BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bauer, Carl Eugene

eRA COMMONS USER NAME (credential, e.g., agency login): CBAUER

POSITION TITLE: Professor and Chairman of Molecular and Cellular Biochemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Minnesota, Mpls., MN	B. S.	1978	Microbiology
Washington State University, Pullman, WA	M. S.	1980	Bacteriology
University of Illinois, Urbana, IL.	M. S.	1982	Microbiology
University of Illinois, Urbana, IL.	Ph. D.	1986	Microbiology

A. Personal Statement

My laboratory has been undertaking continual NIH supported research in the areas of microbial genetics, microbial molecular biology and microbial biochemistry for the past 27 years. We have long held a leadership position in investigating the regulation of purple bacterial gene expression in response to environmental alterations in oxygen tension and light intensity (discussed in more detail in section c). Indeed most of the known transcription factors that control synthesis of the bacterial photosystem were initially identified by my laboratory and have been extensively characterized by my research group (in several cases from the initial genetic discovery all the way to our group solving x-ray crystallographic structures). About 10 years ago, my laboratory initiated analysis of cyst formation in *Rhodospirillum centenum*, a photosynthetic member of the *Azospirillum* clade. This led to the first reported genetic study of encystment in a Gram-negative organism (outside of myxospores which is a very specialized process). These studies gave rise to the identification of a number of transcription factors that control encystment many of which have been biochemically characterized by members of my research group.

During the past funding period, several member of our research group underwent extensive training in transcriptomics which provides genome wide gene expression profiles. This included attending several bioinformatic workshops and active membership in a local transcriptomics work group. Our research group is now well versed in statistical analyses of large ChIP-Seq and RNA-Seq data sets (5 members of my research group are currently undertaking detailed analysis of transcription factors using these techniques). In the past funding period, we have published reports of global gene expression changes that occur when *R. centenum* undergoes development of cysts. We have also published two recent studies that utilize RNA-Seq and ChIP-seq to characterize the extent of the CgrA and FNR regulons, which provides genome wide locations of their respective binding sites. Consequently, all of the methodology that is proposed in this study are areas that we have expertise in undertaking.

B. Positions and Honors

Positions: 1988-97, Fellow, 1997-Current, Senior Fellow, Indiana Molecular Biology Institute; 1988-94 Assistant Professor, 1994-97 Associate Professor, 1997-current Full Professor, Department of Biology, Indiana University; 1997-2007, Clyde Culbertson Professor of Biology; 1993-01, Director, Microbiology Graduate Program; 1995-01, Director, Molecular Biology and Biochemistry Program; 2001-2009, Director,

Interdisciplinary Biochemistry Program (*Founder of this newly accredited graduate program*). 2007-09, Class 54 Professor of Biochemistry (I vacated this Endowed Chair position when I left Biology to form a new Biochemistry department per donors stipulation that the Chair be awarded to a Biology faculty member); 2009-current, Chairman, Department of Molecular and Cellular Biochemistry (*Founder and first Chairman of this newly formed Biochemistry Department-the first new science department on the IU campus in over 30 years!*).

Honors and Professional Service: 1982 Phi Kappa Phi; 1984 Sigma Xi; 1983-86 HEW Cellular and Molecular Biology Training Fellowship; 1992 Marcus Rhoades Outstanding Young Faculty Award; 1993-98 NIH Research Career Development Award; 1994 American Society for Photobiology Young Investigator Award; 1997 Invited Member, Alliance of Distinguished Rank Professors, Indiana University; 1997-07 Recipient, Clyde Culbertson Endowed Professorship; 2002 Recipient, IBASM Outstanding Academic Achievement Award; 1995 co-editor. Anoxygenic photosynthetic bacteria. Kluwer Academic Publishers. 1331 pp; 1991 Session Chairperson, "Regulation of Gene Expression in Response to Oxygen," Annual Meeting for the ASM; 1992, Session Chairperson, Emerging Microbial Systems, Fifth ASM conference on genetics and molecular biology of industrial microorganisms, 1998 Session Chairperson, "Tetrapyrrole biosynthesis," Annual Meeting for ASM; 1995, 1996 Guest lecturer/guest instructor at Woods Hole Marine Biological Laboratory Course on Microbial Diversity; 1996 Chair, Conference Organizing Committee "Diversity, Genetics and Physiology of Photosynthetic Prokaryotes"; 1996 Session Chairperson, "Gene Regulation," Annual meeting of the Society for Industrial Microbiology; 1997-04 Elected member, International Symposium of Photosynthetic Prokaryotes Scientific Advisory Committee; 1995, Ad hoc committee member of the Microbial Physiology Study Section-01, NIH; 1996 Ad hoc committee Member, Bacteriology and Mycology-1 study section, NIH; 1997 Ad hoc Committee Member, NIH Bacteriology and Mycology-1 study section Panel Member, Department of Energy, Division of Biosciences, Study section on photosynthesis; 2003-Member executive committee; Indiana Branch American Society for Microbiology; 2002-2007 Recipient-David and Lucile Packard Foundation Grant; 2004-06 American Society for Microbiology "*Waksman Foundation for Microbiology Lecturer*"; 2009 *Elected Fellow* to the American Academy of Microbiology; 2012 *Elected Fellow* to the American Association for the Advancement of Science (AAAS); Invited speaker at >140 domestic and international meetings-11 as plenary speaker. [*Note that from 2004-07 I was a caregiver to a terminally ill spouse and upon her unfortunate passing in 2007 I became a single parent to two school age children (the youngest went off to college in 2011). During the 2004-11 period, family and IU administrative pressures necessitated that I turn down many speaking engagements, invitations to serve on editorial boards and to join grant review panels].*

C. Contributions to Science

The total number of peer reviewed publications exceeds 130 and can be observed in their entirety at __ or at _____ (Discuss pubs and covers of Science, Cell etc)

1. *The First Genetic And Biochemical Analysis Of Gram-Negative Cyst Development:* Our analysis of encystment by *Rhodospirillum centenum* was initiated approximately one decade ago. During this period we have published numerous manuscripts that provide detailed description of physiological/morphological changes that occur upon cyst development. Our published genetic and biochemical analysis on cyst development is the *only example* of its kind that has been undertaken in a Gram-negative bacterium other than studies on myxospores development by Myxobacteria (which is a very specialized event). In the past funding period, we published the first example of high resolution transcriptome profile changes that occur while these cells transition from vegetative to cyst forms using RNA-Seq methodologies (a technique relevant to the proposal). This has provided the first detailed understanding of genome wide changes in gene expression that occur during encystment. Notable additional discoveries include the first report of genetic and biochemical of a *bona-fide* bacterial guanylyl cyclase and the demonstration that cGMP production is used as a signaling molecule to initiate cyst formation. [Until our report, the production of cGMP was thought to only occur in eukaryotes. The significance of this work was highlighted in a commentary in *Molecular Microbiology*]. We also discovered a CRP homolog (CgrA) that preferentially binds cGMP (instead of cAMP) and demonstrated that a CgrA-cGMP co-complex activates a large set of encystment genes. We have also genetically identified, and extensively biochemically characterized, a novel multicomponent Che-like signal transduction cascade that directly regulates a separate two component encystment signaling cascade via phosphorylation of a REC domain on a histidine kinase (CheS) (this work lead to the invitation to write a minireview for *TIMS* on Che-like signaling systems that control cell survival instead of motility). We have also demonstrated that the cellular

ATP/ADP ratio is one of several inputs that control encystment.

a. Marden JN, JE Berleman & CE Bauer (2011) Cyclic GMP regulates encystment in *Rhodospirillum centenum. Mol. Micro.* 79:600-615 (*This work was highlighted by a commentary of this study in the same issue of Mol. Micro* 79:562-565).
b. He, K., J. M. Marden, E. M. Quardokus & C. E. Bauer (2013) Phosphate Flow between Hybrid Histidine Kinases $CheA_3$ and $CheS_3$ Controls *Rhodospirillum centenum* Cyst Formation. *PLOS Genetics*, DOI: 10.1371/journal.pgen.1004002 (*This work was highlighted by Nature Reviews Microbiology)*
c. He, K. & C. E. Bauer (2014) Chemosensory signaling that controls bacterial survival*. Trends in Microbiology*. 22:389-393 PMCID: PMC4273944
d. Dong, Q., & C. E. Bauer (2015) Transcriptome analysis of cyst formation in *Rhodospirillum centenum* reveals large global changes in expression during cyst development. *BMC Genomics.* 16:68 DOI: 10.1186/s12864-015-1250-9*.*
e. He, K., V. Dragnea, & C. E. Bauer (2015) Adenylate charge regulates sensor kinase $ches_3$ to control cyst formation in *Rhodospirillum centenum mBio*, In Press.

2. *Regulation Of Gene Expression In Response To Redox*: A significant, long-standing, body of work from my laboratory is centered on the regulation of gene expression by redox in the purple photosynthetic bacterium *Rhodobacter capsulatus*. Initially this work was focused on the regulation of photosynthesis (bacteriochlorophyll, carotenoid, light harvesting etc.), electron carrier and respiratory (cytochrome oxidases) genes as well as heme biosynthesis genes. This analysis has expanded from the characterization of individual loci to the analysis of global changes in gene expression using state-of-the-art RNA-seq and ChIP-seq methodologies (methodologies pertinent to this application).

Notable discoveries include the first reported isolation of regulatory mutants that affected photosynthesis gene expression in a photosynthetic bacterium. These early studies led to high visibility publications in *Cell* and *PNAS* as well as invitations for mini-reviews in *Cell* and in *TIBS*. Our discovery and characterization of redox responding RegB-RegA showed that it this is a highly conserved and widely disseminated two-component system (present in most alpha and beta proteobacteria) that is responsible for controlling global aerobic to anaerobic switch in gene expression in response to changes in the redox state of the ubiquinone pool. The sensor kinase RegB has 6 trans-membrane helices and to this day we are the only group that has successfully isolated a full length membrane spanning histidine kinase (i.e. full length RegB) from the membrane with retention of excellent activity. Indeed we are capable of isolating RegB from the membrane in the presence of its effector ligand ubiquinone and have biochemically shown that when the ubiquinone is reduced the kinase activity is on and when it is oxidized the kinase activity is off. We have also discovered and biochemically characterized several other heme and redox responding transcription factors such as (1) CrtJ/PpsR that responds to changes the redox state of a critical Cys located in the HTH DNA binding region (2) HbrL that responds to heme, and (3) FnrL which is a homolog of FNR. These analyses involve both *in vivo* and *in vitro* genetic studies as well as detailed *in vitro* biochemical analyses of DNA and ligand binding activities.

a. Sganga, M. & C.E. Bauer. 1992. Regulatory events controlling light harvesting and reaction center structural gene expression in *R. capsulatus. Cell 68:945-954*
b. Swem, L., B. J. Kraft, D. L. Swem, A. T. Setterdahl, S. J. Masuda, D. B. Knaff, J. M. Zaleski & C. E. Bauer. 2003. Signal Transduction By The Global Regulator RegB Is Mediated By A Redox Active Cysteine. *EMBO J*. 22, 4699-4780
c. Wu J, & Bauer C.E. 2010. RegB kinase activity is controlled in part by monitoring the ratio of oxidized to reduced ubiquinones in the ubiquinone pool. *MBio*. 1. pii: e00272-10. PMID: 21157513
d. Cheng, Z, J Wu, A Setterdahl, K Reddie, K Carroll, L A. Hammad, J A Karty & CE Bauer (2012) Activity of the tetrapyrrole regulator CrtJ is controlled by oxidation of a redox active cysteine located in the DNA binding domain. *Mol. Micro*. 85:734-746 PMID: PMC3418406
e. Wu J, Cheng Z, Reddie K, Carroll K, Hammad LA, Karty JA, & Bauer CE. (2013) RegB kinase activity is repressed by oxidative formation of cysteine sulfenic acid. *J. Biol. Chem.* 288:4755-4762. PMID: 23306201

3. *Regulation Of Gene Expression In Response To Light:* For or nearly two decades we have studied how light regulates prokaryotic gene expression and motility. During that time we have made some seminal discoveries. For example, we were the second group to report the discovery of a phytochrome photoreceptor

in a prokaryote. The first report was in a cyamobacterium (the ancestor to chloroplasts) while our report published in *Science* was the presence of a phytochrome in purple photosynthetic bacterium. Prior to these studies phytochromes were thought to be a plant dedicated photoreceptor that affected the timing and development of plant tissues such as flowers. Since those early reports, (and more recently by sequence analysis of numerous genomes) it is clear that most bacterial species typically contain one or more photoreceptors.

We also reported a novel light regulated antirepressor of CrtJ/PpsR (called AppA) that uses flavin as a blue light absorbing chromophore. This was a notable discovery as AppA constituted a new novel class of photoreceptors (the "Blue Light Using Flavin" or BLUF photoreceptors) that has turned out to be widely disseminated in the prokaryotic Kingdome as well as in alga. This was the first new class of photoreceptor described in over three decades and resulted in a high visibility article that was highlighted on the cover of *Cell*. We have undertaken detailed biochemical, structural and biophysical analyses on several BLUF proteins. For example, my laboratory solved the crystal structure of two BLUF proteins, and in collaboration with several NMR groups, also defined structural changes that occur in solution upon excitation of the flavin. We also collaborated with a biophysics group to define hydrogen bond rearrangements that occur upon excitation of the flavin in the psec (10^{-12}) time frame, events that lead to light driven conformational changes in the peptide backbone.

Beyond the first discovery of a proteobacterial phytochrome and BLUF proteins, our laboratory recently reported the discovery of a novel photoreceptor that binds light excited cobalamine (vitamin B_{12}) to control gene expression in response to blue light intensity [Our work in describing this additional new novel photoreceptor was predated by a similar result in another species that was published just a few months prior to ours]. Like that of phytochromes and BLUF domains, the B12 binding domain in this class of photoreceptor is present in a wide variety of bacteria and can be found as stand alone domains as well as where this B_{12} binding domain constitutes a light absorbing "input domain" that controls a variety of output domains such as histidine kinases or HTH containing DNA binding domains.

a. Jiang, Z-Y, L. Swem, B. Rushing S. Devanathan, G. Tollin & C. E. Bauer. 1999. Bacterial photoreceptor with similarity to both photoactive yellow protein and plant phytochromes. *Science*, *285, 406-409.*
b. Masuda, S. & C. E. Bauer. 2002. AppA is a blue-light photoreceptor that anti-represses photosynthesis gene expression in *Rhodobacter sphaeroides Cell* 110, 613-623. (Featured on cover)
c. Anderson, S., V. Dragnea, V., S. Masuda, J. Ybe, K. Moffat & C. E. Bauer. 2005. Structure of a novel photoreceptor: the BLUF domain of AppA from *Rhodobacter sphaeroides* . *Biochemistry*. 44, 7998-8005
d. Yuan, H. & C. E. Bauer. 2008. PixD promotes dark oligomerization of the BLUF photoreceptor PixD. *Proc. Natl. Acad. Sci. USA 105, 11715-11719.*
e. Cheng, Z., K. Li, L. A. Hammond, J. A. Karty & C. E. Bauer. 2014. B_{12} controls photosystem gene expression by light regulated binding to the antirepressor AerR. *Mol. Microbiol. 91:649-664.* PMCID: PMC3946051 *(This work was highlighted in a companion commentary in the same issue by G. Klug; Mol Microbiol. 91:635-640.)*

4. *The First Reported Characterization Of Chlorophyll Biosynthesis Genes*: Early in my independent scientific career, my laboratory provided the first reported identification of genes involved in chlorophyll biosynthesis in <u>*any*</u> photosynthetic organism. Prior studies reported the isolation of chlorophyll biosynthesis mutants in bacteria, alga and plants that affected chlorophyll biosynthesis, however at that time (early 1990's) there was <u>*no*</u> reported sequence information on genes with a known function in the chlorophyll biosynthetic pathway. My laboratory constructed saturating site directed disruptions in a "photosynthesis gene cluster" in *Rhodobacter capsulatus* that lead to the first reported identification of genes and gene products that were involved in chlorophyll biosynthesis. This work also led us to genetically disrupt several chlorophyll biosynthesis homologs that are present in algal/plant chloroplasts of alga. We also were the first to report the identification of genes that allow bacteria, alga and land plant gymnosperms (non-flowering plants) to synthesize chlorophyll in the dark as well as a loci present in angiosperms (flowering plants) that requires light for chlorophyll synthesis. We also were the first group to isolated and biochemically characterized several novel enzymes in the chlorophyll biosynthetic pathway including a chlorophyll biosynthesis enzyme that is evolutionarily/structurally related to nitrogenase. Overall, our early studies on (bacterio)chlorophyll biosynthesis in bacteria proved to be a "guiding light" for many other groups to identify and characterize chlorophyll biosynthesis genes in a variety of photosynthetic organisms ranging from cyanobacteria, to alga and land plants. [*note that I no longer work on*

this topic as these studies were undertaken by postdoctoral fellows in my group that left to establish their own laboratories in this area.]

a. Suzuki, J.Y. & C.E. Bauer. 1992. Light-independent chlorophyll biosynthesis: Involvement of the chloroplast gene *chlL (frxC). The Plant Cell, 4:929-940*
b. Bauer, C. E., D. W. Bollivar & J. Y. Suzuki. 1993. Minireview-Genetic analysis of photopigment biosynthesis in eubacteria: A guiding light for algae and plants. *J. Bacteriol. 175:3919-3925.*
c. Bollivar, D. W., J. Y. Suzuki, J. T. Beatty, J. Dobrowlski & C. E. Bauer. 1994. Directed mutational analysis of bacteriochlorophyll *a* biosynthesis in *Rhodobacter capsulatus. J. Mol. Biol. 237: 622-640.*
d. Suzuki, J. Y. & C. E. Bauer. 1995**.** A prokaryotic origin for light-dependent chlorophyll biosynthesis of plants. *Proc. Natl. Acad. Sci. U.S.A. 92, 3749-3753.*
e. Suzuki J. Y., Bollivar D. W., & Bauer, C. E. 1997. Genetic analysis of the chlorophyll biosynthesis. *Ann. Review of Genetics 31, 61-89* (Invited review).

5. *Origin and Evolution of Photosynthesis:* During our analysis of chlorophyll biosynthesis genes, I realized that there were a number of theories on the origin photosynthesis but no actual experimental studies that addressed either the origin or the evolution of photosynthesis. Given that nearly all oxygen on earth is derived from photosynthesis, couled with that fact that photosynthetic organisms constitute the bast of the food chain it was surprising how little was known about the evolution of photosynthesis. To address this issue I realized that our work on genes in the chlorophyll biosynthetic pathway could provide unique insight to the evolutionary relationship between various photosynthetic lineages. Consequently, my research group cloned and sequenced chlorophyll biosynthesis genes in each of the known branches of photosynthetic organisms (purple bacteria, green sulfur bacteria, green non-sulfur bacteria, Heliobacteria, etc) and used this information to derive the first ever reported phylogenetic trees that defined the evolutionary relationship between photosystems synthesized between different photosynthetic lineages. This work resulted in several high visibility publications including one article that was featured on the cover of *Science*. [*note that I no longer work on this topic as these studies were undertaken by a postdoctoral fellow in my group that left to establish his own laboratory in this area*.]

a. Xiong, J., K. Inoue & C. E. Bauer. 1998. Tracking molecular evolution of photosynthesis by characterization of a major photosynthesis gene cluster from *Heliobacillus mobilis. Proc. Natl. Acad. Sci. 95, 14851-14856.*
b. Xiong J., K. Inoue, M. Nakahara & C. E. Bauer. 2000. Molecular evidence for the early evolution of photosynthesis. *Science. 289, 1724-1730* (Featured on cover) {discussed in *Science* Perspective in same issue pp1703; in *Trends in Plant Sciences* 6, 4 (2001); in The Scientist, 14, 1 (2001)}
c. Xiong, J. & C. E. Bauer. 2002. A cytochrome *b* origin of photosynthetic reaction centers. *J. Mol. Biol.* 322, 1025-1037.
d. Xiong, J., & C. E. Bauer. 2002. Complex evolution of photosynthesis. *Ann Rev. Plant Physiol.* 53, 503-521. {A figure from this review has been published in "Plant Biochemistry" a textbook by Caroline Bowsher, Martin Steer and Alyson Tobin, Taylor & Francis Group publishers, 2007}.

D. Research Support

Ongoing Research Support

1R01GM099703-01 CE Bauer (PI) 03/01/12-2/29/16
Agency: National Institutes of Health
Title: Regulatory Circuits Controlling Development of Dormant Microbial Cysts (THIS STUDY)
Goal: This is a study to genetically identify and biochemically characterize transcription factors that control cyst development in *Rhodospirillum centenum*.
Role: PI

5 R39 GM40941-21 CE Bauer (PI) 12/01/89 – 03/31/16
Agency: National Institutes of Health MERIT Award (Method to Extend Research Time)
Title: Prokaryotic Gene Regulation by Light and Oxygen
Goal: This is a study to biochemically analyze transcription factors that control *Rhodobacter capsulatus* gene expression in response to alterations in light and oxygen.
Role: PI

Completed Research Support

None to report during the past three years.