken every two hours across a 48 hr time course to observe a double 24 hr diurnal cycle.
- Example shows clear cycling characteristics of nitrogenase enzymes.
- High correlation with previously measured transcriptomic analyses with anticipated protein synthesis lag-time delay.
- Further analyses are revealing other insights into key cycling/non-cycling protein abundance measurements.

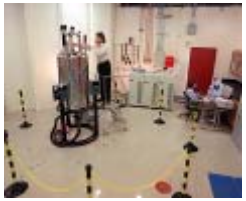


Structural Biology
EMSL High Field Magnetic Resonance Facility (HFMRF)

750 MHz 52 mm

900 MHz 65 mm

800 MHz NMR 63 mm



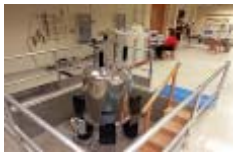
600 MHz 52 mm

600 MHz NMR 52 mm

300 MHz 89 mm

400 MHz 89 mm

300 MHz 89 mm



500 MHz 52 mm

9.5 GHz EPR

500 MHz 52mm

500 MHz 89 mm

MBGC Protein Structures
(14 structures of 8 proteins)

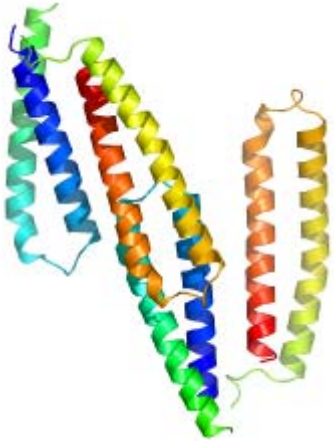
NrtA (2G29)

FutA1 (2PT2, 2PT1)

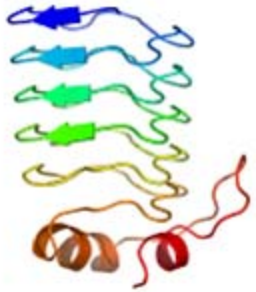
FutA2 (TBD)

CmpA (2I48, 2I4B 2I49, 2I4C)

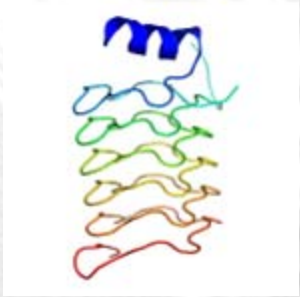
ZnuA (2OV1, 2OV3)



DUF683 (TBD)

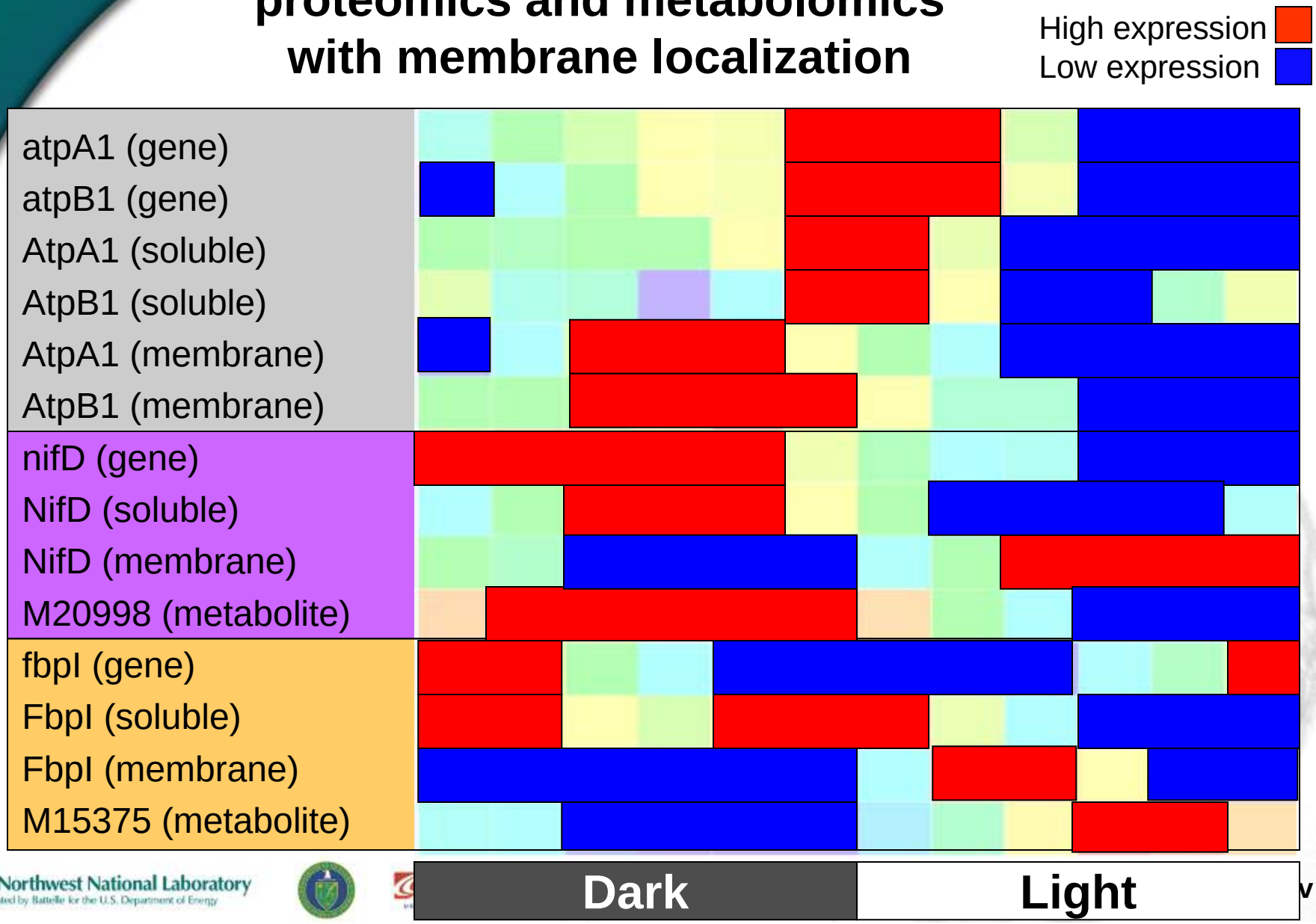


Rfr32 (2G0Y, 2F3L)



Rfr23 (2O6W)

Integration of transcriptomics, proteomics and metabolomics with membrane localization



Measuring Success

- Scientific impact and publications
- New, integrated and enduring capabilities
- Advisory committee feed back
- S&T Awards and recognition
- Biology community recognition
- New users and new types of use

More than 28 Peer Reviewed Publications (to Date)

Protoplasma (2006) 227: 129–138
DOI 10.1007/s00709-006-0145-7

PROTOPLASMA
Printed in Austria

Ultrastructure of the membrane systems in the unicellular cyanobacterium *Synechocystis* sp. strain PCC 6803

Michelle Liberton[1], R. Howard Berg[2], John Heuser[3], Robin Roth[3], and Himadri B. Pakrasi[1,*]

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[2] Donald Danforth Plant Science Center, St. Louis, Missouri
[3] Department of Cell Biology and Physiology, Washington University, St. Louis, Missouri

Protein Science (2006), 15:2579–2595
Copyright © 2006 The Protein Society

Protein Science

Characterization of two potentially universal turn motifs that shape the repeated five-residues fold—Crystal structure of a lumenal pentapeptide repeat

Photosynth Res (2007) 93:69–77
DOI 10.1007/s11120-006-9128-y

REVIEW

Cyanobacterial NADPH dehydrogenase complexes

...ling Mi

...2007, 79, 6081–6093

...llary LC Coupled with High-Mass Measurement ...racy Mass Spectrometry for Metabolic ...ling

...Christina M. Sorensen, Qibin Zhang, Hongliang Jiang, Navdeep Jaitly, Eric A. Livesay, ...ien, Richard D. Smith, and Thomas O. Metz*

...ciences Division, Pacific Northwest National Laboratory, Richland, Washington 99352

PNAS

Atomic structure of a nitrate-binding protein crucial for photosynthetic productivity

Nicole M. Koropatkin*, Himadri B. Pakrasi†, and Thomas J. Smith*‡

*Donald Danforth Plant Science Center, 975 North Warson Road, St. Louis, MO 63132; and †Department of Biology, Washington University, St. Louis, MO 63130

Edited by Robert Huber, University of Chicago, Chicago, IL, and approved May 17, 2006 (received for review March 28, 2006)

Cyanobacteria, blue-green algae, are the most abundant autotrophs in aquatic environments and form the base of all aquatic food chains by fixing carbon and nitrogen into cellular biomass.

Cloning, expression, crystallization and preliminary crystallographi... analysis of a pentapeptide-repeat protein (Rfr23) from the bacterium *Cyanothece* 51142

Garry W. Buchko, Howard Robinson, Shulsong Ni, Himadri B. Pakrasi and M... A. Kennedy

Acta Cryst. (2006). F62, 1251–1254 — Buchko et al. • Pentapeptide-...

nature

Genome sequence of *Cyanothece* 51142 shines new light on the circadian life style of a cyanobacterium

Eric A. Welsh[1*], Michelle Liberton[1*], Jana Stöcker[1], Hanayo Sato[1], Thomas Loh[1], Chunyan Wang[2], Aye Wollam[2], Robert S. Fulton[2], Sandra W. Clifton[2], Jon M. Jacobs[3], Rajeev Aurora[4], Louis A. Sherman[4], Richard D. Smith[3], Richard K. Wilson[2] and Himadri B. Pakrasi[1]

submitted

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*These authors contributed equally to this work

BIOINFORMATICS APPLICATIONS NOTE — Vol. 23 no. 13 2007, pages 1705–1707 doi:10.1093/bioinformatics/btm132

Systems Biology

PQuad—a visual analysis platform for proteomic data exploration of microbial organisms

Bobbie-Jo M. Webb-Robertson[1,*], Elena S. Peterson[1], Mudita Singhal[1], Kyle R. Klicker[1], Christopher S. Oehmen[1], Joshua N. Adkins[2] and Susan L. Havre[1]

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Advance Access publication May 5, 2007
Associate Editor: Thomas Lengauer

740 — IEEE TRANSACTIONS ON PARALLEL AND DISTRIBUTED SYSTEMS, VOL. 17, ...

ScalaBLAST: A Scalable Implementa... of BLAST for High-Performance Data-Intensive Bioinformatics Analys...

Christopher Oehmen, *Member, IEEE*, and Jarek Nieplocha, *Member, IEEE Compu...*

OMICS: A Journal of Integrative Biology

A Network of Genes Regulated by Light in Cyanobacteria

To cite this paper:
Rajeev Aurora, Yukako Hihara, Abhay K. Singh, Himadri B. Pakrasi. OMICS: A Journal of Integrative Biology. 2007, 11(2): 166-185. doi:10.1089/omi.2007.4323.

Supplement

Microscopy and Microanalysis

TEM Study of Manganese Biosorption by Cyanobacterium Synechoc... 6803

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BOOK: The Cyanobacteria: Molecular Biology, Genomics and Evolution
2007
Chapter 12 Carbon Acquisition by Cyanobacteria: Mechanisms, Comparative Genomics and Evolution
Aaron Kaplan, Martin Hagemann, Hermann Bauwe, Shira Kahlon and Teruo Ogawa
In this chapter we mainly focus on the mechanisms of inorganic carbon uptake, photorespiration, and the regulation between the metabolic fluxes involved in photoautotrophic, photomixotrophic and heterotrophic growth. We identify the genes involved, their regulation and phylogeny.

Active NDH-1 Complexes from the Cyanobacterium *Synechocystis* sp. Strain PCC 6803

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Systems biology

SEBINI: Software Environment for Biological Network Inference

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BOOK: The Cyanobacteria: Molecular Biology, Genomics and Evolution
pp.271-287, 2007
Chapter 10 Membrane Systems in Cyanobacteria
Michelle Liberton and Himadri B. Pakrasi
Cyanobacteria are photosynthetic prokaryotes with highly differentiated membrane systems. In addition to a Gram-negative-type cell envelope with plasma membrane and outer membrane separated by a periplasmic space, cyanobacteria have an internal system of thylakoid membranes where the fully functional electron transfer chains of photosynthesis and respiration reside. The presence of different membrane systems lends these cells a unique complexity among bacteria. Cyanobacteria must be able to reorganize the membranes, synthesize new membrane lipids, and properly target proteins to the correct membrane system. The outer membrane, plasma membrane, and thylakoid membranes each have specialized roles in the cyanobacterial cell. Understanding the organization, functionality, protein composition and dynamics of the membrane systems remains a great challenge in cyanobacterial cell biology.

New, Integrated, and Enduring Capabilities

- Proteomics and metabolomics capabilities
  - LTQ Orbitrap mass spectrometer Spectro
  - Metabolomics automated high-pressure liquid chromatography system
  - 12T FTICR Mass Spectrometer for top down proteomics
- Imaging capabilities
  - Cryo-transmission electron microscope
- Controlled cultivation capabilities
  - Photobioreactor developed at EMSL, deployed at three sites
- Data management for systems biology
  - ScalaBLAST – now used by the Joint Genome Institute.

Total capital investment for the Membrane Biology Scientific Grand Challenge: $1.6M

Awards and Recognition

- Alice Dohnalkova receives Diatome Award at Microscopy Society of America national meeting, August 2007
- Himadri Pakrasi installed as Washington University's Freiburg Professor of Biology in Arts and Sciences, October 2007
- Dave Koppenaal inducted as Fellow, American Association for the Advancement of Science, February 2008

Advisory Committee Feedback

- "The ***major science objectives are being realized as expected***; MBGC priorities and DOE/EMSL's expectations as described in the original call for proposals are consistent and being met."

- "Overall, the AC was ***extremely enthused about scientific and technology process***."

- "The AC ***encourages DOE to continue to support and consider expanding the grand challenge concept.*** EMSL, DOE, and its scientific mission will greatly benefit from enhancement of support and continuity."

BERAC Review & Outcomes

- High marks accorded by BERAC review of MBGC:
  - Selection process and initiation of effort
  - Quality of science produced
  - Effectiveness in attracting new users
- BERAC approves MBCG effort as meeting contract goal
- EMSL turns BERAC around on Grand Challenge concept for attracting and engaging users
- EMSL agrees to continue funding MBGC effort for additional 2 yrs
- BERAC invites Himadri Pakrasi to be science speaker at Spring '08 BERAC meeting

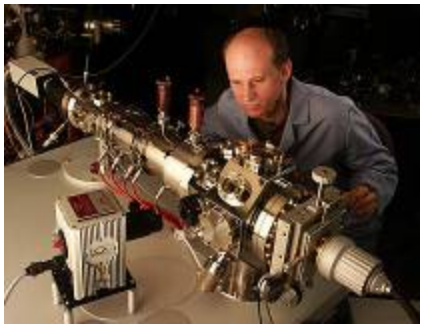
Membrane Biology Grand Challenge Workshop, The Village, Washington University, April, 2007

EMSL Grand Challenges – Lessons Learned (so far)

- GC's were found to be an excellent way to encourage integrated use of EMSL capabilities
- GC's exposed EMSL capabilities to new communities and served as vehicle for creative multi-institutional, collaborative research
- GC's fostered and informed development of new EMSL capabilities
- Lasting impacts TBD
- A way to encourage new facility use and a new type of use
- User Facilities must strive to re-invent and transform themselves to maximize effective use and impact

WR Wiley Environmental Molecular Sciences Laboratory

A national scientific user facility integrating experimental and computational resources for discovery and technological innovation



William R. Wiley
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