“The RNA Binding Protein HuR Regulates Metabolic Flexibility in Skeletal Muscle”

Seminar: November 28, 2022 | 1:00 PM – 2:00 PM | 318 Wolf
Zoom Link: https://udel.zoom.us/j/93807270112

Chalk Talk: November 28, 2022 | 3:00 PM – 4:00 PM | 243 Wolf
Zoom Link: https://udel.zoom.us/j/98287995120

Teaching Round Table: November 28, 2022 | 4:15 PM – 5:00 PM | 119 Wolf

Dr. Warfel is currently a Research Assistant Professor in the Basic Sciences Division at Pennington Biomedical Research Center (PBRC) in Baton Rouge, LA; where his research is broadly focused on determining the molecular mechanisms governing metabolic fuel selection in skeletal muscle, and how inherent defects in this selection might influence the development of insulin resistance.

Abstract: Metabolic flexibility allows for the adaptation of fuel oxidation to fuel availability. This biological phenomenon has been described in skeletal muscle in the physiological literature for roughly 3 decades. However, the molecular mechanisms governing the ability of muscle cells to switch between fuels such as lipids and carbohydrates has yet to be elucidated. My work has identified that the RNA binding protein, HuR, controls metabolic flexibility in skeletal muscle. We have determined that HuR promotes fatty acid oxidation more heavily in males than in females, Our major goals are to investigate the molecular components controlled by HuR that promote fatty acid oxidation, and to understand why this control is more important in male than in female skeletal muscle.

Jaycob Warfel, Ph.D.
Assistant Professor
Basic Sciences Division, Pennington Biomedical Research Center
jaycob.warfel@pbrc.edu
Host: Christopher Trimby (trimby@udel.edu)
PageUp People Applicant Bulk Compile

Date created: 5 Oct 2022, 12:37 pm - Eastern Standard Time

The following document types are provided for each applicant (where available):
- Confidential Letters of Recommendation
- Cover letter
- Other - Applicant
- Resume
- Supporting Applicant documents
- Transcript of results

The following applicants are included in this document:
- Jaycob Warfel

Job Details:
- Requisition Number: 499144
- Posting title: Tenure Track Assistant Professor, Department of Biological Sciences
- College / VP Area: College of Arts & Sciences
- Department: Biological Sciences (02590)

Number of Applicants: 1
September 14, 2022

Dr. Jessica Tanis
Assistant Professor and Faculty Search Committee Chair
Department of Biological Sciences, University of Delaware

Dear Dr. Tanis and Members of the Search Committee,

I am submitting this application for the open Tenure-Track Assistant Professor in Musculoskeletal Biology position in the University of Delaware Department of Biological Sciences. I am an NIH K01 (DK116914) funded Research Assistant Professor in the Basic Sciences Division at Pennington Biomedical Research Center (PBRC) in Baton Rouge, LA; where my research is broadly focused on determining the molecular mechanisms governing metabolic fuel selection in skeletal muscle, and how inherent defects in this selection might influence the development of insulin resistance. I am highly interested in this position for several reasons. 1) My research agenda complements and expands upon your department’s current strengths in metabolism and cellular physiology. 2) The scientific environment is outstanding, hosting NIH funded principle investigators with whom I am highly motivated to collaborate. 3) The very appealing facilities at the University of Delaware such as the Proteomics and Mass Spectrometry Core and Center for Bioinformatics and Computational Biology Core show that I will have the ability to thrive in your department.

My PhD training is in biochemistry through the LSU department of Biological Sciences; and my current research employs transgenic murine and cell culture models to discern the molecular drivers of metabolic flexibility in skeletal muscle. The phenomenon known as metabolic flexibility is concisely defined as an ability to switch between metabolic substrates based on their availability. My laboratory has shown that the RNA binding protein, HuR, which is a master regulator of a variety of cellular processes, controls metabolic flexibility in skeletal muscle through its promotion of lipid metabolism. My group has recently shown that this promotion is specific to male animals, and I am currently revising an R03 application aimed at investigating the role of estrogen cycling in this sex-based difference (DK133616). I developed this project as a T32 postdoctoral fellow (DK6458413) guided by the late Dr. Randy L. Mynatt, and have published 2 senior author manuscripts relating to my K01 funding (See attached). My productivity is evidenced by my total of 9 publications since 2015 (4 as first author), with 2 additional first-author manuscripts under review/revision.

I am highly motivated by the research and teaching activities listed within the job description, and am confident that my qualifications make me a strong candidate for the position. Firstly, my research program is actively externally funded, and focusses on the molecular mechanisms governing fuel selection in skeletal muscle. As a K01 awardee, I also have strong potential of securing future NIH funding through R03 and R01 mechanisms. Secondly, I have been active as a muscular physiologist since August 2014, giving me 8 years of postdoctoral experience within the field. Thirdly, I have over 10 years of total teaching experience, and have developed lecture and laboratory courses in undergraduate biology and biochemistry, and have team taught a graduate course here at PBRC. I have also mentored several undergraduates, graduate students, and postdocs. I am therefore qualified and highly motivated to mentor a diverse group of trainees within my laboratory; and to develop courses in undergraduate and graduate level biology.

As an investigator within a COBRE institution, I am also very familiar with the impact that such a program has on young investigators such as myself. I am therefore very enthusiastic about the potential of joining the COBRE in the University of Delaware Department of Biological Sciences. Thank you for reviewing my application and credentials. I feel that I would make a valuable addition to your department, and I look forward to discussing my qualifications and potential contributions with your committee members at length.

Sincerely,

Jaycob D. Warfel, Ph.D.
CURRICULUM VITAE

Name: Jaycob Dalton Warfel, Ph.D.

Address: Pennington Biomedical Research Center
6400 Perkins Road
Baton Rouge, LA 70808
Office #: (225) 763-2865
Email: jaycob.warfel@pbrc.edu

Education

<table>
<thead>
<tr>
<th>Years Active</th>
<th>Institution and Location</th>
<th>Degree</th>
<th>Field of Study</th>
</tr>
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<tbody>
<tr>
<td>2008-2014</td>
<td>Louisiana State University Baton Rouge, LA</td>
<td>Doctor of Philosophy</td>
<td>Biochemistry</td>
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<tr>
<td>2004-2006</td>
<td>Louisiana State University Baton Rouge, LA</td>
<td>Bachelor of Science</td>
<td>Biochemistry</td>
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<tr>
<td>2002-2004</td>
<td>Parkland College Champaign, IL</td>
<td>Associate of Science</td>
<td>General Science</td>
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Postdoctoral Training

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<th>Years Active</th>
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<th>Fellowship Title</th>
<th>Specific Project</th>
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<tr>
<td>2015-2017</td>
<td>Pennington Biomedical Research Center Baton Rouge, LA</td>
<td>NIH T32 Postdoctoral Fellowship</td>
<td>Identifying molecular modulators of metabolic flexibility in skeletal muscle</td>
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</table>

Professional Employment

<table>
<thead>
<tr>
<th>Years Active</th>
<th>Institution and Location</th>
<th>Position Title and Description</th>
<th>Supervisor/Advisor</th>
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<tbody>
<tr>
<td>2018-Present</td>
<td>Pennington Biomedical Research Center Baton Rouge, LA</td>
<td>Research Assistant Professor: Investigate the way in which proper control of cellular RNA levels by the RNA binding protein, HuR, promotes metabolic flexibility.</td>
<td>Chris Morrison, Ph.D. Associate Executive Director for Basic <a href="mailto:chris.morrison@pbrc.edu">chris.morrison@pbrc.edu</a> (225) 763-3145</td>
</tr>
<tr>
<td>2014-2019</td>
<td>River Parishes Community College Gonzales, LA</td>
<td>Adjunct/Supplemental Instructor: Serve as an adjunct instructor of biology for science majors and a supplemental instructor for math and science students in the TRIO SSS program.</td>
<td>Iris Henry, DPM Biology Division Coordinator <a href="mailto:ihenry@rpcc.edu">ihenry@rpcc.edu</a> (225) 743-8516 G. Chris Magola TRIO SSS Director <a href="mailto:gmagola@rpcc.edu">gmagola@rpcc.edu</a> (225) 743-8515</td>
</tr>
<tr>
<td>2014 – 2018</td>
<td>Pennington Biomedical Research Center Baton Rouge, LA</td>
<td>Postdoctoral Fellow: Perform research to identify molecular modulators of metabolic flexibility in skeletal muscle.</td>
<td>Randy Mynatt, Ph.D. Professor (Deceased)</td>
</tr>
</tbody>
</table>


Under Review:


### Oral and Poster Presentations

1. Warfel, J.D. (Poster Presentation) Lack of HuR in mouse skeletal muscle promotes obesity but heightens insulin resistance in males only. (February, 2021) Keystone Symposia on Molecular and Cellular Biology, Obesity: From Cell to Patient, (Virtual)


4. Warfel, J.D., and LiCata, V. J. (Oral Presentation) Thermodynamics of Short DNA binding by Deinococcus radiodurans and *Escherichia coli* RecA homologues. (September, 2014) Annual Gibbs Conference on Biophysics, Makanda, IL

5. Warfel, J.D., and LiCata, V. J. (Oral Presentation) Thermodynamics of Short DNA binding by Deinococcus radiodurans and *Escherichia coli* RecA homologues. (June, 2014) Mississippi Biophysical Consortium, Jackson, MS


### Funding Support

**Extramural**

**In Revision:**

1 R03 DK133616-01 Warfel, Jaycob (PI) 07/01/23 – 06/30/25 $75,000/Year Direct Cost

“Activated ERα as Compensation for HuR Controlled Lipid Oxidation in Skeletal Muscle”

Metabolic flexibility is the capacity for an organism to adapt fuel oxidation to fuel availability. Male mice lacking the RNA binding protein HuR in skeletal muscle are less metabolically flexible than controls, with a decreased ability to oxidize lipids in skeletal muscle. Female animals lacking HuR in skeletal muscle do not have decreased lipid oxidation relative to controls. This proposal tests the overarching hypothesis that activated ERα can promote lipid oxidation through the transcription factor PPARα, allowing females to bypass HuR-controlled lipid oxidation due to higher levels of circulating 17β-estradiol.
Ongoing:

1 K01 DK116914-01A1, NIDDK 07/01/19 – 06/30/23
Warfel, Jaycob (PI) $104,575/Year Direct Cost

“HuR as a Regulator of Skeletal Muscle Metabolism”
Metabolic flexibility is the ability to switch between fuels based on their availability and is commonly impaired in individuals with type 2 diabetes and obesity. We have shown that systems with decreased HuR action have lower metabolic flexibility. This grant is a mentored training grant which seeks to train me in mouse phenotyping, bioinformatics, and molecular characterization by attempting to understand the mechanisms through which HuR acts to control metabolic flexibility in skeletal muscle.

Intramural

Completed:

1P30GM118430-01, PBRC NIH COBRE P&F 01/01/20 – 07/01/21
Warfel, Jaycob (PI) $34,000 Direct Cost

“Overcoming Metabolic Inflexibility in and HuR Depleted State”
This pilot and feasibility project tested the hypothesis that subjecting mice lacking the RNA binding protein HuR specifically in skeletal muscle to an exercise regime would allow them to overcome the metabolic inflexibility that we have previously shown that they display. Additionally, this project subjected metabolically inflexible human cells to overexpression of HuR in order to determine if this would allow them to achieve greater metabolic flexibility.

P30DK072476, PBRC NIH NORC P&F 01/01/18 – 01/01/19
Warfel, Jaycob (PI) $37,500 Direct Cost

“Transcriptome Changes in Skeletal Muscle During HuR Inhibition”
This grant was aimed at conducting transcriptomics and substrate metabolism assays on mice that are deficient in production of the RNA binding protein HuR specifically in skeletal muscle. Additionally, this project will assess these changes during HuR inhibition in murine and human skeletal muscle cell cultures.

T32DK-6458413, NIDDK PBRC T32 Postdoctoral Fellow 01/15/15 – 01/14/18
Brantley, Phillip (PI) $72,600/Year Direct Cost

“Obesity: From Genes to Man”
This grant focused on training postdoctoral fellows to establish independent scientific careers in investigating various aspects in the development of obesity from both clinical and basic science standpoints.
### Teaching Experience

<table>
<thead>
<tr>
<th>Years Active</th>
<th>Course and Institution</th>
<th>Role</th>
<th>Class Size</th>
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<tbody>
<tr>
<td>2021</td>
<td>NFS 7006 Obesity: Biology, Brain and Behavior</td>
<td>Guest Lecturer</td>
<td>15 Students</td>
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<td>Pennington Biomedical Research Center</td>
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<td>2017-2019</td>
<td>BIOL 1201 Principles of Biology I</td>
<td>Primary Instructor</td>
<td>15-25 Students</td>
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<td></td>
<td>River Parishes Community College</td>
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<tr>
<td>2014-2018</td>
<td>TRIO Student Support Services</td>
<td>Supplemental Instructor</td>
<td>1-3 Students</td>
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<td></td>
<td>River Parishes Community College</td>
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<tr>
<td>2014</td>
<td>HNRS 1007 Introduction to Life Sciences for Non-Majors Louisiana State University</td>
<td>Lab Instructor</td>
<td>10 Students</td>
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<tr>
<td>2011-2014</td>
<td>BIOL 4385 Biochemistry Laboratory</td>
<td>Primary Instructor</td>
<td>10-15 Students</td>
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<td></td>
<td>Louisiana State University</td>
<td></td>
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<tr>
<td>2010-2013</td>
<td>Biology Intensive Orientation for Students</td>
<td>Graduate Mentor</td>
<td>20-30 Students</td>
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<td>Louisiana State University</td>
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<tr>
<td>2008-2014</td>
<td>BIOL 1208 Biology Laboratory for Science Majors</td>
<td>Primary Instructor</td>
<td>20-30 Students</td>
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### Mentoring Experience

| Years Active | Mentee Name                   | Mentee Position and Institution | Institution | |
|--------------|-------------------------------|---------------------------------|-------------|
| 2018-Present | Elizabeth Labarre, BS         | Research Associate              | Pennington Biomedical Research Center | |
|              | Paola Olivares-Nazar          | Undergraduate Research Assistant| Pennington Biomedical Research Center | |
| 2020-2021    | Samuel Velazquez, BS          | Research Associate              | Pennington Biomedical Research Center | |
| 2018-2021    | David Bayless, PhD            | Postdoctoral Fellow             | Pennington Biomedical Research Center | |
| 2018-2021    | Allison Stone, MS             | Graduate Assistant              | Pennington Biomedical Research Center | |
| 2018         | Olga Dubuisson, PhD           | Research Associate              | Pennington Biomedical Research Center | |
| 2016-2017    | Sydney Hodgeson, MD           | Undergraduate Research Assistant| Pennington Biomedical Research Center | |
| 2012-2014    | Katelyn Jackson, BS           | Undergraduate Research Assistant| Louisiana State University | |

### Honors and Awards

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<thead>
<tr>
<th>Year Awarded</th>
<th>Title</th>
<th>Description</th>
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<tbody>
<tr>
<td>2016</td>
<td>Louisiana Research Summit Pennington Biomedical Research Center Postdoctoral Representative</td>
<td>Meeting with NIH Director Dr. Francis Collins</td>
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<td>2015</td>
<td>Simon Chang/Ezzat Younathan Outstanding Biochemistry Teacher</td>
<td>Teaching Assistant Award</td>
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<td>2008</td>
<td>Economic Development Assistantship</td>
<td>Graduate Assistantship</td>
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<td>2002</td>
<td>Parkland Board of Trustees full tuition scholarship</td>
<td>Undergraduate Scholarship</td>
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<tr>
<td>2002</td>
<td>Tolono Lions Club annual scholarship</td>
<td>Undergraduate Scholarship</td>
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### Extramural Service

<table>
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<tr>
<th>Journals Reviewed For</th>
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<tbody>
<tr>
<td>Animals</td>
<td>MDPI</td>
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<td>Antioxidants</td>
<td>MDPI</td>
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<tr>
<td>Applied Sciences</td>
<td>MDPI</td>
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<tr>
<td>Biochimica et Biophysica Acta – Molecular Basis of Disease</td>
<td>Elsevier</td>
</tr>
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<td>Biomedicines</td>
<td>MDPI</td>
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<tr>
<td>Genes and Nutrition</td>
<td>Biomed Central Ltd.</td>
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<td>Geriatrics</td>
<td>MDPI</td>
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<tr>
<td>International Journal of Molecular Sciences</td>
<td>MDPI</td>
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<td>Journal of Advanced Research</td>
<td>Elsevier</td>
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<td>Mayo Clinic Proceedings</td>
<td>Elsevier</td>
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<tr>
<td>Nutrients</td>
<td>MDPI</td>
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<td>Obesity</td>
<td>Wiley</td>
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### Intramural Service

<table>
<thead>
<tr>
<th>Years Active</th>
<th>Committee and Institution</th>
<th>Position</th>
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<tbody>
<tr>
<td>2021-Present</td>
<td>Institutional Animal Care and Use Committee Pennington Biomedical</td>
<td>Committee Member</td>
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<tr>
<td></td>
<td>Research Center</td>
<td></td>
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<tr>
<td>2012-2013</td>
<td>Biograds Graduate Student Committee Louisiana State University</td>
<td>Secretary</td>
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### Professional Memberships

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<tr>
<th>Years Active</th>
<th>Association</th>
<th>Position</th>
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<tr>
<td>2015-Present</td>
<td>American Association for the Advancement of Science</td>
<td>Member</td>
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<tr>
<td>2015-Present</td>
<td>American Diabetes Association</td>
<td>Member</td>
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</table>

### Research Skill Set

- Animal Husbandry
- Plasmid and DNA Transfections
- Bacterial Cell Cultures
- Primary Myocyte Isolation
- Bioinformatics Analyses
- Protein Biochemistry Assays
- Colorimetric Spectrophotometric Assays
- Protein Isolation
- ELISA Assays
- Quantitative PCR
- High Resolution Respirometry
- Radioactive Isotope Metabolism Assays
- Mammalian Cell Culture
- Radioactive Tracer Animal Injections
- Mouse Genotyping
- Rat Dissection
- Mouse Dissection
- Rodent Indirect Calorimetry
- Nucleic Acid Isolation
- UV Absorption Spectrophotometric Assays
- O₂/CO₂ Breath Gas Analysis
- Western Blotting
Delivering effective scientific training within the biological sciences has presented a welcome challenge to me. Because the study of physiology and cell biology involves detecting phenomena at the molecular level, this material is often quite conceptual, and can therefore be both troublesome to convey, and difficult for scientists to retain and responsibly report to the public. The comprehensive understanding of biology necessary for scientists in training relies upon a working knowledge of current perspectives, applicable instrumentation, and methods of data interpretation. It is for this reason that I work with my trainees throughout the course of their development in order to: 1) enhance their comprehension of the subject matter; 2) encourage their presentation of novel ideas; 3) ensure research integrity; and 4) promote personal and professional development through appropriate work/life balance.

As a mentor I adopt a very in depth approach in order to deliver information regarding the theoretical knowledge behind the experimentation, especially with students new to science. These students may have limited knowledge concerning the purpose of each component within an experimental design, and walking them through the experiments step-by-step allows them to gain practical knowledge which enhances their comprehension of the concepts in an impactful and lasting way. This helps them to learn more efficiently than when only engaged in lecture courses, enhancing their understanding, which thereby enhances their ability to succeed. Consistent engagement with trainees in my lab through this type of interaction has aided in the development of my mentees, and in my development as a principle investigator.

In addition to ensuring that my trainees gain a deep level of insight through this hands on training, I also understand the importance of allowing mentees to contribute their own ideas. The feedback of my trainees often guides the progress within the lab, and strengthens the development of each trainee. I have mentored undergraduates, graduate students, and postdoctoral fellows by encouraging them to present their research at meetings and to colleagues, which familiarizes them with obtaining critique and feedback in order to improve their projects prior to publication. Being able to help these individuals complete projects and secure publications has been one of the most rewarding experiences of my career.

The duties associated with responsible scientific investigation must also be faced with integrity, given the often immense pressure to maintain a certain level of performance. Direct involvement of my trainees with scientific research opens to them a realistic expectation of the incremental nature of scientific discovery and hypothesis testing. As my students develop this new perspective of the forefront of biological research, they can understand the importance of carefully and thoughtfully designing experiments and presenting results in an open and truthful manner.

Finally, as a mentor I remember that each of my mentees has a diverse set of life circumstances that are important to consider as part of personal and professional development. I therefore strive to mentor students not only in science, but also in work/life balance. It is critical for me to be understanding of the variety of challenges that young trainees must face outside of the lab, and being understanding of life circumstances allows me to create a work environment where my employees feel safe and secure. This level of understanding also aids in promoting diversity, which is of utmost importance to me as a scientist. The novel ideas generated in my lab often come from a variety of different individuals with varying perspectives and life circumstances.

Mentoring is an extremely important part of my function as a scientist in order to ensure the next generation of trainees is taught how to confront scientific exploration with integrity and curiosity. Being able to see my mentees develop personally and professionally makes the value of responsible mentoring clear; and progress within my research agenda would be minimal without continuous involvement of trainees presenting new ideas and working with intention to complete projects. I will thus continue to interact with each of my mentees on both personal and professional levels in order to ensure the growth of all, and the responsible execution of cutting edge research.
Jaycob D. Warfel, Ph. D. – Diversity Statement

The importance of diverse perspectives and experiences throughout life cannot be overstated. Diversity within my life has allowed me to better advance scientific knowledge, and to enjoy a more versatile and fulfilling life in general. I apply this philosophy to my workmanship in order to continually grow both professionally and personally. Not only do my personal experiences drive me to support a diverse and inclusive environment, but strong evidence supports the idea that diversity and inclusion within a given setting is key to increasing the variety of ideas aimed at positing solutions to complex problems (McKinsey & Company, May 19, 2020 Report). I therefore strive to implement diversity and inclusion in every aspect of my life, and will continue to do so within my educational program, my scientific research, and within my personal life.

Educational Program

As an educator, especially within the Trio SSS program at River Parishes Community College, I have learned the value of getting to know my students as individuals in order to understand how diverse they truly are. Not only do we have to consider demographic variables such as race and gender, but also deep-level diversity markers such as individual personality and values (Torchia, et. al., 2015). I established relationships with students of different genders, ethnic backgrounds, physical abilities, and religious traditions. Devoting time to each student allowed me to understand the deep-level differences that contribute to the way each student learns and works. These personal relationships have been invaluable for shaping the quality and content of my lectures, leading to the growth of myself and my students. As the University of Delaware boasts a student-to-faculty ratio of only 12:1, it is clearly an institution where such relationships can be achieved. Such an environment will therefore allow me to seek the feedback of a diverse student population in order to understand how best to enhance my educational program.

Scientific Research

My research agenda explores the diverse ways in which biological systems maintain homeostasis. I focus on the differences in energy processing by males and females in order to understand how biological diversity makes some populations more susceptible to metabolic disease (Stone et. al., 2021). My most recently submitted grant proposal further explores this topic, and I will continue my investigation of metabolic processing differences between biological sexes throughout my career.

Learning the perspective of individuals from a variety of scientific research backgrounds is also essential for properly exploring the universe, and allows me to consider possible solutions that I could not arrive at on my own. Throughout my research career, I have engaged in research and collaboration with investigators within fields ranging from biochemistry to clinical and translational physiology, and the new perspectives gained from each has been essential for my success. The incorporation of such diversity is even imbedded into the scientific review process; and I welcome the extremely valuable feedback received following submission of manuscripts and grant applications. I will therefore always rely on fruitful collaboration and the critical feedback of peers with diverse perspective in order to broaden my thought process in the pursuit of knowledge.

Personal Life

Living a life full of interactions with people from diverse backgrounds has always been of high importance to me, and the primary influence in my decision to move from rural Illinois to the culturally diverse city of Baton Rouge. As an adult, I have developed relationships with people from a myriad of socioeconomic circumstances, from the professional scientists by whom I was trained, to those with whom I have gratefully volunteered to spend time. Some notable examples include several Baton Rouge inner city youths for whom I have served as a Court Appointed Special Advocate, and inmates whom I have visited with and helped educate at Elayn Hunt State Correctional Center. In addition, as an Orthodox Christian I attend church in a parish largely composed of immigrants to the United States. Engaging in a variety of culturally distinct activities with people from all backgrounds has yielded a greater quality of life and a more empathetic perspective toward humanity.

As a young scientist, I also realize that continued education in facilitating diversity and inclusion are important for my individual growth and to ensure a productive and diverse working environment. I note that the University of Delaware Office of Institutional Equity webpage promotes several programs and services aimed at enhancing faculty development and diversity, such as the LEAD Ally Certificate program. I am highly driven to engage in educational training such as this for personal growth and to gain new perspectives on enhancing diversity and inclusion. Having experienced firsthand the success that diversity and inclusion yields within my professional and personal life, I will always welcome a variety of intellectual perspectives in order to promote personal and community growth.
**Research Vision Statement**

**Career Research Goals:**

Metabolic flexibility allows for the adaptation of fuel oxidation to fuel availability. My research focuses on cellular control points regulating the ability to sense and switch between metabolic substrates. Specifically, I am interested in the way in which metabolic flexibility is controlled by the RNA binding protein HuR. My overall research career goal is to answer the following biological questions:

1) Through what molecular mechanism is HuR regulating the ability of cells to switch between lipids and carbohydrates as a fuel source?
2) How does HuR regulation of metabolic flexibility within cells influence the development of insulin resistance?

**Research Background:**

As a graduate student at Louisiana State University my work was guided by Dr. Vince LiCata and focused on the *in vitro* thermodynamics of nucleic acid binding proteins. My research in protein-nucleic acid biochemistry showed that RecA recombinase acts within the radiation resistant organism *Deinococcus radiodurans* to specifically target damaged DNA. This period of intense biochemical focus facilitated my training in many of the enzymatic assays that I now use to answer questions in cellular and mammalian physiology.

Following completion of graduate school I began a T32 Fellowship as a postdoctoral researcher at Pennington Biomedical Research Center (PBRC), where I studied HuR and its maintenance of cellular metabolism and metabolic physiology. As a postdoctoral researcher in the laboratory of the late Dr. Randy Mynatt I developed an expertise in comparative metabolic physiology by characterizing mouse and human models with a decreased ability to switch between lipids and carbohydrates as a fuel source.

Decreased metabolic flexibility is often seen in patients with obesity and type 2 diabetes, who show a blunted capacity to shift toward lipid oxidation in the fasted state (Kelley and Mandarino, Diabetes, 2000). Skeletal muscle is one of the most significant sites of glucose clearance, and it is thus imperative to understand how intrinsic changes in metabolic processing by skeletal muscle can contribute to the development of metabolic disease. By comparing gene expression datasets generated within Dr. Mynatt’s laboratory from skeletal muscle of metabolically flexible and inflexible humans, I found that many transcripts controlled by HuR are enriched in metabolically flexible humans (Figure 1A-B). Primary myotubes from metabolically inflexible participants do not oxidize lipid as well as those from metabolically flexible humans. This result is recapitulated in healthy myotubes

![Figure 1](image-url)
HuR has classically been acknowledged for its ability to bind to and stabilize cellular RNA in order to ensure their delivery to the ribosome. As part of my K01 project, I am testing the hypothesis that knockout of HuR impairs this delivery. I have employed a TRAP (translating ribosome affinity purification) capable mouse model which has a Cre-activated GFP-L10a construct. This allows for ribosomal pulldown via interaction with GFP antibodies (Figure 2). We have collected all tissues from these mice, and are currently submitting ribosomal RNA samples for RNA-seq analysis. This project employs bioinformatics for final analysis, and I have trained in several programs including Ingenuity Pathway Analysis, Gene Set Enrichment Analysis, and coding in Linux. Much of my focus is on the acquisition and analysis of these new data. As HuR is known to interact with metabolic regulators such as rictor, pgc1α; and the Ppar pathway in skeletal muscle, RNA associated with the mTORC/Ppar/Pgc1α pathway are of high interest for these analyses.

Figure 2: Strategy to test that HuR knockout results in decreased ribosomal delivery of its mRNA targets: I have pulled down skeletal muscle ribosomes and isolated RNA to which they are bound using a GFP-L10a expressing mouse. I am now using RNA-seq to determine differences between HuR<sup>−/−</sup> and control mice.

Figure 3: Taken from Stone et. al, 2021, Biology. A) Fat mass/Lean mass relative to controls is shown for female HuR<sup>−/−</sup> mice (N=14-17, *P<0.05). B) Serum insulin levels are shown for control and HuR<sup>−/−</sup> female mice (N=8). C) Palmitate oxidation is shown for female HuR<sup>−/−</sup> and control mice (N=7-8) (N=17-20), *P<0.05. D-E) Expression of genes regulated by the transcription factor Ppares are decreased in male HuR<sup>−/−</sup> mice (D) but not female HuR<sup>−/−</sup> mice (D) relative to controls (N=14-16, *P<0.05). All data are mean ± SEM.

Current Research Focus:

My laboratory has found that female HuR<sup>−/−</sup> mice also display increased fat mass gain relative to controls. However, unlike male animals, female HuR<sup>−/−</sup> mice do not develop greater hallmarks of insulin resistance relative to controls (Figure 3). HuR<sup>−/−</sup> female mice also do not display decreases in lipid metabolism in skeletal muscle as great as those in males. Our current findings suggest that HuR may promote Ppar controlled transcript expression, which is higher in female HuR<sup>−/−</sup> mice than in males. Ppar's promote lipid oxidation, and can also be controlled stimulated by estrogen-bound Estrogen Receptor α (ERα). I hypothesize that female HuR mice activate lipid metabolism via estrogen signaling in the absence of HuR. This compensation could prevent ectopic lipid accumulation and lessen the development of insulin resistance in female mice lacking skeletal muscle HuR. I submitted a R03 application in October 2021 (DK133616) aimed at testing the ability of 17β-estradiol to enhance lipid oxidation in skeletal muscle in the absence of HuR by activating ERα, and this application is currently in revision for resubmission in November, 2022.

HuR has been exposed to HuR siRNA (Figure 1C). To study the way in which HuR regulates lipid oxidation, I generated a novel knockout mouse model lacking HuR specifically in skeletal muscle (HuR<sup>−/−</sup>). These mice show significantly higher fat mass, serum insulin, and blood glucose relative to controls (Figure 1D-F). Similar to results in humans, lipid oxidation is also significantly decreased in HuR<sup>−/−</sup> male skeletal muscle (Figure 1G). My greatest research accomplishment thus far is in demonstrating that HuR regulates metabolic flexibility at the tissue level, prior to the onset of metabolic disease. This provides evidence for the idea that metabolic flexibility can be intrinsically decreased, rather than simply being a consequence of insulin resistance. My laboratory operates under a NIDDK K01 training grant (DK116914) aimed at further characterizing the metabolic physiology of systems lacking HuR.
Future Research Goals:

Given that male HuR<sup>−/−</sup> mice do not oxidize lipids as well as controls in skeletal muscle, I am investigating how HuR<sup>−/−</sup> mice might compensate through glucose oxidation. Several lines of evidence from our preliminary data suggest that HuR inhibition in skeletal muscle may result in increased glucose utilization. Though Figure 1 shows that male HuR<sup>−/−</sup> mice display greater blood glucose than controls during GTT, our published data indicate that this is an artifact of these mice becoming more obese than controls at 20 weeks of age (Figure 4A). However, when only 10 weeks of age, HuR<sup>−/−</sup> males display decreased blood glucose relative to controls (Figure 4B). We also see consistently higher respiratory quotients and higher skeletal muscle glycogen levels in male HuR<sup>−/−</sup> mice relative to controls, suggesting an increased reliance on glucose (Figure 4C-D). Previous clinical studies have suggested that metabolically inflexible humans have an increased reliance on glucose, as glycolysis and lactic acid fermentation are increased in skeletal muscle (San-Milan and Brooks, 2017, Sports Medicine). Consistent with the clinical models, HuR<sup>−/−</sup> male mice show higher levels of serum lactate relative to controls (Figure 4D). Again in agreement with clinical data, metabolically inflexible human participants have a transcriptomic signature consistent with higher levels of glycolysis in skeletal muscle (Figure 4C-D). In addition, transcriptomic analysis reveals that HuR<sup>−/−</sup> mouse skeletal muscle also shows enrichment of glycolytic genes, and decreased expression of oxidative phosphorylation genes relative to controls (Figure 4E). Increased muscle glycolysis and serum lactate could suggest increased glucose utilization and regeneration via the Cori cycle. I hypothesize that glucose regeneration in the liver is increased in order to meet glycolytic demand in HuR deficient skeletal muscle; and I am using these data to develop an R01 proposal to submit in June, 2023.

My work reveals HuR<sup>−/−</sup> mice as a valuable translational model for decreased metabolic flexibility, and these mice will provide insight into the molecular mechanisms regulating glucose preference in a metabolically inflexible state. My research agenda moving forward will be focused on discerning these mechanisms by acquiring data from mouse tissues, as well as from Human and Murine cell culture models. I believe that my research agenda fits well within the scope of projects within the University of Delaware Department of Biological Sciences COBRE, and anticipate the potential for many productive collaborations with the investigators therein. Through these exciting new research avenues I aim to maintain a robust, NIH funded research program while mentoring a diverse group of students and postdoctoral trainees.
Statement of Teaching Experience and Philosophy
Jaycob Dalton Warfel, Ph. D.

My primary research focus concerns the cellular mechanisms governing metabolic flexibility, which can be concisely described as the ability to switch between metabolic substrates based on their availability. This requires a complex working knowledge of cell biology, biochemistry, and molecular physiology. Active instruction in these subjects is therefore of utmost importance for my career. Including my time as a teaching assistant in graduate school, I have accrued greater than 10 years of teaching experience at both the undergraduate and graduate levels while also developing my research focus, and have greatly enjoyed the educational component of my career. I aim to be involved with student instruction at all levels of biological study, from first year undergraduate students up through graduate students.

The vast majority of my experience with collegiate education is through undergraduate instruction. Through acting as a teaching assistant during graduate school, and as an adjunct instructor during my postdoctoral training, I have gained competency with the formulation of lecture and laboratory based courses from freshman to senior level. Following techniques adapted from my teaching mentors during graduate school at Louisiana State University, I have utilized online learning management systems, including Blackboard, Canvas, and Moodle, to continually stay up to date with course materials and to post instructional summary videos of key concepts accessible to students as powerful tools to increase retention (available upon request). During undergraduate lectures I have implemented active learning techniques (Freeman, et al., 2014, PNAS) such as group discussions to arrive at solutions; and in-class interactive multiple-choice questions to ensure engagement of all. I also recognize that biology education is a continually changing field, and have a history of dynamically adapting classroom presentations to ensure that course lectures contain the most current information.

For the remainder of my career, I will incorporate the above mentioned strategies in order to engage in every level of biological education. I am interested in learning new teaching formats such as Course-Based Undergraduate Research Experiences (CUREs), and in extracurricular strategies aimed at increasing student comprehension and engagement. For example, I participated for several years in the Biology Intensive Orientation for Students (BIOS) while a graduate student at Louisiana State University, which is designed to manage incoming student expectations about the nature of collegiate coursework (Wischusen and Wischusen, 2007, CBE Life Sci Educ). I am very interested in collaborating with my colleagues to develop similar programs in the future. In addition, one-on-one interaction with undergraduate, graduate, and professional students within my laboratory will be of utmost importance for delivering in depth training to young trainees.

I have experience in graduate level instruction through team teaching a graduate level nutrition course at Pennington Biomedical Research Center, and have served many graduate student and postdoctoral trainees as a mentor. For graduate instruction, I will develop courses that deeply investigate the fields of cell biology and metabolic fuel selection. This was the subject matter of my previous graduate lectures; and an entire course devoted to this topic is of high interest to me. Novel studies are continually being published, some of which support the idea that substrate fuel selection can be impaired prior to the onset of metabolic disease, while still others suggest that it is metabolic disease itself which impairs the ability to switch between metabolic fuels. I am therefore interested in developing graduate courses which comprehensively investigate these research perspectives.

Scientific instruction at all levels is an essential part of my career as a cellular physiologist. Though I am currently an assistant professor at a research-intensive facility that requires no teaching commitment, I have elected to engage in teaching part time for 5 of my 8 years here at Pennington Biomedical Research Center (PBRC). My continued involvement in education has allowed me to develop courses that integrate the techniques discussed above as a valuable resource for enhancing student comprehension; and I intend to establish myself in a tenure track position that allows for an interactive coordination between groundbreaking scientific research and outstanding education.