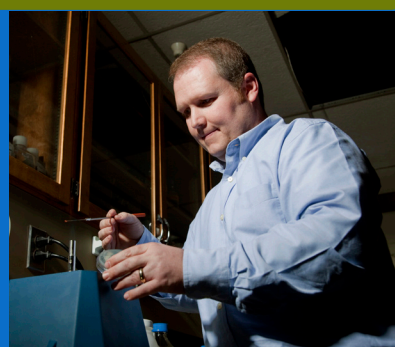
Faculty Research Guide

BYU Department of Microbiology and Molecular Biology



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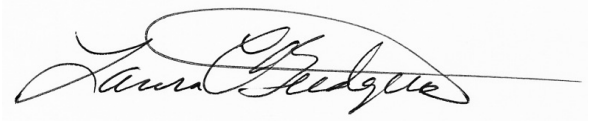
From the Chair : Laura Bridgewater

Brigham Young University's location at the foot of the majestic Rocky Mountains means we're only minutes away from skiing, lakes, camping, hiking, rock climbing, and a host of other outdoor activities—welcome diversions for hard-working graduate students. We also boast a wholesome campus environment that's second-to-none, with over 30,000 students who are committed to the principles of personal integrity, academic excellence, clean living, and service to others. Research facilities on campus include centers for DNA sequencing, electron microscopy, mass spectrometry, chromatography, confocal microscopy, and flow cytometry.

The Department of Microbiology and Molecular Biology is home to a faculty recruited from graduate programs and postdoctoral fellowships at some of the best research institutions in the nation including Stanford, Princeton, Yale, Washington University, MD Anderson Cancer Center, UC San Diego, and UC Berkeley. Our faculty members maintain connections with these institutions, providing expanded opportunities for our students.

We invite you to consider our graduate programs in Microbiology and Molecular Biology as you plan your future—BYU just might be the perfect place for you.



Laura C. Bridgewater, Ph.D.
Department Chair

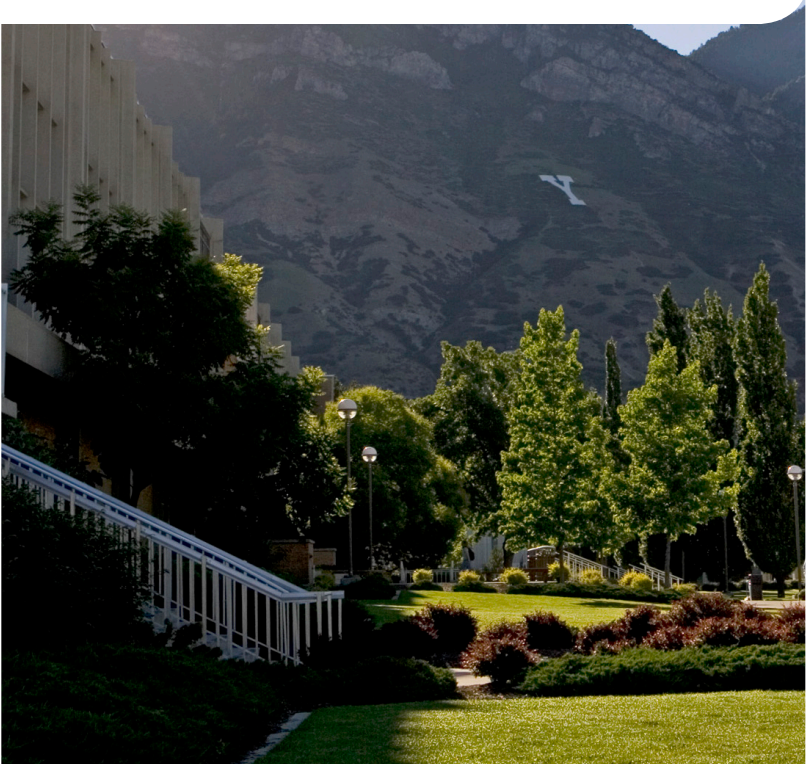
laura_bridgewater@byu.edu
801-422-2434

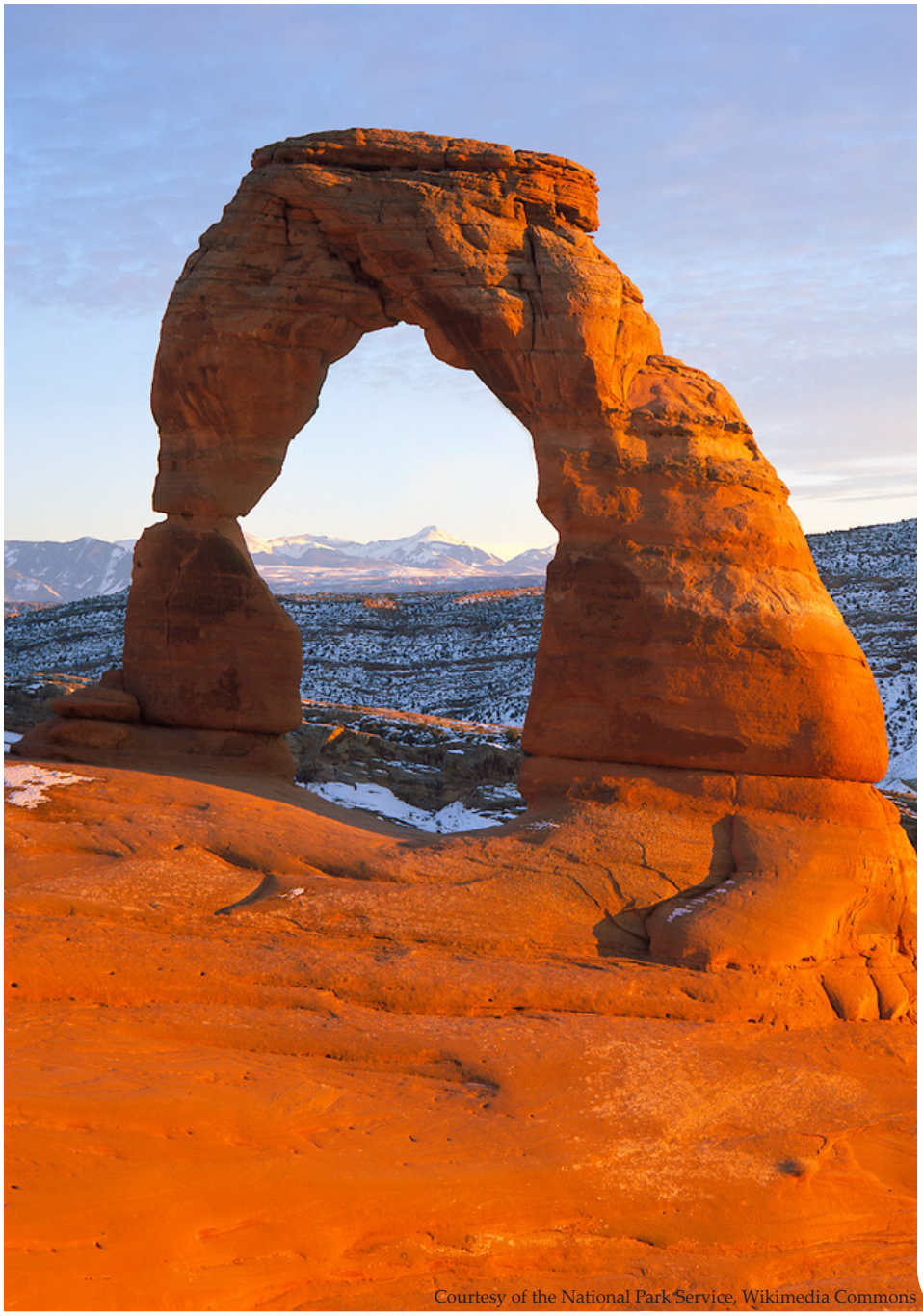
Courtesy of BYU Photography

Welcome to Brigham Young University

Enter to learn, go forth to serve: this is the attitude Brigham Young University strives to instill in its students. BYU seeks to develop students of faith, intellect, and character who have the skills and the desire to continue learning and to serve others throughout their lives. The university provides an outstanding education in an atmosphere consistent with the ideals and principles of its sponsor, The Church of Jesus Christ of Latter-day Saints.

Known for its excellent academics, internationally-experienced student body, world-class teaching and beautiful mountain location, BYU is also recognized for its extensive language programs, talented preforming arts ensembles, outstanding sports programs and devotion to combining solid scholarship with the principles of the gospel of Jesus Christ.





Courtesy of the National Park Service, Wikimedia Commons

Courtesy of Spforticus, Wikimedia Commons

Welcome to Utah

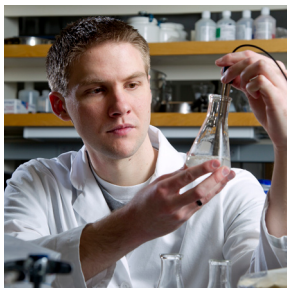
Utah is a paradise for tourists and residents alike, boasting a diverse geographic environment. Whether enjoying Utah's breath-taking scenery or experiencing the variety of exciting outdoor activities, there is never a lack of entertainment.

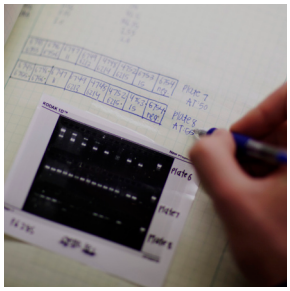
From mountain biking in Moab among the famous red rock arches, to skiing or snowboarding on "the greatest snow on earth" in one of 14 ski resorts, to golfing year round in St. George, to listening to the Mormon Tabernacle Choir on Temple Square, Utah will surprise you with its variety of things to see and do.

Courtesy of Turboed, Wikimedia Commons

Courtesy of Sandstein, Wikimedia Commons

Program of STUDY





The fields of microbiology and molecular biology are closely intertwined and are at the center of some of the most exciting current advances in the biological sciences. From microbial metabolism to eukaryotic gene regulation to multi-organism molecular interactions, these fields encompass a broad range of issues that are important for fundamental understanding as well as the development of biological technologies.

The Department of Microbiology and Molecular Biology offers four degrees:

Microbiology MS
Microbiology Ph.D.
Molecular Biology MS
Molecular Biology Ph.D.

Coursework

Coursework requirements are designed to maximize scientific knowledge and research experiences. All graduate students are required to take:

- Molecular Biology of the Cell, MMBIO 661
- Genomics, Molecular Evolution, and Developmental Biology, MMBIO 662
- Research Orientation, BIO 503
- One MMBIO 500 or 600 level course
- MMBIO Seminar, MMBIO 691R

Ph.D. students are also required to take one of the following Quantitative skill courses:

CHEM 468, CHEM 489, CS 618, PWS 633, STAT 535, or STAT 641

- Research and Thesis/Dissertation Credits

Students, along with their advisory committee, may also select graduate classes from other departments, including Biology, Chemistry and Biochemistry, and Physiology and Developmental Biology.

Choosing a Faculty Advisor

Ph.D. students choose their faculty advisors no later than the end of the second semester, whereas M.S. students choose their advisors after their first semester. These arrangements are made by mutual agreement between the advisor and student. The low student/faculty ratio in the department contributes to a high degree of student choice and allows for a high level of interaction with faculty members.

Laboratory Rotations

New Ph.D. students are encouraged to participate in two to three laboratory rotations in the first year of study. These rotations help students choose a faculty advisor and laboratory, and they also expose students to areas of research they may not have otherwise considered. In addition, students develop a network of contacts and learn a variety of experimental techniques that may prove useful in their subsequent thesis research.

Financial Support

All Ph.D. students in the department are awarded financial support including stipend (through research and teaching assistantships), tuition, and student insurance. M.S. students are awarded research and teaching assistantships on a competitive basis. Departmental support continues for five years for Ph.D. students and two years for M.S. students, provided that progress is satisfactory. Students may also compete for fellowships and awards provided by other entities such as the University Office of Graduate Studies and the BYU Cancer Research Center. Most students work as teaching assistants at least one semester of each year to earn department support, but this requirement is waived for students who secure fellowships or awards through other sources.

Research FACILITIES

Research Instrumentation Core Facility

Sandra Burnett, Ph.D., Director

http://ricfacility.byu.edu

This departmental facility contains shared equipment for protein purification, separation, and analysis. It is equipped with a flow cytometer, image analysis system for gels and blots, a high-speed centrifuge, a fluorescent microscope, a spectrophotometer and two plate readers.

DNA Sequencing Center

Michael F. Whiting, Ph.D., Director

http://dnasc.byu.edu/

This facility provides automated DNA sequencing at affordable prices. Services offered include custom DNA sequencing, DNA fragment analysis, sequencing and PCR troubleshooting and training workshops, SNP analysis, primer walking, and contig assembly and editing.

Proteomics and Mass Spectrometry Facility

Sarah Warburton, Ph.D., Interim Director

massspec@byu.edu

This facility, housed in the Department of Chemistry and Biochemistry, contains a QqToF mass spectrometer with interchangeable electrospray, nanospray, and MALDI ion sources for proteomic analyses (applied Biosystems QSTAR Pulsar I).

Electron Optics Laboratory

John Gardner, Ph.D., Director

john_gardner@byu.edu

Using this facility, students can accomplish all standard electron optics procedures. The laboratory has transmission and scanning electron microscopes equipped with X-ray microanalysis capabilities, plus accessory equipment for freeze-fracture, freeze drying, and necessary support facilities, including confocal laser scan microscopy.

Miscellaneous Campus Facilities

Students also have access to world-class libraries, a supercomputer, a specific pathogen free (SPF) rodent facility, stockrooms, an instrumentation shop, tissue culture rooms, and greenhouses. In addition, students receive free access to university facilities for personal fitness including weight room, pool, track, and exercise equipment.

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Brad Berges

Assistant Professor
Ph.D., University of Pennsylvania

Research Interests:

Viral Disease Mechanisms, Viral Vaccines

Our group seeks to understand how viruses cause disease in humans. A better understanding of these mechanisms can lead to the development of vaccines to prevent new infections and antiviral drugs to treat current infections. The lack of animal models that can be infected with human viruses and exhibit similar disease has seriously hampered these areas of research. In order to study viral infections of human cells in vivo, we use "humanized mice." A humanized mouse is one in which human cells have been transplanted. We transplant mice with human hematopoietic stem cells; this leads to production of a variety of human blood cell types and development of a human immune system in the mouse. Antibody and cellular immune responses of human origin can then be generated in the mouse.

We are interested in studying viral pathogens that infect human blood cells in our humanized mice. Examples include Dengue Virus (DV), Human Immunodeficiency Virus (HIV), Human herpesvirus 6 (HHV-6), and Kaposi's Sarcoma Herpesvirus (KSHV). DV infects approximately 100 million worldwide per year and the rate is rapidly increasing. Infection can lead to hemorrhagic fever and death, but no vaccines or antiviral are available. About 34 million people worldwide are HIV+, and millions die each year from complications due to AIDS. No vaccines exist, and although effective antiviral drugs are available, they have undesirable side effects and the virus can mutate to escape. One side effect of AIDS is HIV-associated lymphoma (cancer of white blood cells) which commonly arise in patients co-infected with gammaherpesviruses like KSHV. No vaccine is available for KSHV, and we have little understanding of how immunosuppression leads to development of cancer.

The lack of good animal models to study how these viruses cause disease has prevented research and development of vaccines and antiviral therapies. Our humanized mice support infection with each of these viral pathogens. Further, human immune responses can be detected against the pathogens, making this a promising model to study vaccines. Work in our lab involves infecting humanized mice with various viral pathogens, and then studying how disease is caused. Immunization strategies are being investigated to develop potential vaccines for humans. Additionally, antiviral drugs can be tested for efficacy and toxicity. Those who work in the lab gain valuable experience in the areas of laboratory mouse handling/manipulation, mouse injections, mouse dissections, drawing blood, production of virus stocks, virus titering, tissue culture, handling infectious substances, RNA in situ hybridization, immunostaining, flow cytometry (FACS), DNA and RNA extraction, PCR, RT-PCR, and Quantitative PCR, ELISA, and analysis of human immune responses (antibody and cellular).

Selected Publications

Berges, B.K., and Rowan, M.R. "The utility of the new generation of humanized mice to study HIV-1 infection: transmission, prevention, pathogenesis, and treatment". *Retrovirology*, 2011; 8:65.

Akkina R., Berges, B.K., Palmer, Brent E., Remling L., Neff, Charles P., Kuruvilla, J., Connick, E., Folkvord, J., Gagliardi, K., Kassu, A., and Akkina, S.R. "Rag1-/-γc-/- mice support multilineage human hematopoiesis and are susceptible to HIV-1 infection via systemic and vaginal routes". *PLoS One*, 2011. 6(6):e20169.

Berges, B.K., Akkina, S.R., Remling, L., and Akkina, R. "Humanized Rag2-/-γc-/- (RAG-hu) mice can sustain long-term chronic HIV-1 infection lasting more than a year." *Virol*, 2010. 397(1):100-3.

Berges, B.K., Akkina, S.R., Folkvord, J.M., Connick, E., and Akkina, R. "Mucosal transmission of R5 and X4 tropic HIV-1 via vaginal and rectal routes in humanized Rag2-/-γc-/- (RAG-hu) mice." *Virol* 2008 Apr;373(2):342-51.

A bacteriophage isolated as part of the Phage Hunters program.

Don Breakwell

Professor
Ph.D., Purdue University

Research Interests:

Microbial Ecology, Scholarship of Teaching and Learning

Bacteriophages are viruses that infect and kill bacteria and, since they only infect specific types of bacteria, they are unable to harm humans, plants, animals, insects, or the environment. Using phages to control pathogenic bacteria has historical precedence, but has recently received increased attention in the United States. The process includes spraying or ingesting cocktails of phages and then allowing time for incubation, phage amplification and subsequent lysis of bacteria to reduce or eliminate the bacterial population. Using phages to treat bacterial diseases, therefore, is a viable alternative to antibiotics or heavy metals. The need for an alternative form of bacterial control is imperative as bacterial resistance to antibiotics has increased, and as farmers attempt to decrease the use of antibiotics in agriculture while still maintaining healthy, productive crops and animals.

This avenue of research was opened to us in 2009 when we began working with the Science Education Alliance at Howard Hughes Medical Institute. As part of this program, we capture, tame, and dissect phage isolated from soil and other environmental samples. Following DNA isolation and sequencing, we analyze the phage genomes, examine, and share the information with others in the alliance and the public at large. Since 2009, we have isolated over 70 bacteriophages that infect a variety of hosts. To date we have contributed 7 genomes to NCBI's GenBank and the list is growing rapidly. Our analysis has led to more than 15 student presentations at regional meetings of the American Society for Microbiology and several manuscripts are being prepared for publication.

The specific objective that we have is to construct and characterize phage cocktails that can be used to treat disease in plants and animals. We do this by evaluating the lytic activity of the isolated phages, determining their effectiveness in treating bacteria isolated from the field, checking their stability for storage, and determining their unique genetic properties.

In addition to phage research, I am also actively involved in the scholarship of teaching and learning. My students and I examine the implementation of active learning strategies in introductory microbiology courses.

Selected Publications

Peter Shen, Matthew Domek, Eduardo Sanz-Garcia, Aman Makaju, Ryan Taylor, Ryan Hoggan, Michele Culumber, Craig Oberg, Donald Breakwell, John Prince, and David Belnap. 2012. Sequence and Structural Characterization of Great Salt Lake Bacteriophage CW02, a Member of the T7-like Supergroup" *J. Virology* (in press).

Graham F. Hatfull, the Science Education Alliance Phage Hunters Advancing Genomics and Evolutionary Science Program, the KwaZulu-Natal Research Institute for Tuberculosis and HIV Mycobacterial Genetics Course Students and the Phage Hunters Integrating Research and Education Program. 2012. Complete Genome Sequences of 138 Mycobacteriophages. *J. Virology* 86:2382-2384

Jordon K. March, Kyle C. Jensen, Nathan T. Porter, and Donald P. Breakwell. 2011. Authentic Active Learning Activities Demonstrating the Use of Serial Dilutions and Plate Counts. *Journal of Microbiology and Biology Education* 12: 152-156.

Laura Bridgewater

Associate Professor,
Department Chair
Ph.D., George Washington University

Research Interest:

Regulation of Gene Expression

The Bridgewater Lab has three major areas of focus:

Cartilage-specific gene regulation. Previously, the Bridgewater Lab focused on the regulation of cartilage-specific genes including those coding for type XI collagen, type IX collagen, and type XXVII collagen. We have identified enhancer elements in each of these genes that increase transcription in cartilage but not in other cell types. The enhancers all share a common structure, and each binds dimeric SOX9 at inverted heptameric repeats. The transcription factor SOX9 is required for normal cartilage development, and prevention of SOX9 binding inactivates all these enhancers. We have also identified other proteins that work with SOX9 to regulate gene expression.

Nuclear bone morphogenetic protein 2 (nBMP2). Our work with potential transcription factors in the nuclear mileau led to the discovery of a novel variant of BMP2 in the nucleus. BMP2 has previously been recognized as a secreted growth factor that participates in bone and cartilage formation, limb formation, patterning, heart development, apoptosis, and cancer. We discovered a form of BMP2 that is translated from an alternative downstream start codon, which eliminates the N-terminal signal peptide and thus prevents ER localization and secretion. Instead, translation occurs in the cytoplasm and a nuclear localization signal directs translocation to the nucleus. We have generated a "knock-in" mouse line in which nuclear translocation of nBMP2 is blocked while secreted BMP2 is produced normally. Preliminary studies on this mouse line suggest that nBMP2 plays a role in intraceullular calcium handling in hippocampus and in skeletal muscle, affecting learning, memory, and muscle endurance. We are focused now on characterizing the molecular pathways that lead to this phenotype.

Osteoarthritus. The third project in the lab has recently produced evidence suggesting that cartilage cells from mice that are predisposed to osteoarthritus (OA) show activation of the unfolded protein stress response (UPR). We are investigating the hypothesis that apoptosis and inflammation triggered by the UPR contribute to OA.

Selected Publications

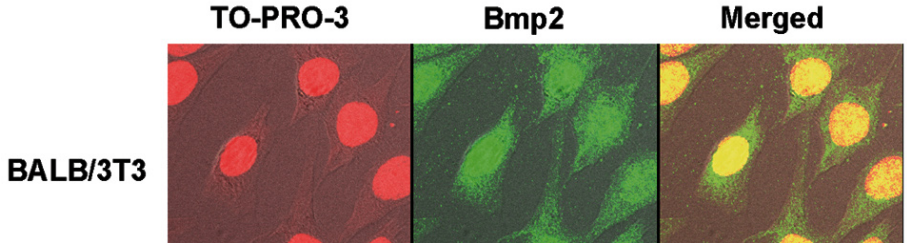
Holt, D.W., Henderson, M.L., Stockdale, C.E., Farrell, J.T., Kooyman, D.L., Bridgewater, L.C., & Seegmiller, R.E. "Osteoarthritis-like changes in the heterozygous sedc mouse associated with the HtrA1-Ddr2-Mmp-13 degradative pathway: a new model of osteoarthritis." Osteoarthritis and Cartilage. 20:430-439 (2012).

Felin, J.E., Mayo, J.L., Loos, T.J., Jensen, J.D., Sperry, D.K., Gaufin, S.K., Meinhart, C.A., Moss, J.B., Bridgewater, L.C. "Nuclear variants of bone morphogenetic proteins." BMC Cell Biology. 11:20 (2010). http://www.biomedcentral.com/1471-2121/11/20.

Mayo, J.L., Holden, D.N., Barrow, J.R., and Bridgewater, L.C. "The transcription factor Lc-Maf participates in Col27a1 regulation during chondrocyte maturation." Experimental Cell Research. 315:2293-2300 (2009).

Genzer, M.A., Bridgewater, L.C. "A COL9A1 enhancer element activated by two interdependent SOX9 dimers." Nucleic Acids Research 35:1178-1186 (2007).

nBMP2 (green) is visible in the nuclei (red) of cultured mouse BALB/3T3 cells.

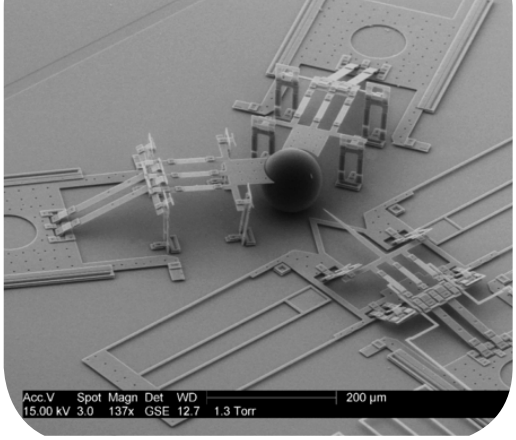


Sandra Burnett

Associate Professor,
Director of the Instrumentation Core Facility
Ph.D., University of Kentucky

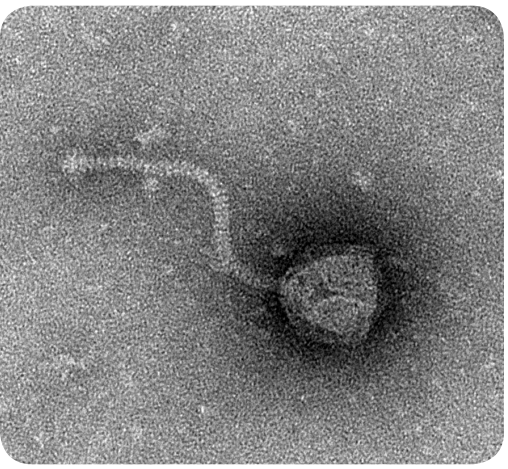
Research Interests:

Transgenic Technology, Immunology



A nanoinjector is built on a small silicone chip and is used to deliver DNA into a mouse zygote to generate a transgenic mouse.

Transfer of DNA into cells is used for bacterial transformation, eukaryotic tissue culture cell or primary tissue cell transfection, as well as production of transgenic animals. The Burnett Lab is involved in collaborative projects with the BYU Department of Mechanical Engineering to pursue new technologies in macromolecule transfer using micro-electro-mechanical systems on the nanometer scale utilizing small silicone chips and nanotechnology. This collaboration has resulted in the development of 'nanoinjection,' a new method for producing transgenic mice using simplified operational techniques and resulting in reduced cell trauma.



The Burnett Lab is also actively engaged in the study of mycobacteriophage and phage hosted by other bacteria. The research is in continuation of an undergraduate research course titled, "Phage Hunters," which attempts to capture, purify, and sequence whole genomes of novel phage from environmental samples such as soil.

A mycobacteriophage is captured and imaged by electron microscopy. The virus contains its genetic information in the capsid head and uses the tail to bind to and infect a bacterial cell.

Selected Publications

Aten, Q.T., Jensen, B.D., Tamowski, S., Wilson, A.M., Howell, L.L., and Burnett, S.H. (2012) Nanoinjection: Pronuclear DNA Delivery using a Charged Lance. Transgenic Research, DOI 10.1007/s11248-012-9610-6.

Aten, Q.A., Jensen, B.D., Burnett, S.H., and Howell, L.L. (2011) Electrostatic accumulation and release of DNA using a micromachined Lance, J. Microelectromechanical Systems, 20, 1449-1461.

David, R.A., Jensen, B.D., Black, J.L., Burnett, S.H., Howell, L.L. (2011) Effects of dissimilar electrode material and electrode position on DNA motion during electrophoresis, J. Nanotechnology in Engineering and Medicine, 2 (2), 021014.1-021014.6.

Graham F. Hatfull, the Science Education Alliance Phage Hunters Advancing Genomics and Evolutionary Science Program, the KwaZulu-Natal Research Institute for Tuberculosis and HIV Mycobacterial Genetics Course Students and the Phage Hunters Integrating Research and Education Program. (2012) Complete Genome Sequences of 138 Mycobacteriophages. *J. Virology* 86:2382-2384

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David Erickson

Associate Professor
Ph.D., University of Calgary

Research Interests:

Pathogenesis and Transmission of Bacterial Diseases

Our laboratory is focused on questions related to pathogen evolution, gene expression, and adaptation to different environments. We are especially interested in understanding how bacterial pathogens disrupt, avoid, or otherwise compromise the innate immune systems of their hosts. We primarily work with bacteria in the genus *Yersinia*, which includes *Y. pestis*, the cause of bubonic plague, as well as *Y. pseudotuberculosis* and *Y. enterocolitica*, which cause food-borne illnesses.

Some of the current research questions we are pursuing are:

1. How is biofilm production in *Yersinia* regulated?

Biofilm formation is a key factor in transmission of *Y. pestis* by fleas and may increase *Y. pseudotuberculosis* and *Y. enterocolitica* survival in the environment. We have characterized several regulatory genes that affect biofilms produced by these species.

2. What are the components of the insect innate immune system that affect *Y. pestis* growth?

Fleas transmit *Y. pestis* to susceptible mammals and the bacteria must adapt to both hosts. We have characterized the changes in gene expression that occur in fleas following infection and are investigating the role of specific immune defenses in establishing a transmissible infection.

3. How do *Yersinia* and other Gram-negative bacteria resist killing by antimicrobial chemokines?

Several chemokines are directly antimicrobial and are prevalent at mucosal sites where the bacteria colonize. We are investigating how specific bacterial genes affect chemokine binding and bacterial survival.

4. How do the normal bacterial residents in fleas affect the survival or transmission of *Y. pestis*?

Bacterial pathogens must not only overcome host defenses but also must co-exist with or eliminate complex microbial communities. We are characterizing the normal flora of fleas and how *Y. pestis* interacts with this community.

Selected Publications

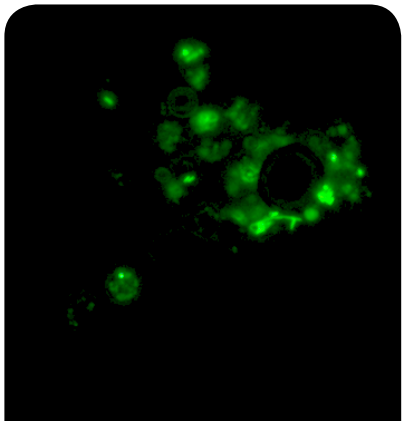
Zhou, W., Johnson, K.L., Mortensen, R.D, and Erickson, D.L. 2012. Gene expression analysis of *Xenopsylla cheopis* fleas suggests a role for reactive oxygen species in response to Yersinia pestis infection. *J. Med. Entomol* 49(2):364-70

Erickson, D.L., Russell, C.W., Johnson, K.L., Hileman, T., and Stewart, R.M. 2011. PhoP and OxyR transcriptional regulators contribute to *Yersinia pestis* virulence and survival within *Galleria mellonella*. *Microb. Pathog*. 51(6):389-95

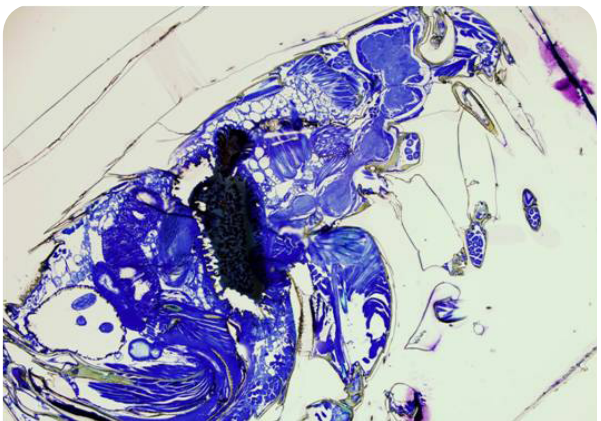
Erickson, D.L. Anderson, N.A., Cromar, L.M., Jolley, A.,2009. Bacterial Communities Associated with Flea Vectors of *Yersinia pestis*. *J. Med. Entomol*. 46:1532-1536

Erickson, D.L., Jarrett, C.O., Callison, J.A., Fischer, E.R., and Hinnebusch, B.J. 2008. Loss of a biofilm-inhibiting glycosyl hydrolase during the emergence of *Yersinia pestis*. *J. Bacteriol*. 190:8163-70.

Yersenia survive inside insect phagocytes.



Xenopsylla cheopis fleas are the arthropod vector of *Yersinia pestis*.



R. Paul Evans

Assistant Professor
Ph.D., Medical College of Virginia, Virginia Commonwealth University

Research Interests:

Molecular Biology

Our research activities are focused on the nexus of molecular biology and the application of phylogenetic analyses to understand the generation and maintenance of biodiversity and to reconstruct evolutionary history.

Current research topics include:

- distribution and genetic diversity of cutthroat trout
- whole-genome analysis of aquatic insects
- next generation sequencing and transcriptomes for the development of diagnostic markers
- human genetics and forensic pathology of the ancient Egyptian Fag el Gamous cemetery population as a part of the BYU Egypt Excavation Project
- conservation genetics of endemic western American fishes
- phylogenetic status of the Acanthocephalans (thorny headed worms)

Selected Publications

Evans, R. P. and D. Whitchurch. In Press. Rethinking Burial Dates at a Graeco-Roman Cemetery: Fag el Gamous, Fayoum, Egypt. 7th World Congress on Mummy Studies.

Amin, O., R. P. Evans, R. Heckmann, A. El-Naggar. Submitted. The description of *Mediorhynchus africanus* n. sp. (Acanthocephala: Gigantorhynchidae) from galliform birds in Africa

Houston, D., R. P. Evans, D. Shiozawa. 2012. Evaluating the genetic status of a Great Basin endemic minnow: the relict dace (*Relictus solitarius*). *Conservation Genetics*. 13:727-742

Stutz, H. L., D. Shiozawa, R. P. Evans. 2010. Inferring dispersal of aquatic invertebrates from genetic variation: a comparative study of an amphipod and mayfly in Great Basin springs. *Journal of the North American Benthological Society*. 9: 1132-1147

Joel Griffitts

Associate Professor
Ph.D., University of California, San Diego

Research Interests:

Bacterial Genetics,
Symbiotic Nitrogen Fixation

Nitrogen (N) fixation is the conversion of atmospheric nitrogen to biologically accessible ammonium. Accomplished solely by prokaryotes, biological N fixation is of fundamental importance in supporting life on earth. N-fixing soil bacteria known as rhizobia have the unique ability to engage in a permissive infection process on compatible host plants, leading to a special plant-derived structure called the root nodule, where N-fixation takes place. This cooperative interaction occurs in diverse biomes, is a driving force in global nitrogen cycling, and is fundamental to the agricultural technique of crop rotation.

Beyond the ecological and economical importance of this symbiosis, it presents us with a profoundly complex developmental process, programmed into the genes of both plant and microsymbiont. What are the genes that allow the bacteria to navigate the nodule environment and then differentiate into N-fixing entities within the nodule cells? How do plants and N-fixing bacteria recognize each other as compatible? Our research addresses these and other questions, using modern molecular genetic approaches.

In one approach we study various wild strains of the bacterium *Sinorhizobium meliloti*, in hopes of understanding why some strains produce abundant N for host plants, while some do not. In some of these strains we have identified specific DNA segments that actively reduce N fixation efficiency on certain plants. In a second project, we are seeking to understand how rhizobia control the expression of genes that are required for symbiotic N fixation. Elaborate teams of proteins are constantly engaged in listening to the outside world and passing information on to the inside of the cell. In a third project, we are investigating the retention of symbiotic capabilities in rhizobia that are grown for thousands of generations in the absence of a plant host. This project addresses the question of how genetically dedicated rhizobia are to assisting plant growth. Finally, our laboratory works with local high school students to explore the microbial world, in what is known as the Symbiosis Learning Consortium (SymLC). Our current SymLC objective is to identify and characterize isolates of *Sinorhizobium meliloti* from Utah soils.

Selected Publications

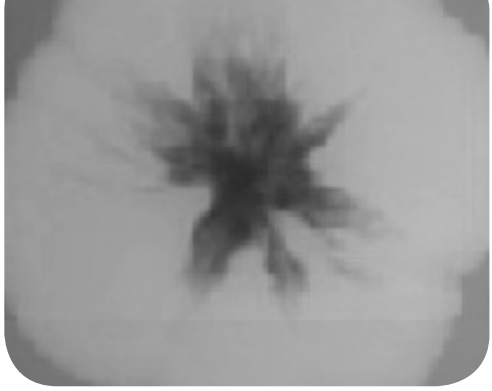
Crook, M.B, Lindsay, D.P., Biggs M.B., Bentley, J.S., Price, J.C., Clement, S.C., Clement, M.J., Long, S.R., and Griffitts, J.S. Rhizobial plasmids that cause impaired symbiotic nitrogen fixation and enhanced host invasion. *Mol Plant Microbe In* (in press, 2012).

Harrison, C.L., Crook, M.B., Peco, G., Long, S.R., and Griffitts, J.S. Employing site-specific recombination for conditional genetic analysis in *Sinorhizobium meliloti*. *Appl Environ Microbiol* (Epub, 2011).

Carlyon, R.E., Ryther, J.L., VanYperen, R.D., and Griffitts, J.S. FeuN, A novel modulator of two-component signaling identified in *Sinorhizobium meliloti*. *Mol Microbiol* 77:170-82 (2010).

Wang, D., Griffitts, J.S., Starker, C., Federova, E., Limpens, E., Ivanov, S., Bisseling, T., and Long, S.R. A nodule specific protein secretory pathway required for nitrogen-fixing symbiosis. *Science* 327:1126-9 (2010).

A jumble of root material that has been nodulated with ineffective rhizobial strain B069. While this strain generally yields small white nodules that fix little N, it occasionally mutates to become quite effective (large pink nodule at the center of the image). Understanding mechanisms of rhizobial ineffectiveness could have important agricultural implications.



A colony of *Salmonella typhimurium* undergoing duplication segregation. The chromosomal duplication is of the essential NAD kinase gene and contains the gene encoding LacZ, which turns colonies blue on plates containing X-gal. Thus, colonies that have lost the duplication through segregation have lost the LacZ gene and are white.

Julianne Grose

Assistant Professor
Ph.D., University of Utah

Research Interest:

Metabolic Regulation in Microbial Systems

Cells have evolved complex mechanisms that allow them to sense their nutritional status and regulate cellular metabolism appropriately. A dysfunction in metabolic regulation is the root of a variety of diseases. Our lab utilizes *Saccharomyces cerevisiae* and *Salmonella typhimurium* to study how cells regulate key metabolic pathways in response to the availability of nutrients and other factors affecting growth. Since the proteins and pathways of central metabolism are often conserved our findings may aid in understanding metabolic regulation in higher organisms.

Our lab focuses on two aspects of metabolic regulation. The first is the study of PAS kinase and is a highly conserved sensory protein kinase that regulates glucose metabolism linked to the development of Maturity Onset Diabetes (MODY). The PAS kinase protein has both a sensory and a regulatory domain. The sensory component consists of a PAS domain that may bind small molecule effecters. This domain regulates an attached serine/threonine protein kinase domain which modulates the activity of other proteins through phosphorylation. Our goal is to further characterize the role PAS kinase plays in metabolic regulation by identifying specific mechanisms involved in its activation and function.

The second aspect of metabolism we are studying is control of NAD and NADP levels within the cell. The vitamin niacin (B3) is a precursor to both NAD and NADP, which serve as cofactors in over 300 cellular reactions that are central to basic metabolism. Thus it is not surprising that defects in NAD(P) metabolism result in a variety of diseases including diabetes, cancer, cardiomyopathy and neurodegenerative diseases. Our lab focuses on the role of NAD(P) misregulation in the development of cardiomyopathy. In addition, we are working on identifying novel pathways involved in the biosynthesis and recycling of NAD(P).

Selected Publications

Grose, J.H., Rutter, J. The role of PAS kinase in PASsing the glucose signal. *Sensors (Basel)*. 2010;10(6):5668-82.

Grose, J.H., Sundwall, E., Rutter, J. Regulation and function of yeast PAS kinase: a role in the maintenance of cellular integrity. *Cell Cycle*. 2009 Jun 15;8(12):1824-32.

Grose, J. H., Smith, T.L., Sabic, H., Rutter, J.R. "Yeast PAS kinase coordinates glucose partitioning in response to metabolic and cell integrity signaling." *EMBO*. Nov. 2007.

Grose, J.H., Joss, L., Velick, S.F., Roth, J.R. "Evidence that feedback inhibition of NAD kinase controls responses to oxidative stress." *PNAS*. May 2006.

Grose, J.H., Bergthorsson, U., Xu, Y., Sterneckert, J., Khodaverdian, B., Roth, J.R. "Assimilation of nicotinamide mononucleotide requires periplasmic AphA phosphatase in Salmonella enterica." *J. Bacteriol*. July 2005.

Grose, J.H., Bergthorsson, U., Roth, J.R. "Regulation of NAD synthesis by the trifunctional NadR protein of Salmonella enterica." *J. Bacteriol*. Apr. 2005.

Alan R. Harker

Professor
Ph.D., University of Utah

Research Interest:

Microbial Ecology of the Great Salt Lake

Microorganisms have either arisen in or adapted to almost all niches on earth. Included in these are peculiar environments that seem hostile or at least non-conducive to life. The Great Salt Lake is the major remnant of ancient Lake Bonneville, varying by locality between 5 and 27% salinity.

The enormous size of the lake offers a variety of unique microenvironments (petroleum seeps, thermal springs, salt and freshwater springs, etc). Each of these microenvironments offers a combination of physical and chemical parameters secondary to salinity. Each dissipates from a central source creating gradient effects and potential metabolic island effects. We assume that organisms adapted to the elevated hydrocarbon levels at Rozel Point might be restricted in their ability to occupy space in other parts of the lake. Conversely, the microflora of the main body of the lake might have difficulty at Rozel. The combination of hydrocarbon utilization/tolerance and salt tolerance may make them unique in many other ways.

Classical biological and microbiological studies have found in the lake a limited variety of identifiable halophiles that have adapted to the various levels of salinity. Modern molecular techniques have been applied in only a limited way to the study of the Great Salt Lake and the unique sites described in this proposal have never been explored. We are engaged in an integrated exploration of these sites based on molecular, genetic, physiological, and physical characterization. We are creating integrated models of the site ecosystems to account for determined populations, metabolic activities, resource utilization and flux, gene flow, etc. These are to be collated across seasonal variations.

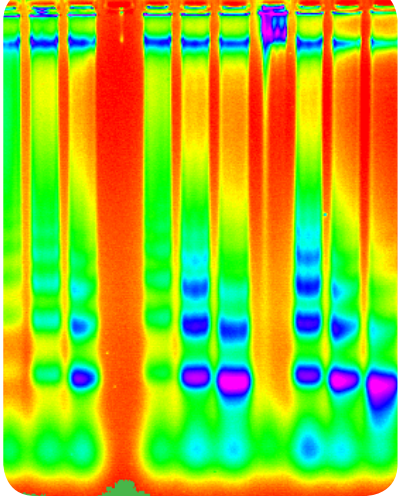
Selected Publications

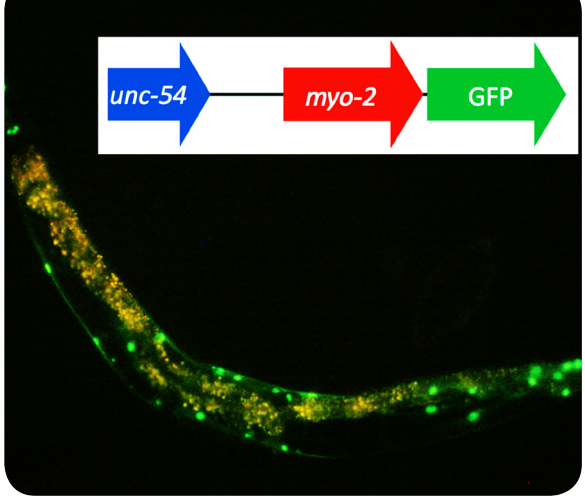
Microbial Diversity in Extreme Environments: Novel Lineages in Great Salt Lake, Utah. L. Tazi, D.P. Breakwell, A.R. Harker, and K.A. Crandall. (In Review).

A.R. Harker (2001) Full Application of the Scientific Method in an Undergraduate Teaching Laboratory: A Reality Based Approach to Experiential Student-Directed Instruction. In: Practicing Science, The Investigative Approach in College Science Teaching. J. Cusick, ed. NSTA Press, Arlington VA, pp. 39-42.

P. Ayoubi and A.R. Harker (1998) Whole Cell Kinetics of Trichloroethylene Degradation by Phenol Hydroxylase in Ralstonia eutropha JMP134. Appl. Environ. Microbiol. 64:4353-4356.

Our study site at Rozel Point, Great Salt Lake, Utah





Steven Johnson

Assistant Professor
Ph.D., Yale University

Research Interests:

Epigenetics, Chromatin Architecture, Nucleosome Positioning and Gene Expression

Six feet of DNA is contained in almost every cell of your body. In order to fit into a nucleus with a diameter of 1/300,000th its length, the DNA is highly compacted with proteins to form chromatin. This extreme compaction must be highly ordered to allow DNA to function in its roles in transcription and replication. The first order of this compaction is the nucleosome composed of 147 base pairs of DNA wrapping around a core of eight histone proteins. The position and density of nucleosomes on the genome play a major role in regulating genic expression. Densely packed, tightly bound nucleosomes form heterochromatin (which is transcriptionally inactive) and less dense, loosely packed nucleosomes form euchromatin in which the genes can be turned on and off as appropriate. Many decades of research in several labs has demonstrated that the underlying DNA sequence itself can influence where nucleosomes form in the genome.

In my lab we study chromatin architecture (specifically by looking at nucleosome positioning and its relation to the underlying DNA sequence in the genome) with the goal of learning how to modulate chromatin architecture by subtly manipulating the underlying DNA sequence so as to regulate gene expression. We are using both *in vivo* and *in vitro* approaches in our studies coupled with ultra-high-throughput DNA sequencing technologies. We have comprehensive nucleosome position maps for human tissues as well as for the nematode worm *C. elegans* (a common model organism for human genetics and disease), and are continuing studies to look at nucleosome positioning in specific cell types at different developmental stages. We are also using *in vitro* nucleosome reconstitution assays to define and test putative nucleosome attractive or repulsive sequences. These sequences can then be tested *in vivo* in the worm for their potential to regulate genic expression both temporally and spatially in *C. elegans*. Because of the highly conserved nature of histone proteins within the domain Eukaryotae and the absolute conservation of the chemical structure of DNA between all forms of life, what we learn from these basic studies in the worm may enable us to subtly manipulate gene expression in human cells and tissues with the potential to overcome the universal problem of gene silencing which occurs with DNA-based disease treatments such as those seen in current applications of gene-therapy.

Selected Publications

Kundaje, A., Kyriazopoulou-Panagiotopoulou, S., Libbrecht, M., Smith, C.L., Raha, D., Winters, E.E., Johnson, S.M., Snyder, M.P., Batzoglou, S., and Sidow, A. (2012) Ubiquitous heterogeneity and asymmetry of the chromatin environment at regulatory elements. *Genome Res.*, (In Press)

Valouev, A., Johnson, S.M., Boyd, S., Smith, C.L., Fire, A.Z., and Sidow, A. (2011) Determinants of nucleosome organization in primary human cells. *Nature*, 474, 516-520.

Johnson, S.M. (2010) Painting a perspective on the landscape of nucleosome positioning. *J Biomol Struct Dyn.*, 27, 795-802.

William R. McCleary

Associate Professor
Ph.D., University of California, Berkely

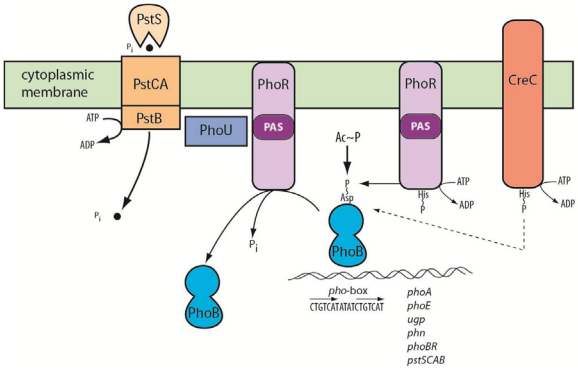
Research Interest:

Prokaryotic Signal Transduction

Our lab is currently engaged in research to understand the molecular mechanisms by which the simple bacterium, *Escherichia coli* senses and responds to changes in environmental phosphate. We are studying this question because it is an extremely useful model to understand complex regulatory schemes in all living organisms. At the heart of this question is a two-component signal transduction system that senses environmental phosphate and controls the expression of many genes for the high affinity acquisition of phosphate and the utilization of alternate sources of phosphorous.

Our current model for the regulation of this response is that the PstSCAB transporter (a high affinity ABC transporter of phosphate) senses phosphate levels and communicates through the PhoU protein to the bifunctional histidine kinase, PhoR, which interacts with and controls the steady state phosphorylation level of the response regulator, PhoB. Phospho-PhoB binds to specific DNA sequences upstream of Pho regulon genes, interacts with the sigma70 subunit of RNA polymerase and stimulates transcription. Phosphate sufficiency generates a signal that shuts off the Pho regulon by activating the phospho-PhoB phosphatase activity of PhoR. However, when phosphate is limiting or when mutations eliminate any component of the PstSCAB transporter or PhoU, the Pho regulon is turned on. This low-phosphate signal stimulates the kinase activity of PhoR allowing it to serve as an efficient phospho-donor to PhoB. Phosphate starvation also triggers the general stress response in which cells become increasingly resistant to many environmental stresses. The master regulator of this response is sigmaS (RpoS), an alternate sigma factor that competes with sigma70 to direct the transcription of genes under its control. The regulation of sigmaS is very complex and has numerous inputs. Its cellular levels are controlled at the levels of transcription, translation, protein turnover and activity.

We are currently using genetic, molecular genetic, biochemical and biophysical techniques to determine the molecular mechanisms of signal transduction in the Pho regulon. Students who work and study in our lab gain experience in mastering multiple techniques and in learning to address difficult problems through a multifaceted approach.



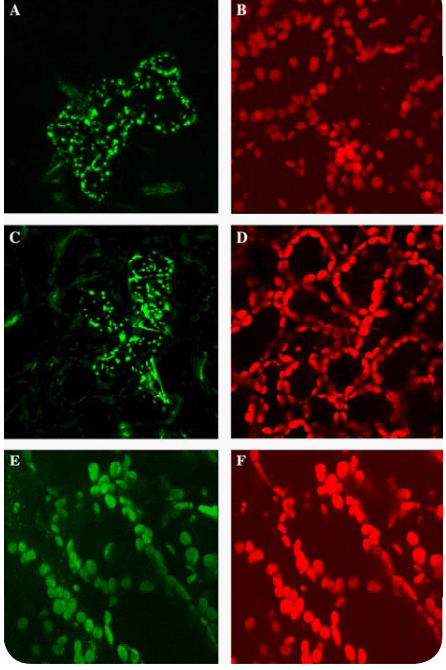
Selected Publications

McCleary, W. R. 2009. Application of promoter swapping techniques to control expression of chromosomal genes. *Appl Microbiol Biotechnol* 84:641-8.

Rice, C.D., Pollard, J.E., Lewis, Z.T. and McCleary, W.R. 2009. "The employment of a promoter swapping technique shows that PhoU modulates the activity of the PstSCAB2 ABC transporter in Escherichia coli." *Applied and Environmental Microbiology*. 75:573-82

Schurdell, M.S., Woodbury,G.M. and McCleary, W.R.. 2007. "Genetic evidence suggests that the intergenic region between pstA and pstB plays a role in the regulation of rpoS translation during phosphate limitation." *Journal of Bacteriology*.189:1150-3.

McCleary, W. R. 2005. "No Phobias about PhoB Activation." *Structure.* 13: 1238-1239.



The localization of proteins can be visualized by tagging them with GFP (green fluorescent protein). A and C show proteins targeted to mitochondria, E to chloroplasts. B, D, and F show chloroplast autofluorescence.

Brent L. Nielsen

Professor
Ph.D., Oregon State University

Research Interests:

Plant and Organelle Molecular Biology, Molecular Analysis of Depression and Fibromyalgia Disorders

There are three research projects in my laboratory: plant organellar DNA maintenance, proteomics and gene expression in halophytes, and the association of point mutations in the human genome with depression and anxiety disorders and the association of fibromyalgia with mitochondrial mutations.

Mitochondria are the powerhouses of eukaryotic cells and produce ATP for cellular processes. Mitochondria contain DNA (mtDNA) that encodes a few genes, while most proteins for mitochondrial function are encoded in the nucleus and imported into mitochondria. MtDNA is susceptible to damage from oxygen free radicals that are produced during respiration, and mutations leading to mitochondrial diseases have been identified in humans. We are studying one family that has an inherited fibromyalgia that shows mitochondrial linkage to identify the mutation(s) involved.

We are also analyzing specific genetic markers associated with anxiety, depression, and other mood disorders in healthy, athletic senior citizens in comparison with a general population of senior citizens. We are using PCR to classify the genetic markers and are comparing the results with written survey and other data collected from the participants to evaluate correlations of the markers with each condition.

Our laboratory has been working for many years to study plant genes encoding mitochondrial and chloroplast DNA replication and recombination proteins and to determine their role in the maintenance of the organelle genomes during plant development and also in response to DNA damage. We are analyzing T-DNA insertion mutants for each of these genes to determine the effect of disruption of expression of each on plant development. Our findings indicate that mitochondrial DNA recombination is involved in the response to DNA damage and is likely involved in replication and maintenance of the mitochondrial genome.

Halophytes are plants that grow optimally in salty soils and have potential for development as agricultural crops. However, little is known about the changes in proteins expressed in these plants when grown under optimal salt conditions. We are using MudPIT analysis to characterize proteins expressed in plants grown at different salt levels. We are also conducting transcriptome analysis to identify the genes expressed under each condition.

Selected Publications

Lassen, M.G., S. Kochhar, B.L. Nielsen. 2011. Identification of a soybean chloroplast DNA replication origin-binding protein. *Plant Molecular Biology* 76:463-471.

Nielsen, B.L., J.D. Cupp, J. Brammer. 2010. Mechanisms for maintenance, replication, and repair of the chloroplast genome in plants. *J. Exp. Botany* 61:2535-2537.

Khan, M.A., R. Ansari, H. Ali, B. Gul, B.L. Nielsen. 2009. *Panicum turgidum*, a potentially sustainable cattle feed alternative to maize for saline areas. *Agriculture, Ecosystems and Environment* 129:542-546.

Manchekar, M., K. Scissum-Gunn, L.A. Hammett, S. Backert, B.L. Nielsen. 2009. Mitochondrial DNA recombination in *Brassica campestris*. *Plant Sci*. 177:629-635.

Kim O'Neill

Professor
D.Phil. University of Ulster
Northern Ireland

Research Interest:

Tumor Immunology

Our Lab focuses on three main aspects of cancer research:

1. Prevention through education.

Our laboratory focuses on the benefits that can be obtained through a diet rich in fruit and vegetables. We are investigating the many different plant chemicals that are involved in reducing cancer risk. It is a well-established fact that many cancers can be prevented by proper attention to diet. We are investigating phytochemicals at the molecular level to establish the mechanisms of protection. Current studies involve gene expression by certain phytochemicals, the effect of certain phytochemicals on DNA repair and immune function enhancement. We promote education by publishing our research findings in scientific journals, giving presentations at conferences and authoring chapters in scientific books.

2. Enhancing the body's own defense systems, particularly the immune system and DNA repair mechanisms.

The body has natural defenses against cancer. We study the immune system and help with the development of possible vaccines that could be used against certain forms of cancer. We are currently studying the interface between the immune system and the cancer cell, focusing on tumor associated macrophages and their role in the cancer process. We have developed new methods to study angiogenesis and metastasis. Currently we are investigating the immune response to tumor cell microenvironment and see the effect on macrophages when placed in different tumor microenvironments. We have also developed the DNA repair assays that allow the measurement of certain cells repair capacity which aid in studies of apoptosis and DNA repair.

3. Early detection of disease.

Cancer is generally easier to treat, and a better outcome is assured, if the tumor growth is found early in its development. If it is discovered before metastatic spread, then generally a more favorable outcome is achieved. We have discovered a tumor marker found in serum that will aid in diagnosis, prognosis and tumor management. This maker accurately reflects tumor presence, and tumor stage. Several other laboratories working in this field have confirmed this research. We have developed and accurate test method for this marker, BYU has patented the discovery and it has been licensed to a biotech company for commercial development.

Selected Publications

Gaytri Gupta Elera, B.Sc.; Andrew R Garrett, B.Sc; Martinez Martinez, B.Sc; Richard Robison, Ph.D.; Kim O'Neill, D.Phil. 2010. The antioxidant properties of the Cherimoya (Annona cherimola) fruit. Food Research International Volume 44, Issue 7, August 2010, Pages 2205-2209.

March, Jordon; Cohen, Marissa; Lindsey, James; Millar, D; O'Neill, Kim; Schaalje, G.; Robison, Richard, 2011. The disinfectant susceptibility of virulent and attenuated Bacillus anthracis spores varies with disinfectant type. Applied Microbiology

Gupta-Elera, Gaytri; Garrett, Andrew R.; Robison, Richard A.; O'Neill, Kim L. 2012 The role of oxidative stress in prostate cancer. European Journal of Cancer Prevention. 21(2):155-162, March 2012.

Gaytri Gupta-Elera, Andrew Garrett, Andres Martinez, Ryan D. Kraus, Richard Robison and Kim O'Neill, 2012. A Comparison of Antioxidant Properties in Organic and Conventional Blueberries. Journal of Food Research, Vol 1, #3 p1-7

M. Alegre, R. Robison, and K.L. O'Neill, 2012. Thymidine kinase 1 upregulation is an early event in breast tumor formation. Journal of Oncology, (in Press)

Brian Poole

Assistant Professor
Ph.D., Pennsylvania State University

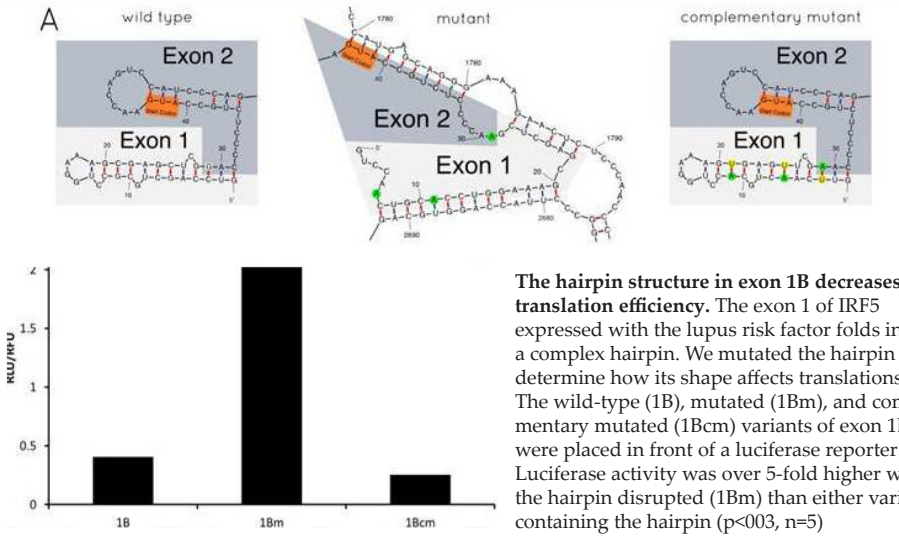
Research Interest:

Cell-Virus Interactions

Systemic lupus erythematosus is a common, debilitating autoimmune disease in which components of the body's own cells are targeted and attacked by the immune system. The origins of the disease are still unclear, but it is known that genetic, environmental, and hormonal factors are all involved in causing lupus. We are studying the molecular mechanisms of genetic risk factors and how they contribute to lupus.

Although there is a strong genetic component to lupus, not much is known about how genes influence the development of the disease. We are focusing on lupus-associated variations in the IRF5 gene. The IRF5 protein is a key intermediary in the response to viral infection. People with lupus tend to have certain variations in their IRF5 gene, that cause it to be either expressed at a higher level or spliced differently than in people without lupus. We hypothesize that the modifications to the IRF5 gene associated with lupus leads to increased interferon production and disruption of several cellular pathways. This disruption results in the production of antibodies against normally occurring parts of cells and can lead to lupus. Through studying these interactions, we hope to identify markers for people who are at high risk for lupus, and early indicators that autoimmunity is developing. Early intervention in the disease has shown promise in slowing its effects. We also hope to evaluate the role of interferon in lupus and evaluate the potential of blocking interferon as a treatment for the disease.

Another interest of our laboratory is virology, especially Epstein-Barr virus and Herpes Simplex virus. We are currently exploring how infection with these viruses affects gene expression in the infected cells.



The hairpin structure in exon 1B decreases translation efficiency. The exon 1 of IRF5 expressed with the lupus risk factor folds into a complex hairpin. We mutated the hairpin to determine how its shape affects translations. The wild-type (1B), mutated (1Bm), and complementary mutated (1Bcm) variants of exon 1B were placed in front of a luciferase reporter gene. Luciferase activity was over 5-fold higher with the hairpin disrupted (1Bm) than either variant containing the hairpin ($p<003$, $n=5$)

Selected Publications

Guthridge, Joel M.; Clark, Daniel N.; Templeton, Amanda; Dominguez, Nicolas; Lu, Rufei; Vidal, Gabriel; Kelly, Jennifer A; Kauffman, Kenneth; Harley, John B.; Gaffney, Patrick; James, Judith A.; Poole, Brian D. Effects of IRF5 lupus risk haplotype on pathways predicted to influence B cell functions. Journal of Biomedicine and Biotechnology. 2012: 594056

Clark, Daniel N.; Poole, Brian D.; Hedman, Tyler J.; Hammond, Daniel V.; Catts, Daniel S.; Stewart, Amanda; Johnson, F. Brent. Characterization of herpes simplex virus clinical isolate Y3369 and its bearing on HSV typing. Virology Journal 2011 8:290

Poole, Brian D.; Templeton, Amanda K.; Guthridge, Joel M.; Brown, Eric J.; Harley, John B.; James, Judith A. Aberrant Epstein-Barr viral infection in systemic lupus erythematosus. Autoimmun Rev. 2009 8(4):337-42.

Poole, Brian D., Schneider, Rebecca I.; Guthridge, Joel M.; Velte, Cathy; Reichlin, Morris; Harley, John B.; James, Judith A. Early Targets of nRNP Humoral Autoimmunity in Human Systemic Lupus Erythematosus. Arthritis and Rheumatism 2009 60(3):848-59.

Richard Robison

Professor
Ph.D., Brigham Young University

Research Interests:

Bacterial Pathogens - Genetic Diversity, Detection, and Host Immune System Interaction

Bacterial agents that cause disease in man and animals are the focus of our research. Pathogenic mechanisms these organisms use to evade host immune mechanisms and cause disease is a specific focus. We are interested in all CDC select agents as well as pathogens within the genera *Streptococcus*, *Pasteurella* and *Myobacterium*. The genetic diversity of these pathogens, their virulence factors, and the development of multiplexed real-time PCR assays for their detection and differentiation, are some areas in which we are currently working. Particular species in which we are interested include: *Burkholderia pseudomallei* (the etiologic agent of melioidosis), *Burkholderia mallei* (the etiologic agent of glanders), *Pasteurella multocida* (the agent of fowl cholera), and pathogenic members of the genus *Mycobacterium* including *M. ulcerans* (the etiologic agent of Buruli ulcer) and drug-resistant isolates of *M. tuberculosis*.

In addition to the above, we also maintain an active interest in the areas of decontamination, disinfection, and infection control. We are currently performing research on compounds and devices that are capable of high-level disinfection (with an emphasis on tuberculocidal activity) and/or sterilization. We are also interested in natural products that are capable of killing or inhibiting the growth of pathogens, or stimulating the immune system to prevent disease.

Current Research Support

Department of Homeland Security
Several commercial companies

Professional Affiliations

American Society for Microbiology (ASM)
American Association for Cancer Research

Selected Publications

Stewart, A., B. Satterfield, M. Cohen, K. O'Neill, and R. Robison. 2008. A quadruplex real-time PCR assay for the detection of *Yersinia pestis* and its plasmids. Journal of Medical Microbiology 57(3):324-331.

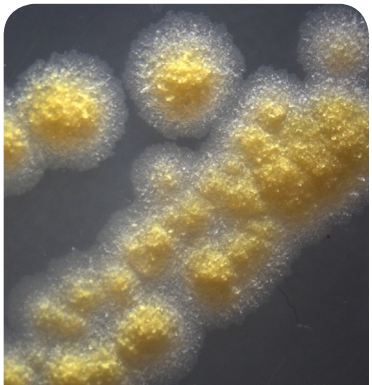
Murray, B.K., S. Ohmine, D.P. Tomer, K.J. Jensen, F.B. Johnson, J.J. Kirsi, R.A. Robison, and K.L. O'Neill. 2008. Virion disruption by ozone-mediated reactive oxygen species. Journal of Virological Methods 153:74-77.

El-Etr, S.H., J.J. Margolis, D. Monack, R.A. Robison, M. Cohen, E. Moore, A. Rasley. 2009. *Francisella tularensis* type A strains cause the rapid encystment of *Acanthamoeba castellanii* and survive in amoebal cysts for three weeks post infection. Applied and Environmental Microbiology 75:7488-7500.

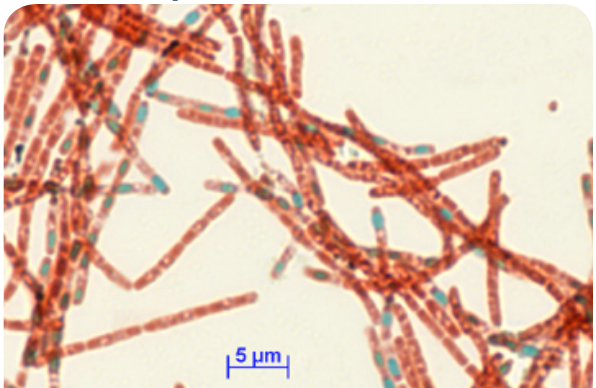
Mitchell, A.M., G.A. Strobel, E. Moore, R. Robison, and J. Sears. 2010. Volatile antimicrobials from *Muscodor crispans*, a novel endophytic fungus. Microbiology 156:270-277.

Satterfield, B.A., A.F. Stewart, C.S. Lew, D.O. Pickett, M.N. Cohen, E.A. Moore, P.F. Luedtke, K.L. O'Neill, and R.A. Robison. 2010. A quadraplexed real-time PCR assay for rapid detection and differentiation of the *Clostridium botulinum* toxin genes A, B, E and F. Journal of Medical Microbiology 59:55-64. Note: This paper was featured in the 'Highlights of Hot papers in Recent SGM Journals" section of Microbiology Today, February, 2010, p. 60.

Colonies of *Mycobacterium marinum*



Spore stain of *Basillus anthrasis*



K. Scott Weber

Assistant Professor
Ph.D., University of Illinois

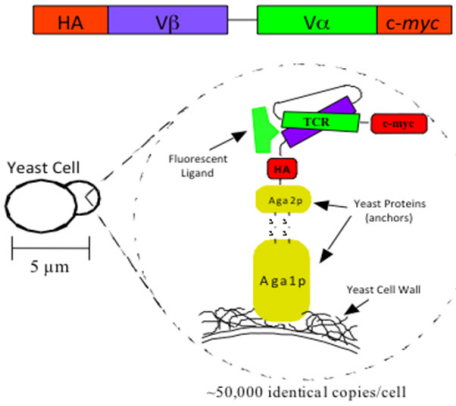
Research Interest:

T cell Activation and Memory, Immunity to Infectious Disease

Upon infection, many components of the host immune response are involved in recognition and removal of the pathogen. T cells play a critical role in infectious disease protection by recognition of pathogen specific epitopes. After a primary infection the antigen specific T cells dramatically expand, contract, and become short-lived effector cells or are maintained as long-lived memory cells. Memory cell formation is a hallmark of the adaptive immune system and memory T cells rapidly respond to a secondary challenge and are critical for numerous vaccine strategies. CD4+ T cells play a central role in the coordination of the adaptive and innate immune responses and deliver essential survival signals for the generation of CD8+ memory T cells, recall responses, and protective immunity. In recent years our understanding of memory CD8+ T cells has increased substantially, but our understanding of memory CD4+ T cells remains incomplete. It is clear that the pathways for CD4+ memory formation are distinct and a better understanding of the parameters for CD4+ help and CD4+ memory formation provides an opportunity to effectively improve vaccines and protection from infectious disease.

My lab is focused on understanding the necessary signals for proper development and function of CD4+ T cell memory. To better understand what these conditions are, we have recently generated two CD4+ T cell receptor transgenic mice specific for the same naturally occurring epitope from *Listeria monocytogenes*. These transgenic mice, called LLO118 and LLO56, have dramatically different primary and secondary responses to infection. LLO118 has a strong primary response relative to LLO56, whereas LLO56 has a much better memory response compared to LLO118. Understanding why these dramatic differences between primary and secondary responses exist could provide important insights into why some T cells are better at providing immunity to infection and generating memory cells and how this can be improved.

A second focus of my lab is to understand how high affinity T cell receptors differ in their ability to recognize antigen and cause T cell activation. High affinity T cell receptors are engineered using yeast display and directed evolution and also represent a novel tool for targeting T cell epitopes that are not recognized by antibodies. High affinity T cells may be useful as therapeutics in an infectious disease setting when coupled with pro-inflammatory cytokines or in an autoimmune setting when coupled with anti-inflammatory cytokines.



Engineering T cell receptors with yeast display. A library of single chain T cell receptors (Vβ-Vα) expressed as Aga-2 fusion proteins on the surface of yeast can be screened via directed evolution to isolate high affinity T cell receptors.

Selected Publications

Weber, K.S., Li, Q.J., Persaud, S.P., Campbell, J.D., Davis, M.D., and Allen, P.M. (2012) Distinct populations of CD4+ helper T cells mediate CD4+ and CD8+ memory responses to infection. Proceedings of the National Academy of Sciences. U S A. 109(24):9511-9516

Weber, K.S., Hildner, K., Murphy, K.M., and Allen, P.M. (2010) Trpm4 differentially regulates Th1 and Th2 function by altering calcium signaling and NFAT localization. *Journal of Immunology*. 185(5):2836-2846

Weber, K.S., Miller, M.J., and Allen, P.M. (2008) Th17 cells exhibit a distinct calcium profile from Th1 and Th2 cells and have Th1-like motility and NFAT nuclear localization. *Journal of Immunology*. 180(3):1442-145

Weber, K.S., Donermeyer, D.L., Allen, P.M., and Kranz, D.M. (2005) Class II-restricted T cell receptor engineered in vitro for higher affinity retains peptide specificity and function. *Proceedings of the National Academy of Sciences. U S A.* 102(52):19033-19038.

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Eric Wilson

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Research Interests:

Cell Immunology

The mammalian immune system is extremely complex, consisting of both innate and adaptive constituents. The complex and varied nature of the immune system is necessary to effectively protect the host from the constant barrage of microbial assaults we all face on a daily basis. Our laboratory focuses on elucidating and understanding the role of chemokines in the immune system. Chemokines are small proteins shown to be involved in two distinctly different aspects of immunity. One function of chemokines is to help direct migrating immune cells to appropriate tissues. A second function of chemokines is to act as antimicrobial proteins (AMPs) which directly kill or inhibit microbes.

Specifically one aim of our laboratory is to understand how migrating antibody secreting cells accumulate in the appropriate tissue. Our previous work has shown that the chemokine CCL28 plays an indispensable role in directing the homing of IgA secreting B cells (IgA ASC) to the lactating mammary gland. Interestingly, although CCL28 plays a vital role for IgA ASC recruitment to the lactating mammary gland this chemokine apparently plays no role in the accumulation of T cells to the same tissue. This specificity of chemokine involvement in B cell vs. T cell homing to a specific tissue is an excellent illustration of the complex and intricate nature of lymphocyte homing to mucosal tissues. Currently our laboratory is working to understand, at the molecular level, what directs IgA ASC to specific mucosal tissues (especially exocrine glands). For mucosal vaccines to reach their full potential in disease prevention, it is imperative that we understand the molecular mechanisms of lymphocyte homing to mucosal tissues. This is particularly true if vaccines are to be designed in which a vaccine is administered via one mucosal surface but where antibody protection is also desirable at other mucosal sites.

The chemokine CCL28, in addition to mediating efficient migration of IgA antibody secreting cells to mucosal tissues, has also been shown to function as an AMP. Using CCL28 as a model antimicrobial chemokine we are studying the mechanisms by which bacteria defend themselves from the mammalian produced AMPs. Working with the laboratory of Dr. David Erickson we have developed a flow cytometry based assay to quantitate the ability of AMPs to bind and kill bacteria. Using this assay, we have screened hundreds of mutant bacteria and identified several bacterial genes involved in protecting bacteria from the action of AMPs.

Both of these projects are funded through National Institutes of Health grants through 2015.

Selected Publications

Kathryn Distelhorst, Jovanka Voyich and Eric Wilson. 2010. Partial Characterization and Distribution of the Chemokines CCL25 and CCL28 in the Bovine System. *Vet. Immunol. and Immunopathol*. 138:134-138.

Elisabeth Low, Benjamin Martino, Lauren Zagieboylo and Eric Wilson. 2010. IgA ASC Accumulation to The Lactating Mammary Gland is Dependent on VCAM-1 and alpha4 Integrins. *Molecular Immunol.* 47:1608-12.

Bin Liu and Eric Wilson. 2010. The Antimicrobial Activity of CCL28 Is Dependent on C-Terminal Positively Charged Amino Acids. *Eur. J. Immunol.*40:186-96.

Olivier Morteau, Craig Gerard, Bao Lu, Sorina Ghiran, Miriam Rits, Yuko Fujiwara, Yuetching Law, Kathryn Distelhorst, Elizabeth M. Nielsen, Erica D. Hill, Raymond Kwan, Nicole H. Lazarus, Eugene C. Butcher, and Eric Wilson. 2008. An Indispensable Role for the Chemokine Receptor CCR10 in IgA Antibody Secreting Cell Accumulation. *J. Immunol.* 181:6309-15.

Questions?

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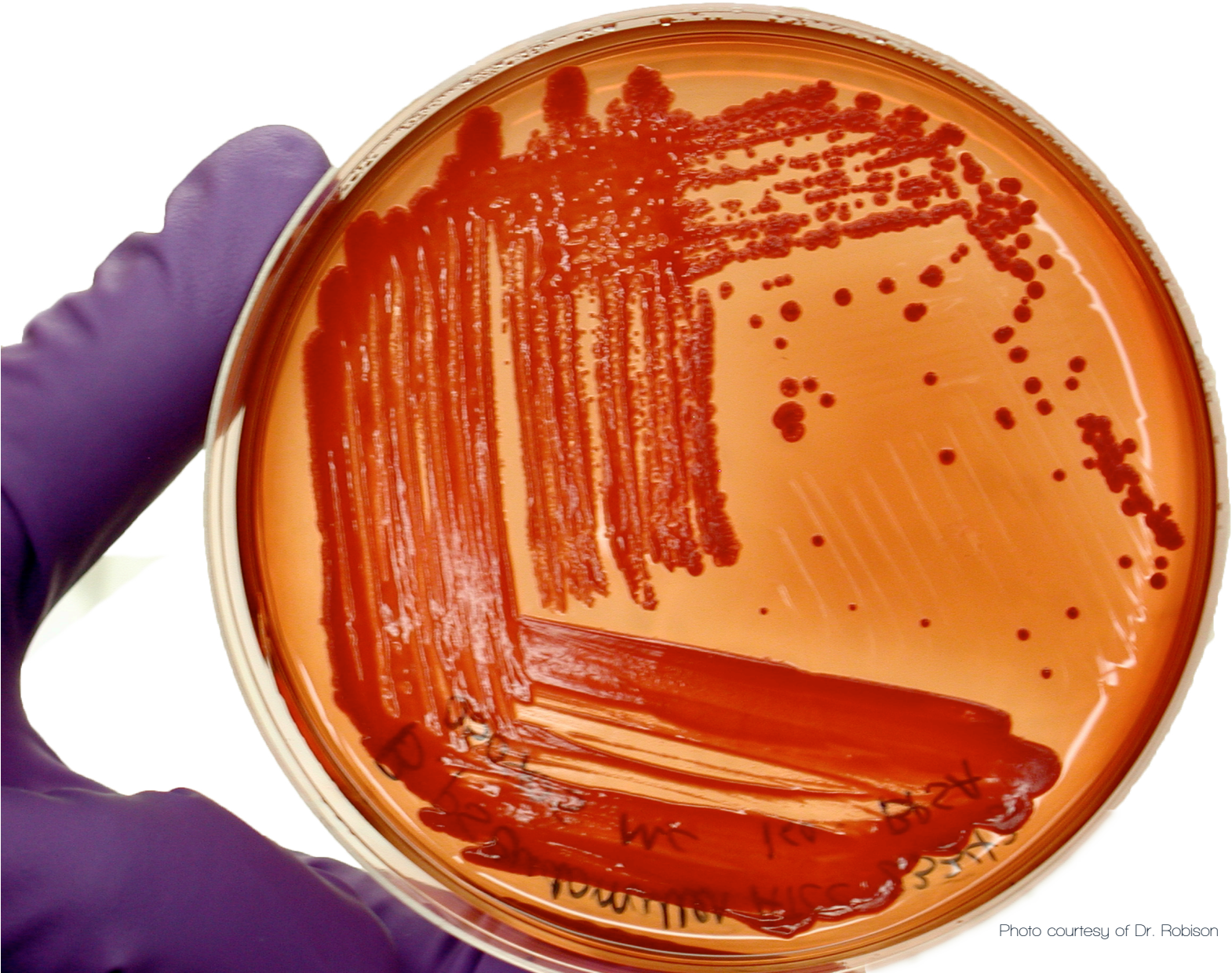
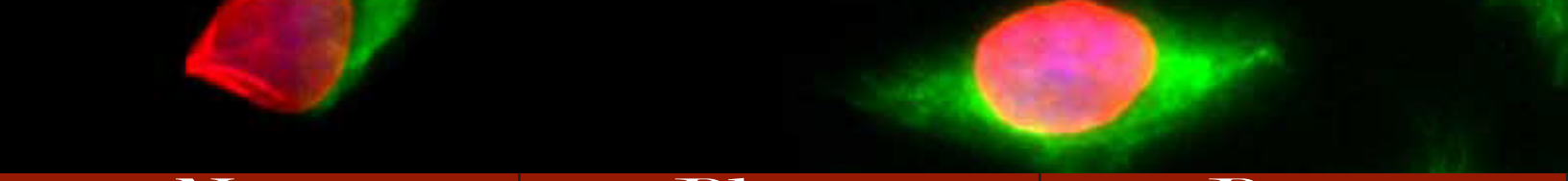


Photo courtesy of Dr. Robison



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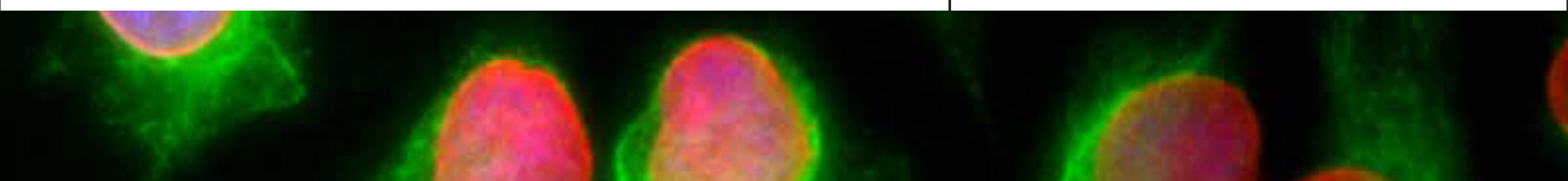

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