BIOGRAPHICAL SKETCH

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NAME: David A. Dubnau

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

POSITION TITLE: Professor

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
Lafayette College, Easton, PA	AB	9/56	Biology/chemistry
Columbia University, New York, NY	MA	6/58	Biology
Columbia University, New York, N	PhD	6/61	Biology

A. Personal Statement

My laboratory investigates the biology of the model organism *Bacillus subtilis* in the belief that this powerful model reveals fundamental aspects of biology with wide application to other fields, including the study of pathogens. My lab focuses on two areas. The first is the regulation of developmental processes, including genetic competence, sporulation and biofilm formation. A second major goal is to gain an understanding of how transforming DNA is internalized. For all of our studies we use a combination of microbiological, microscopic, biochemical, genetic and biophysical approaches, based on the conviction that adopting a variety of experimental avenues of attack greatly expands the power of our research. Our work has been consistently productive and NIH has continuously funded us for 50 years. For many years I have had two grants, one devoted to regulatory studies and the other on the mechanisms of DNA uptake during transformation. This MIRA proposal combines the two areas of investigation, both of which deal with aspects of bacterial development.

I believe strongly in a team approach to research. My group meets weekly so that students and postdocs may present their work and valuable ideas emerge from these discussions. I also believe strongly in collaborations when progress requires an expertise that is lacking in my group. These practices have served us well for many years and have made our work both productive and enjoyable. Over the years I have helped train many doctoral and postdoctoral students, several of whom have gone on to successful careers in academia, in the private sector and as editors of premiere journals. Several of these individuals have taken possession of projects that were initiated in our lab and this practice continues.

B. Positions and Honors

9/61 - 2/64 Postdoctoral Fellow (National Cancer Institute), National Institute for Medical Research, London, England (with Dr. M.R. Pollock)

3/64-12/65 Postdoctoral Fellow (National Cancer Institute), Dept. of Biochemistry, Albert Einstein College of Medicine, Bronx, New York (with Dr. J. Marmur)

7/66-8/71 Research Assistant, Professor, Department of Microbiology, New York University School of Medicine, New York, New York

9/71-8/79 Research Associate Professor, Department of Microbiology, New York University School

of Medicine, New York, New York

9/79-1/04 Research Professor, Department of Microbiology, New York University School of Medicine, New York, New York

1/66-6/70 Associate, Department of Microbiology, The Public Health Research Institute, New York, New York

7/70-6/79 Associate Member, Department of Microbiology, The Public Health Research Institute, New York, New York

7/79-Present Member, Department of Microbiology, The Public Health Research Institute, Newark, New Jersey

7/84-6/88 Member of the Microbial Physiology & Genetics Study Section, NIH

7/86-6/88 Chairman, of the Microbial Physiology & Genetics Study Section, NIH
5/90-1993 Member, Genbank Advisory Committee, NIH

1996-present Fellow of AAAS

2003-2016 Professor, Department of Microbiology and Molecular Genetics, New Jersey Medical School, University of Medicine and Dentistry of New Jersey

2016-present Professor, Department of Microbiology, Biochemistry and Molecular Genetics, New Jersey Medical School, Rutgers University

2008 Mentor of the Year Award, voted by UMDNJ Graduate students.

C. Contributions to Science

a. As a postdoctoral fellow I generated the first nearly contiguous genetic map of the *Bacillus subtilis* chromosome. This study helped establish *B. subtilis* as the most widely used Gram-positive bacterial model system.

Dubnau D, Goldthwaite C, Smith I, Marmur J. Genetic mapping in Bacillus subtilis. J Mol Biol. 1967 Jul 14;27(1):163–185.

Dubnau D, Smith I, Marmur J. Gene conservation in Bacillus species. II. The location of genes concerned with the synthesis of ribosomal components and soluble RNA. Proc Natl Acad Sci U S A. 1965 Sep;54(3):724–730.

b. As a newly independent investigator my lab isolated and characterized the first systematically derived set of mutants deficient in transformation. These carried either regulatory mutations (see "d") or mutations in the genes that encode DNA uptake proteins. The DNA uptake proteins identified in these studies have now been found in all the eubacterial transformation systems (except for the pilus-related proteins that are absent from *Helicobacter*) and are still being actively investigated in many labs. This subject is the focus of Project 2 in the current application and we believe that we are poised to make significant gains in our understanding of the mechanism of DNA transport across the cell membrane.

Hahn J, Albano M, Dubnau D. J Bacteriol 1987; 95:876–885 Isolation and characterization of Tn917lac-generated competence mutants of Bacillus subtilis.

Draskovic I, Dubnau D. Biogenesis of a putative channel protein, ComEC, required for DNA uptake: membrane topology, oligomerization and formation of disulphide bonds. Mol. Microbiol. 2005 55:881-896. PMC3835657

Hahn J, Maier B, Haijema BJ, Sheetz M, Dubnau D. Transformation Proteins and DNA Uptake Localize to the Cell Poles in *Bacillus subtilis*. Cell 2005 Jul; 122(1): 59-71. PMC4442496

Briley K, Jr., Dorsey-Oresto A, Prepiak P, Dias MJ, Mann JM, Dubnau D. The secretion ATPase ComGA is required for the binding and transport of transforming DNA. Mol Microbiol 2011; 81: 818-830. PMC3781931

c. We identified the enzyme that methylates bacterial 23S rRNA to confer resistance to macrolide antibiotics and discovered a unique mechanism of regulation of this enzyme by translational attenuation. These studies have expanded our understanding of resistance to an important class of antibiotics.

Shivakumar AG, Dubnau, D. Characterization of a plasmid-specified ribosome methylase associated with macrolide resistance. Nuc. Acids Res. 1981; 9(11): 2549-2562.

Hahn J, Grandi G, Gryczan TJ, Dubnau D. Translational attenuation of *ermC*: a deletion analysis. Mol Gen Genet. 1982;186(2):204-16.

Dubnau D. Induction of *ermC* requires translation of the leader peptide. EMBO J. 1985 Feb; 4(2): 533–537.

Narayanan CS, Dubnau D. An in vitro study of the translational attenuation model of ermC regulation. J Biol Chem. 1987 Feb 5;262(4):1756-65.

d. Our laboratory has been a leader in elucidating the complex network of protein-protein and protein-DNA interactions that regulates the expression of competence genes. This network is embedded in an even more complex set of interactions that governs spore and biofilm formation, and we have continued to investigate this expanded regulatory system. Project 1 in the current application continues our investigations of this network.

Turgay K, Hahn J, Burghoorn J, Dubnau D (1998) Competence in Bacillus subtilis is controlled by regulated proteolysis of a transcription factor. EMBO J 17: 6730-6738. PMC1171018

The Rok protein of Bacillus subtilis represses genes for cell surface and extracellular functions. Albano M, Smits WK, Ho LT, Kraigher B, Mandic-Mulec I, Kuipers OP, Dubnau D. Journal of bacteriology. 2005; 187(6):2010-9. PMC1064057

Prepiak P, Dubnau D (2007) A peptide signal for adapter protein-mediated degradation by the AAA+ protease ClpCP. Mol Cell 26: 639-647. PMC2041856

Miras M, Dubnau D (2016) A DegU-P and DegQ-Dependent Regulatory Pathway for the K-state in *Bacillus subtilis.* Frontiers in Microbiol 22:1868. PMC5118428

e. We were among the first to recognize that the expression of competence development is governed stochastically and that cells are selected on the basis of transcriptional noise. Our investigations of the bistable expression of competence genes stimulated much related work in other labs and are often cited as a model for other developmental systems.

Maamar, H., and Dubnau, D. (2005) Bistability in the *Bacillus subtilis* K-state (competence) system requires a positive feedback loop, *Mol. Microbiol. 56*, 615-624. PMC3831615

Maamar H, Raj A and Dubnau D (2007) Noise in gene expression determines cell fate in Bacillus subtilis. Science 317: 526-529. PMC3828679

Mirouze N, Prepiak P and Dubnau D. Fluctuations in spo0A transcription control rare developmental transitions in *Bacillus subtilis*. PLoS genetics. 2011; 7(4):e1002048. PMC3084206

Mirouze N, Desai Y, Raj A, Dubnau D (2012) Spo0A~P imposes a temporal gate for the bimodal expression of competence in Bacillus subtilis. PLoS Genet 8: e1002586. PMC3297582

f. Recently we have discovered a complex of three proteins (RicAFT) needed for biofilm formation, sporulation and genetic competence in *B. subtilis*. This complex carries two Fe-S clusters as well as a single molecule of FAD. These proteins are widely conserved among the firmicutes and although their precise roles are still poorly understood, they are clearly important for developmental processes. Understanding them is a major goal of Project 1.

Carabetta VJ, Tanner AW, Greco TM, Defrancesco M, Cristea IM, Dubnau D (2013) A complex of YlbF, YmcA and YaaT regulates sporulation, competence and biofilm formation by accelerating the phosphorylation of Spo0A. Mol Microbiol 88: 283-300. PMC3781937

Dubnau, EJ, Carabetta VJ, Tanner AW, Miras M, Diethmaier C, Dubnau D (2016) A protein complex supports the production of Spo0A-P and plays additional roles for biofilms and the K-state in *Bacillus subtilis*. Mol. Microbiol. 101:606-624. PMC4978174

Tanner, AW, Carabetta, VJ, Martinie, RJ, Mashruwala, AA, Boyd, JM, Krebs, C, Dubnau, D. (2017) The RicAFT ((YmcA-YlbF-YaaT) complex carries two [4Fe-4S$^{]+2}$ clusters and may respond to redox changes. Mol Microbiol 104: 837-8500. PMC5444954

g. We have initiated an ongoing study of protein acetylation and its roles in bacterial physiology and development. We began by characterizing the acetylome of *B. subtilis*. We have discovered a potential role for acetylation in the control of DNA compaction in the nucleoid. My postdoc Valerie Carabetta will eventually seek independent funding for this project. I have therefore not included this project in the current application.

Carabetta VJ, Greco, TM, Tanner AW, Cristea IM, Dubnau D (2016) Temporal Regulation of the Bacillus subtilis Acetylome and Evidence for a Role of MreB Acetylation in Cell Wall Growth. mSystems 1(3). pii: e00005-16. Epub 2016. PMC4927096

h. We are investigating the role of the bacterial flagellum as a sensing device for the regulation of gene expression and have identified viscous drag on the flagellum as a signal that regulates the phosphorylation of DegU. The control of gene expression by mechanosensing signaling involving flagella and cilia is widespread biology but the signal transduction pathways are not well understood in bacteria. This work continues as part of Project 1.

Diethmaier, C, Chawla, R, Canzoneri, A, Kearns, DB, Lele, PP, Dubnau D (2017) Viscous drag on the flagellum activates Bacillus subtilis entry into the K-state. Mol Microbiol 106: 367-380. PMC5653444

i. We have shown that competent cells of *B. subtilis* are arrested in growth and DNA replication, reminiscent of persistent cells during antibiotic exposure. In fact competent cells are tolerant of antibiotics. We have identified two proteins that are required for the growth arrest and are characterizing their modes of action. This work continues as part of Project 1.

Briley, K Jr, Prepiak, P, Dias, MJ, Hahn, J, Dubnau D. (2011) Maf acts downstream of ComGA to arrest cell division in comptent cells of *B. subtilis*. Mol. Microbiol. 81:23-39. PMC3781949

Hahn J, Tanner AW, Carabetta VJ, Cristea IM, Dubnau D. (2015) ComGA-RelA interaction and persistence in the *Bacillus subtilis* K-state. Mol. Microbiol. 81:23-39. 97: 454-471. PMC4722805

Complete list of publications in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41438987/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

RO1 GM057720 D. Dubnau (PI) Last Funding Period: 07/01/2014 - 06/30/2018
Title Regulation of genetic competence in *Bacillus subtilis*
The goal of this study is to understand the regulation of stationary phase developmental pathways in *Bacillus subtilis*, particularly genetic competence. Role: PI

RO1 GM043756 D. Dubnau (PI) Last Funding Period: 05/01/2013 - 02/28/2017
Title Genetic competence apparatus of *Bacillus subtilis*
The goal of this study is to understand the mechanisms of transformation in *Bacillus subtilis*. Role: PI