OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
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NAME: Robert Allen Britton

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

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 |
| --- | --- | --- | --- |
| University of Nebraska | B.S. | 1985-1989 | Biology |
| Baylor College of Medicine | Ph.D. | 1990-1996 | Cell and Molecular Biology |
| Massachusetts Institute of Technology | Postdoc | 1996-2002 | Bacterial genetics/genomics |
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**A. Personal Statement.**  The role of bacteria in human and animal health has undergone a renaissance in the past decade. The overall focus of my laboratory is therapeutic microbiology, in which we aim to develop both traditional probiotic bacterial strains for the prevention and treatment of disease as well as engineer bacterial communities to express therapeutic proteins. During my PhD work under James Lupski at Baylor College of Medicine and my postdoctoral training under Alan Grossman at MIT I received excellent training in microbial genetics, physiology and genomics. I trained extensively in both Gram-negative and Gram-positive model systems and it is this expertise that I now bring to the current work in the areas of probiotic bacteria and the intestinal microbiota. My laboratory has been investigating microbial community structure and function using next generation sequencing technology to address how microbial ecology impacts health. We also have developed powerful genetic tools for the exploration of mechanistic insights into the benefits of probiotic lactic acid bacteria. Recently, we have invented human fecal Mini-Bioreactor Arrays (MBRAs) to investigate how human intestinal microbiota interacts with *C. difficile* as well as a humanized microbiota (Hmb) mouse model of *C. difficile* disease. The MBRAs completely reproduce the *C. difficile* invasion dynamics that are observed in humans and animal models as well as other aspects of human intestinal communities. We also use MBRAs to study microbiome:diet interactions, drug metabolism by the microbiota and other infectious disease interactions with microbial communities. Thus, I am well-positioned to act at Co-PI on this proposal.

**B. Positions and Honors**

**Positions and Employment**

1988-1990 Research Assistant with Robert Klucas, Ph.D., in the Dept. of Biochemistry, Univ. of Nebraska, Lincoln, NE.

1989-1990 Research Assistant with Anne Vidaver, Ph.D., in the Dept. of Plant Pathology, Univ. of Nebraska, Lincoln, NE.

1995 Guest Researcher in the laboratory of Dr. Donald Court, Laboratory of Chromosome Biology and Gene Expression, NCI/FCRDC, Frederick, MD.

1991-1996 Completed Ph.D. Thesis Research with James R. Lupski, M.D./Ph.D., Dissertation Title: Suppressor Analysis of *E. coli* *dnaG* Mutations. Baylor College of Medicine, Houston, TX.

1996-2002 Postdoctoral fellow in the laboratory of Dr. Alan Grossman, Department of Biology, MIT, Cambridge, MA.

2003-2008 Assistant Professor, Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI.

2008-2014 Associate Professor, Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI.

2014-2014 Professor, Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI.

2014-present Professor, Department of Molecular Virology and Microbiology; Member, Center for Metagenomics and Microbiome Research, Baylor College of Medicine, Houston, TX.

**Professional Memberships**

1999-present American Society for Microbiology

**Honors and Service**

2016 International Ocular Surface Society Award Lecture, Seattle, WA.

2010 Teacher-Scholar Award, College of Natural Science, Michigan State University

2009 NSF Fall Genetics Panel, Reviewer

2008-present Participant in the Joint Genomes Institute Undergraduate Annotation Research

Initiative.

2005-2010 Editor, Gene – Functional Genomics

2006-2009 Delegate, International Society of Probiotics and Prebiotics

2005-2007 Scientific Foundation of Ireland, Reviewer, Genetic Panel and Equipment grants

2000-2002 Co-director of the MIT Microarray Club.

1994 O.B. Williams Award Winner, Best Oral Presentation, Texas Branch American Society for Microbiology.

**C. Contributions to science.**

**1. Characterization of the mechanisms of action of *Lactobacillus reuteri* 6475 as a probiotic organism for the improvement of human health.** *L. reuteri* 6475 is a probiotic organism that has anti-inflammatory properties and produces the anti-microbial compound reuterin. My lab has been focused on how *L. reuteri* impacts health and disease in animal models and in vitro assays. In collaboration with James Versalovic (Baylor College of Medicine) we have shown that *L. reuteri* 6475 can turn down TNF production from activated monocytes by the production of histamine. Based on this anti-inflammatory property we have recently shown this strain can reduce osteoporosis in a mouse model of menopause and are currently investigating the molecular basis for this suppression from both the host and bacterial perspectives. Our work has also discovered the molecular bases for acid and bile resistance in *L. reuteri*, as well as the mechanism of action of reuterin in killing bacteria. *L. reuteri* 6475 is currently available as a probiotic supplement and we hope to provide evidence for specific use of this strain in osteoporosis and other chronic, inflammatory diseases.

**1.** **Britton RA**, Irwin R, Quach D, Schaefer L, Zhang J, Lee T, Parameswaran N, McCabe LR (2014). Probiotic *L. reuteri* Treatment Prevents Bone Loss in a Menopausal Ovariectomized Mouse Model. J Cell Physiol. 2014 Mar 27. doi: 10.1002/jcp.24636

**2.** Quach D, Collins F, Parameswaran N, McCabe L, **Britton RA**. (2018). Reconstitution Does Not Cause Bone Loss in Germ-Free Mice. mSphere. 2018 Jan 3;3(1). pii: e00545-17. doi: 10.1128/mSphereDirect.00545-17. eCollection 2018 Jan-Feb. PMID:29299532

**3.** Jones SE, Whitehead K, Saulnier D, Thomas CM, Versalovic J, **Britton RA** (2011). Cyclopropane fatty acid synthase mutants of probiotic human-derived *Lactobacillus reuteri* are defective in TNF inhibition. Gut Microbes. 2(2):1-11.

**4.** Walter J, **Britton RA**, and Roos S. (2011) Microbes and Health Sackler Colloquium: Host-microbial symbiosis in the vertebrate gastrointestinal tract and the *Lactobacillus reuteri* paradigm. PNAS. 2011 Mar 15;108 Suppl 1:4645-52. Epub 2010 Jun 25.

**2. Development of precision genome editing tools for lactobacilli and lactococci.** A major challenge for the field of probiotics is elucidating the mechanisms by which these organisms impact human health. The lack of sophisticated genetic tools in lactic acid bacteria has limited the ability to use genetic approaches in uncovering key probiotic functions. My lab adapted recombineering technology for use in *Lactobacillus reuteri* and *Lactococcus lactis*, which allows for the introduction of point mutations, deletions, and insertions directly into the chromosome without the need for antibiotic selection. The number of mutations that can be constructed in a single organism is essentially limitless, and the ability to create single basepair mutations enables the alteration of gene expression, enzyme function, and protein interactions in addition to generating null mutations. This method was successfully used to prove the histamine decarboxylase operon of *L. reuteri* 6475 is responsible for histamine production and anti-inflammatory capabilities of this strain. We have also altered the sensitivity of *L. reuteri* 6475 to the antibiotic vancomycin by making a single amino acid change in the *ddl* gene. We have shared this technology with dozens of laboratories around the world.

**1.** van Pijkeren, JP and **Britton RA**. (2012). High-efficiency recombineering in lactic acid bacteria. Nucleic Acids Research. May;40(10):e76. doi: 10.1093/nar/gks1472012 Feb 10. [Epub ahead of print]

**2.** van Pijkeren JP, Neoh KM, Sirias D, Findley AS, **Britton RA** (2012).Exploring optimization parameters to increase ssDNA recombineering in *Lactococcus lactis* and *Lactobacillus reuteri.* Bioengineered Bugs. Jul-Aug;3(4):209-17. doi: 10.4161/bioe.21049. Epub 2012 Jul 1.

**3.** Stockdale SR, Mahony J, Courtin P, Chapot-Chartier MP, van Pijkeren JP, **Britton RA**, Neve H, Heller KJ, Aideh B, Vogensen FK, van Sinderen D (2013). [The lactococcal phages Tuc2009 and TP901-1 incorporate two alternate forms of their tail fibre into their virions for infection specialization.](http://www.ncbi.nlm.nih.gov/pubmed/23300085) Journal of Biological Chemistry. Jan 8. [Epub ahead of print]. PMID: 23300085.

**4.** van Pijkeren JP, **Britton RA**. (2014). Precision genome engineering in lactic acid bacteria. Microb Cell Fact. 2014 Aug 29;13 Suppl 1:S10. doi: 10.1186/1475-2859-13-S1-S10. Epub 2014 Aug 29.

**3. Investigating the interaction between the intestinal microbiota and *Clostridium difficile*.** We are interested in understanding how the intestinal microbiota provides a barrier to incoming pathogens and how perturbations of the microbiota result in an established infection. We have focused most of our attention on the pathogen *Clostridium difficile*, which is the most common cause of antibiotic associated diarrhea and is quickly becoming the most common cause of nosocomial infections. We have developed mini-bioreactor arrays (MBRAs) and mice colonized with a human intestinal microbiota to address which members of the community are responsible for inhibiting *C. difficile* invasion. The MBRAs are capable of harboring complex, human derived microbial communities that suppress *C. difficile* invasion unless treated with antibiotics. Our ultimate goal is to develop a probiotic cocktail derived from the human intestinal microbiota that will suppress *C. difficile* invasion.

**1.** Collins J, Robinson C, Danhof H, Knetsch CW, van Leeuwen HC, Lawley TD, Auchtung JM, **Britton RA.** (2018) Dietary trehalose enhances virulence of epidemic *Clostridium difficile*. Nature. 2018 Jan 18;553(7688):291-294. doi: 10.1038/nature25178. Epub 2018 Jan 3. PMID: 29310122

**2.** Robinson CD, Auchtung JM, Collins J, **Britton RA**. (2014). Epidemic *Clostridium difficile* Strains Demonstrate Increased Competitive Fitness Compared to Nonepidemic Isolates. Infect Immun. 2014 Jul;82(7):2815-25. doi: 10.1128/IAI.01524-14. Epub 2014 Apr 14

**3.** Collins J, Auchtung JM, Schaefer L, Eaton KA, **Britton RA**. (2015). Humanized microbiota mice as a model of recurrent *Clostridium difficile* disease. Microbiome. 2015 Aug 20;3:35. doi: 10.1186/s40168-015-0097-2

**4.** Auchtung JM, Robinson CD, **Britton RA**. (2015). Cultivation of stable, reproducible microbial communities from different fecal donors using minibioreactor arrays (MBRA). Microbiome. 2015 Sep 30;3:42. doi: 10.1186/s40168-015-0106-5. PMID: 26419531.

**4. The role of essential GTPases in the control of bacterial ribosome biogenesis and cell cycle control.** GTPases play an important role in the assembly of ribosomes in all three kingdoms of life. The molecular mechanisms by which they function are largely unknown. We are studying the ribosome assembly GTPase RbgA in *Bacillus subtilis* in an attempt to understand how these proteins act in the maturation of the large ribosomal subunit using a combination of biochemical, structural and genetic approaches. Interestingly, mutation or depletion of RbgA results in the accumulation of a ribosome assembly intermediate that is arrested at a very late stage of development. Work on eukaryotic homologs of RbgA suggests that these proteins are involved in a late assembly step of the large ribosomal subunit. The results from this bacterial work will have important implications for the formation of cytoplasmic, mitochondrial, and chloroplast ribosomes.

**1.** Gulati, M, Jain, N, Davis, JH, Williamson, JR and Britton RA (2014). Functional interaction between ribosomal protein L6 and RbgA during ribosome assembly. PLoS Genetics. 2014 Oct 16;10(10):e1004694. doi: 10.1371/journal.pgen.1004694. eCollection 2014 Oct. PubMed PMID: 25330043; PubMed Central PMCID: PMC4199504.

**2.** Jomaa A, Jain N, Davis JH, Williamson JR, **Britton RA**, Ortega J. (2013). Functional domains of the 50S subunit mature late in the assembly process. Nucleic Acids Res. 2013 Dec 13. [Epub ahead of print].

**3.** **Britton, RA**. Role of GTPases in ribosome assembly. (2009). Annual Review of Microbiology 2009 May 1. [Epub ahead of print].

**4.** Schaefer, L., Uicker, W. U., Wicker-Planquart, C., Foucher, AE, Jault JM and **Britton, R.A.** (2006). Multiple GTPases participate in the assembly of the large ribosomal subunit in *Bacillus subtilis*. Journal of Bacteriology. **188**:8252-8258.

Full publication record available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/1TKIVdmmlv5/bibliography/41856232/public/?sort=date&direction=descending

**D. Research Support**

**Ongoing research support:**

R01GM110248 (Britton - PI) 3/1/15 – 2/28/19

NIH/NIGMS

**GTPase control of large ribosome subunit biogenesis**

The goal of this project is to investigate the role of RbgA in assembly of the 50S subunit.

U19AI116482 (Britton - collaborator) 3/1/15 – 2/29/20

NIH/NIAID

**Engineered human intestinal organoids: a modular system to model enteric disease**

The goal of this project is to interface human intestinal organoids with intestinal microbes.

U01 AI124290-01 9/1/16-8/31/21

NIH/NIAID (Savidge, Britton, Sorg, Garey, Iliopoulus multi-PI)

**Decoding antibiotic-induced susceptibility to *Clostridium difficile* infection**

The goal of this project is to study *C. difficile* pathogenesis using a systems biology approach.

R01DK103759 (Britton) 12/1/15 – 11/30/18

NIH/NIDDK

**Sex, serotonin & visceral hypersensitivity**

The goal is to identify the molecular basis of how serotonin contributes to IBS with a focus on finding microbial therapeutics to alleviate IBS symptoms.

P01CA039542 (Ferrara; Britton-BCM PI) 06/01/16 – 05/31/20 0.6 CM

NIH/NCI $44,977

**Cellular and Molecular Studies of Bone Marrow Transplant**

We are engineering probiotic L. reuteri strains to deliver human biotherapeutics that will combat intestinal GVHD.

R01EY026893 (de Paiva) 09/01/17-08/31/22 0.8 CM

NIH/NEI $100,000

**Commensal microbiota modulates ocular surface mucosal inflammation**

We are investigating the impact of the microbiota on dry eye syndrome in mice and humans.

Research to Prevent Blindness Foundation (Britton) 01/01/17-12/31/19 0.12 CM

**RPB Stein Innovation Award** $150,000

Investigating the role of intestinal microbes on progression of inflammatory diseases of the eye.

We are investigating the of the role of the intestinal microbiota in dry eye and uveitis. This honor is aimed at getting researchers that do not work in eye research to initiate a project in this area.

Gates Foundation (Britton) 09/07/17-10/01/19 0.5 CM

Bill and Melinda Gates Foundation $268,454

**Upstream acceleration of preclinical discovery efforts that target the gut microbiota for treatment of childhood undernutrition: testing the utility of mini-bioreactor arrays (MBRAs)**.

The objective of this proposal is to test if we can reconstitute undernourished microbial communities in vitro to be used for testing therapeutic compounds.

R66361 William Marsh Rice University (Britton-BCM PI) 05/04/17-10/03/18 0.5 CM

Caribou Biosciences, Inc.$98,686

**Screening a DBD-Swapped human gut microbiota TCS library to discover novel sensors of gastrointestinal inflammation.**

The objective of this proposal is to identify novel biosensors of gut inflammation.

R01AI123278 (Britton) 11/17/17 – 10/31/22 2.0 CM

NIH/NIAID $250,000

**Diet driven evolution of epidemic ribotypes of *C. difficle***

The goal of this project is to study the impact of dietary trehalose on epidemic *C. difficile*.

R33AI121522 (Britton) 12/01/15 – 11/30/20 1.56 CM

NIH/NIAID $300,000

**Defined microbial communities for the treatment of recurrent C. difficile infection**

The goal of this project is to isolate intestinal bacteria that, when administered as a cocktail, suppress

*C. dfficile* invasion.