APPLICATION FOR FEDERAL ASSISTANCE

SF 424 R&R

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION

❍Pre-application ●Application ❍Changed/Corrected Application

2. DATE SUBMITTED

Applicant Identifier

4. a. Federal Identifier

b. Agency Routing Identifier

c. Previous Grants.gov Tracking ID

5. APPLICANT INFORMATION **Organizational DUNS:** [redacted]

[redacted]

Person to be contacted on matters involving this application

Prefix: First Name: [redacted] Middle Name: [redacted] Last Name: [redacted] Suffix:

[redacted] Title: [redacted]

[redacted]

6. EMPLOYER IDENTIFICATION NUMBER*(EIN) or (TIN)*: [redacted]

7. TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ❍Women Owned ❍Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:

●New ❍Resubmission

❍Renewal ❍Continuation ❍Revision

If Revision, mark appropriate box(es).

❍A. Increase Award ❍B. Decrease Award ❍C. Increase Duration

❍D. Decrease Duration ❍E. Other*(specify)*:

Is this application being submitted to other agencies? ❍ Yes ● No What other Agencies?

9. NAME OF FEDERAL AGENCY:

National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Contextualizing Chaotic Metabolic Networks and Their Regulation

12. PROPOSED PROJECT:

Start Date	Ending Date
07/01/2020	06/30/2026

13. CONGRESSIONAL DISTRICT OF THE APPLICANT:

[redacted]

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
	JORDAN	[redacted]	BERG	

Position/Title: Graduate Research Assistant
Organization Name: University of Utah
Department: Biochemistry
Division:
Street1: [redacted]
Street2:
City: Salt Lake City
County/Parish: Salt Lake
State: UT: Utah
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 84112-8930
Phone Number: [redacted]
Fax Number:
Email [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	$366,586.00
b. Total Non-Federal Funds	$0.00
c. Total Federal & Non-Federal Funds	$366,586.00
d. Estimated Program Income	$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree

The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or other Explanatory Documentation. File Name: Mime Type:

19. Authorized Representative

Prefix:	First Name:	Middle Name:	Last	
	[redacted]		[redacted] Brown	[redacted]

Position/Title: [redacted]
Organization Name: [redacted]
Department: [redacted]
Division: [redacted]
Street1: [redacted]
Street2:
City: Salt Lake City
County/Parish: Salt Lake
State: UT: Utah
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 84112-8930
Phone Number: [redacted]
Fax Number: [redacted]
Email: [redacted]

Signature of Authorized Representative **Date Signed**

20. Pre-application File Name: Mime Type:

21. Cover Letter Attachment File Name: Cover_Letter1029235290.pdf Mime Type: application/pdf

The University of Utah
Department of Biochemistry

Division of Receipt and Referral
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive
Rockledge II, MSC-7768
Bethesda, MD 20892-7768
(301) 435-1115

03 Dec 2019

Dear Selection Committee,

I am pleased to submit the enclosed fellowship proposal, "**Contextualizing Chaotic Metabolic Networks and Their Regulation**", for consideration for the NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00). The following application contains all of the required agency approval documentation as issued in **RFA-CA-19-057**. This proposal seeks to build tools to aid in contextualizing complex and dynamic data in metabolic networks and use these tools to answer previously unanswerable questions related to the aggregate regulation of metabolism. These tools and regulatory mechanisms will be vital to deconvoluting cancer metabolism behavior. I appreciate the opportunity to be considered for this fellowship.

List of referees:
[redacted]
Distinguished Professor, Department of Biochemistry, University of Utah

[redacted]
Assistant Professor, Department of Oncological Sciences, University of Utah

[redacted]
Associate Professor, Department of Microbiology and Molecular Biology, Brigham Young University

Sincerely,

[redacted]

Jordan A. Berg
Ph.D Candidate
Department of Biochemistry
University of Utah
[redacted]

Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: University of Utah

* Street1: [redacted]		Street2:
* City: Salt Lake City	County: Salt Lake	* State: UT: Utah
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: [redacted]
DUNS Number: [redacted]	* Project/Performance Site Congressional District: [redacted]	

File Name	Mime Type

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ❍ Yes ● No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If yes, check appropriate exemption number

Exemption Number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If no, is the IRB review Pending? ❍ Yes ❍ No

IRB Approval Date:

Human Subject Assurance Number

2. * Are Vertebrate Animals Used? ❍ Yes ● No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ❍ Yes ● No

4.a. * Does the Project have an Actual or Perceived Impact – positive or negative – on the environment? ❍ Yes ● No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5.a. * Is the research performance site designated, or eligible to be designated, as a historic place? ❍ Yes ● No

5.b. If yes, please explain:

6.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? ❍ Yes ● No

6.b. If yes, identify countries:

6.c. Optional Explanation:

7. Project Summary/Abstract	Project_Abstract1029235300.pdf	Mime Type: application/pdf
8. Project Narrative	Project_Narrative1029235299.pdf	Mime Type: application/pdf
9. Bibliography & References Cited	Bibliography_References_Cited1029235369.pdf	Mime Type: application/pdf
10. Facilities & Other Resources	Facilities_Other_Resources1029235291.pdf	Mime Type: application/pdf
11. Equipment	Equipment1029204466.pdf	Mime Type: application/pdf
12. Other Attachments	Institutional_Nomination_Letter1029235330.pdf	Mime Type: application/pdf

Project Summary/Abstract

Cancer metabolism is a complex network of perturbations to essential chemical and enzymatic reactions; however, the past century has seen a largely reductionist approach to understanding this system. While previously this approach was necessary due to technological limitations, current computer age technological advances allow us to survey, model, and explore the biological details of individual cells and populations of cells. Scientific fields, such as RNA biology and metabolism, have experienced massive strides in recent decades with the advent of RNA-seq and mass spectrometry-based metabolomics, yet our ability to contextualize and extract the full extent of these enormous datasets continues to lag and often results in focusing on only a handful of entities from a dataset. This effectively causes “big data” to become “little data”. This is problematic as these experiments are often expensive and time-consuming to produce, yet we only use a fraction of the total data produced by a given experiment. For the F99 phase of my proposal, I will address these limitations by leading the development of *Metaboverse*, a multi-omic computational analysis framework built upon our previous work to contextualize -omics datasets within customizable and global metabolic network representations. This framework will lay the foundation allowing for the exploration of complex forms of metabolic regulation in cancer. For example, we will analyze the ability of metabolic networks to undergo dispersed and low-magnitude regulation, where, rather than one or two components acting as the core regulatory actors, regulation is performed by dispersed groups of genes, proteins, or metabolites. **This framework and related regulatory research will revolutionize our ability to more holistically understand temporal metabolic shifts and gene-metabolite intra-cooperativity, as well as ensure we obtain the maximum amount of information from our data**. For the K00 phase of my proposal, I will work with a postdoctoral mentor at an NCI-Designated Cancer Center or affiliated institution that will supplement my training in machine learning and network biology to develop models that improve our ability to predict metabolic state from transcriptomic state. Doing so will allow us to harness the vast transcriptomics databases in cancer biology to better understand the role of metabolism across heterogeneous tumor cell populations. **My ultimate goal is to become a tenured professor and run an independent, NIH-funded research lab that focuses on computational cancer metabolism research and that develops methods for interrogating this emerging domain of biology.**

Project Narrative

While cancer metabolism is a robust and well-developed research field, approaches to its holistic understanding are still under-developed and hinder our ability to contextualize these complex metabolic states and their consequences. During the F99 phase, I will develop tools and methods that allow researchers to explore data in a more holistic manner than previously possible, which will be essential to elucidating more complicated regulatory mechanisms within cancer metabolism. During the K00 phase, I will develop novel machine learning algorithms that will improve our ability to predict the metabolic state from the transcriptional state, allowing us to harness the rich transcription datasets found in cancer biology for therapeutic benefit.

Bibliography

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Facilities & Key Resources

Scientific Environment: The University of Utah School of Medicine has a long history of excellence in biochemistry, genetics, oncology, and neuroscience. NIH training grants support interdepartmental research and training in these and other areas, and the University continues to attract outstanding new faculty, students, and postdocs. Basic science and clinical faculty interact regularly at interdepartmental research meetings and at seminars with intramural and extramural speakers. These include weekly Journal Club meetings, Research in Progress meetings, and weekly Metabolism Interest Group meetings. Speakers at this meeting include members of each participating lab as well as invited external speakers from major research institutions around the country, providing a rich intellectual environment that will support the proposed project. The scientific community at the University of Utah is very open and collaborative. Investigators, postdoctoral fellows, and graduate students alike are very open and willing to share ideas and collaborate. There is a wealth of interdisciplinary science occurring at the University of Utah, which was another draw for me to come to the University for graduate school. Based on my interest in leveraging computational biology and big data to be able to ask previously difficult-to-answer questions, I chose to come to the University of Utah and work in the Rutter lab where opportunities to unlock this synergy. My dissertation committee is also highly reflective of the interdisciplinary nature of the university and my research as I have experts in cancer biology, cellular quality control and signaling regulation, metabolism, RNA biochemistry and RNA-Seq, and computational biology on my committee with appointments in Biochemistry, Oncological Sciences, and Human Genetics. My committee members are all well-established in their respective fields with a diversity of experience. Speaking to this point, Dr. Jared Rutter is currently an HHMI Investigator and members of my committee, Drs. Brenda Bass and Carl Thummel, were both HHMI Investigators for over 15 years each and Dr. Brenda Bass is a member of the National Academy of Sciences. Drs. Jason Gertz and Adam Hughes are considered leaders in their respective fields and each member is essential to the success of my dissertation. This committee has been enriched by collaborators and mentors, such as Drs. Aaron Quinlan, Bei Wang Phillips, and James Cox. To further illustrate the interdisciplinary nature of the university and research environment, Dr. Jared Rutter is a Professor in the Department of Biochemistry, holds an Ida Smith Endowed Chair of Cancer Research, and is a co-leader of the Nuclear Control and Cell Growth and Differentiation program at the Huntsman Cancer Institute and organizes the Seminars in Metabolism. This proposed project will benefit from outstanding core facilities supported by the University of Utah, such as the High-Throughput Genomics and Metabolomics Cores. All core services are provided through centralized facilities at reasonable recharge rates (http://cores.utah.edu/).

Laboratory: The Rutter laboratory (3461 sq ft) is in the 14-year old Emma Eccles Jones Medical Research Building at the University of Utah School of Medicine. The Rutter lab has adjacent 30°, 37°, 4°, tissue culture, radioactivity and common equipment rooms. This building houses both the Department of Biochemistry as well as the Department of Pathology and is located central to the other medical research buildings under the School of Medicine as well as many of the research cores, such as the Metabolomics core, drug discovery core, a CRISPR core, and the bioinformatics core to name a few. This setup allows for easy access to collaborators and equipment to facilitate my research projects. The Rutter lab contains the needed equipment to perform yeast genetics, molecular biology and biochemistry, equipment and resources needed to prepare high-throughput sequencing libraries, as well as the necessary BSL-2 cell and tissue culture facilities to culture, transfect, and treat the cell lines to be used in this proposal. I have a large computer desk with sufficient space for my personal workstation, along with available wet bench space.

Computer: The office of Dr. Rutter is equipped with a MacBook Pro with a studio display. Each member of the Rutter laboratory has either a Macintosh or PC computer, which is networked with access to an HP laser printer and remote access to a lab server for storage and exchange of data within the lab. The PI of this proposal has a 2018 15” Macbook Pro, 2.9 GHz Intel Core i9 laptop with 32 GB of DDR4 RAM, along with two external monitors. All workstations also have the necessary software for common laboratory functions, databases, word processing, and graphics.

Office: Dr. Rutter has a 120 sq. ft. office adjacent to the laboratory. Lab members have desk space in the laboratory and access to a dedicated trainee office for writing and reading. Administrative and accounting support and support equipment (copier, fax, conference room) are in the nearby department office.

Other: The Department of Biochemistry provides full centralized support for purchasing, accounting, and human resource management. The Rutter laboratory shares two technicians with other adjacent laboratories for yeast media preparation and glassware cleaning.

Facilities: The following facilities are available through the University of Utah: confocal microscope; flow cytometry; DNA and peptide synthesis core; electron microscopy; small animal imaging; mass spectrometry core for proteomics and metabolomics; biorepository with access to >30,000 specimens collected from cancer patients undergoing surgery at the Huntsman Cancer Institute; and a high-throughput genomics core for RNA-seq, ChIP-seq, etc.

High-Throughput Genomics Core: The University of Utah High Throughput Genomics Core is housed at the Huntsman Cancer Institute, proximal to the Emma Eccles Jones Medical Research Building where our lab is located. This core provides access to state-of-the-art Illumina sequencing platforms, as well as an Aligent Technologies 2200 TapeStation for quality control of ribosome profiling sequencing libraries. The sample-to-sequence turnaround time is reasonable, data access is easy, and the sequencing quality is reliable. In fact, the High-Throughput Genomics Core was recently part of a study comparing University sequencing cores and was shown to output the most aligning reads per sequencing run of the sequencing cores analyzed (https://www.nature.com/articles/s41467-018-03751-6).

Metabolomics Core: The Metabolomics Core, located in the Emma Eccles Jones Research Building, where the Department of Biochemistry and the Rutter lab are located, specializes in metabolomics sample preparation, metabolome profiling, and data analysis. The core has equipment capable of handling GC-MS, LC-MS, NMR, lipidomics, and metabolic flux analysis. The Rutter lab's SCIEX X500R QTOF MS is also housed in the Metabolomics Core.

Center for High Performance Computing (CHPC): The University of Utah CHPC manages over 22,000 high performance computing cores and over 13 petabytes of RAID configured spinning disk storage. CHPC frequently holds training workshops to aid users in leveraging their resources. Users can either purchase private computing nodes and data storage space or submit quarterly allocation requests for priority access to these freecycle nodes. The Rutter lab is currently allocated a generous 50,000 wall-clock hours per quarter. The Rutter lab also has allocated freecycle computing privileges with 5TB dedicated lab storage available in a protected environment for processing sensitive data. These resources are essential and sufficient for the processing of the data associated with this proposal.

Equipment

University of Utah Center for High-Performance Computing:

- Lab allocation of 50,000 general computing hours per quarter
- General free-cycle nodes available for all lab members with CHPC registration
- Protected computing environment free-cycle nodes and 5 TB lab project space for protected data processing and short-term storage
- Other non-allocation compute nodes available for use

Basic Lab Equipment: The Rutter lab is fully equipped to perform routine laboratory procedures involving molecular biology, yeast genetics and biochemistry, mouse husbandry and manipulations, tissue and cell culture, and standard light and fluorescence microscopy. Equipment available within the Rutter laboratory includes:

- SCIEX X500R QTOF mass spectrometer with a Shimadzu LC20 ADXR HPLC
- Zeiss LSM 880 Confocal Microscope with Airyscan
- Zeiss AxioObserver inverted microscope and ZenPro imaging system with DIC and fluorescence (including six different fluorescence filters), deconvolution, time-lapse, and tiling capabilities
- Seahorse XFe96 Analyzer for measurement of mitochondrial respiration, glycolysis, and fatty acid oxidation in live cells
- Three fridges, a deli case, a walk-in cold room
- Six -20^{o} C freezers
- Three –80^{o} C freezers
- Shimadzu SPD M10A VP HPLC for peptide and small molecule purification
- Roche LightCycler 480 for real-time PCR
- BioMek NX Laboratory Automation Workstation for automated microtiter plate liquid handling
- OceanOptics oxygen electrode for oxygen consumption experiments
- Eppendorf Biospectrometer kinetic spectrophotometer
- One MJ Research thermocycler and two BioRad T100 thermocyclers
- Thermo Speedvac
- Three cryostorage tanks for long term storage of cultured cells
- Five water-jacketed CO_2 incubators
- Three Thermo Sorval Legend Mirco 21 microfuges, one Eppendorf 5417C microfuge, and one Eppendorf 5415C microfuge
- Eppendorf 5424 centrifuge, Eppendorf 5417R centrifuge, Eppendorf 5810R centrifuge, a Beckman C515R centrifuge, and two Thermo Sorvall Primo centrifuges
- Balances (including analytical balance), pH meter, incubators, power supplies, protein and nucleic acid electrophoresis equipment including equipment for both semi-dry and wet transfer, heat blocks, stir plates, vortexes, orbital shakers, water baths, vacuum aspirators, Bunsen burners, light microscope, microwave oven, fume hood, and equipment for storing and handling radioactive isotopes including two handheld Geiger counters.

Biochemistry Department Equipment:

- Preparative centrifuges including ultracentrifuges
- SPEX SamplePrep 6870 Freezer/Mill
- Tetrad dissection setup
- Freeze-dryers
- Liquid scintillation counter
- Developer for Western blots and autoradiography
- Licor Odyssey IR imaging system
- NanoDrop for microvolume UV-Vis measurements
- Water bath and probe sonicators
- Dish washing/autoclaving facilities

HUNTSMAN
CANCER INSTITUTE
UNIVERSITY OF UTAH

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

November 26, 2019

Re: NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00)

[redacted]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | First Name*: JORDAN | Middle Name [redacted] | Last Name*: BERG | Suffix:

Position/Title*: Graduate Research Assistant
Organization Name*: University of Utah
Department: Biochemistry
Division:
Street1*: [redacted]
Street2:
City*: Salt Lake City
County: Salt Lake
State*: UT: Utah
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI | Other Project Role Category:

Degree Type: BS | Degree Year: 2016

	File Name
Attach Biographical Sketch*:	Biosketch_Berg1029235351.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: | First Name*: Jared | Middle Name [redacted] | Last Name*: Rutter | Suffix:

Position/Title*: Professor
Organization Name*: University of Utah
Department: Biochemistry
Division:
Street1*: [redacted]
Street2:
City*: Salt Lake City
County: Salt Lake
State*: UT: Utah
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted] E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other (Specify) | Other Project Role Category: Sponsor

Degree Type: [redacted] | Degree Year: [redacted]

	File Name
Attach Biographical Sketch*:	[redacted]
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: | First Name*: Bei | Middle Name | Last Name*: Wang-Phillips | Suffix:

Position/Title*:	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Street2:	
City*:	Salt Lake City
County:	Salt Lake
State*:	UT: Utah
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	[redacted]

Phone Number*: [redacted]	Fax Number:	E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]	
Project Role*: Other (Specify)	Other Project Role Category: Co-Sponsor
Degree Type: [redacted]	Degree Year: [redacted]

	File Name
Attach Biographical Sketch*:	[redacted]
Attach Current & Pending Support:	

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: Berg, Jordan A.

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Graduate Research Assistant, Ph.D Candidate

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Brigham Young University, Provo, UT	B.S.	06/2010	05/2016	Molecular Biology
University of Utah, Salt Lake City, UT	Ph.D.	08/2016	05/2022	Biochemistry

A. Personal Statement

While human metabolism has been elementally understood and appreciated since the time of Aristotle with the publication of “Parts of Animals”, and vigorously dissected over the past two centuries, a holistic and systematic understanding of metabolism, and particularly cancer metabolism, is incomplete. Often, cancer metabolism research takes a reductionist stance by perturbing a gene or protein in a pathway to determine its effect. But even in these scenarios, the systematic consequences are difficult to parse out. Interestingly, Drs. Ralph DeBerardinis and Navdeep Chandel (*Sci Adv*, 2016) recently published a review on cancer metabolism, where they, in their conclusions, pointed to a lack of computational methods for deconvoluting and analyzing the complex metabolic behaviors of tumor cell populations. In order to improve our understanding in this realm, my aims are two-fold. 1) Develop automated, robust tools for performing complex, system-wide interrogations of metabolism, and 2) Use these tools to address questions related to the regulation of metabolism that without such tools would be impossible to answer. With these tools, the pace of scientific discovery can modernize and accelerate, expanding the yield of our insights into the complex pathology of cancer. This information will then be used to develop novel therapeutic options that address the metabolic state of cancer.

I chose to work with Dr. Rutter due to his expertise in the mechanistic dissection of cancer metabolism and his enthusiasm to leverage computational methods to ask new and difficult questions. I chose Dr. Bei Wang Phillips as a co-mentor for her expertise in network biology, topographical data analysis, machine learning, and signal deconvolution. **With this dual-training strategy, I will be able to provide a much-needed mechanistic approach to computational dissection of cancer metabolism**. After my graduate training, I will find a position as a postdoctoral research fellow in a lab with expertise in network biology and machine learning to allow me to continue to expand this toolkit. My driving goal behind all of these career stages is to lead my own computational cancer metabolism lab where we will develop novel tools to deconvolute noisy and complex datasets and provide a more holistic view of cancer metabolism.

B. Positions and Honors

Positions and Employment

2014 iGEM Project Leader, 2014 iGEM Team, Brigham Young U.
2013-2016 Undergraduate Research Assistant, Julianne Grose Lab, Brigham Young U.
2014-2016 Teaching Assistant, HHMI SEAPHAGES Program, Brigham Young U.
2018, 2020 Teaching Assistant, Lit. & Problem Solving, U. of Utah
2016-present Graduate Student, Molecular Biology Program, U. of Utah
2017-present Graduate Research Assistant, Jared Rutter Lab, U. of Utah

Other Experience and Professional Memberships

2015 Member, American Society for Microbiology
2014-2016 Youth Mentor, Provo Youth Mentoring
2018 Lead Recruitment Host, Molecular Biology Graduate Program, U. of Utah
2018 Volunteer, Adventure Scientists

2018-present Member, SACNAS
2018-present SACNAS Webmaster/Social Media Outreach Officer

Reviewer for Bioinformatics, NAR Genomics and Bioinformatics, Journal of Emerging Investigators. See https://bit.ly/2DLqcsk for records.

Academic and Professional Honors

2014 iGEM World Jamboree, Silver Medal
2016 Outstanding Research Award, Dept. of Microbiology and Molecular Biology, Brigham Young U.
2018-2020 T32 Training Grant in Computational Approaches to Diabetes and Metabolism, U. of Utah

C. Contributions to Science

1. *Brevibacillus/Paenibacillus* Bacteriophage/Host Evolution (Undergraduate)

During my undergraduate degree, my research focus centered around the isolation, genomic characterization, and evolutionary analysis of bacteriophage infecting the bee probiotic *Brevibacillus laterosporus,* the bee pathogen *Paenibacillus larvae*, and the Rosaceae pathogen, *Erwinia amylovora*. **I was the first author of two published peer-reviewed papers**. I mentored 22 undergraduate research assistants and students, 16 of whom contributed as co-authors on published papers and/or primary authors on posters presented at external conferences. Additionally, I was the first author or a co-author for the annotation of 51 phage genome annotations published in NCBI's Genbank (see https://bit.ly/2NWJ25Q for a complete listing). I was selected to present a talk on my *Erwinia* phage research at 2015 Tri-Branch American Society for Microbiology (ASM) conference. In collaboration with the U.S. Environmental Protection Agency (EPA), I developed phage therapy cocktails for treating *Erwinia amylovora* infections. I was also a member of Brigham Young University's 2014 International Genetically Engineered Machine (iGEM) team and served as one of the project leaders.

Abstracts (selected list, 7 total):

1. **Berg JA**, Esplin IND, Brundage BM, Crockett JT, Esplin KP, Evans MR, Heaton KE, Hilton JA, Hyde JR, McBride MS, Schouten JT, Simister AR, Thurgood TL, Merrill BD, Ward AT, Breakwell DP, Burnett SH, Grose JH. (2015) Isolation of six novel Paenibacillus larvae bacteriophage and characterization of five Brevibacillus laterosporus bacteriophages to understand their evolutionary relationship to Brevibacillus and other bacteriophages. **Poster presentation**. 7th Annual HHMI SEA-PHAGES Symposium, Janelia Farms, Ashburn, VA, USA.
2. McBride M, Evans MR, Brundage BM, **Berg JA**, Merrill BD, Burnett SD, Breakwell DP, and Grose JH. (2015) Comparing Protein Structures of a Transcriptional Regulator Repeated in Brevibacillus Phages. **Poster presentation**. Tri-branch ASM meeting, Colorado State University, Fort Collins, CO, USA. Third place, **Best poster presentation.**

Oral Presentations (1 total):

1. **Berg JA**, Simister, AR, Thurgood TL, Grose JH. (2015) Characterization and analysis of six novel Erwinia phages reveals relationship to Enterobacteriaceae family members. **Oral presentation**. Tribranch ASM meeting, Colorado State University, Fort Collins, CO, USA.

Research Articles (selected list, 6 total):

1. **Berg JA**, Merrill BD, Breakwell DP, Grose JH, Hope S. A PCR-based method for distinguishing between two common beehive bacteria, *Paenibacillus larvae* and *Brevibacillus laterosporus*. (2018) ***Journal of Appl Environ Microbiol***. 84:e01886-18. DOI: 10:1128/AEM.01886-18.
2. Sharma R, **Berg JA**, Beatty NJ, Choi MC, Cowger AE, Duncan SG, Fajardo C, Ferguson HP, Galbraith T, Herring JA, Hoj TR, Hughes J, Hyde JR, Jensen GL, Ke K, Keele BR, Killpack S, Lawrence EEK, Nwosu I, Roark BJ, Thompson DW, Tueller JA, Ward MEH, Webb CJ, Wood ME, Wynne H, Yeates EL, Baltrus D, Breakwell DP, Hope S, Grose JH. Genome Sequences of 10 *Erwinia amylovora* Bacteriophages. (2018) ***Microbiol Resour Announc***. 7(14):e00944-18. DOI: 10.1128/MRA.00944-18.
3. Esplin IND, **Berg JA**, Sharma R, et. al. Genome sequences of 19 novel *Erwinia amylovora* bacteriophages. (2017) ***Genome Announc*.** 5(46):e00931-17. DOI: 10.1128/genomeA.00931-17.
4. **Berg JA**, Merrill BD, Crockett JT, Esplin KP, Evans MR, Heaton KE, Hilton JA, Hyde JR, McBride MS, Schouten JT, Simister AR, Thurgood TL, Ward AT, Breakwell DP, Burnett SH, Grose JH.

Characterization of five novel *Brevibacillus* bacteriophages and genomic comparison of *Brevibacillus* phages. (2016) ***PLoSONE*** 11(6): e0156838. DOI: 10.1371/journal.pone.0156838.

2. Computational Approaches to Deconvoluting and Understanding Metabolism (Graduate)

I have worked in a variety of labs from different fields during my rotations, but the two that were most impactful to me and my career trajectory were with Drs. Jason Gertz and Jared Rutter. During my rotation with Dr. Gertz, I developed analytical and predictive computational methods to identify patients with endometrial cancer that would respond positively to progesterone treatment. My rotation with Dr. Rutter distilled in me an amazement and excitement of metabolism and its complexity. While I still collaborate closely and often with Dr. Gertz, I like complexity and being able to make sense of complex systems, which is why I decided to do my thesis in Dr. Rutter's lab. Understanding these systems require large amounts of biological data that has been processed uniformly. To enable these scaled analyses, I developed *XPRESSyourself*, which was a collaborative project with Drs. Aaron Quinlan and Jason Gertz, as well as members of the Rutter and Quinlan labs. In this toolkit, we provide standardized and automated sequence data processing and introduced new open source tools for ribosome profiling analysis, where such tools and standardization were still missing.

With Drs. Bei Wang, James Cox, and others, we are building upon this first toolkit to create *Metaboverse*, which will standardize and enhance proteomics and metabolomics data analysis, supplemented with RNA-Seq and ribosome profiling data. We also recently completed two manuscripts where we investigated the topographical structure of the metabolic network, presented key considerations for analyzing and visualizing metabolic networks (***GigaScience*, In Press**), and identified systematic changes to glucose metabolism in colorectal cancer that drives tumorigenesis (***Cell Metabolism*, 2019**). These observations will serve as a foundation for visualizing and contextualizing complex metabolism and its regulation in *Metaboverse*.

Abstracts (3 total):

1. **Berg JA,** Belyeu JR, Morgan JT, Ouyang Y, Bott AJ, Quinlan AR, Gertz J, Rutter J. (2019) XPRESSyourself—Enhancing, standardizing, and automating ribosome profiling computational analyses yields improved insight into data. **Poster presentation**. Genome Informatics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA.
2. **Berg JA**, Nuebel E, Rutter JP. (2018) Ribosome profiling reveals translation-level regulation of peroxins in response to loss of peroxisomes. **Poster Presentation**. Frontiers in Metabolism, Madison, WI, USA.
3. **Berg, JA**, Rutter JP. (2018) RiboPipe: A ribosome profiling pipeline optimized for easy assembly and data analysis. **Poster Presentation**. RECOMB2018, Paris, FR.

Oral Presentations (3 total):

1. **Berg JA**, Zhou Y, Waller TC, George I, Cox J, Wang B, Rutter J. (2019) Contextualizing chaotic metabolic networks and their regulation. **Selected Talk**. EMBL/EMBO Epigenetics Meets Metabolism, Heidelberg, DE.
2. **Berg JA,** Belyeu JR, Morgan JT, Ouyang Y, Bott AJ, Quinlan AR, Gertz J, Rutter J. (2019) XPRESSyourself—Enhancing, standardizing, and automating ribosome profiling computational analyses yields improved insight into data. **Lightning Talk**. Genome Informatics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA.
3. **Berg JA**. (2019) XPRESSyourself: Enhancing, Standardizing, and Automating Ribosome Profiling Computational Analyses Yields Improved Insights. **Invited Talk**. Bioinformatics Seminar Series, Center for Computational Biology & Bioinformatics, University of California San Diego, San Diego, CA, USA.

Research Articles (&co-corresponding authors; *equal contributors; selected list, 5 total):

1. **Berg JA&**, Belyeu JR, Morgan JT, Ouyang Y, Bott AJ, Quinlan AR, Gertz J, Rutter J&. *XPRESSyourself*: Enhancing, Standardizing, and Automating Ribosome Profiling Computational Analyses Yields Improved Insight into Data. (2019) ***bioRxiv***. 704320. DOI: 10.1101/704320. **Under review**.
2. Hughes CE, Coody TK, Jeong M, **Berg JA**, Winge DR, Hughes AL. Amino acid toxicity drives age-related mitochondrial decline by altering iron metabolism. **In Press at *Cell***.
3. Bensard CL*, Wisidigama DR*, Olsen KA, **Berg JA**, Krah NM, Schell JC, Nowinski SM, Fogarty S, Bott AJ, Wei P, Dove KK, Tanner JM, Panic V, Cluntun A, Lettlova S, Earl CS, Namnath DF, Vázquez-Arregun K, Villanueva CJ, Tantin D, Murtaugh LC, Evason KJ, Ducker GS, Thummel CS, Rutter J. Regulation of Tumor Initiation by the Mitochondrial Pyruvate Carrier. (2019) ***Cell Metabolism***.

4. Waller TC[&], **Berg JA**, Lex A, Chapman BE, Rutter J[&]. Compartment and Hub Definitions Tune Metabolic Networks for Metabolic Interpretations. **In Press at *GigaScience***.

Complete list of publications is available on Google Scholar: https://bit.ly/33Wu2KV

D. Scholastic Performance

Brigham Young University

YEAR	COURSE TITLE	GRADE
[redacted]	[redacted]	[redacted]

YEAR	COURSE TITLE	GRADE
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Cumulative Undergraduate GPA=3.23

*Undergraduate grades based on an A-E scale, E equaling a failing grade; or reported as Pass (P), Fail (F)

University of Utah

YEAR	COURSE TITLE	GRADE
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Cumulative Graduate GPA=3.807

*Graduate grades based on an A-D, F scale or reported as Pass (P), Fail (F)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: Rutter, Jared

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bei Wang Phillips (publish under Bei Wang)

[redacted]

[redacted]

[redacted]

[redacted]

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction

1. Introduction
(for Resubmission applications)

Fellowship Applicant Section

2. * Applicant's Background and Goals for Fellowship Training	Applicants_Background_Goals1029235350.pdf

Research Training Plan Section

3. * Specific Aims	Specific_Aims1029235347.pdf
4. * Research Strategy	Research_Strategy1029235348.pdf
5. * Respective Contributions	Respective_Contributions1029235289.pdf
6. * Selection of Sponsor and Institution	Selection_Sponsor_Institution1029235295.pdf
7. Progress Report Publication List (for Renewal applications)	
8. * Training in the Responsible Conduct of Research	Training_Responsible_Conduct1029204555.pdf

Sponsor(s), Collaborator(s) and Consultant(s) Section

9. Sponsor and Co-Sponsor Statements	Sponsors_Statement1029235297.pdf
10. Letters of Support from Collaborators, Contributors and Consultants	Letter_Support1029235352.pdf

Institutional Environment and Commitment to Training Section

11. Description of Institutional Environment and Commitment to Training	Institutional_Environment_Training1029235287.pdf

Other Research Training Plan Section

Vertebrate Animals

The following item is taken from the Research & Related Other Project Information form and repeated here for your reference. Any change to this item must be made on the Research & Related Other Project Information form.

Are Vertebrate Animals Used? Yes ✔ No

12. Are vertebrate animals euthanized?

If "Yes" to euthanasia
Is method consistent with American Veterinary Medical Association (AVMA) guidelines?
If "No" to AVMA guidelines, describe method and provide scientific justification

13. Vertebrate Animals

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Other Research Training Plan Information

14. Select Agent Research

15. Resource Sharing Plan Resource_Sharing_Plan1029235293.pdf

16. Authentication of Key Biological and/or Chemical Resources

Additional Information Section

17. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* Yes ✔ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s):

18. Alternate Phone Number: [redacted]

19. Degree Sought During Proposed Award:

Degree:	If "other", indicate degree type:	Expected Completion Date (MM/YYYY):
PHD: Doctor of Philosophy		06/2022

20. * Field of Training for Current Proposal: 104 Computational Biology

21. * Current Or Prior Kirschstein-NRSA Support? Yes ✔ No

If yes, please identify current and prior Kirschstein-NRSA support below:

Level*	Type*	Start Date (if known)	End Date (if known)	Grant Number (if known)

22. * Applications for Concurrent Support? Yes ✔ No

If yes, describe in an attached file:

23. * Citizenship

U.S. Citizen U.S. Citizen or Non-Citizen National? ✔ Yes No

Non-U.S. Citizen With a Permanent U.S. Resident Visa

With a Temporary U.S. Visa

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here:

24. Change of Sponsoring Institution Name of Former Institution:*

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Budget Section

All Fellowship Applicants:

25. * Tuition and Fees:

None Requested ✔ Funds Requested

Year 1	$5,945.00
Year 2	$5,945.00
Year 3	
Year 4	
Year 5	
Year 6 (when applicable)	
Total Funds Requested:	$11,890.00

Senior Fellowship Applicants Only:

26. Present Institutional Base Salary: Amount | Academic Period | Number of Months

27. Stipends/Salary During First Year of Proposed Fellowship:

a. Federal Stipend Requested: Amount | Number of Months

b. Supplementation from other sources: Amount | Number of Months

Type (e.g., sabbatical leave, salary)

Source

Appendix

28. Appendix

Applicant's Background and Goals for Fellowship

A. Doctoral Dissertation and Other Research

My ultimate career goal is to become an independent investigator and a tenured professor. I envision the research program of my future lab to be a harmonious synthesis of computational metabolism and software development, enriched by collaborations with wet lab researchers and clinicians. In a recent review article by Drs. DeBerardinis and Chandel (*Sci Adv*, 2016), these leading scientists point to three primary bottlenecks to unlocking the keys of cancer metabolism for therapeutic advancement. One of the highlighted challenges was the lack of analytical and computational tools and approaches to be able to deconvolute the complex metabolic phenotypes that exist between cell populations within a tumor. My research plan is to develop the necessary tools and algorithms that would enable a more holistic understanding of the underpinnings of cancer metabolism and would eventually lead to more effective and personalized treatment options. I have already had success achieving the requisite milestones. Specifically, I have contributed significantly to collaborative projects as a co-author on manuscripts that interrogate these complex metabolic landscapes and help form the foundation of my proposed F99 phase research plan (***Mol Cell*, 2018; *Cell Metabolism*, 2019; *GigaScience*, In Press; *Cell*, In press**), and I have prepared a first-author manuscript currently under its second round of review (***bioRxiv*, 2019**) that presents a tool for the uniform and automated processing and analysis of sequence data and a validation of its performance in both cancer and neurological contexts. In this package, I also introduced vital open-source tools currently missing from the computational toolkit to handle the inherent biases in ribosome profiling data. This will be followed by my final dissertation publications wherein we will present *Metaboverse*, and where we will deconvolute and validate complex, dispersed regulatory events and signals in cancer metabolism. To date, I have presented four posters at local conferences, three posters at national and international conferences, one selected talk at a local conference, one short talk at a national conference, one selected talk at an international conference, and one invited seminar talk at the University of California San Diego. **My background and skills, augmented with the additional training outlined in this proposal, will enable me to become a leader at the intersection of cancer metabolism, computational metabolism, network biology, and machine learning**. I began preparing for these career goals early and my research experience is summarized below:

Fall 2013 - Summer 2016 (undergraduate) – *Undergraduate Research Assistant* (**Advisor: Julianne Grose, Ph.D**) – At the start of my second year during my undergraduate education, I began research with Dr. Julianne Grose. There I learned basic laboratory procedures and isolated novel bacteriophage that infect *Erwinia amylovora*, a fruit tree pathogen. I learned how to prepare genome sequencing libraries for this and other phages and then annotated and characterized their genomes. During my time in the Grose lab, **I published a first author paper in PLoS ONE** in collaboration with Dr. Sandra Hope describing the genomic characteristics and evolution of several *Brevibacillus* phages. Additionally, **I published another first author paper in the Journal of Applied and Environmental Microbiology** that introduces a combined computational-wet-lab methodology for distinguishing environmental microbial strains from other, closely related strains. I was also a co-author on 4 other publications related to this research. In total, I was the **first author or co-author on 51 phage genome publications** in NCBI's GenBank. While I was an undergraduate research assistant, **I mentored 22 undergraduate researchers, 16 of which were co-authors on publications or posters**. I helped prepare and present 7 posters at scientific conferences and was **selected to give a talk at the 2015 Tri-Branch American Society for Microbiology conference**.

Spring 2014 - Fall 2014 (undergraduate) – *iGEM Team Project Leader* (**Advisor: Julianne Grose, Ph.D**) – I was a member of the 2014 BYU International Genetically Engineered Machine (iGEM) team. For this project, we synthetically redesigned a common wastewater bacterium, *Nitrosospira multiformis*, to more efficiently break down sewage biofilm. As a part of this project, we talked with local wastewater reclamation workers to discuss key components in the design of this synthetic organism to improve the efficiency of the bioreactor and help address some of the biggest challenges in wastewater reclamation. I led the project improving the biofilm degradation ability of this organism and the design and creation of our team's website. At the end of this project, we traveled to the 2014 iGEM Giant Jamboree in Boston to present our work via an oral team presentation.

Summer 2016 (graduate) – *Rotation Project* [redacted]

[redacted]

Fall 2016 (graduate) – *Rotation Project* [redacted]

Fall 2016 (graduate) – *Rotation Project* (**Advisor: Jared Rutter, Ph.D**) – During my rotation with Dr. Jared Rutter, my project focused on defining the role of different proteins identified as potential actors in peroxisomal disorders. In particular, I was interested in proteins that presented a mitochondrial phenotype upon perturbation, as the role of these factors are less characterized in peroxisomal disorders. During this project, I generated several yeast strains and genetic tools that aided in our determination of these candidate proteins' role in a model of Peroxisomal Biogenesis Disorder when challenged with the deletion of the mitochondrial quality control factor, *MSP1*/*ATAD1*.

Spring 2017 (graduate) – *Rotation Project* [redacted]

Summer 2017 – Present (graduate) – *Ph.D Dissertation Research* (**Advisor: Jared Rutter, Ph.D**) – I joined Dr. Rutter's lab for a variety of reasons – his emphasis on independence and student-driven projects, the freedom he would give me to blend my dual-training in both computational and wet lab biology, and his expertise in cancer metabolism. An early collaboration (***Cell Metabolism*, 2019**) made me start thinking of the challenges of contextualizing the complex cancer metabolism network. In this manuscript, we described the consequences the loss of a mitochondrial metabolite transporter, initially characterized in our lab, on tumorigenesis. In our models I began to notice interesting and complex metabolic patterns between the different stages of tumorigenesis and realized there was a void in available computational tools required to dig deeper into these questions. This project also intertwined nicely with the first phase of my dissertation research, which involved building a software package that standardized, enhanced, and automated ribosome profiling and RNA-Seq computational analysis. Early in my dissertation, I analyzed several ribosome profiling datasets and realized that, unlike RNA-seq, the standards for computational analysis of ribosome profiling data had not been established yet and a culture of analysis transparency (open source scripts) has been slow to be adopted by the community. Working with Dr. Jeffrey Morgan, an expert in ribosome profiling; Drs. Aaron Quinlan and Jay Gertz, experts in RNA-Seq and computational tool design; and other collaborators, **we built *XPRESSyourself* to meet these needs. The paper describing this tool is currently available as a pre-print (DOI: 10.1101/704320) and is under a second round of peer-review at *PLoS Computational Biology***. **This paper, for which I was a corresponding author, has also helped establish me in the computational biology field and has led to reputable journals, such as *Bioinformatics*, reaching out to me to review papers**. These projects, and another project (***GigaScience*, In Press**) will feed directly into my next project, *Metaboverse* (github.com/Metaboverse; metaboverse.github.com/demo; **Aim 1.1-3**), where I will standardize and improve the methods available for the integrated analysis of sequence, proteomics, and metabolomics data.

Members of the metabolism community often struggle to make sense of their data, especially as current trends in analysis tend to focus on a list of differentially expressed entities. Understanding how these components fit into the larger network is difficult, and contextualizing these data becomes an extremely laborious and tedious task. Having assembled a team containing experts in metabolism, metabolomics, topological data analysis, network biology, and cancer biology, we are building this tool and the appropriate analytical methods to aid a user in contextualizing their data. The tool will additionally allow for the multi-omic integration of sequencing data, or any -omic for which features can be mapped to gene identifiers. Based on feedback from presentations I have given, this tool is in high demand and we are set to have a strong user base once the beta-version is released in early to mid 2020. Once this tool is finalized and published in a peer-review journal, I will focus my remaining F99 phase efforts on phase 3 of my thesis (**Aim 1.4**), in which I will use these tools developed over the past couple of years to answer new, complex, and exciting problems in metabolic regulation. It is important to note that once we have established a sufficient user base for the tools we are creating, Dr. Rutter and I will begin applying for funding support to continue to maintain and improve these tools. I will also continue to provide support for this tool and *XPRESSyourself*, regardless of funding throughout the duration of my F99 and K00 phases as they will be central in the work I will propose. As discussed above, I have presented my research at multiple venues during my graduate career, but I will highlight a selected talk on *Metaboverse* at the EMBO/EMBL Metabolism Meets Epigenetics meeting in Heidelberg, Germany, and an invited talk on *XPRESSyourself* hosted by the Center for Computational Biology & Bioinformatics at the University of California San Diego.

Aside from my research experience, several characteristics uniquely position me for excellence in computational metabolism, which I discuss in some detail below:

- Dual Training: I come from both computational and biology backgrounds. I completed my undergraduate degree in Molecular Biology and supplemented this training with computer science and genomics training. During my graduate career, I have focused on computational approaches, but continue to receive wet lab training and have performed my own high-throughput experiments. This background is supplemented by Dr. Rutter, who pushes me to think more mechanistically about the biological questions I pursue so I can offer unique perspectives to cancer and metabolism.
- Leadership: I have naturally fallen into leadership roles. During my undergraduate career, I was a project leader for our University's iGEM team and led the team wiki page design and execution. During my undergraduate training, I mentored 22 undergraduate students over three years, in addition to my service mentoring elementary school children. During my graduate career, I have continued to assume leadership roles. For example, I have assembled two separate teams with the necessary expertise for the *XPRESSyourself* and *Metaboverse* projects. I serve as a SACNAS officer and have mentored two undergraduate students.
- Collaboration: The teams that I have assembled have been valuable collaborators, enabling success during my research career. In addition to intra-lab collaborations, I have independently established collaborative relationships with other labs. I also attend conferences with the intention of establishing new collaborations. For example, from my interactions with others during the 2019 Genome Informatics conference, I established a connection with one of the lead PIs of the Galaxy project who requested that I work with him to integrate the *XPRESSyourself* tool into the Galaxy webserver.
- Endurance: I am able to persist, regardless of the barriers and difficulties I face. This was largely instilled to me during my undergraduate and graduate hobbyist running career. After running multiple marathons, each time shaving tens of minutes off of my previous personal records through discipline and training, I eventually ran a 50-mile race in the harsh southern Utah desert. While unfortunately I did not complete this race, I ran until I could hardly walk, blistered and beaten, and only stopped when I missed my final cut-off time by minutes. I have seen this same tenacity pay dividends during my research career, allowing me to publish two first-author papers on my undergraduate research, and leading the team that published my first first-author paper during my graduate career, involving weekend, 20 hours/day coding sprees to complete the project when we discovered we had a competitor. When a challenge is in front of me, I have a laser-like focus and am able to push forward. An essential part of learning endurance has been learning balance as well, where, perhaps unlike my running career where I over-trained for the 50-mile race and ran those 40 miles through the desert on a torn ligament, I have been able to find an optimum performance level in my research that allows me to drive my research forward while mitigating burn-out.

B. Training Goals and Objectives

There is great strength in the co-application of wet lab research and computational biology. While the integration of these two fields is improving, a disconnect remains and limited computational tools for handling complex datasets continues to stifle advancement. My overarching goal is to provide a bridge between these fields and further close the gap between cancer metabolism and computational biology. Completion of my goals outlined in this proposal will provide me with the training I need to provide this bridge. I have chosen a mentor, Dr. Rutter, and other collaborators, who all have expertise in metabolism, cancer biology, computational biology, network analysis, and machine learning. Both my wet lab and computational background has been a benefit to my research. I have chosen mentors with expertise across scientific domains to allow me to answer difficult and complex questions in cancer metabolism, and to approach cancer metabolism mechanistically through systems-wide approaches. The University of Utah has incredible statistical genomics and computer science communities. Members of these communities, such as my collaborators from the *XPRESSyourself* project, Dr. Aaron Quinlan, and current or continuing collaborators such as Drs. Bei Wang Phillips (see sponsor/co-sponsor statement), Jason Gertz (see letter of recommendation), and James Cox (see letter of support), have been and will be essential collaborators to ensure the research I perform is robust and high-quality. I meet with Dr. Bei Wang Phillips bi-weekly as able and with my other core collaborators at least monthly to discuss progress and generate ideas for future project directions.

I am extremely fortunate to work in Dr. Rutter's lab, where I am given a great amount of trust and independence with my project and the its direction. I meet with Dr. Rutter one-on-one once a week to discuss ideas and experimental plans, and also frequently in person or via email other times throughout the week. Dr. Rutter has always provided prompt feedback that has been invaluable as I develop my projects. Dr. Rutter has truly become a mentor in every sense of the term, and someone I have learned from immeasurably. I also meet with the Rutter lab Big Data group every week to discuss the ideas proposed in this application and their progress. I am also able to provide feedback for my peers in this venue. I present my research often in lab meeting to get feedback on the direction of my projects. These meetings have been consequential to the development of my ideas as the members of the lab come from diverse backgrounds and have valuable perspectives. Additionally, I have cultivated a network of computational biologists at the University of Utah and often reach out to them with questions. The University of Utah has a strong collaborative spirit, therefore when my established network is unable to provide the necessary guidance, it is easy to reach out to someone with the necessary expertise at the University and they have always welcomed these interactions. For example, before presenting my research to a more computational audience, I meet with this network to hone my presentation for scientists from a computational background. Not only do these interactions help improve the research that I perform, but they also provide me with training to present my ideas and results in a concise and clear manner and defend those ideas in front of experienced graduate students, postdoctoral fellows, and senior scientists.

The F99 and K00 phases of my training will be vital to developing the skills I need to run a successful computational metabolism lab in the future. To ensure I obtain the proper training, I have outlined the following goals. Component steps planned to achieve these goals are detailed in Table 1 of Section C in this document.

1. <u>Research Development</u>: While I have years of experience in bioinformatics and computational biology, there are still several skills I am lacking in my toolkit. For instance, in order to deconvolute data within complex metabolic networks, I will need to lean on principles of graph theory. In order to develop these skills, I have partnered with Dr. Bei Wang Phillips (see co-sponsor statement) and her graduate student, Youjia Zhou, to master and implement these principles in the *Metaboverse* software package. Another principle that will be essential for the projects proposed in this application is machine learning. While some view machine learning as the cure-all in medicine, improper implementation is rampant. As during the *XPRESSyourself* project, where I worked closely with Drs. Jay Gertz and Aaron Quinlan to ensure I implemented statistical and computational principles correctly, I will work with Dr. Bei Wang Phillips to develop the necessary intellectual foundation.

Various aspects of this proposal will require wet lab validation. During my training in the Rutter lab, I have learned how to prepare high-throughput sequencing libraries. I am also fortunate to be in a lab consisting of individuals from diverse backgrounds and experiences. We currently have nine post-doctoral fellows who bring expertise in sequencing and mass spectrometry, as well as yeast genetics, mammalian cell culture, and biochemistry. I intend to continue to strengthen my wet lab skills by preparing sequencing libraries and samples for mass spectrometry (with the support of others in the Rutter lab who do this routinely) to carry out the validation studies proposed in this application. My wet lab background and training will profit immensely from these relationships and training from others in the Rutter lab.

In addition to the papers I will publish as first author, and to make full use of my unique background in computational metabolism, I plan to work on 2-4 collaboration projects per year that will lead to additional co-

author papers. While I have been able to contribute significantly to each of these projects, it has not deterred me from maintaining a high level of productivity on my personal projects.

2. Computational Training: While originally trained in C++, I primarily use Python and R for my research. These programming languages, while incredible useful, have limitations. Thus, I have begun teaching myself other programming languages, such as Julia for its speed and efficiency for data processing tasks and JavaScript for the dynamic visualization libraries available. I have also been refreshing my HTML and CSS skills to aid in design and implementation of the user front-end experience of the *Metaboverse* project. I will continue to develop these skills, as I have done with Python and R over the past several years, to ensure that I have a broad, yet firm, grasp over these languages.

3. Science Communication: In order to continue to develop my science communication skills, I will approach growth in this area through a handful of avenues. First, grant writing will be an essential skill that I must continue to work on, especially as I will run my own lab at some point in the future. While I have taken a grant writing course and successfully applied for and received a T32 training grant, Jared will also help me find opportunities to aid in grant writing for applications related to my project. The second avenue will be through publications. Dr. Rutter has already been incredibly helpful in this regard by allowing me to take the lead on drafting, submitting, and revising the manuscript for *XPRESSyourself*. I will continue to take the lead on future manuscripts for my project and write 1-2 review articles related to the developing field of computational metabolism. The third and final avenue will be in relation to presentation skills. To date, I have attended 4 external conferences while in the Rutter lab, where I have presented 3 posters and 1 talk on my research. I was also fortunate enough to be invited to present my research to the UCSD Center for Computational Biology & Bioinformatics. I will continue to attend conferences related to metabolism and complex systems and seek opportunities to give talks at these venues. I will also use these experiences to continue to build my collaborative network. I believe that clinical experiences are essential for grounding and focusing our research. As such, I will continue shadowing Dr. Stephen McKeller, a heart surgeon, and Dr. Bill McKean, an oncological physician, both of whom are associated with the Rutter lab, to ensure I develop this critical human-centered grounding to guide my research.

4. Leadership: To develop the skills I need to become a successful PI, I have taken several approaches in the development of my training plan. I am currently an officer for the SACNAS chapter at the University of Utah, where I manage the group's webpage design and upkeep and social media outreach. I also regularly review for the Journal of Emerging Investigators, a peer-reviewed journal dedicated to mentoring middle- and high-school students as they publish their own research. A central goal and task as a reviewer for this journal is to assist these young researchers in developing essential scientific communication skills. My expertise has also been solicited for peer-review at reputable journals.

I have been actively sought out opportunities for providing in-person mentorship. This past Summer I mentored an intern through the Native American Summer Research program, with whom I taught computational methods for investigating cancer metabolism regulation. I also mentor an undergraduate student who is planning on attending graduate school. They are currently assisting on the *Metaboverse* project and will soon be beginning an independent project of their own design. I will aid them as they prepare their graduate school applications and other appropriate fellowship applications. I also take the lead in meetings with collaborators and have secured computational resources through the University of Utah's Center for High Performance Computing allocation award submission project for the past three years for all projects carried out in the Rutter lab.

Dr. Jared Rutter, Dr. Bei Wang Phillips, and I are confident that this training plan will be fundamental and sufficient to prepare me for my transition from Ph.D student to postdoctoral fellow, and eventually a tenure-track professor. Upon completion of my degree, I will apply for postdoctoral positions in academic research where I can continue to develop my interdisciplinary computational/wet lab training and prepare myself for a position as a principle investigator at an NCI-Designated Cancer Center. There, I will apply systems biology approaches to complex, mechanistic questions in cancer metabolism and will continue developing methods and tools that span and bridge the computation-biology gap. To ensure I stay on track to meet these goals, and aside from our weekly meetings and day-to-day communication, Dr. Rutter and I hold a yearly progress meeting. While we discuss my goals weekly, this yearly meeting gives us the opportunity to reflect on the past year, revise training plans, and evaluate whether I am on target to achieve my goals. These meetings have been a significant in my development as a scientist.

C. Activities Planned Under this Award

The milestones and benchmarks listed in Table 1 will keep me on schedule to achieve the goals discussed in my training plan (Section B). The F99/K00 award will be consequential in providing me with the independence and confidence to drive my own cancer research program and make a lasting impact in computational metabolism and cancer biology.

Table 1. Timeline and Milestones for F99/K00 Training

	F99		K00			
Activity	**Y1**	**Y2**	**Y1**	**Y2**	**Y3**	**Y4**
Research Activities:	80%	80%	87%	87%	80%	80%
- Maintain *XPRESSyourself* software	O	O				
- Complete development of *Metaboverse* software (Aim 1.1-3)	O					
o Expression Pattern Search Engine (Aim 1.1)	O					
o Mechanistic and regulatory curation (Aim 1.1)	O	O				
o k-NN time-aware search algorithm (Aim 1.1)	O					
o Documentation and usability	O					
o Perform validation studies (Aim 1.2)	O					
o Prepare and submit manuscript for peer review	O	O				
- Explore and validate amplifying regulatory events in metabolic networks (Aim 1.4)	O	O				
o Develop statistical network methods for exploring complex regulatory events within *Metaboverse* (Aim 1.3)	O	O				
o Curate time course datasets (Aim 1.3)		O				
o Interrogate temporal and spatial networks for regulatory events (Aim 1.3)		O				
o Validate regulatory networks (Aim 1.3)		O				
o Prepare and submit manuscript for peer review		O	O			
- [redacted]			O	O		
[redacted]			O	O	O	O
[redacted]					O	O
[redacted]				O	O	O
Intellectual Training:	8%	5%	3%	3%	3%	3%
- Attend weekly seminars	O	O	O	O	O	O
- Complete advanced seminar coursework	O					
- Complete 5th year graduate journal club	O					
- Complete ethics in research course	O				O	
- Complete machine learning course		O				
- Attend lab meeting (weekly)	O	O	O	O	O	O
- Attend department Research in Progress (weekly)	O	O	O	O	O	O
- Clinical shadowing	O	O	O	O	O	O
Professional Development:	5%	5%	5%	5%	5%	5%
- Attend cancer metabolism conferences (1-2x/yr)	O	O	O	O	O	O
- Attend systems/computational biology conferences (1-2x/yr)	O	O	O	O	O	O
- Write review article(s)		O	O			
- Volunteer as peer-reviewer	O	O	O	O	O	O
- Student mentorship	O	O	O	O	O	O
- Complete TAship requirement	O					
- Meet with faculty interviewees	O	O	O	O	O	O
- Attend local metabolism and cancer conferences/symposia	O	O	O	O	O	O
Milestones:	2%	5%	0%	0%	5%	5%
- Prepare and submit *Metaboverse* and metabolic regulation manuscripts	O	O				
- Prepare and defend dissertation		O				
- Prepare K00 transition application and develop K00 research plan		O				
- Apply for NIH Pathway to Independence (K99/R00) or other R-level grants					O	O
- Identify, interview for, and obtain tenure-track faculty position						O
Mentorship Plan:	5%	5%	5%	5%	7%	7%
- Meet with sponsor (weekly)	O	O	O	O	O	O
- Meet with co-sponsor (bi-weekly)	O	O	O	O	O	O
- Attend and receive feedback at sub-group meetings (weekly)	O	O	O	O	O	O
- Present at lab meeting (3x/yr)	O	O	O	O	O	O
- Present at department Research in Progress (1x/yr)	O	O	O	O	O	O
- Present at Seminars in Metabolism or similar venue (1x/yr)	O	O	O	O	O	O
- Meet with dissertation committee (1-2x/yr)	O	O				
- Progress report and planning meeting with sponsor (yearly)	O	O	O	O	O	O
- Identify K00 mentor		O				
- Prepare for faculty interviews					O	O

Specific Aims

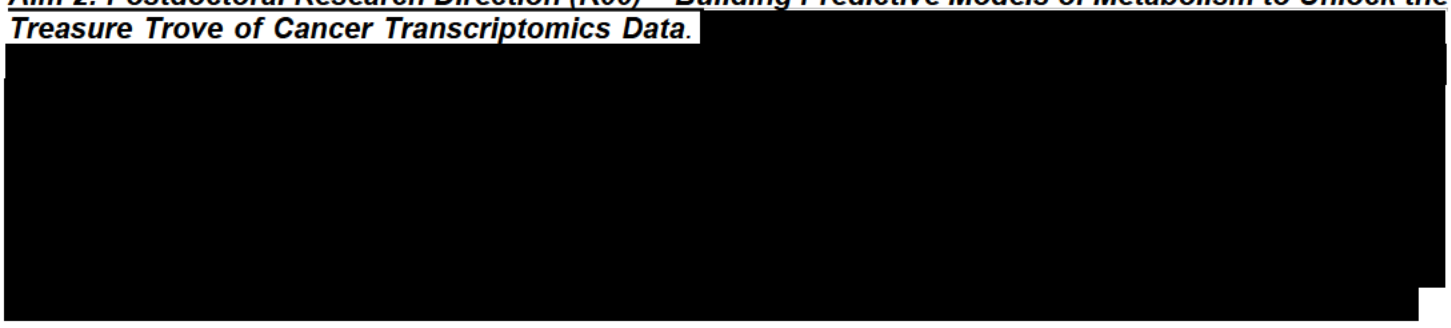
Metabolism is a complex network of chemical reactions. These reactions are required to sustain life and involve a multitude of actors, namely metabolites, proteins, and the genes that encode these proteins[1]. The dysregulation of metabolism is one of the hallmarks of cancer[2–4]. Much of the research in cancer metabolism has sought to understand this complex network using reductionist approaches by interfering with a single gene, protein, or metabolite to determine its effect[2]. While valuable, this approach limits the overall understanding of how this perturbation and its outcomes fit into the larger network. To approach this system holistically, computational tools and more sophisticated analyses are needed to properly deconvolute these networks[5]. High-throughput methods enable us to probe these networks systematically, but it is difficult to contextualize these data on the metabolic network[6]. Additionally, researchers tend to use only a limited number of datapoints from a dataset and only focus on entities that are regulated above an arbitrary threshold[7,8]. While this approach helps identify large magnitude changes, it neglects essential information that is encoded within lower magnitude changes within the network.

To begin to address these challenges in -omics data contextualization, we built *XPRESSyourself* to uniformly process and analyze ribosome profiling and RNA-Seq data[9]. Our collaborator and Director of the University of Utah Metabolomics Core, Dr. James Cox, has built an automated pipeline for processing metabolomics raw signal data. Together, these two software packages will form the operational foundation of *Metaboverse*, a software package for contextualizing multi-omic data on the global metabolic network. It will also allow the systematic searching of regulatory patterns within the network. For example, we are interested in identifying reactions where input abundance is high and output abundance is low, indicating some regulatory change at a reaction. We will also build more sophisticated search algorithms for identifying temporal regulatory events. Using these tools, we will be able to interrogate low magnitude changes within the network. By using the pathway neighbors of the changed entity, we can also strengthen our confidence in whether these smaller changes are a result of noise or are meaningfully changing[10]. Identifying and understanding these regulatory principles will allow for improved statistical confidence in metabolic events, will describe the regulatory landscape of metabolism with improved clarity, and will describe these changes within the context of tumorigenesis.

My primary goal is to become an independent investigator leading a lab that bridges the gap between mechanistic wet-lab and computational cancer metabolism research. During the F99 phase, I will lead the team developing *Metaboverse* and interrogate these more complex forms of temporal metabolic regulation. During the K00 phase, I will develop robust machine learning models to extract the metabolic state from transcriptomic data, a staple platform in cancer biology research[11].

Aim 1: Dissertation Research Project (F99) – Visualizing, Contextualizing, and Analyzing Chaotic Metabolic Networks and their Regulation. (**1.1**) I will complete development of *Metaboverse*, implementation of novel expression pattern search algorithms, and curation of metabolic interactome databases to allow identification of novel regulatory events and infer their mechanisms. (**1.2**) I will demonstrate the utility of *Metaboverse* by identifying previously missed regulatory events from publicly available biological data. I will analyze flux metabolomics datasets in metabolic perturbation models generated in our lab. (**1.3**) I will develop improved statistical methods for deconvoluting real, low-magnitude changes within the metabolic network from noise. I will curate high-quality time course datasets, identify temporal regulatory events, and validate these events.

Aim 2: Postdoctoral Research Direction (K00) – Building Predictive Models of Metabolism to Unlock the Treasure Trove of Cancer Transcriptomics Data.



With my dual training possible with my background and the unique combination of my sponsor and co-sponsor, I will be able to bring a more mechanistic perspective to computational approaches for cancer metabolism than previously possible and establish a pioneering lab in computational metabolism.

Research Strategy

A. Significance

Cancer metabolism is complex, dysregulated, and difficult to deconvolute. Metabolism is the sum total of the chemical reactions that occur within a cell to build the necessary units for a cell to function and survive[14]. While commonly viewed as the "powerhouse of the cell", mitochondria do more than just generate energy and act as a hub for cellular metabolism[15,16]. The consequences of aberrant metabolism are far-reaching, playing a significant role in inborn errors of metabolism, diabetes, and in particular, cancer. In some cancers, altered glucose utilization leads to perturbations in metabolism and contributes to metabolic states favorable for tumorigenesis[3]. While a variety of pharmacological methods have been proposed to alleviate dysregulated metabolism in this context, we are far from a full understanding of the intricate dynamics of cancer metabolism systems and the consequences of their disruption[2,3,14].

In order to better understand cancer metabolism and develop more targeted treatment options that restore native metabolic homeostasis and discourage tumorigenesis, we must approach a tumor's metabolism systematically to deconvolute its complex nature[17,18]. However, a major bottleneck in metabolism research is contextualizing data within the global metabolic network[12], and analysis of these data and their place in the global metabolic system is difficult. Over the last decade, tools have been created to address this issue of data contextualization, yet they suffer from a variety of problems. All are either limited in scope of the analyses they are able to perform, unable to integrate multi-omics data, or are simply outdated, inoperable, and unusable for the general user[19–23]. Therefore, in order to make better sense of a tumor's metabolism system, we need to develop better computational tools that will allow for this deconvolution.

A holistic model of cancer metabolism relies on utilizing the entire dataset. Along with improvements to the way we contextualize data, we must make sense of the entire system's ability to adapt its behavior upon perturbation. However, current analytical tools are unavailable to extract the required data, particularly in metabolomics data where missing values for metabolites are common[24]. Additionally, analyses tend to focus on a limited list of large magnitude changes that fall outside of established, arbitrary thresholds. For example, in a metabolomics experiment, a researcher is often provided with a list of measured metabolites that fall outside a fold change greater than 2 or less than -2. However, we know that noise is inherent to biology[25–27], and that ignoring entities that do not change by the arbitrary magnitude discards valuable data describing the entire state of metabolism and the genetic environment. By extracting more from our data and moving beyond reductionist approaches[18], we will be able to better understand the intricate details of metabolism in cancer.

Our new computational framework currently in development, *Metaboverse*, will deconvolute and contextualize multi-omic data and shed light on complex regulatory events in cancer metabolism. This computational strategy builds on two foundational projects from the Rutter lab. The first is *XPRESSyourself*, a computational pipeline I developed for automating the processing and analysis of transcriptomic and translatomic sequence data[9]. Paired with the work of our collaborator, Dr. James Cox, the University of Utah Metabolomics Core Director, who developed a pipeline for the automation and uniform processing of metabolomics data, these software packages will be fundamental in analyzing data for this proposal. The second is a recent manuscript from our lab where we investigated the fundamental metabolic network structure and described important considerations for contextualizing data within this complex structure[28]. In sum, these projects will allow us to visualize multi-omic metabolic data correctly.

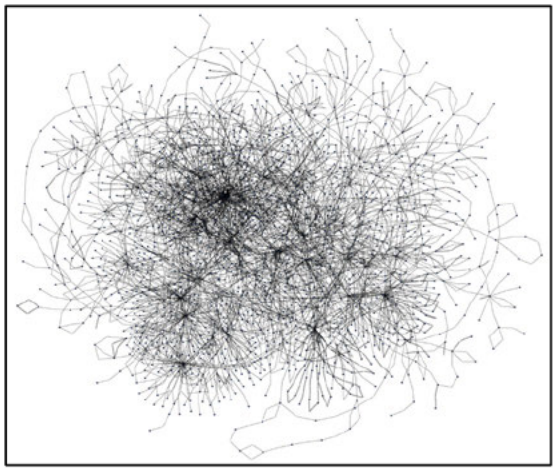


***Figure 1: The Metabolic Network**. A representation of metabolism without organelle compartments or central metabolite hubs from Waller et. al., In Press. One can appreciate the complexity of the metabolic network and the challenge of contextualizing data within this structure. Each node (point) represents a chemical entity. Each link (line) represents a relationship between nodes.*

Metaboverse will be an open-source, interactive, and scalable framework for multi-omic data visualization and analysis on the global metabolic network **(Aim 1.1-3)**. With this tool, we will be able to answer questions related to more complex regulatory mechanisms in cancer metabolism. For example, I hypothesize that dispersed regulation across a network can culminate in larger downstream metabolic changes **(Aim 1.4)**. I will also discuss plans for optimizing metabolic predictive models from sequence data in a postdoctoral lab specializing in network biology and machine learning **(Aim 2)**.

B. Approach

Aim 1: Dissertation Research Project (F99) – Visualizing, Contextualizing, and Analyzing Chaotic Metabolic Networks and their Regulation. To date, my dissertation has been marked by several collaborative efforts, and my own effort to standardize and enhance sequence analysis, particularly for ribosome profiling data. Each of these projects, discussed below, contribute significantly to the remaining F99 work I will propose.

Dissertation progress report

a) Regulation of Tumor Initiation by the Mitochondrial Pyruvate Carrier. As part of a collaborative project, we described how tumorigenesis is drastically increased by the loss of the mitochondrial pyruvate carrier (MPC) in mouse and fly colon cancer models[29]. I curated and analyzed the mouse model and human patient data to identify the systematic consequences of MPC-loss on pyruvate metabolism and became interested in developing methods that would allow for a more integrated analysis of cancer metabolism. During this project I developed *XPRESSplot*, a component of *XPRESSyourself*, that provides an easy-to-use package for plotting biological data[9]. Methods included in this package and used for this project included principle component analysis, differential expression analysis, systematic analysis of gene regulatory patterns, and more.

b) Compartment and Hub Definitions Tune Metabolic Networks for Metabolic Interpretations. In this work, we described key considerations for analyzing metabolic networks and data[28]. As metabolic networks are complex and pathways are often entangled, we described the topographical structure of the network and determined that removal or simplification of "hubs" (metabolites that participated in more than 50 reactions), aided in the disentanglement of this network and made visualization and interpretation of metabolic data easier. These improvements were demonstrated by reanalyzing existing data and extracting new metabolic insights from the data using these improvements. During this project, I began developing the foundation for *Metaboverse*.

c) XPRESSyourself: Enhancing, Standardizing, and Automating Ribosome Profiling Computational Analyses Yields Improved Insights. Early into my dissertation, I noticed a lack of standardized and automated methods for processing and analyzing sequence data. This was particularly apparent for ribosome profiling, where the experimental methodology has been available for a decade, yet computational approaches are incomplete and inconsistent. I developed *XPRESSyourself* as an all-in-one toolkit for ribosome profiling, standard single-end, or paired-end RNA-Seq data processing and analysis[9]. Along with learning software development best practices, I filled voids in the ribosome profiling toolkit where publicly available options were missing, such as fast and efficient quality control modules and a curation tool that allowed for the removal of systematic biases present in ribosome profiling data[30,31]. This project allowed me to master methods for sequence data analysis in RNA-Seq and ribosome profiling[32]. As part of the validation of this tool, we benchmarked *XPRESSyourself* to publicly available data. We showed that our methods could extract additional supporting biological information.

Development, Validation, and Release of Metaboverse. A challenge within the metabolomics community since its inception has been contextualizing data[6]. While it is simple to determine up- or down-regulated components of metabolism from most experiments, making sense of how these changes contribute to the larger story has traditionally been performed manually through the curation of a graphical pathway representation with the data overlaid by hand. While some tools have emerged to handle this challenge, they are severely limited in capability[19–23]. For example, one of the most popular options, *Cytoscape*, offers robust visualization and a certain level of customizable analysis[19]. However, in order to perform more complex searches in a network, like those proposed in this Aim, additional infrastructure needs to be built from the ground up.

Five essential challenges remain for which a comprehensive tool is missing. First, how do we develop a metabolic network visualization tool that is easy to use and then how do we understand its output? Second, how do we integrate the full extent of available regulatory information to infer the mechanism behind the events we observe? Third, how do we parse out relevant information from the global network when massive amounts of data and annotated relationships are involved? Fourth, how do we strengthen our confidence in changes and relationships across the global metabolic network? Fifth, how to we integrate cross-species reaction information in a way that might inform identification of a novel reaction in our organism of interest? The development of *Metaboverse* will address each of these challenges (alpha version under development at github.com/Metaboverse). *Metaboverse* is designed to be a simple tool to help users integrate single or multi-omic datasets into the metabolic network, contextualize their data within the global network, and search the network for interesting regulatory information. It is capable of processing data for every model organism, and its network structure is customizable. To date, the basic structure of *Metaboverse* is in place and we have developed proof-of-concept tests for the majority of planned features; however, several key features are still in active

development, which will compose the sub-aims for **Aim 1.1-3**. A working demo demonstrating some of these planned features is available online (metaboverse.github.io/demo). **Completion of these sub-aims will provide me with thorough training in metabolomics data analysis and processing, network biology, machine learning, and database curation**. **These sub-aims will also require tailored statistical method development. These supplementary training components will be guided by my co-sponsor, Dr. Bei Wang Phillips, with additional mentorship from Dr. Jason Gertz.**

Aim 1.1: Complete analytical platform and database curation for Metaboverse. In order to allow for the robust multi-omic integration and analysis of data in the context of the metabolic network, we will build advanced capabilities into *Metaboverse* that will allow for the systematic analysis of regulatory events in cancer metabolism and improve our ability to generate hypotheses and infer regulatory mechanisms from data. Throughout this proposal, I will generally refer to a regulatory event as a reaction where input is high and output is low, or vice versa. If an event is accompanied by data for modifiers of that reaction, such as a catalyst or inhibitor, these reactions will be prioritized for the user. However, more complex regulatory events will be analyzed by *Metaboverse*.

- *Expression and abundance pattern search engine (PaSEN)*: In collaboration with Dr. Bei Wang Phillips and Youjia Zhou, we are developing *PaSEN* using principles from network topology searches for rapidly analyzing the global metabolic network for interesting regulatory events[33,34]. In Figure 2A, the transition between L-Arginine (L-Arg) and L-Argininosuccinate (ARSUA) shows a large difference in relative abundances across the reaction (>2 fold). *PaSEN* will search for changes across a reaction using similar and more complex criteria. *PaSEN* will interrogate the entire network for potential regulatory events, and therefore avoid the bias originating from a researcher focusing on a few familiar pathways. The current metabolic model includes modifier information for reactions. In this same example in Figure 2A, we see that gene expression for *ASL*, whose gene products form the ASL tetramer which acts as a catalyst in this reaction, is down regulated. It could be inferred that the reduction of this catalyst is driving the change across the reaction. Results such as these will be returned to the user as a prioritized results table based on these and other considerations. This output will allow the user to quickly identify the highest confidence regulatory events to help them focus their follow-up and validation experiments on network-wide changes. The ability to track regulatory patterns across time will also be incorporated into the search engine.
- *k-Nearest Neighbors searche*s: Once a regulatory event is identified, a user may want to explore how a change affects distal reactions. For example, does the decrease in glycerol (center) lead to changes in pathways other than in glucose metabolism? Using k-nearest neighbors (k-NN) search principles[35], users will be able to explore various reaction neighborhoods of their entity of interest (Figure 2B). This capability expanded to multiple nearest neighbors and its ability to perform trend analysis across the reaction neighborhood will be essential for monitoring regulatory waves across time and between pathways (Aim 1.3). For cases where network coverage is sparse, we will develop a reaction collapse module that will allow for summarization of reactions with missing data to bridge these gaps. Each reaction bridge will be maintained in the network representation as a separate pseudo-relationship so a user can identify these missing steps for further interrogation of those components if desired.
- *Regulatory predictions*: The current database used by *Metaboverse* is derived from Reactome[36] and contains reaction modifier information that can be helpful in adding context behind the patterns identified by *PaSEN*. We will

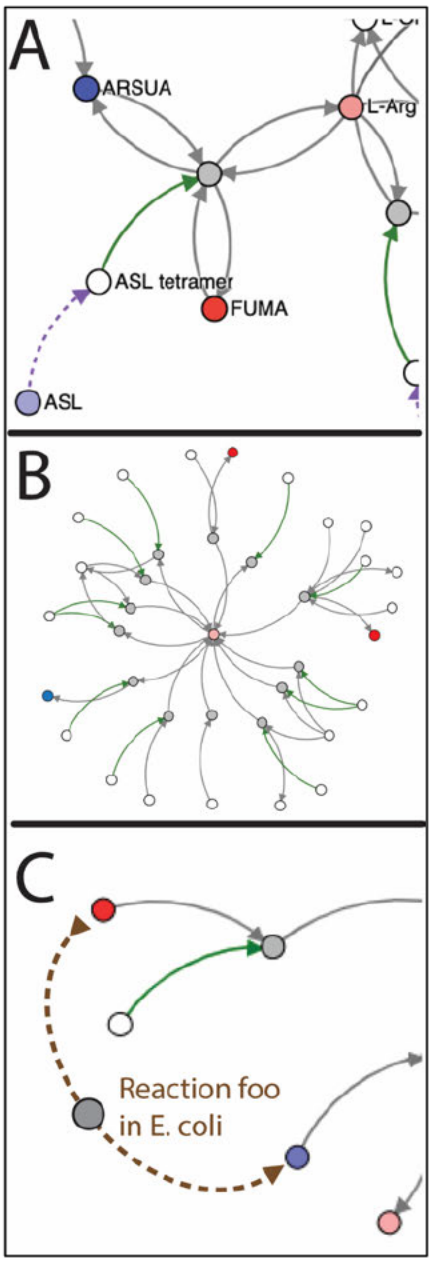


Figure 2: Features of Metaboverse. *(A) Metaboverse demo displaying test metabolomics and transcriptomics data overlaid on the Urea Cycle. Grey circles indicate reactions. White circles indicate missing data or no change. Red circles indicate up regulation, while blue circles indicate down regulation. Green curved arrows indicate a reaction catalyst. Dotted purple curved arrows indicate a gene component of a protein involved in the reaction. (B) Example of k-NN search to explore distal participation of metabolite in reactions across all pathways and between pathways. (C) Example of a regulatory event across a reaction not annotated in human but found in other organisms.*

supplement this information with BRENDA, a comprehensive database for enzyme interactions across organisms[37]. This will further improve the ability of *Metaboverse* to provide mechanistic predictions from events identified by *PaSEN*. *PaSEN* will also search putative reactions in, for example humans, that have only been identified (with high confidence) in other organisms (see Figure 2C). This may be useful in cases where a regulatory activity across an unannotated reaction in an organism exists, implying existence of an unannotated metabolic feature. These databases will be supplemented with findings from MIDAS[38], a platform continuing to be developed in the Rutter lab in collaboration with Calico Life Sciences, which identifies novel protein-metabolite and RNA-metabolite interactions.

Aim 1.2: Demonstrate Metaboverse's ability to extract novel regulatory events from public and new data. Using high-quality metabolomics datasets I identify with Dr. James Cox, I will compare the original analyses of these data with those derived from *Metaboverse* using the features described in Aim 1.1. We expect that *Metaboverse* will recapitulate the original findings and identify novel regulatory events missed in the original study using conventional analysis methods. In collaboration with Drs. Cox and Waller, we have also produced flux metabolomics datasets in yeast with varying levels of MPC expression. As described before, we have observed that MPC amplifying tumorigenesis in the colon[29]. Using these data and the search features available in *Metaboverse*, we will interrogate the mechanistic roles of MPC loss on glucose utilization to better understand its role in tumorigenesis.

Alternative Strategies: While the amount of public metabolomics data is increasing, there is currently no NIH mandate for their publication as with gene expression data. Therefore, we may find that the number of total metabolomics datasets we can use for Aim 1.2 is limited. If this is true, we will generate paired yeast RNA-Seq and metabolomics datasets under various conditions to generate the needed data. Another source of data useful for this application is being generated by Dr. Alex Bott in the Rutter lab, where a series of amino acid drop-out human cell culture models are being profiled using paired RNA-Seq and metabolomics to understand how cancer responds to nutrient availability.

Aim 1.3: Develop improved statistical methods for deconvoluting real, low-magnitude changes within the metabolic network from noise. Metabolic networks are inherently complex. The complexity of these networks allows for features such as redundancy, particularly within essential pathways, to give rise to the ability to thrive[39]. However, classical studies of metabolism have long focused on these reactions and their roles in a piece-meal fashion. For example: a researcher supplements their model with an excess amino acid. They collect the perturbed cells and perform RNA-Seq and metabolomics to discover how these programs changed in the model. By running differential expression analysis, they discover 30 genes and 15 metabolites are differentially regulated upon amino acid stimulus. The researcher performs additional experiments to better understand the consequences and causes of these changes, publishes their results, and then moves on. But what about the changes that occurred with the other ~20,000 genes and ~2,000 metabolites? Were they simply noisy bystanders, or were they more involved?

Recent work has shown that the bystander role for entities in a biological context may be limited and that trans effects in gene expression networks influence trait inheritance[40]. In this model, the authors demonstrated that changes to auxiliary entities of the gene network could influence or drive the phenotypes accompanying the perturbation of core genes. They term this the "*omnigenic*" model of inheritance, or the theory that all genes in the cell influence the resulting phenotype. However, how these trans-acting elements act upon the entire metabolic network, and especially how they drive stimulus responses, is unexplored.

In order to deconvolute low change patterns throughout a network, high-quality time course experiments are needed. While publicly accessible gene expression data is plentiful, this standard is not as well established in the metabolomics community. With Dr. James Cox, we will identify and/or develop the datasets needed to analyze these regulatory events in metabolic networks. We will prioritize datasets that are from synchronized cell populations to reduce extrinsic (global) noise and amplify intrinsic (local) noise in the data[27].

I will then use the k-NN and *PaSEN* search features of *Metaboverse* to rapidly identify longer range patterns of regulation within metabolic networks across space or time using real data (see Figure 3 for an example). To aid in this exploration, we have begun building interactive time course exploration capabilities into *Metaboverse*, which will need to be further developed to be fully operational for this task. Another approach we will use to identify these

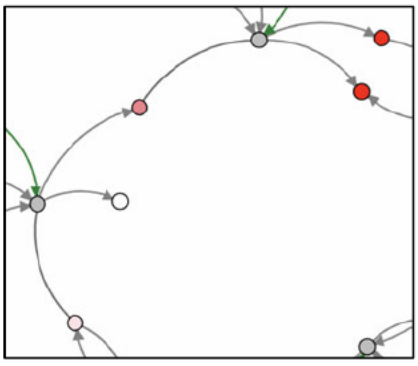


Figure 3: A simulated example of regulation across a network, either in space or time.

patterns will be to perform differential expression analysis on RNA-Seq and metabolomics datasets at a terminal time-point, identify each differentially expressed entity's position in the metabolic network and upstream reactions at earlier timepoints. By using this unique platform only available through *Metaboverse*, we will be able to better describe the regulatory environment of cancer metabolism and identify new methods of regulation. These may be temporal regulation events, where a pathway ramps up regulation gradually. These could also be spatial regulatory events, where we see broad regulation across several features, where individually these regulated events would not be considered important because they do not meet the arbitrary thresholding criteria. Regardless of the events we identify, **completion of this sub-aim will allow for a better representation and more complete understanding of how a metabolic network is regulated in cancer and will open up new avenues for improved treatment that modulates metabolism to decrease a tumor's ability to proliferate**.

Once high confidence temporal or spatial patterns are identified, we will identify drugs using the CMap database[41] that target upstream elements of the terminally changed gene or metabolite. Where drugs are available, they will be used to target and inhibit earlier pathway elements. We expect that ablation of the upstream element will lead to reduced change in downstream elements of the pathway. Ideally, we will be able to find very trans-related regulatory patterns that can be inhibited by a drug and then measure to see if the core gene or metabolite was unable or reduced in its ability to be differentially regulated. By doing so, this trans-inhibition will act as a strong model for temporal regulation in a metabolic pathway. Additionally, we will perform single-cell sequencing in these models as able to determine if distinct sub-populations of cells undergo temporal regulation, or perhaps whether these sub-populations are able to arrive at the same terminal downstream effect via various routes.

Alternative Strategies: Where inhibitory drugs are not available for an upstream component of a strong trend motif, we will use conditional inhibition for that entity. It is possible that missing connections in the metabolic network (unknown associations) will obfuscate trends. We can fill these missing gaps using data from the MIDAS project, as mentioned above[38].

Statistical significance determination is challenging, particularly in metabolomics data, which is far more transient and sparser than other -omics data types. In order to determine statistical significance of these changes we observe in the network, we will apply two well-established methodologies:

- *Monotonic trend analysis*: For each identified temporal or spatial pattern identified by our search algorithm, we will perform Mann-Kendell trend analysis on each returned series. Mann-Kendell (M-K) trend analysis tests whether a non-parametric data series follows a linear, monotonic trend[42]. This test is often used in climate change studies to test whether the climate is appreciably changing over time[43]. A key advantage of this method is that it allows for missing data, which is particularly important for metabolomics data where missing data is common due to methodological limitations[24]. Monotonic trend analysis across a network may also be informative in statistical significance and prioritization of measurements in the network. For example, in Figure 3, if we notice consistent trends across reactions in pathway, either at a static time point or across time, we can be more confident in their existence. We can also modify these approaches to allow for some level of variability in the monotonic trend. For example, in climate data, temperatures naturally fluctuate, but generally we see periodic increases or decreases in general temperature. We expect to see similar characteristics in biological data.
- *Sub-network inference*: Metabolism is a complex system of multi-dimensional, highly interdependent functional relationships between metabolites, proteins, and other biomolecules. Hence, it is inaccurate to assume that these measurements are all independent, as many false discovery rate correction methods assume[44]. Doing so would decrease resolution at the expense of Type II (false negative) errors. We will therefore utilize updated methods for significance testing and correction that account for this network dependence to minimize both Type I and Type II errors[44,45]. Network biology has also demonstrated promising methods that use the functional network as prior covariates by which to test hypotheses. One popular modern example of this is the *jActiveModules* package which approaches this challenge with a sub-network-centric approach[46]. Using a modified, sub-network-centric approach, we can more accurately analyze the network and its members' roles in metabolic regulation.

Completion of the F99 phase of my research will provide a new software package for the integrated multi-omic analysis of metabolic data. Using this tool, we will explore the role of MPC and pyruvate flux on glycolysis and better understand how MPC impairment promotes tumorigenesis. We will also describe the role of more complex and dispersed regulatory events, either across the network or across time, on cancer metabolism and validate these events.

Aim 2: Postdoctoral Research Direction (K00) – Building Predictive Models of Metabolism to Unlock the Treasure Trove of Cancer Transcriptomics.

[redacted]

A project such as this will require world-class machine learning, network, and computational biology experts. I have identified potential postdoctoral advisors for this stage such as [redacted] or [redacted]. [redacted] Finding the correct mentor during this stage will be vital to my intellectual foundation as there are numerous pitfalls to machine learning methods and is often abused or misused in medical sciences. Ensuring I obtain the proper training from experts in the field will be essential to my intellectual and technical growth.

This award will be essential in my progress by allowing me the flexibility and independence needed in my research to answer questions such as those posed in this Aim and will help establish myself as an expert and pioneer in computational metabolism and cancer metabolism.

Respective Contributions

Respective contributions to the research plan

The research strategy was developed and conceived by the PI (Jordan Berg) with insight from the sponsor (Dr. Jared Rutter) and co-sponsor (Dr. Bei Wang Phillips). The proposed experiments were conceived and designed by the PI.

Respective contributions to the experiments

Yeast metabolomics data used in *Metaboverse* validation were generated by Drs. T. Cameron Waller and James Cox. *Metaboverse* is developed by the PI, with support from Dr. Bei Wang Phillips, Youjia Zhou, and Ian George. Data curation and analysis for the metabolic regulation studies proposed in this document will be performed by the PI. [redacted]

Selection of Sponsor and Institution

To establish myself in the field of computational metabolism, the selection of my sponsor, co-sponsor, and institution were essential and each decision came with extensive introspection and discussion. Preparing myself for my career requires several components: 1) Mentoring from an expert metabolism researcher who appreciates systematic approaches to untangling the complex features of metabolism and its role in cancer and who will train me to approach metabolism as a thoughtful biologist, 2) Mentoring from a computational expert with a background in graph theory and machine learning who will challenge and train me to think analytically about the proper computational and statistical approaches associated with this proposal, and 3) An institutional environment that will allow me to develop rich collaborative relationships and that has the resources necessary to allow me to ask important questions in cancer metabolism.

Selection of Sponsor: While I was impressed by all of the professors with whom I rotated, what ultimately drew me to choose Dr. Rutter as my mentor was his expertise in metabolism and metabolic regulation, his willingness to explore metabolism in novel, inter-disciplinary ways, and his rigor in publishing high-quality, foundational research papers. After my dissertation work, I will pursue a postdoctoral research position and a position as a tenure-track professor in academia, and I was certain Dr. Rutter would provide me with the best opportunities and mentorship to prepare myself for these career stages. This has been true manifold. Dr. Rutter's approach to thinking about biology and driving the field to new limits has been consequential in my training and will be essential to ensure I have a solid foundation in cancer biology and metabolism before my postdoctoral training in a more computationally focused lab for the K00 training phase. I also appreciate Dr. Rutter's approach to mentoring where he provides his mentees with complete independence and freedom to explore and think creatively. These combined qualities will allow me to take full advantage of my dissertation training and will help me establish the needed connections within the cancer, metabolism, and computational biology communities. Dr. Rutter has been fantastic in making himself available whenever needed for advice or administrative purposes. If he or I are traveling, he will make a point to schedule time to talk virtually while the other is in transit. In the Rutter lab, I will also be able to establish myself in the systems biology and computational metabolism fields by publishing foundational papers in the field of metabolic regulation, along with publishing papers presenting tools needed for processing and analyzing ribosome profiling, RNA-Seq, proteomics, and metabolomics datasets.

Selection of Co-Sponsor: I selected Dr. Bei Wang Phillips as my co-sponsor due to her expertise in topological data analysis, graph theory, and machine learning. It was important in the development of my training plan that I surround myself with an expert with a computational background. I was especially impressed with Dr. Phillips enthusiasm and vision when we initially discussed the *Metaboverse* project. Already, I have seen incredible dividends in my personal and intellectual growth from this relationship, along with the bolstered ability to innovate in new ways at the intersection of computer science and cancer metabolism. The training Dr. Phillips will provide will be vital to my success as a postdoctoral fellow as I will need a solid foundation in machine learning and graph theory in order to hit the ground running at the start of the K00 phase of my training.

Selection of Institution: I was drawn to the University of Utah because of its strong collaborative spirit and its multi-disciplinary approach to biomedical and basic science. I was impressed by the multiplicity of fields I could explore within the Molecular Biology/Biochemistry Graduate School Program. During my interviews at the University of Utah, I could see how excited and creative the professors in each department were, and this was encouraging to me as I saw the potential to apply my own expertise in creative and forward-thinking manners. I was also impressed with the caliber of scientists at the University of Utah. The University has been home to a Nobel Prize winner and several other prestigious scientists, and is an NCI-Designated Comprehensive Cancer Center, which speaks to the quality of science at this institution.

Another consideration in my decision to attend the University of Utah for my dissertation work was the numerous resources available. For example, in the Emma Eccles Jones Building, where the Rutter lab is located, we are a short walk away from the Metabolomics Core. This is an essential resource for the projects I have proposed and the proximity to Dr. James Cox, the core director, and his willingness to discuss ideas is consequential for this project. I have also had similar interactions with the sequencing core and the Center for High-Performance Computing. Feedback and resources from both groups have been invaluable. The close proximity to the Huntsman Cancer Institute, where my long-time collaborator, Dr. Jason Gertz, is located, is also important as there are numerous world-class cancer biologists in addition to Dr. Gertz with whom I can discuss and develop my ideas.

Training in Responsible Conduct of Research

Introduction

Training in the Responsible Conduct of Research (RCR) is an ongoing process at the University of Utah. Trainees receive informal training from faculty and mentors, and formal training through the Research Education Department's RCR courses. The Research Education RCR courses are designed to meet or exceed all NIH and NSF requirements for RCR training. All individuals who are covered by this mandate and working under this grant will either complete a 9-week Research Ethics course (PHIL 7570/1.0 credit hours) and/or complete Research Education RCR courses. Compliance is administered under the University Office of the Vice President for Research, which is responsible for administration of grants and contracts, management of intellectual property, oversight of human subject and laboratory animal research, and implementation of the university's policies on research. Mr. Jordan Berg successfully fulfilled this requirement by completing the PHIL 7570 course during the Fall 2016 semester and will continue to complete an RCR course through the University of Utah every four years, thus is scheduled to complete an RCR course Fall 2020 to fulfill this additional goal.

Instructional Components of the University of Utah Responsible Conduct of Research Course

1. **Format**: The Research Education Department offers a certificate that consists of a minimum of 10 hours of instruction including live lectures, group discussions, assigned readings, and a comprehensive online class with a proficiency examination.
2. **Subject Matter**: The program includes (but is not limited to) the following instructional areas:
   a. Protection and Use of Human Subjects in Research
   b. Conflict of Interest in University Research
   c. Data Acquisition, Management, Sharing and Ownership
   d. Research Misconduct
   e. Publication Practices and Responsible Authorship
   f. Mentoring/Trainee Responsibilities
   g. Peer Review
   h. Collaborative Research
3. Animal Care and Use in Research is also taught but is not a requirement of the Research Education Department's RCR certificate.
4. **Faculty Participation**: All live lecture and small group discussions are taught by University faculty and staff with extensive experience in the subject matter. Faculty members in charge of research training programs frequently contribute to presentations and discussions.
5. **Duration of Instruction**: Instruction consists of at least 10 hours, made up of eight (8) hours of live lecture, face-to-face instruction and supplemented by a two-hour comprehensive online course with a proficiency examination.
6. **Frequency of Instruction**: Trainees must participate in the RCR program at the earliest opportunity, at least once every four years, and at least once during their early career stage. Once the required 10 hours of RCR instruction have been successfully completed, the trainee receives a dated "Certificate of Achievement."

How Participation in RCR Instruction is Monitored

Participation in Research Education's RCR courses is monitored in several ways: signed and dated class attendance rosters, electronic transcripts, online class registration, and a dated "Certificate of Achievement". Trainees enrolled in the online RCR class are required to successfully complete review quizzes at the end of each of the 9 units and a final proficiency examination with a minimum passing grade of 85%. Upon successful completion of the online class, a Record of Class Completion is provided to the trainee. Trainees are also expected to attend all required live lecture and small group discussion sessions. Attendance rosters are the primary way to ensure that trainees have completed the appropriate training requirements. In addition to attendance, trainees are expected to be actively involved in all class discussions and activities. Because research is being done in a multitude of subject areas, having input from all trainees is essential to having a discussion that sees a situation from multiple viewpoints.

Provided by Brent Hill, AVP Research Integrity & Compliance (updated 5/31/2019)

Sponsor and Co-Sponsor Statements

Sponsor: Dr. Jared Rutter, PhD

[redacted]

Co-Sponsor: Dr. Bei Wang Phillips, PhD

[redacted]

A. Research Support Available:

Table 1: Current Support

Title	Source and PI	Amount (Annual Direct)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

B. Sponsor's Previous Fellows/Trainees:

[redacted]

Table 3: Representative Trainee Information

Faculty Member	Past Trainee Name	Training Period (Degree)	Prior Academic Degree Institution	Prior Academic Degree(s)/Year(s)	Title of Research Project	Current Position of Past Trainees
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C. Training Plan, Environment, Research Facilities:

Training Plan

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Environment and Research Facilities

[redacted]

D. Number of Fellows/Trainees to be Supervised During Fellowship

Table 4: Current Trainees of Sponsor and Co-Sponsor

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

E. Applicant's Qualifications and Potential for a Research Career

UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

Core Administration

DNA Peptide Core Facility
581-4051

DNA Sequencing Core Facility
585-2976

Electron Microscopy Core Facility
581-4571

Fluorescent Imaging Core Facility
587-7964

Flow Cytometry Core Facility
585-7382

Genomics Core Facility
585-2977

Mass Spectrometry Core Facility
581-5018

Metabolomics Core Facility
587-7779

Metabolic Phenotyping
Core Facility
585-0400

MRI Imaging Core Facility
587-8357

Mutation Generation Core Facility
585-3391

NMR Core Facility
585-7363

Small Animal Ultrasound
581-7715

SOM Machine Shop
581-3180

Zebrafish Core Facility
585-1381

November 23, 2019

Re: Letter of Support, Jordan Berg F99/K00 Fellowship Application

[redacted]

Institutional Environment and Commitment to Training

Program Overview and Resources

Mr. Jordan Berg matriculated into the Biosciences Graduate Program at the University of Utah in August 2016 and joined the Department of Biochemistry as a PhD student in the laboratory of Dr. Jared Rutter in May 2017. The Department of Biochemistry is one of ten departments at the University of Utah participating in the Biosciences Graduate Program and is currently composed of 15 Tenure Track Faculty, 14 Research Career Track Faculty, and 18 Adjunct Faculty. The University of Utah provides an excellent environment to mentor and train young scientists, and very few limitations exist in terms of the resources available to trainees for professional and intellectual development. Faculty in the Biochemistry Department as well as the nine other departments comprising the Biosciences Graduate Program are fully commited to student training, mentoring, and success. Resources avaible to the PI to achieve his research and professional goals are described below.

Research Facilities: The PI has access to all the necessary resources provided by the sponsor (Dr. Jared Rutter) to carry out the work and training proposed in the application. For more details on facilities and equipment available to the PI see the “Facilities and Other Resources” section. In addition, the PI also has access to over 40 exceptional core facilities at the University, including Cell Imaging, DNA/Peptide Synthesis, DNA Sequencing, Electron Microscopy, Flow Cytometry, Mass Spectometry & Proteomics, Metabolic Phenotyping, Metabolomics, Nuclear Magnetic Resonance, Small Animal Imaging, High Throughput Genomics, Transgenic & Gene-Targeting Mouse Facility, a state of the art Comparative Medicine Department, and many more. Those necessary for the current application are highlighted in the “Facilities and Other Resources” section.

Reagents and Intellectual Support: The PI has access to all necesary reagents and intellectual support to carry out the experiments outlined in the proposal. These include access to the bioinformatics and high-throughput genomics (sequencing) cores, CHPC supercomputing clusters, and all necessary sequencing, yeast genetics, cell culture, biochemical, and molecular biology tools and resources as outlined in the “Facilities and Other Resources” and “Equipment” sections of this application. The PI has assembled a world-class mentoring support network, led by Dr. Jared Rutter and Dr. Bei Wang Phillips who will provide the intellectual support needed for this proposal spanning computation and metabolism.

Meetings, Seminars, and Journal Clubs: Because of the close-knit and interdisciplinary nature of the faculty and departments here at the University of Utah, students are provided with a wealth of opportunites to interact with faculty and other trainees in settings such as seminar series, research interest groups, and journal clubs. Upon joining the Biochemistry Department, all students present their research annually to the department through a formal “Research in Progress” (RIP) seminar series. These presentations begin in the student’s third year in the department, and students are provided feedback on their presentation by a committee of faculty. Trainees in the department also participate in a journal club in their second and fifth years, and attend a biweekly outside speaker seminar series hosted by the department. In addition, students are welcome to attend and speak at numerous interest groups on campus, including the Genetics Interest Group, the Membrane Trafficking Group, the Seminars in Metabolism Group, the Metals Interest Group, and many more. Other local opportunites for rich interaction amongst students and faculty occur at annual symposia hosted on campus. These include the annual Biosciences Symposium, a Biochemistry Departmental Retreat, an annual student retreat, and retreats hosted by various training grants and interest groups on campus including metabolism, genetics, membrane trafficking, and developmental biology. Mr. Jordan Berg has already attended and/or presented at 6 internal symposia, and actively participates in the Metabolism Interest Group. In addition to local seminars and interest groups, students in the Department are strongly encouraged to attend and present their research at national and international meetings focused on their research topic, and monetary support is available to students to support their attendance at these meetings through University Travel Awards.

Professional Development: The University hosts many worksops and courses on professional development available to the PI, spanning topics such as grant writing, publishing, and employment networking/exploration opportunities both within and outside of academia.

Educational Information

As stated above, Mr. Jordan Berg joined the Universty of Utah’s Biosciences Graduate Program in the fall of 2016. Students enter this program through one of two tracks, the Molecular Biology program or Biological

Chemistry Program. Each is comprised of faculty across multiple departments on campus. The PI started their graduate career in the Molecular Biology program. Each program has a slightly different first year curriculum which caters to the specific topic of study. In the first year, students take a set of core and elective courses unique to each program along with courses on Research Ethics, Literature Review & Problem solving, and Guided Grant Preparation. The end of the first year culminates with an oral capstone exam in which the students defends a written proposal in front of a faculty committee. The proposal is constructed during the Guided Grant Preparation Course. In addition, students also complete three seven-week laboratory rotations during their first year, which gives them the opportunity to conduct research in different departments and allows them to select a thesis faculty advisor. Mr. Jordan Berg successfully completed all of his first year coursework, and joined the lab of Dr. Jared Rutter in May 2017.

After completion of the first year, Mr. Jordan Berg officially became a student of the Biochemistry Department and will be awarded a PhD in Biochemistry at the culmination of his studies. In addition to the first year coursework, Biochemistry students are also required to take at least 1.5 semesters of additional coursework in addition to their thesis research. Mr. Jordan Berg is in his fourth year in the Department, and has completed one semester of this coursework thus far, leaving one advanced seminar class which he will enroll in during the Winter 2020 semester. He has completed half of his TAship requirement and will complete the remaining half during the Winter 2020 semester for Drs. Adam Hughes and Nels Elde.

Graduate Students in the Department of Biochemistry are required to take a Qualifying/Preliminary Examination by the end of the Fall Semester during their first year in the department (second year in graduate school). This exam is conducted by the student's Supervisory Committee and takes place over a 5-week period. After passing their Preliminary Exam, students advance to PhD candidacy. The student's advisor and research mentor use this entire process, starting well before the five week period, to assist with the development and refinement of a thesis proposal by reviewing draft documents, arranging practice talks, discussing relevant background literature, as well as honing plans for future research. This process follows the same format and development process that is used when submitting a research grant proposal with the intention of aiding students to formulate and express their scientific research interests in a manner that is focused and comprehensible to the peers in their community. Mr. Jordan Berg successfully passed his qualifying exam on 02 April 2018.

During their dissertation work, students continue to have regular meetings with their faculty advisor as well as feedback and assessment meetings with their thesis committee on at least an annual basis. Students are also required to present their work on an annual basis to the entire department during the weekly Research in Progress Seminar Series, which is attended by all faculty, postdocs, research staff, and graduate students in the department. During this presentation, students field questions about their research, and our faculty provide each presenter with both written and oral feedback. Biochemistry graduate students are also required to serve one semester as a teaching assistant to provide teaching experience, and participate in a journal club in their second and fifth years in the Department. At the end of their studies, students write and defend their dissertation.

The progress of our PhD candidates is closely monitored by the individual's direct advisor, the Director of Graduate Students, Dr. Adam Hughes, as well as the department's co-chairs, Drs. Wesley Sundquist and Christopher Hill. Our current faculty to student ratio is approximately 1:1.3, which helps to ensure close mentoring and faculty availability for all of our students. The current average time to completion of the doctoral degree in Biochemistry over the past ten years is approximately six years from the date students enter the department.

This information has been provided by Department co-chairs Drs. Christopher Hill and Wesley Sundquist, and Director of Graduate Students Dr. Adam Hughes.

Resource Sharing Plan

Software: I am fully committed to open-source software development and have a track record of adhering to this commitment (see Berg, *et. al*., *bioRxiv*, 2019; github.com/j-berg). Software is made available under a GNU General Public License, which allows for broad use and re-use. Whenever possible, projects in development are immediately open source during their development to ensure transparency and encourage contribution from the broader community.

Data: As with developed software, any data created and used for this proposal will be made publicly available via a repository such as the Gene Expression Omnibus or Metabolomics Workbench. All scripts developed for data analysis will be made available (see github.com/j-berg for examples). Analysis code associated with a published work will be open-access to facilitate reproducibility and will be given a digital object identifier (DOI) to act as a persistent identifier to make sure that the resource is perpetually available and free to access.

Publications: All work from this proposal will be published in peer-reviewed open-access journals under CC-BY, or similarly open, licenses. Manuscripts in review will be made immediately available via a pre-print server, such as *bioRxiv*. NIH and other resources will be acknowledged in all derivative works.

Other: Any lab reagents or cell lines generated for use as part of this proposal will be stored and managed by Dr. Jared Rutter, who will handle requests for these reagents. The Rutter lab has a rich history of making its resources available for others and has benefited from many rich collaborations as a result. To aid in dissemination of knowledge, presentations I give regarding this and related work will be made publicly available via github.com/j-berg/presentations.

PHS Human Subjects and Clinical Trials Information

Are Human Subjects Involved	❍Yes		●No					
Is the Project Exempt from Federal regulations?	❍Yes		❍No					
Exemption Number	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8
Does the proposed research involve human specimens and/or data	●Yes		❍No					
If Yes, provide an explanation of why the application does not involve human subjects research	Human_Subjects1029235292.pdf							
Other Requested information								

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

Human Subjects

The accompanying proposal outlined by the PI (Mr. Jordan Berg) will be completed using yeast strains generated within the Rutter lab, or commercially available mammalian cells lines. A large portion of this work will be completed by way of secondary analysis of sequencing, proteomics, or metabolomics datasets that are already publicly available by way of another published study. These datasets will be obtained through NIH-sponsored databases, such as the Gene Expression Omnibus (GEO), Metabolomics Workbench, or similar NIH-supported data repositories where proper protections for human patient data will have been taken. If protected patient data is used, it will only be accessed through the dbGAP portal where data has already been de-identified, and only after the PI and sponsor have submitted the proper request form to access the data.

In the cases outlined above where de-identified patient data is used, processing and analysis of data that could in any way be traced back to the individual will be accessed directly from the dbGAP portal, processed on the Rutter lab protected computing environment at the University of Utah Center for High-Performance Computing, and promptly destroyed after use. These data files will be accessed only through proper secure channels and will only be used if the original study followed the appropriate NIH standards for data acquisition and storage.