Before my junior year of high school, I was involved in an automobile accident and suffered severe facial trauma. I underwent several procedures to repair the damage, including maxillofacial reconstruction (Figure 1) and extensive dental surgery. During my recovery, I became fascinated with the sophistication of the materials used in my repairs and became deeply interested in orthopedic and dental biomaterials. This interest, combined with my strengths in physics and mathematics, led me to pursue my undergraduate education in bioengineering with an emphasis in materials science at The Pennsylvania State University.

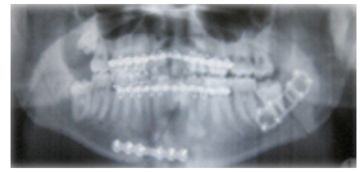

Figure 1.

Through my educational, teaching, leadership and outreach activities, I have since formulated my career aspiration to become a professor at a research institution. My desires to address biomedical challenges creatively, to advance my education, and to share my knowledge are perfectly suited to this profession.

Educational Experiences. In addition to maintaining a high GPA, I have participated in academic activities to prepare myself for graduate study. For example, I joined the Schreyer Honors College my sophomore year to gain experience in writing an honors thesis. Being in the honors college also has afforded me the opportunity to take higher-level courses that incorporate my research interests. For instance, I enrolled in a graduate-level musculoskeletal mechanics course for the spring. I am also a scholar in the Ronald E. McNair Post-Baccalaureate Achievement Program, a federal TRIO program designed to prepare low-income, first generation, and underrepresented students for doctoral study. The program initially appealed to me because it organizes professional development activities for its scholars and financially supports a nine-week summer research internship with a faculty advisor. This program was a unique opportunity to develop my career objectives and gain valuable research experience. In the spring of 2007, I was accepted into the program and joined the laboratory of two faculty advisors whose research aligned with my interest in orthopedic biomaterials: [redacted] from Materials Science and Engineering and Bioengineering and [redacted] from Biochemistry and Molecular Biology. These two professors collaborate on studying breast cancer metastasis to bone.

Teaching Experiences. As a low-income, first-generation college student, I work to support my education and have sought opportunities where I both can be compensated and can reinforce concepts from my coursework. For instance, I have served as a grader for the Math Department in six differential equations courses over two semesters and have volunteered to run chemistry, physics and calculus study groups for the Women in Engineering Program. During this time, I also accepted an internship with the Chemistry Department, which combined research, volunteer and teaching components. Under the advisement of [redacted], I researched the life and scientific achievements of George Washington Carver, focusing on his experiments with peanuts. Extracting information from farming bulletins, Carver's patents and my own laboratory experiments, I developed a laboratory curriculum for students in general chemistry, and implemented the curriculum in the form of a make-up laboratory. The curriculum was later adapted into a calorimetry laboratory for an honors introductory chemistry course. Because I also wanted to be

Teaching Experiences
- Physiology Teaching Assistant
- Engineering Design Lab Assistant
- WEP Facilitator – Chemistry, Calculus, Physics groups
- Chemistry Dept. internship
- Grader, Differential equations
- 400 level Bioengineering course

involved in teaching activities more closely related to my academic pursuits in bioengineering, I accepted a position as a laboratory assistant for an engineering design course, helping students in the development and presentation of design projects.

As my teaching skills strengthened, I wanted to challenge myself to lead a classroom. For that reason, I became a teaching assistant for an introductory physiology laboratory, a role in which I could teach independent from a faculty instructor. I have taught six sections of this course over the past two years. Each semester, I manage approximately 60 students. As the only TA studying bioengineering, I also mentor bioengineering students from other sections. My responsibilities for the course include preparing and instructing pre-laboratory lectures, developing weekly quiz questions, demonstrating laboratory techniques, leading post-laboratory discussions, and formulating instructions for written reports. I have received Institutional Animal Care and Use Committee (IACUC) training for the use of animals in the laboratory. With the help of another TA, I developed an academic writing tutorial as a supplement for the course. I will further challenge myself in the spring as an assistant for a 400-level bioengineering course by teaching more difficult material.

Leadership Activities. In addition to assuming leadership roles in the previously mentioned activities, I currently serve as treasurer for the Penn State chapter of the Biomedical Engineering Society. I help coordinate volunteer activities and professional development workshops for our members, including an American Red Cross blood drive, an H1N1 vaccination clinic, and a graduate school portfolio workshop. Our chapter has also established "Lunch and Learn" activities, which give bioengineering students an opportunity to learn about the research and career paths of department and adjunct faculty members. Additionally, I am presently working with other bioengineering students and faculty to establish a chapter of AEMB, the National Biomedical Engineering Honor Society.

BMES
Penn State University

Outreach. I have also participated in numerous educational outreach activities. Currently, I work with a program called Engineering Ambassadors to encourage high school students, particularly women, to pursue an education in science or engineering. In this program, I travel to biology, chemistry, and physics courses at high schools across Pennsylvania and give presentations about research emerging at the intersection of science and engineering. I was one of two students to pilot this program over the past summer and present the results of the pilot to administrators in the College of Engineering. Positive feedback from our presentation has allowed the program to expand to include 15 female presenters, with plans for visits to schools across the state throughout the year.

While I was taking a physiological systems bioengineering course, I observed that a considerable amount of time was spent reviewing basic physiology because it was being presented from the engineering perspective. This academic year, I am re-designing pre-laboratory PowerPoint presentations used in the physiology course that I teach in order to approach the basic physiology from this engineering perspective. These modified materials may be incorporated into a bioengineering-section of the course in the future. I have also contributed to an engineering communications course by recording a class presentation as an educational web resource for students in a wide variety of engineering disciplines. Additionally, the slides I developed for the class are now used by course instructors as strong examples.

As I near the end of my undergraduate career, I look forward to working toward a Ph.D. and a career as an academic. The NSF fellowship would provide me with the resources to achieve this goal.

In the spring of 2008, I began undergraduate research in the laboratories of [redacted] and [redacted], who collaboratively study breast cancer metastasis to bone using an engineered three-dimensional bone tissue developed in a compartmentalized bioreactor. This research offered me the opportunity to learn fundamentals of osteobiology and osteopathology that would translate to studies of orthopedic biomaterials later in my career. I was fascinated by the simplicity of the bioreactor design, the sophistication of the tissue it supported and the potential for this *in vitro* model to enhance the investigation of metastatic bone disease. I have since dedicated myself to this research by working full-time throughout the summers of 2008 and 2009 as well as throughout the past two academic years to complete my honors thesis.

Background. The American Cancer Society estimates that one in eight women will be diagnosed with breast cancer in the course of their lifetime. Breast cancer is the second most commonly diagnosed cancer in women in the United States, accounting for nearly 27% of all female cancers in 2009.[1] Breast cancer frequently metastasizes to bone (Figure 1), with bone metastases occurring in approximately 70% of patients with advanced breast cancer.[2] Breast cancer disrupts normal bone remodeling by suppressing the function of osteoblasts (bone-forming cells) and increasing the activity of osteoclasts (bone-resorbing cells), resulting in increased bone degradation coupled with the release of factors from the bone matrix that support tumor growth. Current therapies target this "vicious cycle" between tumor cells and the skeleton.[3] Bisphosphonates are a family of drugs that bind avidly to mineralized bone where they are internalized by osteoclasts and signal osteoclast destruction, resulting in reduced bone degradation. They are often administered alongside chemotherapy drugs (taxanes).[4] The interaction of bisphosphonates with osteoclasts is well understood, but little is known about effects of bisphosphonates on osteoblasts.

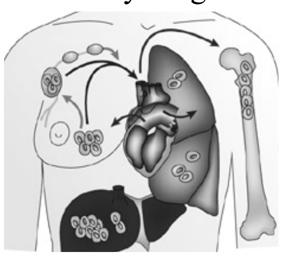

Figure 1.

Undergraduate Thesis Research. My research involves the study of these drugs with considerations for their effects on osteoblasts. The purpose of this study is to characterize the effect of a bisphosphonate (zoledronic acid) and a taxane (docetaxel), alone and in combination, on osteoblasts in conventional tissue culture and osteoblasts challenged with metastatic breast cancer cells in the compartmentalized bioreactor. I hypothesize a combination therapy will show synergistic antitumor effects but have little effect on the integrity of osteoblast tissue.

In the summer of 2008, I gained valuable skills in cell culture and maintenance by assessing the effects of these drugs on osteoblast proliferation and differentiation in conventional tissue culture. During this time, I was supported by the Ronald E. McNair Summer Undergraduate Research Program and fulfilled all program requirements, which included documenting a minimum 40 hours of research each week, writing a research paper for the Penn State McNair journal, and presenting the research at the annual McNair summer conference. Throughout the 2008-2009 academic year, I became skilled in developing osteoblastic tissue in the bioreactor, challenging that tissue with breast cancer cells, and monitoring cancer progression with confocal microscopy (Figure 2A). I participated in the McNair program again the following summer and was additionally supported by the Undergraduate Summer Discovery Grant awarded through the university. I enhanced my previous data by optimizing cell viability assays and expanded my

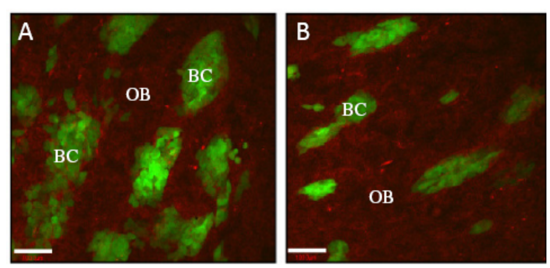

Figure 2.

experiments to the bioreactor, evaluating the effects of zoledronic acid on this model of breast cancer in bone. I discovered a single dose of zoledronic acid at 0.50 μM administered three days after co-culture reduced the formation of breast cancer colonies and disrupted cancer cell alignment with osteoblast tissue (Figure 2B). This finding suggests that, in addition to effects on osteoclasts, zoledronic acid may have a direct antitumor affect on breast cancer cells. These findings will be published in the next McNair journal and were presented at the McNair summer conference in 2009. My abstract was also accepted for poster presentations at two professional conferences, one in the field of engineering and the other in bone metastasis research. The opportunity to engage in conversations with engineers, biologists, and oncologists and receive their feedback was a rewarding experience that taught me the value of being an active member of the scientific community.

This academic year, I will complete my thesis research by evaluating the combination bisphosphonate and taxane therapy in the bioreactor model. I am currently supported by the Pennsylvania Space Grant Consortium Sylvia Stein Memorial Scholarship and Federal Work Study. In addition to detailing my research project, a portion of my thesis will be devoted to evaluating the potential for the bioreactor to serve as a system for testing therapeutics. I have also begun a small research project in collaboration with [redacted], a bioengineering professor, to investigate the effects of surface topography on osteoblast development in the bioreactor. We predict that microfabricated surface topographies will accelerate or enhance maturation of osteoblastic tissue in the bioreactor.

While I work alongside my advisors, a graduate student, and a laboratory technician to develop my research skills, my application of these skills is original and my research is independent. Perhaps the most important thing I learned throughout this experience is that approaching a research problem from only one perspective is inefficient. I truly value my capacity to work within a highly interdisciplinary team and my ability to leverage skill sets from different fields to achieve a more holistic understanding of my research problem. Additionally, the experience of working with the bioreactor has taught me that successful strategies in research do not necessarily have to be complex – success can sometimes be achieved through simplicity.

Publications and Presentations

[redacted]

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[1]American Cancer Society, *American Cancer Society, Inc.* 2009, 1-72.
[2]Coleman RE, *Cancer* 1997, 80(S8): 1588-94.
[3]Steeg P; Theodorescu D, *Nature Clinical Practice Oncology* 2008, 5(4): 206-19.
[4]Green J, *The Oncologist* 2004,9(suppl 4):3-13.

Engineered Bone Tissue for the Study of Mechanotransduction in Osteocytes

Numerous studies have shown that micro-gravity conditions induce bone loss during long-term inhabitation of space; decreased mechanical stimulation of bone results in uncoupled bone remodeling favoring bone resorption.[1] Efforts to prevent or treat micro-gravity induced bone loss typically involve resistive exercise to impart mechanical loads on the skeleton. While some studies indicate that exercise may reduce the uncoupling of bone remodeling, exercise has yet to effectively reduce bone loss.[1] Thus, an understanding of the mechanisms by which external loads are sensed by bone cells and translated to cellular signals may elucidate targets for pharmaceutical interventions.

Proposed Research. The objective this study is to investigate osteocyte mechanobiology using principles of tissue engineering and to ascertain mechanisms by which osteocytes respond to mechanical loading. I propose to study the effects of small-magnitude, high-frequency fluid shear stresses on the maturation of osteocytes cultured in a compartmentalized bioreactor.

Background. Osteocytes are stellate cells abundant in cortical bone that develop from osteoblasts that become entrapped in secreted extracellular matrix (Figure 1). Osteocytes occupy lacunar spaces within bone matrix and are thought to influence their surroundings via cytoplasmic intercellular processes that extend through microscopic canals in the bone called canaliculi.[2] It is widely accepted that osteocytes are responsible for sensing mechanical signals (mechanosensation), but the mechanisms by which those mechanical signals are translated to the cells (mechanotransduction) are still unclear.[2]

Figure 1.

Osteocytes are difficult to study *in situ* because they are embedded in mineralized matrix and relatively inaccessible. Similarly, demineralization of bone matrix for *in vitro* studies fails to reproduce tissue with an appropriate three-dimensional architecture and a complex lacunocanalicular network.[2] Principles of tissue engineering may lend improvements to developing biologically relevant bone models for mechanobiology studies.[3] My undergraduate thesis research involved engineering osteoblastic tissue in a compartmentalized bioreactor (Figure 2) and challenging that tissue with breast cancer cells.[4] Through this experience, I gained an appreciation for the ability of engineered tissues to serve as *in vitro* models of osteopathologies and developed an interest in applying these models for studying osteobiology. Krishnan et al. recently reported that pre-osteoblasts proliferate in the bioreactor to form a three-dimensional mineralizing osteoblastic tissue that progressively develops an osteocytic phenotype.[5] Cobblestone-shaped osteoblasts mature into stellate cells embedded in a dense matrix with numerous intercellular processes.[5] Therefore, the bioreactor provides access to the continuum of osteocyte development *in vitro*, including the aforementioned lacunocanalicular network.

Figure 2.

Previous studies have indicated that external forces are transduced to osteocytes by means of “fluid shifts” within the lacunocanalicular network.[2] This theory (the poroelastic model) accounts for the effects of low-amplitude, high-frequency forces associated with the majority of daily human activities, such as sitting, standing and changing posture, as well as effects of high-strain activities such as exercise.[2,6] While the effects of shear stresses have been evaluated *in vivo* and on osteocyte-like cell lines such as MLO-Y4, effects of fluid shear on the progressive maturation of osteocytes have yet to be investigated.[2]

Materials and Methods. Compartmentalized bioreactors based on the principle of simultaneous growth and dialysis[7] will be assembled to develop engineered bone tissue that can be mechanically manipulated. Murine calvarial osteoblasts (MC3T3-E1) can be cultured in the bioreactor for up to 10 months to progressively develop an osteocyte-like phenotype.[5] Cells can be microscopically monitored throughout the culture interval using confocal microscopy.

The bioreactor can be inserted into a mechanical device (Figure 3) that produces small-magnitude deformations in the membrane encasing the device. This external force will generate a pressure gradient within the cell-culture medium, and incorporation of a flow-loop for each compartment will allow the fluid to shift within the lacunocanalicular network. This system, once fully developed, can be used to investigate proposed mechanotransduction pathways and biochemical markers, such as ATP, prostaglandin E_2 and nitric oxide.[8] I am particularly interested in quantifying the expression of the protein sclerostin, an osteocyte-specific product of the SOST gene that inhibits bone formation.[8] Murine models have shown decreased sclerostin expression following loading, suggesting another potential mechanism for mechanotransduction in osteocytes.[9]

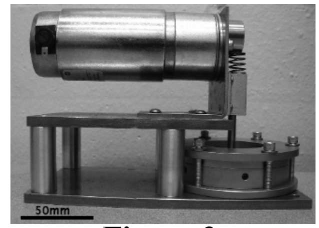

Figure 3.

Agenda. In the first year of my fellowship tenure, I will design and construct the bioreactor and characterize the development of osteocytes in the culture system. Throughout the second year, I will determine a protocol for mechanically loading the bone tissue and investigate proposed mechanotransduction pathways. I will focus on developing quantitative methods of measuring signaling pathways in the bioreactor system. The final year will be devoted to analyzing effects of mechanical stimulation on osteocyte biomarkers and inducing mechanisms of osteocyte mechanotransduction in bone.

Broader Impact. The aim of this project is to gain an understanding of the complex mechanisms underlying mechanotransduction in bone. Discovering these mechanisms could contribute to the development of therapies to treat micro-gravity induced bone loss experienced by astronauts during space travel. This research also has implications for the treatment of other bone diseases, such as osteoporosis and Paget's disease. The collaborative nature of the [redacted] will allow for numerous perspectives to contribute to this work and my doctoral studies. Furthermore, participation in the [redacted] would guide my research and enhance my understanding of space medicine.

I have actively participated in educational outreach activities during my undergraduate studies and will continue to do so throughout my graduate career by mentoring underrepresented students as a McNair alumna and encouraging high school students to pursue careers in science and engineering. As I continue to pursue my aspiration of becoming a professor, I look forward to probing new research questions and sharing my knowledge and experiences with students from a variety of disciplines and backgrounds.

[1] LeBlanc A.D. et al., *J Musculoskelet Neuronal Interact* 2007, 7(1): 33-37.
[2] Allori A.C. et al., *Tissue Engineering: Part B* 2008, 14(3): 285-293.
[3] Freed L.E. et al., *Tissue Engineering* 2006, 12(12): 3285-3305.
[4] Dhurjati R. et al., *Tissue Engineering* 2006, 12(11): 3045-3054.
[5] Krishnan V. et al., *In Vitro Cell.Dev.Biol – Animal* 2009, Accepted 3 Sept. 2009.
[6] Hwang S.J. et al., *Clin Orthop Relat Res* 2009, 467: 1083-1091.
[7] Rose G.G., *Int. Rev. Exp. Pathol.* 1966, 5: 111-178.
[8] Riddle R.C.; Donahue H.J., *Journal of Orthopaedic Research* February 2009, 143-149.
[9] Robling A.G. et al., *The Journal of Biological Chemistry* 2008, 283(9): 5866-5875.

Rating Sheet 1:

Overall Assessment of Intellectual Merit: Very Good
Explanation to the applicant:

Student's proposed plan of research was well organized and well presented. She documented several awards and scholarships as well as a few publications and presentations Noteworthy that she researched accomplishments of Geo. Washington carver and then developed lab curriculum for students in general chemistry. Also noted that she mentored students in bioeng. and became TA for physiology lab excellent letters of recommendation

Overall Assessment of Broader Impacts: Very Good
Explanation to the applicant:

active in Biomed Engin. Society as treasurer and helped coordinate volunteer outreach activities Sought to motivate more young women to go into engineering and other STEM fields by creating 20-minute presentation served as Engineering Ambassador and presented data from pilot program to administrators which brought about funding for the group. Applicant demonstrated leadership through this initiative and spearheaded visits to her former high school

Rating Sheet 2:

Overall Assessment of Intellectual Merit: Excellent
Explanation to the applicant:

excellent academic performance excellent leadership and outreach activities Honors college student Chemsitry intern-includes research, volunteer and teaching components a number of publications and presentations - both oral and poster excellent research experiences innovative course/curriculum slides, example approach basic physiology from engineering perspective and other similar ones good communication skills, very good write-up with suitable figures for previous and proposed research studies Excellent choice of institution excellent references

Overall Assessment of Broader Impacts: Very Good
Explanation to the applicant:

excellent prior accomplishments excellent community outreach-volunteer for Red cross blood drive, H1N1 vaccination clinic, engineering ambassador-to encourge high school students especially girls, to pursue carrers in science/engineering very good future plan excellent individual experience very good inegration research and education very good leadership experiences and skills and got the potential to be a future leader, considering first generation, low-income college student involved in Women In Eng society activiites Designed an innovative lab course which was used for honors degree

Rating Sheet 3:

Overall Assessment of Intellectual Merit: Excellent
Explanation to the applicant:

The student is strong academically, with an extremely strong supportive package. She has maintained an excellent standard of work while simultaneous working at many jobs. She does not merely fulfill the obligations of her jobs, but goes above all expectations to develop new processes, teaching materials, etc. The applicant has substantial research experience leading to a poster presentation. The work is with tissue engineering, but not in order to produce replacement tissues. Instead, the engineered tissue is used to study the role of osteoblasts, osteocytes, and pharmaceuticals in diminishing the potential of breast cancer cells to metastasize. Her previous experience will translate directly to her proposed research project. Again, she will use tissue culture as a means of studying bone formation and loss. In this case, she will look at the mechanisms of bone loss and the interaction of exercise with bone loss. The proposal mentions that the mechanisms of cell signaling will be investigated. I would have liked to see those outlined more clearly, and I highly recommend that the student have a clear protocol before beginning the task of building the bioreactor.

Overall Assessment of Broader Impacts: Excellent
Explanation to the applicant:

As previously mentioned, the student has held several jobs where she has not only completed her duties, but has worked to improves processes, teaching materials, etc. I have the opinion that she has done this not to further her own ambitions, but out of extreme conscienciousness. In addition to many hours of work, a rigorous academic schedule, and participation in research, the student has also contributed as a leader in the BMES club and is helping to charter an AEMB Honor Society. She has shown her capability to disseminate scientific results through preparation of a manuscript, presentation of a poster, and being a "poster child" of oral presentation skills. I believe that she has the ability to make a meaningful impact in the field of biomedical engineering.