Project Title:

Diabetes, Arthritis, and Alzheimer's disease:
chronic inflammatory conditions with common origins and treatments

Principal Investigator(s) (full-time faculty)

Name (PI listed first)	Department	College
Richard Watt	Chemistry & Biochemistry	CPMS
Ben Bikman	PD Bio	Life Sciences
Lance Davidson	Exercise Sciences	Life Sciences
David Kooyman	PDBio	Life Sciences
William Pitt	Chemical Engineering	Engineering

Abstract

Diabetes, arthritis and Alzheimer's disease are some of the fastest growing challenges facing the medical field. An alarming observation is that patients with one of these disorders have more than a 50% higher probability of developing one of the other disorders. Treatments to prevent the development of each of these diseases and medications to treat these diseases once they are manifest are minimal or absent altogether. Our research plan employs well-defined experimental models for arthritis, diabetes, infection and obesity. Remarkably, each model shows secondary symptoms of a related disease. For example, the arthritis model shows symptoms of diabetes. We will use these overlapping models with multiple disease manifestations to map the signaling pathways that cause the original diseases and our research plan is designed to allow us to find the connecting pathway that triggers the secondary disease. Given the etiological similarities, we propose each of these diseases might be disparate and tissue-specific manifestations of the same chronic inflammatory condition. If this is the case, our work will identify drug targets that will treat the initial disorder and prevent the development of the secondary disease. As a first example of potential treatments, our team has outlined a treatment regime for treating chronic inflammation associated with pain and damage of arthritis. We propose that treating arthritis will slow or prevent the progression of diabetes and Alzheimer's disease because treatments that minimize inflammation in arthritis have been shown to lower the probability of developing Alzheimer's disease by 50%.

The cross-disciplinary research team is composed of Dr. Watt from Chemistry and Biochemistry, Dr. Kooyman and Dr. Bikman from Physiology and Developmental Biology, Dr. Davidson from Exercise Science and Dr. Pitt from Chemical Engineering. Combined these faculty have experience studying arthritis, diabetes, obesity and the related bariatric surgery to treat obesity and diabetes, oxidative stress, anemia of inflammation, Alzheimer's disease and drug delivery.

Summary of Plans for External Funding

List target sources of external funding and proposed timeline for proposal submission.

The team will meet monthly and evaluate data and organize data, plan subsequent steps to prepare grant submissions. We will submit an Alzheimer's Association grant in 2020 and a National Institutes of Health – Institute of Arthritis and Musculoskeletal And Skin Diseases in October 2020. If needed, we plan to submit a resubmission or related proposal in April 2021.

Project narrative (up to 5 pages).

Background and Significance:

Scientists increasingly refer to Alzheimer's disease as Type 3 Diabetes, in part because over half of Type 2 Diabetes patients develop Alzheimer's disease and they share common biochemical changes in glucose and insulin (1). Diabetes also raises the risk of developing arthritis by 50% (2). Patients with rheumatoid arthritis or osteoarthritis have a 50% higher probability of developing diabetes and eventually Alzheimer's disease (2). The inter-connected nature of diabetes, arthritis and Alzheimer's disease suggests that progression of these diseases occurs through common biochemical signaling pathways. The activation of the first disease initiates the activation of the secondary disease. If this is the case, treating one disease might prevent the development of other related diseases. Also identifying the connecting pathways can identify new therapeutic targets to prevent cross-over. The **long-term goals** are to identify related biochemical pathways among these diseases and identify targets of interventions that can prevent the progression of both the primary and secondary diseases. Our **short-term objectives** use established disease models that manifest symptoms of multiple diseases and inhibitors/drugs that block the progression of one disease will be used to evaluate the effect on the secondary disease.

Evidence that this strategy has merit comes from observations that anti-inflammatory drugs used to treat arthritis lower the probability of developing Alzheimer's disease by 50% (3). Studies also show that early detection of diabetes and aggressive treatment lowers the probability of developing dementia (4). These observations show that chronic inflammation is highly associated with developing diabetes and arthritis and eventually Alzheimer's disease. The observation that treating chronic inflammation in these studies gives additional strength to our hypothesis that these diseases share common inflammation related triggers for initiating this family of diseases.

Inflammation is intimately linked to oxidative stress. Inflammation disrupts normal iron processing and increases free iron in some tissues. Iron is a catalyst for oxidative stress through reactions called "Fenton chemistry" that form reactive oxygen species (ROS), which cause oxidative stress and inflammation (5). Disrupted iron metabolism is a well-established problem in each of these three diseases (6, 7). Individuals with the iron overload disease hemochromatosis, experience elevated oxidative stress and inflammation and have increased risk of developing diabetes, arthritis and Alzheimer's disease (6, 7).

The combinations of inflammation and oxidative stress and the related iron dysregulation have been complicating factors in understanding these diseases. However, in joining forces, our team, which has been independently working on different aspects of these diseases, has now identified some very important common ground we can use to connect the causes of these diseases.

Our new innovative research plan is based on work from our labs and from experimental models and treatments found in the literature that sets a backdrop for our proposed studies. We can use the following experimental models for each of these diseases to follow the progression and treatment of the secondary diseases. These models include:

- Bariatric Surgery patients as a model for obesity and type 2 diabetes.
- Three distinct animal models for arthritis, diabetes and anemia that each shows a related secondary disease.
- Inhibitory treatments for specific biochemical pathways or symptoms of each disease.
- Drug delivery models and expertise that allows drug delivery to specific target tissues.
- Complimentary cross-disciplinary research expertise.

Research Team Unique Qualifications:

A valuable component of this interdisciplinary team is our access to patients with obesity and type 2 diabetes who undergo gastric bypass surgery. **Dr. Davidson** from Exercise Sciences has over a decade of experience studying and working with these patients, who commonly become insulin sensitive (and maintain normal blood glucose levels) within weeks of their surgery – even prior to significant weight loss – and who remain in diabetes remission at rates of 77% at 2 years, 66% at 6 years and 51% at

12 years postoperatively (8, 9). A key observation from studies of human obesity is that iron overload is associated with increased diabetes risk (10). We propose that studying the cytokine and iron profile of serum from these patients, prior to and after surgery, will allow us to identify signaling pathways related to diabetes that changed after surgery. By understanding these changes, we will be able to identify signaling pathways that cause Type 2 diabetes and understand how to modulate these pathways as treatments.

To leverage knowledge of these inflammatory pathways, another team member, **Dr. Bikman** has previously found that post-bypass patients have a pronounced reduction in plasma markers of inflammation (11). A common thread woven throughout these seemingly distinct disorders is the sphingolipid ceramide. Ceramides are known to mediate metabolic complications, including insulin resistance, in response to inflammatory signals, which provides an obvious relevance to type 2 diabetes and Alzheimer's disease. Moreover, ceramides are powerful activators of apoptosis, which is relevant to osteoarthritis and, again, Alzheimer's disease. Thus, in multiple proposed models (including cell cultures and rodents), we will utilize a work-horse inhibitor of ceramide biosynthesis, myriocin. **Dr. Bikman** has extensive published experience with myriocin and ceramide metabolism (12).

Another important connection with bariatric surgery is that the surgery bypasses the section of the intestine where iron absorption occurs. This observation further connects elevated iron levels as an important contributor to the oxidative stress and inflammation that activates pathways for diabetes. The **Watt** Lab has been studying the hormone hepcidin, which is the master regulator of iron. Inflammation increases serum hepcidin concentrations and hepcidin causes iron to be trapped in tissues leading to elevated oxidative stress and additional inflammatory cytokine production. Hepcidin inhibitors have been identified that lower serum hepcidin during inflammation and allow iron accumulated in tissues to be released and lowers oxidative stress. The proof-of-concept study demonstrating that hepcidin inhibitors lowered iron levels was done in an arthritis model of inflammation (13). Similar lipopolysaccharide treatments are known to trigger inflammatory diabetes modes in animals (14). This animal model will allow us to conduct experiments to connect inflammation to arthritis, diabetes and iron processing. Our team can use this **first** animal model and repeat this study to evaluate how lowering iron levels using hepcidin inhibitors alters the arthritis and diabetic symptoms of these rats. We predict that hepcidin inhibitor treatment will minimize the arthritis and diabetes symptoms.

The **Kooyman** lab uses a **second** rat as well as mouse model where surgery causes osteoarthritis. In this model, inflammation caused by joint damage can be treated using anti-inflammatory, pain reducing treatments. Inflammatory pathways are activated by injury to the joint causing secondary-effects on the health of the animal. In one study, the eyes of mice with and without surgery were examined and the mice with surgery leading to arthritis expressed early molecular markers of macular degeneration. Macular degeneration in the eye has many symptoms similar to Alzheimer's Disease and we will use macular degeneration as a simplified, early indicator that the rats have activated signaling pathways similar to Alzheimer's disease. This model allows us to monitor signaling pathways that connect arthritis and macular degeneration and we will also test these rats for symptoms of diabetes using glucose tolerance tests.

We will evaluate a **third** rat model for type 2 diabetes is produced by feeding the rats a high fat, high sucrose diet (15). This model triggers metabolic syndrome was also shown to induce infiltration of inflammatory macrophages into the synovium promoting arthritis. We will use this third model as a system to monitor simultaneous progression of diabetes, arthritis and iron dysregulation. By following all three conditions simultaneously, we will be able to map biochemical pathways through cytokine activation. We will use this model and compare it to the other two animal models and also the cytokine profiles for the bariatric surgery patients. Once cytokines and pathways are identified we can move to the inhibition and treatment phase.

An important aspect of this proposal is to deliver treatments that specifically target one ailment and evaluate if the treatment also blocks the development of the secondary ailment. **Dr. Pitt** is an expert in drug delivery and his expertise will be critical to design treatments that will allow our team to deliver a medication or inhibitors for one ailment and observe if the treatment has a beneficial effect on the

secondary ailment. We will also attempt to identify pathways that diverge between the two ailments and deliver drugs to target one pathway without interacting with a secondary pathway. Careful drug targeting will be essential to distinguish between disease states. For example, in the arthritis surgery model, anti-inflammatory drugs will be delivered transdermally from a patch where the medication will absorb directly into the joint. Targeted treatment of the joint will lower the local inflammation. This will be compared to direct targeting by drug injection into the synovial capsule of the knee. Rats treated to have arthritis and treated with anti-inflammatory drugs targeted to the knee will be evaluated for decreased macular degeneration by comparison to rats with arthritis but not treated with a localized anti-inflammatory drug. These animals will be compared to a third group of arthritic animals treated with a systemic anti-inflammatory treatment (via tail vein injection). Such experimental design will allow us to identify the connections between the diseases and the inflammatory pathways that cause the disease.

Research Plan - Methodology:

Our team has begun studying the connections between arthritis, diabetes and disrupted iron regulation with rat models of chronic inflammation. Three independent rat models, each with a different treatment to initiate a disease state, show connections between arthritis, diabetes and Alzheimer's-like symptoms. The first is a surgery model, destabilization of the medial meniscal ligament (DMM) that causes arthritis but has symptoms of macular degeneration [the eye is a simplified model of the brain and expresses amyloid beta, the hallmark of Alzheimer's in macular degeneration] (16). The second is a high fat, high sugar diet that causes diabetes but also results in arthritis (15). The third model mimics a bacterial infection that results in arthritis (13) but also shows hallmarks of diabetes (17).

We realized that we could use these three different models to identify the cytokines that cause the primary condition, but these models would also allow us to verify which cytokines cause the secondary condition. Our first research Aim will examine the three models, identify the cytokines that trigger the initial inflammatory condition and validate that the cytokines elevated in the first condition create secondary effects that cause damage in other tissues.

Bariatric surgery, and more specifically gastric bypass surgery, was originally performed as a method for weight loss (18), but is now considered a metabolic surgery due to its powerful effects on diabetes, dyslipidemia, and cardiovascular disease morbidity and mortality (19). After bariatric surgery, patients almost immediately become insulin sensitive or they respond to insulin and can clear glucose from the bloodstream (20). In essence, bariatric surgery stops type II diabetes. The fact that these patients are no longer insulin resistant gives an ideal model to study the physiological changes that occur after a patient experiences bariatric surgery. Dr. Davidson has serum samples from bariatric surgery patients and severely obese controls before and after surgery, and is able to recruit surgery patients with diabetes to conduct new analyses on samples prior to and soon after surgery.

Specific Aim #1 – Identify elevated cytokines common to diabetes and arthritis rat models.

Serum obtained from the three rat models described above will be tested for changes in: cytokine levels in untreated control groups, inflamed groups, in groups treated to inhibit inflammation and pain, groups treated with inhibitors for specific signaling pathways, groups treated with myriocin to inhibit ceramides or groups treated to have altered iron levels. Treatments will include systemic drug and inhibitor treatment with myriocin, protease inhibitors, iron chelators, and anti-inflammatory treatments. Other treatments will be localized patch treatments or topical cream or ointment where anti-inflammatory drugs and arthritis inhibitors will be delivered through the skin to joints. Finally, targeted drug delivery will be attempted to deliver treatments to specific organs or joints.

Enzyme Linked Immunosorbent Assays (ELISAs), mass spectrometry or PCR will be used to identify changes in the cytokine levels caused by inflammation. Important cytokines that will be measured include: IL-1β, TNF-α, IL-6, BMP-6, BMP-9, hepcidin, homocysteine and ceramide. Serum iron levels will be measured by inductively coupled plasma emission (ICP). Plasma ceramides will be quantified via lipidomics analysis. Glucose and insulin levels will also be measured to verify Type 2 diabetes are caused by arthritis or iron dysregulated conditions. Rat joints will be evaluated for arthritis

by established methods. Matrix Metallo Proteinase enzymes indicative of arthritis will also be measured. The pancreas, eyes, brain and joints will be tested by western blots for inflammation, mitochondrial respiration and oxidative stress and amyloid production showing each disease shares common etiology in these markers. Other markers for specific tissues related to inflammation and oxidative stress will be measured. Changes in iron related proteins such as ferritin, transferrin and ferroportin will be measured in each group using western blot techniques.

Aim #2 – Cytokine analysis of serum from bariatric surgery patients.

Serum from bariatric patients will be tested for the same cytokines, iron and other biomarkers listed in Aim #1. The cytokine levels in serum taken prior to bariatric surgery will be compared to serum taken after bariatric surgery (1-day, 1-week and 1-month with subsequent follow up blood draws over several years). We expect to see changes in inflammatory cytokine levels and iron biomarkers when comparing pre-surgery versus post-surgery serum. These changes will allow us to identify the cytokines and iron biomarkers that allow bariatric surgery patients to overcome the Type 2 diabetes conditions that existed prior to bariatric surgery.

The cytokine and iron profiles obtained from the different animal models for anemia, diabetes and arthritis will be compared to the bariatric surgery patient data to map the inflammatory pathways involved in each disease. We will also use the inhibitory data from different treatments to identify which pathways can be targeted by existing treatments and identify other pathways that have not yet been targeted for developing treatments for arthritis, diabetes and Alzheimer's disease.

Expected Outcomes – Expected Milestones:

1. We expect to find important differences in cytokines and iron biomarkers when we analyze and compare serum taken before and after bariatric surgery. This study will identify pathway(s) that can be targeted for treating Type 2 diabetes.
2. Inflammation caused by ceramides signaling is known to occur in each of these diseases. The bariatric surgery work will be the first study to measure ceramides in post-bariatric surgery patients. We anticipate that inflammation caused by ceramides will change and provide and important target for future treatments.
3. Elevated iron levels are associated with each of these diseases. Bariatric surgery bypasses the part of the intestines, the duodenum, where iron absorption occurs. We expect lower levels of serum iron and iron biomarkers and lower levels of oxidative stress in post-bariatric surgery serum.
4. Two of the animal models show evidence of a second disorder. We expect our work will show similarities in cytokine and iron biomarker activation. We also expect to show that treatments targeted to alleviate problems caused by the first disorder will also have a beneficial effect on the second disorder.
5. We expect that comparing the cytokine pathways and iron biomarkers among all of the animal studies and the bariatric surgery patients will allow us to map common pathways for the development of each disease and the accompanying secondary disorders. This map will allow us identify inhibition points that will allow us to develop treatments for all three disorders.

Mentoring environment:

The **Watt lab** has 2 graduate students that each act as mentors for 3-4 undergraduate students. He meets individually with the graduate students each week. He also has team meetings with the graduate student and their undergraduate team. Opportunities for oral presentations to share data take place in weekly lab meetings with the entire Watt research group. Additionally, he spends time in the lab mentoring both the graduate and undergraduate students.

Dr. Kooyman has a PhD student that interacts with the undergraduate students in his lab on a

daily basis. His lab is organized into four teams of undergraduate students, each with a team leader. His lab has a formal laboratory meeting once a week in which he and the students rotate through the program, which consists of an opening prayer, spiritual thought, journal article and research presentations.

Students are exposed to a wide range of experiences in the Kooyman laboratory. They are directly involved with the discovery process in research that is consequential. Techniques that they routinely perform include: qRTPCR, PCR, western blot, cell culture, tissue fixation, embedding, sectioning and staining, mouse & rat husbandry, micro-surgery, operating the micro CT scanner and MRI.

The first author on 4/7 papers and 4/6 abstracts from the Kooyman lab over the past three years were undergraduate students. Dr. Kooyman has arranged for funding such that undergraduates with data that wish to attend either a national or international scientific conference have been able to attend and present their work.

Currently the **Pitt lab** has 2 graduate students that each mentor several undergraduate students. The lab is divided into a "bacterial diagnosis" group and a "drug delivery" group. Dr. Pitt has individual weekly mentoring with each graduate student and 1 or 2 key undergraduate students. The other students are mentored by Dr. Pitt in one of 2 weekly group meetings. The students also present their research and discuss a pertinent research topic in each group meeting.

The **Bikman lab** currently has one PhD student, one MS student, and seven undergraduates. Students interact daily in the lab based on project 'teams' and the lab meets as a whole weekly to discuss projects, share latest results, and explore related research (i.e., journal club).

The Davidson Lab currently has 3 MS students that each mentor 3-5 undergraduate research assistants. Dr. Davidson meets with these teams on a weekly basis and individually mentors other undergraduates working on writing projects. These research assistants present the results of their work at national conferences and are now working on producing peer-reviewed manuscripts.

The students from each lab will have extensive overlap and interaction with the students from the other labs and this will create a cross-disciplinary training opportunity for all students. The PIs will have regular meetings to share progress occurring in their labs and will evaluate the progress of the entire project. Additional experiential learning will occur through multi-group lab meetings where update reports will be given so the entire group can see the overall progress of the project.

Budget and budget narrative (up to 1 page). Teams can propose up to $60K per year for two years.

Year 1 and Year 2 will follow the same budget:

1.	Graduate Student Research Assistantships	$20,000.00
2.	Undergraduate Salary	$2,500.00
3.	Human Subject Enrollment Fee	$1,000.00
4.	Blood collection supplies	$1,000.00
5.	Animal purchase, care and feeding	$18,000.00
6.	ELISAs and Antibodies	$10,000.00
7.	Drugs/Inhibitors	$2,500.00
8.	PCR	$1,000.00
9.	Mass Spec fees for lipidomics and cytokine detection	$1,000.00
10.	Glucose/Insulin testing	$1,000.000
11.	Iron assays	$1,000.000
12.	Drug Delivery Supplies	$1,000.000
	1st – year Total	$60,000.00
	The same funding needs will be followed for year #2	
	2^{nd} – year Total	$60,000.00
	Grand Total	**$120,000.00**

Justifications:

The greatest cost will be to purchase, feed and care for the animals. This will include the graduate students and undergraduate students participating in the daily care. Other significant costs are for ELISA kits to measure the biomarkers. Additional costs include the drugs and inhibitors to block or alter the biochemical signaling pathways.

References (no page limit). List references cited in the project description.\

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Plans for external funding (up to 1 page). List of potential external funders and a timeline for submitting proposals

How the IDR Origination Award will enable the team to successfully obtain future external support

Our research team will meet in a monthly coordination meeting with all the PIs to report progress. During this meeting we will have brainstorming sessions to cross-fertilize ideas. Students will participate so they can learn proposal-writing strategies from each of these mentors. Assignments for writing different sections of the proposal will be given. Additionally, when sections are completed, they will be shared among the group for review and critical evaluation.

For a timeline, we propose collecting data for an 8-12 month time period for the animals. During the first year we will also analyze the existing serum samples from the Davidson lab on bariatric patients. This will allow us to begin mapping interesting cytokine pathways. During the second year we can use the data from the bariatric surgery and initial animal studies to guide additional experimentation with inhibitors and drugs on the pathways to firm up our hypothesis.

This process will lead to formulating the Specific Aims for the final proposals. We plan 3 months of preparing and refining the proposal, while continuing to collect more data and write publications. We will submit an R01 in about 12-15 months.

Additional effort will be made to approach program directors at the related institutes at NIH to discuss the proper institute to submit our proposal. We hope to get interest from several of the institutes and hope to have shared interest among multiple institute program directors to evaluate our proposal.

After approaching the NIH, we will formulate and submit proposals to the arthritis foundation, the diabetes foundations and Alzheimer's Association. Just as a point of interest, Dr. Kooyman and Dr. Watt met with CSO of the Alzheimer's society and he indicated our idea was new and novel. He indicated that this is a new-cutting edge hypothesis and he is interested in funding research in this area.

Our research plan and aims are designed to quickly obtain the essential data that will support the hypotheses that we can proposal in an NIH R01 proposal. These proposals need solid preliminary data and this plan will provide the data. We are also working in a research space that is new and the NIH likes and element of novelty and well-thought-out creativity. Of course, the research has great potential for high impact on human health, which is the primary funding goal of the NIH.

Biographical Sketches (up to 2 pages per PI)

William G. Pitt

Professor

B.S. Brigham Young University April 1983 Chemical Engineering

PhD University of Wisconsin-Madison December 1987 Chemical Engineering

Sabbatical University of Minnesota – Twin Cities 1994-1995

Sabbatical Montana State University 2001-2001

A. Personal Statement

I have been doing research in drug delivery for 25 years. In my lab we make micelles, liposomes, solid nanoparticles, gas bubbles, and other nanostructures for drug delivery. I also do polymer synthesis to make needed polymers for drug delivery devices. I have over 50 publications in the area of drug delivery.

B. Positions and Honors

Positions and Employment

1982, 1983	Project Engineer, Terra Tek Research, Salt Lake City, UT : corrosion research, geochemistry
1983-1987	Research Assistant, Teaching Assistant, Dept of Chem. Eng., University of Wisconsin-Madison
1987-1993	Assistant Professor, Dept. of Chemical Engineering, Brigham Young University
1988-present	Adjunct Asst, Assoc, Full Professor, Department of Bioengineering, University of Utah
1993-1998	Associate Professor, Chemical Engineering Dept., Brigham Young University
1998-present	Professor, Chemical Engineering Dept., Brigham Young University

Honors

1994-1995	Lasby Visiting Professor, Dept. of Oral Sciences, Univ. of Minnesota, Minneapolis
1998	Outstanding Faculty Award, College of Engineering, Brigham Young University
2007-2012	Pope Professor of Chemical Engineering (endowed chair), Brigham Young University
2010	Outstanding Faculty Award, Department of Chemical Engineering, Brigham Young Univ.
2013	Maesar Research and Creative Works Award, Brigham Young University
2016	Wesley P. Lloyd Award for Distinction in Graduate Education, Brigham Young University

C. Contributions to Science

1. Ultrasonically-Activated Chemotherapeutic Delivery. Building on our success of using ultrasound to enhance antibiotic delivery to biofilms, and using my background in colloidal chemistry, we synthesized submicron-sized l micelles and liposomes that are responsive to ultrasound – responsive in that these carriers sequester the cancer chemotherapeutic until ultrasound is applied. Thus ultrasound can be applied to a cancerous tissue and the drug released as the carriers circulate through the target tissue. Our most novel carrier is a 100-nm liposome that contains drug and a nanodroplet of non-toxic liquid perfluorocarbon that is triggered by ultrasound to change from a liquid to a gas phase, thus disrupting the liposomes. By placing endocytosis-activating ligands on the liposome surface, these are taken into the endosome and then disrupted, thus releasing drug directly to the cytosol. We also delivered plasmids and proteins with these liposomes. We successfully used some of these constructs in 2 NIH-funded research projects using a mouse model of colon cancer. Key papers in the area of drug delivery are listed below.

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132. Husseini, G.A.*, Pitt, W.G., and Martins, A.M., "Ultrasonically triggered drug delivery: breaking the barrier", Colloids & Surfaces B: Biointerfaces, **123**, 364-386 (2014). http://dx.doi.org/10.1016/j.colsurfb.2014.07.051
129. Lin, C.-Y., Javadi, M., Belnap, D.M., Barrow, J.R., and Pitt, W.G.*, "Ultrasound Sensitive eLiposomes Containing Doxorubicin for Targeted Drug Therapy", *Nanomedicine: Nanotechnology, Biology, and Medicine*", **10**(1), 67-76 (2014). http://dx.doi.org/10.1016/j.nano.2013.06.011

Complete list of published work by W.G. Pitt in MyBibliography (showing 97 of 153 publications): https://www.ncbi.nlm.nih.gov/sites/myncbi/william.pitt.1/bibliography/41164705/public/?sort=date&direction= descending

Lance E. Davidson
Assistant Professor
B.S. Brigham Young University April 2000 – Physical Education
M.S. Brigham Young University April 2002 – Exersice Science
PhD. Queen's University Kingston Ontario Canada September 2007
Postdoc Columbia University, New York, NY 2008-2009
Postdoc, University of Utah, 2009-2010.

A. Personal Statement

This IDR project aligns well with my research interests in severe obesity and its associated health consequences, and I am eager to collaborate with this multi-disciplinary team. My previous training has focused almost solely on human research, and this opportunity to translate compelling evidence from animal models directly to humans is exciting to me. I anticipate that the findings of this project will provide our collaborative group with the pilot data we need to fuel further investigations into therapeutic targets and modalities that may interrupt or reverse the progression of these interrelated chronic diseases.

B. Positions and Honors

Positions and Employment

2010-11 Adjunct Assistant Professor, Cardiovascular Genetics, University of Utah School of Medicine,
Salt Lake City, UT

2011-13 Research Assistant Professor, Cardiovascular Genetics, University of Utah School of Medicine,
Salt Lake City, UT

2013-18 Adjunct Assistant Professor, Cardiovascular Genetics, University of Utah School of Medicine,
Salt Lake City, UT

2018- Adjunct Assistant Professor, Epidemiology, University of Utah School of Medicine,
Salt Lake City, UT

2013- Assistant Professor, Department of Exercise Sciences, Brigham Young University, Provo, UT

Professional Societies

2001- American College of Sports Medicine

2001- The Obesity Society / North American Association for the Study of Obesity

2003-08 Canadian Society of Exercise Physiology

Reviewer for the following journals: JAMA, American Journal of Clinical Nutrition, Obesity, Journal of Physical Activity and Health, Aging Health, American Journal of Clinical Nutrition, BMC Obesity, Obesity Surgery, International Journal of Obesity, Clinical and Experimental Pharmacology and Physiology, American Journal of Human Biology, American Journal of Preventive Medicine, Medicine & Science in Sports & Exercise, PLoS One

C. Selected Publications

Most relevant to the current application

1. Lee S, Kuk JL, **Davidson LE**, Hudson R, Kilpatrick K, Graham TE, Ross R. Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes. *J Appl Physiol*. 99(3):1220-5, 2005. [PMID: 15860689]
2. Kuk JL, **Davidson LE**, Hudson R, Kilpatrick K, and Ross R. Effect of dietary fat intake on the relationship between liver fat and insulin sensitivity in sedentary, abdominally obese older men. *Appl Physiol Nutr Metab,* 33(2):239-245, 2008. [PMID: 18347678]
3. **Davidson LE**, Hudson R, Kilpatrick K, Kuk JL, McMillan K, Janiszewski PM, Lee S, Lam M, Ross R. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. *Arch Intern Med*, 169:122-31, 2009. [PMID: 19171808]

4. Lin WY, Pi-Sunyer FX, Chen CC, **Davidson LE**, Liu CS, Li TC, Wu MF, Li CI, Chen W, Lin CC. Coffee consumption is inversely associated with type 2 diabetes in Chinese. *Eur J Clin Invest*. 41(6):659-666, 2011. [PMID: 21226707]
5. Kolotkin RL, **Davidson LE**, Crosby RD, Hunt SC, Adams TD. Six-year changes in health-related quality of life in gastric bypass patients versus obese comparison groups. *Surg Obes Relat Dis*. 8(5):625-33, 2012. [PMID: 22386053]
6. Adams TD, **Davidson LE**, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC, Strong MB, Vinik R, Wanner NA, Hopkins PN, Gress RE, Walker JM, Cloward TV, Nuttall RT, Hammoud A, Greenwood JL, Crosby RD, McKinlay R, Simper SC, Smith SC, Hunt SC. Health benefits of gastric bypass surgery after 6 years. *JAMA*. 308(11):1122-31, 2012. [PMID: 22990271]
7. Adams TD, **Davidson LE**, Litwin SE, Hunt SC. Gastrointestinal surgery: cardiovascular risk reduction and improved long-term survival in patients with obesity and diabetes. *Curr Atheroscler Rep.* 14(6):606-15, 2012. [PMID: 23054662]
8. **Davidson LE**, Kelley DE, Heshka S, Thornton J, Pi-Sunyer FX, Boxt L, Balasubramanyam A, Gallagher D. Skeletal muscle and organ masses differ in overweight adults with type 2 diabetes. *J Appl Physiol*. 117(4):377-82, 2014. [PMID: 24947030]
9. Priester T, Ault TG, **Davidson L**, Gress R, Adams TD, Hunt SC, Litwin SE. Coronary calcium scores 6 years after bariatric surgery. *Obes Surg*. 25(1):90-6, 2015. [PMID: 24927692]
10. Adams TD, Mehta TS, **Davidson LE**, Hunt SC. All-Cause and Cause-Specific Mortality Associated with Bariatric Surgery: A Review. *Curr Atheroscler Rep*. 17(12):74, 2015. [PMID: 26496931]
11. **Davidson LE**, Adams TD, Kim J, Jones JL, Hashibe M, Taylor D, Mehta T, McKinlay R, Simper SC, Smith SC, Hunt SC. Association of patient's age at gastric bypass surgery with long-term all-cause and cause-specific mortality. *JAMA Surg*. 151(7):631-7, 2016. [PMID: 26864395]
12. Ko G, **Davidson LE**, Brennan AM, Lam M, Ross R. Abdominal adiposity, not cardiorespiratory fitness, mediates the exercise-induced change in insulin sensitivity in older adults. *PLoS One*. 11(12):e0167734, 2016. [PMID: 27936206]
13. Daniels P, Burns RD, Brusseau TA, Hall MS, **Davidson L**, Adams TD, Eisenman P. Effect of a randomised 12-week resistance training programme on muscular strength, cross-sectional area and muscle quality in women having undergone Roux-en-Y gastric bypass. *J Sports Sci*. 36(5):529-535, 2018. [PMID: 28467737]
14. Hopkins JL, Hopkins PN, Brinton EA, Adams TD, **Davidson LE**, Nanjee MN, Hunt SC. Expression of metabolic syndrome in women with severe obesity. *Metab Syndr Relat Disord*. 15(6):283-290, 2017. [PMID: 28657427]
15. Adams TD, **Davidson LE**, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, Gutierrez JM, Frogley SJ, Ibele AR, Brinton EA, Hopkins PN, McKinlay R, Simper SC, Hunt SC. Weight and metabolic outcomes 12 years after gastric bypass. *N Engl J Med*. 377(12):1143-1155, 2017. [PMID: 28930514]
16. **Davidson LE**, Yu W, Goodpaster BH, DeLany JP, Widen E, Lemos T, Strain GW, Pomp A, Courcoulas AP, Lin S, Thornton JC, Gallagher D. Fat free mass and skeletal muscle five years after bariatric surgery. *Obesity.* 26(7):1130-1136, 2018. [PMID: 29845744]
17. Kolotkin RL, Kim J, **Davidson LE**, Crosby RD, Hunt SC, Adams TD. 12-year trajectory of health-related quality of life in gastric bypass patients versus comparison groups. *Surg Obes Relat Dis.* 14(9):1359-1365, 2018. [PMID: 29884519]
18. **Davidson LE**, Hunt SC, Adams TD. Fitness versus adiposity and cardiovascular disease risk. *Eur J Clin Nutr*. [E-pub Oct 8, 2018]. [PMID: 30297762]

David L Kooyman
B.S. California State Polytechnic University – Pomona, CA April 1982
M.S. California State Polytechnic University – Pomona, CA April 1986
Ph. D. Ohio University, Athens OH, 1993
Postdoc DNX, Princeton, NJ. 1995
Personal Statement

Immediately after completing my Master's degree I began a PhD track in the Department of Animal Sciences, College of Agriculture, Food and Natural Resources at the University of Missouri-Columbia, MO. My dissertation was focused on the production of transgenic mice resistant to K99 enterotoxigenic *E. coli*. Two years into my program my major professor took a position at Ohio Univeristy-Athens, OH. I transferred to OU as a PhD student in the multi-disciplinary molecular and cellular biology program housed in the College of Arts and Sciences and worked in the Edison Biotechnology Center. This was a major shift for me that provided a broad background while working in a focused graduate program. These formative years helped shape me into a scientist that is able to look at physiology simultaneously from both a holistic and molecular/cellular perspective. My strong background as a scientist in the biotechnology industry has honed my skills at translational research. For several years after coming to Brigham Young University my research laboratory was focused on studies involving molecular and cellular approaches to animal physiology and genetics. Since 2010 I have focused my interests to cartilage biology. This shift was due most notably because I developed osteoarthritis (OA) and could find no treatment in the medical arena. Initially I studied OA from a purely basic research working off of the accepted dogma that it was a wear and tear disease. I was co-author on several papers that examined the biology of cartilage in animals carrying two genetic defects (*SEDC* & *Dmm*). Because of some observations in these studies I began to look at OA as a metabolically active disease. Shortly thereafter, I was senior author on a landmark paper published in Frontiers of Physiology regarding the development of OA in wildtype and RAGE KO mice after knee destabilization surgery D.J. Larkin, J.Z. Kartchner, A.S. Doxey, W.R. Hollis, J.L. Rees, S.K. Wilhelm, C.S. Draper, D.M. Peterson, G.G. Jackson, C. Ingersoll, S.S. Haynie, E. Chavez, P.R. Reynolds, and **D.L. Kooyman**. 2013. Inflammatory markers associated with osteoarthritis after destabilization surgery in young mice with and without Receptor for Advanced Glycation End-products (RAGE). Frontiers in Physiology. 4 (article121): 1-8). Published in 2013, this paper was given the distinction of "best performing article in Frontiers" by the journal in 2014. My lab has presented results from our OA work at the conference of the International Society of Osteoarthritis or Experimental Biology every year since 2011. We have continued our basic approach by studying the interactions of OA with other diseases including retinopathy, Alzheimer's and metabolic syndrome. We are exploring the role of primary cilia in OA from a basic research approach (Isaac D. Sheffield, Mercedes A. McGee, Steven J. Glenn, Da Young Baek, Joshua M. Coleman, Bradley K. Dorius, Channing Williams, Brandon J. Rose, Anthony E. Sanchez, Michael A. Goodman, John M. Daines, Dennis L. Eggett, Val C. Sheffield, Arminda Suli and **David L. Kooyman**. Osteoarthritis-Like Changes in Bardet–Biedl Syndrome Mutant Ciliopathy Mice (Bbs1M390R=M390R): Evidence for a Role of Primary Cilia in Cartilage Homeostasis and Regulation of Inflammation. 2018. Frontiers in Physiology. 9 (article 708): 1-10). My research has also incorporated a translational aspect that led to three provisional patents. One of which was licensed and developed into an OTC commercial product for treating OA and the pain associated with the disease (Arthritis Wonder®).

B. Positions and Honors

1980-1983 Process Engineer, Synathane-Taylor Corp., Upland, CA
1989-1994 Scientist (Xenotransplantation group). DNX, Inc. Princeton, NJ
1995-1997 Senior Scientist, Project Leader. Nextran (Baxter International), Princeton, NJ
1997-2000 Assistant Professor, Dept. of Animal Science, BYU Provo UT
1998 Who's Who in American Scientists and Engineers

2001-2002 Associate Professor, Dept. of Animal and Veterinary Sciences, BYU Provo UT
2000-2001 Chair, Dept. of Animal and Veterinary Sciences, BYU, Provo UT
2001-2003 Associate Dean, College of Biology and Agriculture, BYU, Provo UT
2003-2013 Associate Professor, Dept. of Physiol. & Dev. Biology, BYU, Provo UT
2010 Coach for BYU iGEM team which were Gold Medalists in Americas Regional Competition
2013 Outstanding Faculty Award Dept. of Physiology and Developmental Biology, BYU Provo UT
2013-Present Full Professor, Dept. of Physiol. & Dev. Biology, BYU, Provo UT
2015 Faculty Distinguished Service Award College of Life Sciences, BYU Provo UT
2016 Abraham O Smoot University Citizenship Award BYU Provo UT (3rd Highest University Honor)

C. Contributions to Science

My research has included studies in xenotransplantation, skeletal muscle physiology and osteoarthritis. In addition, I have extensive experience in project management and project overview.

(1) Xenotransplantation

After my Post-Doc with DNX I transitioned into the first project leader in their xenotransplantion group that was later acquired by Baxter International as a small biotechnology company called, Nextran. As project leader my group had the distinction to be the first ones to successfully transplant a vascularized pig organ (heart) into a baboon. We also discovered a novel mechanism by which GPI anchored proteins transfer from one cell to another. Our work led to many key experiments that resulted with major publications including

Our work significantly advanced the field of xenotransplantation and elucidated an important property of GPI anchored proteins. We eventually transplanted other pig organs into baboons and humans and were poised to begin pre-clinical trials when a moratorium was placed on pig to human xenotransplantation until all zoonotic threats could be identified and nullified.

(2) **Skeletal Muscle Physiology**

Having helped complete the work of re-inventing the college, I left the Deans office and went into the department that most closely reflected my background – Physiology and Developmental Biology. For a period of time I worked closely with a colleague, William R. Winder in studying muscle physiology. I was co-PI on a grant, NIHRO1 Roles and Mechanisms of Activation of LKB1/MO25/STRAD in Skeletal Muscle in Response to Muscle Contraction that was funded for five years with a yearly direct cost of $209,348.00. A portion of the grant in which I was involved resulted in a significant publication in which we characterized a myopathic phenotype in myocin light chain LKB1-KO mice. The paper, referenced below, reported an important role for LKB1 in skeletal muscle function.

(3) Osteoarthritis While the muscle physiology work was interesting and successful, I became interested in osteoarthritis (OA) as a sufferer myself. I came into this field with somewhat naive eyes. While many were still considering OA as primarily a wear and tear disease, we approached it as a metabolic problem associated with inflammation. Our approach initially was to examine the interaction of two key receptors in the inflammation – RAGE and TLR4. The first major break came when we demonstrated that eliminating RAGE using a KO mouse model afforded significant attenuation of OA after knee destabilization surgery in mice. We subsequently discovered that TLR4 is a key receptor associated with pain in the knee joint. We also pioneered a model for studying TMJ OA using alignment of the mouse jaw by bonding a small piece of stainless steel wire to the back molar. Most recently, we have become focused more on the interaction of OA with two of its major comorbidities – Alzheimer's Disease and Type II Diabetes. We are focusing our attention on primary cilia as playing a key role in the initiation and progression of OA. My work in OA has led to some key publications including:

My work in OA has also included translational work that resulted in three provisional patents that were subsequently licensed. A product that treats the pain associated with OA, derived from one of the patents, is currently on the market.List of Published Works in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/57089442/

Brigham Young University
Department of Physiology and Developmental Biology
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Provo, UT 84602
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bikman@byu.edu

EDUCATION

Postdoctoral Fellow, Cardiovascular and Metabolic Diseases, Duke-NUS Graduate Medical School, Singapore, 2011
Ph.D., Bioenergetics, East Carolina University, Greenville, North Carolina, 2008
M.Sc., Exercise Physiology, Brigham Young University, Provo, Utah, 2005
B.Sc., Exercise Science, Brigham Young University, Provo, Utah, 2003

AWARDS, HONORS AND RECOGNITION

Faculty

- APS Research Career Enhancement Award – 2013
- APS/NSF Mentor Award - 2013
- Oroboros Travel Award, O2K Workshop - 2012

PROFESSIONAL AND SCIENTIFIC SOCIETIES

- Mitochondrial Physiology Society
- American Diabetes Association
- American Physiology Society
- American Society for Investigative Pathology

PUBLICATIONS

Manuscripts in Review

1. Fox JC, Evans AT, Blomfield MP, Livingstone SK, Tenney SR, Webster JB, Perry K, Hill JT, **Bikman BT**, Hansen MDH. Resistance mechanisms and cross-resistance for a pyridine-pyrimidine amide inhibitor of microtubule polymerization. *Molecular Cancer Therapeutics*

Published Manuscripts

1. Pape JA, Newey CR, Burrell HR, Workman A, Perry K, **Bikman BT**, Bridgewater LC, Grose JH. Per-Arnt-Sim Kinase (PASK) deficiency increases cellular respiration on a standard diet and decreases liver triglyceride accumulation on a western high-fat high-sugar diet. *Nutrients* 2018 PMID: 30558306
2. DeMille D, Pape JA, **Bikman BT**, Ghassemian M, Grose JH. The regulation of Cbf1 by PAS Kinase is a pivotal control point for lipogenesis versus respiration in *Sacchromyces cerevisiae*. *G3 (Bethesda)* 2018 PMID: 30381292.
3. Parker BA, Walton CM, Carr ST, Andrus JL, Cheung ECK, Duplisea MJ, Wilson EK, Draney C, Lathen DR, Kenner KB, Thomson DM, Tessem JS, **Bikman BT**. β-hydroxybutyrate elicits favorable mitochondrial changes in skeletal muscle. *Int J Mol Sci* 2018 19(8); 10.3390/ijms19082247.
4. Dallon BW, Parker BA, Hodson AE, Tippetts TS, Harrison ME, Appiah MMA, Witt JE, Gibbs JL, Gray HM, Sant TM, **Bikman BT**. Insulin selectively reduces mitochondrial uncoupling in brown adipose tissue in mice. *Biochem J* 2018 475(3):561.
5. Rowley TJ, Bitner BF, Ray JD, Lathen DR, **Bikman BT**, Hansen JM, Dorenkott MR, Goodrich KM, Ye L, O'Keefe SF, Neilson AP, Tessem JS. Monomeric cocoa catechins enhance β-cell function by increasing mitochondrial respiration. *J Nutr Biochem* 2017 49:30-41.
6. Lindsley JE, Abali EE, **Bikman BT**, Cline SD, Fulton T, Lopez B, Rosenthal OD, Uhley VE, Weintraut RJ, Williams PD, Wisco JJ, Thompson K. What nutrition-related knowledge, skills, and attitude should medical students develop? *Medical Science Educator* 2017; 27(4) 579-583.

7. Sampson MJ, Lathen DR, Dallon BW, Draney C, Ray JD, Kener KB, Parker BA, Gibbs JL, Gross JS, Tessem TS, **Bikman BT**. β-Hydroxybutyrate improves β-cell mitochondrial function and survival. *J Ins Resist* 2017; 2(1), a25.
8. Banks CJ, Rodriguez NW, Gashler KR, Pandya R, Mortenson JB, Whited MD, Soderblom EJ, Thompson JW, Moseley MA, Reddi AR, Tessem JS, Torres MP, **Bikman BT**, Andersen JL. Acylation of Superoxide Dismutase 1 (SOD1) at K122 Governs SOD1-mediated Inhibition of Mitochondrial Respiration. *Mol Cell Biol* 2017 Jul 24. pii: MCB.00354-17. doi: 10.1128/MCB.00354-17.
9. Napa K, Baeder AC, Witt JE, Rayburn ST, Miller MG, Dallon BW, Gibbs JL, Wilcox SH, Winden DR, Smith JH, Reynolds PR, **Bikman BT.** LPS from *P. gingivalis* negatively alters gingival cell mitochondrial bioenergetics. *Int J Dent* 2017:2697210.
10. Taylor OJ, Thatcher MO, Hubbard ST, Gibbs J, Trumbull AM, Gray HM, Winden DR, Pearson MJ, Tippetts TS, Holland WH, Reynolds PR, **Bikman BT**. High-mobility group box 1 disrupts metabolic function with cigarette smoke exposure in a ceramide-dependent manner. *Int J Mol Sci.* 2017 18 (5).
11. Sanders NT, Dutson DJ, Durrant JW, Lewis JB, Wilcox SH, Winden DR, Arroyo JA, **Bikman BT**, Reynolds PR. Cigarette smoke extract (CSE) induces RAGE-mediated inflammation in the Ca9-22 gingival carcinoma epithelial cell line. *Arch Oral Bio* 2017 80; 95-100.
12. Lewis JB, Hirschi KM, Arroyo JA, **Bikman BT**, Kooyman DL, Reynolds PR. Plausible Roles for RAGE in Conditions Exacerbated by Direct and Indirect (Secondhand) Smoke Exposure. *Int J Mol Sci*. 2017 Mar 17;18(3)
13. Mathis AD, Naylor BC, Carson RH, Evans E, Harwell J, Knecht J, Hexem E., Peelor III FF, Miller BF, Hamilton KL, Transtrum M, **Bikman BT**, Price JC. Mechanisms of i*n vivo* ribosome maintenance respond to nutrient signals. *Molecular and Cellular Proteomics* 2017 16(2):243-254.
14. Reynolds M, Hancock C, Ray J, Kener K, Draney C, Garland K, Hardman J, **Bikman BT**, Tessem J. β-cell deletion of Nr4a1 and Nr4a3 nuclear receptors impedes mitochondrial respiration and insulin secretion. *Am J Physiol Endocrinol Metab* 2016 311(1):E186-201.
15. Braeder AC, Napa K, Richardson ST, Taylor OJ, Andersen SG, Wilcox SH, Winden DR, Reynolds PR, Bikman BT. Gingival cells exposed to cigarette smoke extract induce muscle cell metabolic disruption. *International Journal of Dentistry* 2016 ID 2763160.
16. Hodson AE, Tippetts TS, **Bikman BT**. Insulin treatment increases myocardial ceramide accumulation and disrupts cardiometabolic function. *Cardiovascular Diabetology* 2015 Dec 18;14(1):153.
17. Hansen ME, Thatcher MO, Simmons KJ, Tippetts TS, Saito RR, Trumbull AM, Taylor OJ, Hubbard ST, **Bikman BT**. Lipopolysaccharide Disrupts Mitochondrial Physiology in Skeletal Muscle via Disparate Effects on Sphingolipid Metabolism. *Shock* 2015 Dec;44(6):585-92.
18. Kwon OS, Tanner RE, Barrows KM, Runtsch M, Symons JD, Jalil T, **Bikman BT**, McClain DA, O'Connell RM, Drummond MJ. MyD88 regulates physical inactivity-induced skeletal muscle inflammation, ceramide biosynthesis signaling and glucose tolerance. *Am J Physiol Endocrinol Metab* 2015 DOI: 10.1152/ajpendo.00124.2015.
19. Nelson MB, Swensen AC, Winden DR, Bodine JS, **Bikman BT**, Reynolds PR. Receptor for advanced glycation end-products (RAGE) signaling reduces cardiomyocyte mitochondrial function in a ceramide-dependent manner. *Am J Physiol Heart* 2015 DOI: 10.1152/ajpheart.00043.2015.
20. Gibby JT, Njeru DK, Cvetko ST, Merrill RM, **Bikman BT**, Gibby WA. Volumetric analysis of central body fat accurately predicts incidence of diabetes and hypertension in adults. *BMC Obesity* 2015; 2:10.

Richard Watt
B.S. Brigham Young University April 1994
Ph. D. University of Wisconsin-Madison July 1998
Postdoc Princeton University 1998-2000

A. Personal Statement

My expertise is metal ion homeostasis and how metals such as iron are handled and sequestered to prevent cellular damage. Throughout my career I have studied Ni, Mn and Fe in biological systems and focused on the chaperone-like proteins and metal ions transporters involved in the proper movement of these metals throughout the organism. My most recent research has focused on the iron proteins, transferrin and ferritin, particularly: 1) mechanisms of iron binding; 2) mechanisms that inhibit iron binding; and 3) mechanism that trigger iron release from these proteins. Failure of the normal iron processing proteins results in free iron that is a catalyst for oxidative stress and radical damage that is prevalent in diabetes, kidney, Parkinson's and Alzheimer's diseases. Our published work has focused on studying physiological conditions present in diabetes and kidney disease but in a recent review article we discussed mechanisms for iron dysregulation associated with atherosclerosis, Parkinson's and Alzheimer's disease (1. Watt, BioMetals, (2011) 24 (3), 489-500).

Our work is unique because we focus on performing iron-loading studies using physiologically relevant phosphate and carbonate buffers that include other molecules present in the serum or cytosol. Our studies have identified that phosphate is inhibitory to iron loading into both ferritin and transferrin and polymeric soluble iron-phosphate complexes form under the conditions tested. We have shown that these polymeric soluble iron-phosphate complexes prevent iron from being a substrate for ferritin or transferrin iron loading. Furthermore, we have proposed that these polymeric soluble iron-phosphate complexes might be part of the non-transferrin bound iron (NTBI) pool present in patients with diabetes and kidney disease.

Based on the Watt lab expertise in iron loading assays (2. Hilton et al. BioMetals (2012) 25 (2), 259-273 and 3. Hilton et al., J. Inorg. Biochem. (2012) 110, 1-7), and review/highlights articles relating to iron loading into ferritin and transferrin (4. Watt, ChemBioChem (2013), 14, 415-419.), we have recently established collaboration with Rockwell Medical to further examine transferrin iron loading and free iron in the serum.

Our lab has developed a new and novel treatment for anemia. We have identified inhibitors of hepcidin, the hormone that regulates iron absorption and redistribution in the body. We are in the process of licensing these ideas and starting a company to treat anemia.

B. Positions and Honors

2000-2006	Assistant professor, University of New Mexico, Albuquerque, NM
2006-2011	Assistant professor, Brigham Young University, Provo, UT
2011 – present	Associate professor, Brigham Young University, Provo, UT

C. Contribution to Science

My research has included studies in biochemistry and biomaterials. My focus in biochemistry has been on metal ion metabolism and has focused on understanding how these mechanisms fail. Iron homeostasis is disrupted with inflammation and causes oxidative stress, which is caused by free iron in the biological system. Biomaterials applications include the design of an artificial photosynthesis cell using ferritin.

(1) Fundamental Metal Binding: The first area the Watt lab has focused relates to metal ion chemistry in physiologically relevant buffers. The ability of metal binding proteins such as transferrin and ferritin to function properly depends on the reaction conditions that occur in biology and how metal ion binding occurs mechanistically. Our lab has contributed by preparing review articles and highlight articles emphasizing that experiments must be done under physiologically relevant reaction conditions in order to

understand the mechanism of metal binding and retention and how metal ions can be released by physiologically relevant conditions. The background surrounding this work is that most studies have been performed using standard laboratory buffers such as the Good's Buffers. These allow the proteins to be studied for iron-binding properties but these studies do not allow the evaluation of physiologically relevant buffers and other molecules to be assessed. Our work has shown that phosphate and other species present in biological buffers such as Ca and Mg interfere with proper iron loading. These studies have been done in my lab and in collaboration with Dr. Jose Dominguez-Vera at the University of Granada, Spain.

(2) Metal Binding Under Altered Physiological Conditions: The second major contribution the Watt lab has made relates to the application of our metal binding studies to altered reaction condition associated with disease states. We observed that in chronic kidney disease that non-transferrin bound iron was present in serum (similar studies showed elevated iron in the labile iron pool in the cytosol of cells). We have examined iron loading into ferritin and transferrin with elevated phosphate levels mimicking conditions that would occur in the serum of chronic kidney disease. Additionally we have examined iron release in the presence of other metal binding proteins under physiological conditions. Finally we have considered other potentially harmful biomolecules that become elevated with disease such as homocysteine. In each instance, we have determined that the molecules identified, have had an important inhibitory effect on iron binding by transferrin or ferritin. We have done these experiments in our lab and in collaboration with Merce Capdevila at the Universitat Autonoma de Carcelona.

(3) BioMaterials Applications: For several years I have studied ferritin as a reactor for synthesizing non-native metal minerals in the 8 nm core of ferritin. Potential applications include bioimaging and drug delivery. The literature indicated that ferritin might be photoactive. As the PI over this project, my lab used ferritin as a photocatalyst in an artificial photosynthesis cell where we have designed a system that absorbs light at multiple wavelengths as a multi-junction light-harvesting cell. Health implications include obtaining energy with fewer pollutants that currently exist from fossil fuels. We are now modifying our system to use ferritin as a source of reducing power (biobattery) in an in vivo system.

List of Published Works in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1pShEHisyou/bibliography/48597933/public/?sort=date&direction=ascending.

Current and Pending Support for William G. Pitt

ACTIVE

Precision Membranes, LLC (Pitt) 10/1/2018 – 3/31/2019 0.5 calendar
Subcontract on Precision Membranes, LLC $50,000
Rapid and Efficient Extraction of Bacteria from Whole Blood for Sepsis Diagnosis
The major goals of this project are to capture bacteria from whole blood using surface-modified magnetic beads.
OVERLAP
There is NO scientific overlap between this liposome project and the current proposal.

NIH NIAID, R01AI116989 Hawkins is PI, Pitt is co-PI 4/1/2015 – 3/31/2020 0.75 calendar $5.6MM in total direct costs. Pitt portion is about $800,000
Multiplexed, Non-Amplified, Nucleic Acid-Based Identification of Multidrug Resistant Pathogens Using an Integrated Optofluidic Platform
My specific research area is to develop the rapid separation technique to separate bacteria from whole blood in less than 10 minutes, and then lyse the bacteria and deliver the DNA to the next stage of the process.
OVERLAP
There is NO scientific overlap between this liposome project and the current proposal.

PENDING

Precision Membranes, LLC (Pitt) 10/1/2019 – 3/31/2020 0.5 calendar
Subcontract on Precision Membranes, LLC $60,000
Rapid Antibiotic-Resistance Phenotyping of Bacteria from Blood Infections

The major goals of this project are to grow bacteria in nanodroplets containing various antibiotic concentrations to determine the antibiotic resistance phenotype.
OVERLAP
There is NO scientific overlap between this liposome project and the current proposal.

NIH Pitt is the PI 10/1/2018 – 9/30/2023 1.5 calendar
NIAID $500,000
"*Rapid Identification of Carbapenem and Colistin Resistance in Blood Infections using Optical Detection*"
The major goals of this project are to isolate bacteria from blood by lysis and filtration, and then recover separately plasmids and genomic DNA in a microfluidic device; then the DNA will be analyzed by Raman spectroscopy to identify bacterial species and presence of resistance genes. My role (Pitt) is to direct the entire project, develop the lysing and DNA collection, and assist in building integrated optical system.
OVERLAP
There is NO scientific overlap between this bacterial recovery project and the proposal.

NIH Mizrachi is the PI, Pitt is a paid consultant 10/1/2018 – 9/30/2020 0.25 calendar
National Institute of General Medical Sciences $750,000
"Engineering soluble tight junction integral membrane proteins to modulate paracellular transport"
The major goals of this project are to re-engineer tight junction proteins to allow passage of small molecules. My role (Pitt) is to develop therapeutic delivery vehicles for protein delivery to cells.
OVERLAP
There is NO scientific overlap between this liposome project and the proposal.

D. Completed Research Support in past 3 years

1. "Co-delivery of doxorubicin and verapamil from eLiposomes to enhance cytotoxicity toward multidrug resistant cancer cells". Simmons Cancer Research Center. $35,000 in total costs. May 1 – August 31, 2015. I was the PI on this project (1 grad student) to encapsulate doxorubicin and verapamil into liposomes for targeted drug delivery. No overlap with the current proposal.

2. "Acoustically Activated Delivery of Small Molecules to the Skin", L'Oreal Inc. $50,000 in total costs. Aug 15, 2016 – Aug 14, 2018. I am the PI on this project to develop drug delivery carriers for delivery of lipids and proteins to the dermis of the skin. No overlap with the current proposal.

Current and Pending Support Lance Davidson

Ongoing Research Support

Intermountain Medical and Research Foundation
(PI: Ted D. Adams; Investigator: Lance E. Davidson, Ph.D.)
02/01/19-01/31/21

Intermountain LiVe Well Center Clinical Record Data Extraction Project

This pre-research project will employ approximately 20 BYU undergraduate students each semester to comb through paper files from attendees of the Intermountain LiVe Well Center's wellness program, which includes a comprehensive physical and lifestyle assessment in clients who are predominantly business executives. The task will generate a rich dataset that features maximal treadmill tests, body composition assessments, and health history questionnaires, sometimes with multiple follow-ups since the program's inception in 1980. When linked with the Utah Population Database, this dataset will yield a wealth of health and fitness data for future students to answer important questions about the effect of lifestyle on chronic disease conditions and mortality.

Current and Pending Support - Bikman

Current

- NIH/NIA R01 – Novel molecular mechanisms of skeletal muscle insulin resistance in physically inactive older adults (R01 AG050781). 04/01/16-03/31/21. Total costs: $1,875,850. Role on project: Collaborator.

In Review

- NIH R01 – The role of ceramides in diabetes-induced fetal complications. Total costs: $1,875,850. Role on project: Collaborator.
- NIH R01 – Investigating how perturbed lipid metabolism predisposes for development of Alzheimer's disease. Total costs: $1,650,500. Role on project: Collaborator.

Sponsored Research

- Unicity – The capacity of a proprietary anti-oxidant cocktail to mitigate ROS. Total costs: $60,000 (with Dr. Jason Hansen).

Completed

- BYU Gerontology Research Grant Award, Title: *A Role for Ceramides in Sarcopenia*. Term: 01/01/12-12/31/12. Total Costs: $10,000. Role on Project: P.I.
- Predoctoral Institutional Training Grant (T32), NIH/NIA, 2005
- BYU Mentoring Environment Grant – TLR4/MyD88 signaling in cigarette smoke-induced heart ceramide accrual. 01/01/16-12/31/16. Total costs: $20,000. Role on project: P.I.
- BYU Life Sciences Translational Research Grant – The efficacy of TGFβ inhibition via SGI-1252 in the prevention and reversal of diet-induced obesity and diabetes. 4/1/16-3/31/17. Total costs: $15,000. Role on project: P.I.

Gifts

- Unicity (2016): $2,000
- Bank of American Fork (2015): $500
- Becton-Dickinson (2015/2016): $4,000
- Mannatech Inc. (2015): $5,000
- College of Physical and Mathematical Sciences (2014): $15,000.

Student Funding

- 2017 BYU ORCA, Title: The Efficacy of Orally Ingested D-hydroxybutyrate in Skeletal Muscle in the Prevention and Reversal of Diet-induced Obesity and Diabetes. Total costs: $1,500. Awardee: Brian Parker
- 2016 BYU Graduate Research Fellowship, Title: The role of insulin in the etiology of Alzheimer disease. Total costs: $10,000. Awardee: Sheryl Carr
- 2016 BYU ORCA, Title: The Efficacy of TGF-Beta Inhibition via SGI-1252 in the Prevention and Reversal of Diet-induced Obesity and Diabetes. Total costs: $1,500. Awardee: Blake Dallon
- 2013 APS/NSF, Undergraduate Research Fellowship, Title: Reactive Oxygen Species and Mitochondrial Fission. Total costs: $4,000. Awardee: Braden Tucker
- 2013 BYU Graduate Research Fellowship, Title: Ceramides as a Mediator of Cigarette Smoke-induced Metabolic Disruption. Total costs: $15,000. Awardee: Mikayla Thatcher
- 2013 BYU ORCA Grant, Title: Ceramides and Oxidative Stress. Total costs: $1,000. Awardee: Braden Tucker
- 2012 BYU ORCA Grant, Title: Ceramides and AMPK. Total costs: $1,000. Awardee: Kate Erickson
- 2012 Graduate Research Fellowship, Title: Ceramides and Mitochondrial Function. Total costs: $15,000. Awardee: Melissa Smith

BYU Diabetes Research Lab

- 2018: $120,000 – Including a $110,000 gift to the established endowments.
- 2017: $114,000 – Inculding a $100,000 gift to the established endowments.
- 2016: $156,000 – Including a donation to establish two endowments to fund student research and conference travel.
- 2015: $12,000

Current and Pending Support - Kooyman

D. Research Support

Current Support:

BYU Gerontology Grant. 2019 - $10,000.00

Completed Research Support

NIHRO1 Roles and Mechanisms of Activation of LKB1/MO25/STRAD in Skeletal Muscle in Response to Muscle Contraction. 2006-2011
Yearly direct cost of $209,348.00
Role: Co-PI

University Mentoring Environment Grant, Structural variations in articular cartilage associated with osteoarthritis. 2013.
$20,000.00
Role: PI

University Gerontology Program Grant, Potential Non-Invasive Treatment for Osteoarthritis. 2016
$6000.00
Role: PI

University Mentoring Environment Grant, The Role of Inflammation in the Progression of Osteoarthritis. 2016.
$20,000.00
Role: PI

College of Life Sciences Technology Transfer Grant, Topical/Transdermal application of wogonin as a treatment for osteoarthritis and pain associated with it. 2017.
$20,000.00
Role: PI

Current and Pending Support - Watt
Current Support:
Rockwell Medical. Trace mineral analysis using the iron drug Triferic. $10,800.00. November 2018 – May 2019.

BYU College High Impact Research Proposal – Development of a Lateral Flow Immunoassay for Hepcidin 2017 – present. $20,000.00.

Gift – Hal and Bonnie Chase – Animal study to use protease inhibitors to prevent anemia. 2018
$30,000.00.

Completed Research Support
Department of Defense – Strategic Environmental Research and Development Program (SERDP)
R. Watt Co-PI with Andrew Nelson (PI) – China Lake Naval Weapons Laboratory, Ridgecrest, CA.
Title: Novel Lead Free Ballistic Modifiers for improved, IM-Compliant Minimum Signature Propellants
The Watt lab devised novel synthesis methods to encapsulate explosives inside ferritin. This allowed the development of ferritin as a bio-nano-propellant. Grant period 8/1/2011- 8/1/2014
Role: Co-PI

NASA Watt (PI) 12/1/2011 – 12/1/2012
Development of an Aluminum Ferritin-Peroxide Bio-nano-propellant.
The Watt lab devised novel synthesis methods to encapsulate peroxide inside ferritin. This allowed the development of ferritin as a bio-nano-propellant. Role: Co-PI

Clene Nanomedicine 1/10/ 2016 – 1/9/2018
Analysis of Cuprizone binding to gold nanoparticles. The Watt lab verified that cuprizone does not bind strongly to, or chelate gold ions from gold nanoparticles. Clene Nanomedicine is using gold nanoparticles to treat multiple sclerosis and they use cuprizone to induce demyelination. Our work showed that the drug effect of the gold nanopartcles was not simply inactivating cuprizone. Role: PI.