Biology 5960: Understanding Peer-Reviewed Literature: Focus on Mitochondrial Metabolism

Prerequisites: BIOL 2020 (Cell Biology) and BIOL 3510 (Biochemistry I)

2018 Summer Session 2
2 Credits
Tu/Th 9:30a-12:30p
Class Location: JTB120

Course Instructors
Casey Hemmis, PhD (hemmis@biochem.utah.edu)
Sara Nowinski, PhD (sara.nowinski@biochem.utah.edu)
Esther Nuebel, PhD (enuebel@biochem.utah.edu)

Office location: TBD
Office hours will be by appointment. Contact one of the instructors to schedule.

Expected Learning Outcomes
By the end of this course you will be able to:

1. Read a scientific paper, be able to understand and summarize it, and have an opinion about it.
2. Understand the different research approaches that fall under the umbrella of biochemistry (structural, bioenergetics, metabolic pathways, signaling, more)
3. Explain specific, cutting-edge topics relating to mitochondrial metabolism (TCA cycle, electron transport chain, the proton gradient, ATP production, reactive oxygen species, mitochondria in disease).
4. Use scientific databases to search for research papers and review articles.

Course Description
This course will be taught using a mixture of reading, discussion, quizzes (individual and team-based) and student presentation modalities, with an emphasis on active learning. While introducing cutting edge topics in mitochondrial metabolism, this course will develop the ability to critically read, process, and challenge scientific publications. Topics will range from structural biology to bioenergetics and mitochondrial metabolic pathways, finally expanding into errors of metabolism in disease.

Course Resources
Canvas: Class expectations, materials, scores, announcements, attendance tracking and discussions will all be provided on Canvas.

Primary Literature: Research articles will be posted on Canvas for each course session. In addition to required reading, textbook chapters, online videos, and/or review articles that can be utilized as supplemental reading will be provided for each session.
Textbook for supplemental reading: For background knowledge about biochemistry and central metabolism, we will sometimes refer to chapters or sections in the textbook Biochemistry by Berg, Tymoczko, Gatto, and Stryer. A PDF of this textbook is available for free online at: http://medsmart.ir/2017/07/26/biochemistry-8th-edition-berg-tymoczko-gatto-stryer/. A hard copy can be accessed for a 2h loan period at the Marriott Library via Health Sciences Closed Reserve (Request at Eccles Library Service Desk) (QU 4 B493 2012).

Teaching and Learning Methods
This course will be taught using team-based learning. Reading will be assigned to be completed before each class. At the start of each class, students will complete an in-class individual assessment about the reading. After this, students will complete the same assessment in their teams. Then, we will go through the paper together in a discussion format with a focus on the section indicated (for example, the abstract), however, the entire paper will be read and discussed. Discussion will be initiated using questions submitted from students during the pre-class assignments and will be tailored to the needs of the students each class. Some sections may have games or other team-based activities, student presentations, etc.

Course Policies
Attendance and participation: This course is based on active discussion and participation within the classroom. Therefore, attendance and participation are required and graded. You will receive 2 points for every class that you attend. Your classroom participation grade will be based on the following criteria: 1) contributed fully to the class discussion of problems, 2) behaved in a professional and respectful manner towards classmates and faculty, and 3) successfully completed any in-class activities. You will not be able to earn points for attendance, participation, or in-class quizzes for unexcused absences, however, it may be possible to make up some missed points by completing an alternative assignment when an absence is excused with a written letter from a medical or legal professional.

Preparation for class: Assigned readings are to be completed prior to each class meeting. Each student will be required to post at least 2 thoughtful questions for discussion on the class Canvas page by 10PM the night before class (Mon or Wed). Completion of this will be reflected in the pre-class exercise grade.

Electronic Devices in Class: An electronic device, preferably a laptop/tablet, will be required for the class. These devices will be used for taking assessments online via Canvas. Searching external materials such as assigned readings, web resources, Wikipedia, etc. is NOT PERMITTED while taking assessments. During group activities/discussions, use of devices to search/utilize external resources, however, will be encouraged. The instructors will clearly indicate which activities permit the use of electronic devices. We expect that devices are silenced or turned off and put away at all other times. Use of any electronic device for non-class activities or in a disruptive manner is NOT PERMITTED.
Student Assessment
Grades will be based on the following criteria:

<table>
<thead>
<tr>
<th>Attendance</th>
<th>15%</th>
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<tbody>
<tr>
<td>Classroom participation</td>
<td>15%</td>
</tr>
<tr>
<td>Pre-class exercise</td>
<td>10%</td>
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<tr>
<td>In-class individual quizzes</td>
<td>15%</td>
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<tr>
<td>In-class group quizzes</td>
<td>15%</td>
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<tr>
<td>End exercise</td>
<td>30%</td>
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<tr>
<td><strong>Total</strong></td>
<td>100%</td>
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</tbody>
</table>

Evaluation Scheme

<table>
<thead>
<tr>
<th>Letter Grade</th>
<th>Percentage</th>
<th>Letter Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>94-100</td>
<td>C-</td>
<td>70-72</td>
</tr>
<tr>
<td>A-</td>
<td>90-93</td>
<td>D+</td>
<td>67-69</td>
</tr>
<tr>
<td>B+</td>
<td>86-89</td>
<td>D</td>
<td>64-66</td>
</tr>
<tr>
<td>B</td>
<td>82-85</td>
<td>D-</td>
<td>60-63</td>
</tr>
<tr>
<td>B-</td>
<td>79-81</td>
<td>E</td>
<td>Below 60</td>
</tr>
<tr>
<td>C+</td>
<td>76-78</td>
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<tr>
<td>C</td>
<td>73-75</td>
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Scores will be rounded:
Example 94.4=94, 94.5=95

Class Schedule
All classes will be held in JTB 120 from 9:30 am to 12:30 pm on Tuesdays and Thursdays.

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Class Title</th>
<th>Primary Reading (additional reading for each class listed below)</th>
<th>Primary Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/21</td>
<td>Th</td>
<td>Intro, preliminary exercise</td>
<td>In class (Title, Abstract, and Introduction from Andrezejewski et al. 2014)</td>
<td>Esther &amp; Casey</td>
</tr>
<tr>
<td>6/26</td>
<td>Tu</td>
<td>Targeting Metabolism in Cancer – analyzing an abstract</td>
<td>Andrezejewski et al. 2014</td>
<td>Esther</td>
</tr>
<tr>
<td>6/28</td>
<td>Th</td>
<td>Complex I: the ETC components – reading an introduction</td>
<td>Davies et al. 2018</td>
<td>Esther</td>
</tr>
<tr>
<td>7/3</td>
<td>Tu</td>
<td>ATP production: Results and Materials &amp; Methods</td>
<td>Srivastava et al. 2018</td>
<td>Casey</td>
</tr>
<tr>
<td>7/5</td>
<td>Th</td>
<td>ATP as an energy and signaling molecule: Results and Materials &amp; Methods</td>
<td>Ross et al. 2016</td>
<td>Casey &amp; Esther</td>
</tr>
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</table>
Learning Objectives and Readings for Class Sessions

**Class 1 (June 21)**
**Primary Reading:** In-class: Andrezejewski et al. 2014 “Metformin directly acts on mitochondria to alter cellular bioenergetics.”

**Objectives:**
- Introduce students and instructors to one another.
- Describe the overall course structure.
- Understand course expectations and policies from instructors.
- Explain modes for assessment and grading.
- State and discuss learning goals and expectations of the students.
- Describe the key concepts of team-based learning.
- Form teams and participate in introductory team activity.
- Read scientific content and classify key words and nomenclature.
- Define unknown nomenclature and summarize new vocabulary in glossary.

**Class 2 (June 26)**
**Primary Reading:** Andrezejewski et al. 2014 “Metformin directly acts on mitochondria to alter cellular bioenergetics.”

**Required Background Material:** “How to Read Scientific Papers” videos (links provided on Canvas)

**Objectives:**
- Use online resources such as PubMed and Google Scholar to search for review or research articles.
- Recognize the different sections of a standard research article.
- Identify main components of each section of a research article.
• Discuss different strategies for reading a scientific article.
• Clarify the purpose of an abstract.
• Develop active reading strategies.
• Introduce concept maps.
• Develop a map that illustrates concepts required to understand assigned readings.

Class 3 (June 28)
Primary Reading: Davies et al. 2018 “Conserved in situ arrangement of complex I and III2 in mitochondrial respiratory chain supercomplexes of mammals, yeast, and plants”

Required Background Material: Berg, Tymoczko, Stryer - Chapter 18

Objectives:
• Describe the protein complexes which compose the respiratory chain and introduce supermolecular structures.
• Explore the compartments of mitochondria and match complexes to their appropriate localization.
• Diagram the flow of electrons through the respiratory chain.
• Explore how electron flow is connected to the transport of protons.
• Explain the membrane potential and predict what may minimize this potential.
• Identify how reactive oxygen species occur.
• Introduce concept of signaling.
• Explain the components and aim of the Introduction in a scientific article.
• Identify what is known in the field and what are the major questions this paper will be addressing.

Class 4 (July 3)
Primary Reading: Srivastava et al. 2018 “High-resolution cryo-EM analysis of the yeast ATP synthase in a lipid membrane.”

Required Background Material: TBD

Objectives:
• Explain the importance of establishing a proton gradient in the mitochondria.
• Explore how the mitochondrial ATP synthase is connected to the respiratory chain.
• Discuss basic mechanism of how mitochondrial ATP synthase makes ATP.
• Discuss the use of cryo-electron microscopy as a structural tool.
• Explain how oligomycin disrupts ATP synthase activity
• Use Chimera as a tool for visualizing protein structures.
• Discuss basics of protein structure: how primary sequence leads to 3D molecules.
• Explain how protein structure informs biochemical and cell biological experiments and data such as sites of oligomycin/drug binding.
• Understand how to read Results section while appropriately referencing Materials and Methods.
Class 5 (July 5)
Primary Reading: Ross et al. 2016 “Differential regulation by AMP and ADP of AMPK complexes containing different γ subunit isoforms”
Required Background Material: TBD

Objectives:
- Discuss the concept of phosphorylation as a cellular signal.
- Explain the competing functions of kinases and phosphatases.
- Recognize the role of AMP-kinase as a master regulator of metabolism.
- Understand how cells “sense” ATP levels and how this affects cell growth/energy metabolism.
- Connect effects of exercise to increased ATP production.
- Introduce protein isoforms and discuss how different isoforms can alter function in protein complexes/signaling pathways.
- Understand how to read Materials and Methods, especially in the context of Results section.
- Explain the concept and use of Western Blots.

Class 6 (July 10)
Primary Reading: Vander Heiden et al. 2009 “Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation.” (Review Article)
Required Background Material: Berg, Tymoczko, Stryer Chapter 15.1, Chapter 16.1, 16.2:
Aerobic glycolysis is a property of rapidly growing cell.

Objectives:
- Explain the overall context of glycolysis and mitochondrial metabolism in human physiology.
- Analyze why 2-deoxyglucose labelling is so effective in tumors.
- Diagram the four types of macromolecules found in cells and what they are composed of.
- Explain the concept of “building block” molecules
- Draw how cancer cells alter their metabolism in favor of “aerobic glycolysis.”
- Describe why aerobic glycolysis is advantageous for cancer cells.
- Predict why cancer cells still need their mitochondria at all.
- Describe how and why targeting metabolism is an effective strategy to target cancer cells.
- Explain the difference between a review article and a research article.
- Describe the strengths and uses of a review article.

Class 7 (July 12)
Primary Reading: Pecqueur et al. 2008 “Uncoupling protein-2 controls proliferation by promoting fatty acid oxidation and limiting glycolysis-derived pyruvate utilization.”
Required Background Material: Video about chemical uncoupler dinitrophenol (DNP)
Berg, Tymoczko, Stryer Chapter 22.
Objectives:
- Describe the process of fatty acid oxidation.
- Explain the phrase “fats burn in the flame of carbohydrates.”
- Explain the concepts of metabolic “coupling” and “un-coupling.”
- Diagram the process by which uncoupling proteins produce heat.
- Explain why a high level of mitochondrial uncoupling is disadvantageous to cell growth.
- Predict how drugs targeting mitochondria would affect cancer cell growth.
- Evaluate results section in the context of the rest of the paper:
  - Do the figures support the claims made in the text and other parts of the paper?
  - How is this paper different from others we have read?
- Introduce respirometry as a biochemical tool.

Class 8 (July 17)
Primary Reading: Guimaraes et al. 2018 “Chemosensitizing effects of metformin on cisplatin- and paclitaxel-resistant ovarian cancer cell lines.”
Required Background Material: - BioNinja website on Enzyme Inhibition; Cisplatin and Paclitaxel YouTube videos

Objectives:
- Outline the major ways in which drugs act in cells.
- Explain the difference(s) between a competitive inhibitor, a non-competitive inhibitor, and drugs with other modes of action.
- Describe how traditional chemotherapeutic drugs kill cancer cells.
- Explain what “chemosensitizing” means.
- Discuss benefits of “additive” drug effects.
- Effectively read paper Discussion section, answering questions such as:
  - Does your interpretation of the data match the authors’ interpretation?
  - Do the authors over-interpret their findings?
  - Have the authors fulfilled what they set out to do?
  - What are the next steps/future directions?
- Explain flow cytometry as a scientific tool.

Class 9 (July 19)
Primary Reading: Andrezejewski et al. 2014 “Metformin directly acts on mitochondria to alter cellular bioenergetics.”
Required Background Material: TBD

Objectives:
- Revisit and evaluate concept map developed by students in Class 2 for assigned reading.
- Discuss major effects of metformin in cells.
- Explain stable isotope labeling.
- Predict molecular target of metformin
- Explain the benefits or caveats of targeting mitochondria for cancer therapies.
Class 10 (July 24)
No class, Pioneer Day

Class 11 (July 26)
Readings: TBD
Objectives: TBD

Class 12 (July 31)
Primary Reading: Paper for final activity.
Objectives: Wrap up, final activity and evaluation. Final questions, concluding remarks, evaluation forms.

University Policies

1. The Americans with Disabilities Act. The University of Utah seeks to provide equal access to its programs, services, and activities for people with disabilities. If you will need accommodations in this class, reasonable prior notice needs to be given to the Center for Disability Services, 162 Olpin Union Building, (801) 581-5020. CDS will work with you and the instructor to make arrangements for accommodations. All written information in this course can be made available in an alternative format with prior notification to the Center for Disability Services.

2. Addressing Sexual Misconduct. Title IX makes it clear that violence and harassment based on sex and gender (which includes sexual orientation and gender identity/expression) is a civil rights offense subject to the same kinds of accountability and the same kinds of support applied to offenses against other protected categories such as race, national origin, color, religion, age, status as a person with a disability, veteran’s status or genetic information. If you or someone you know has been harassed or assaulted, you are encouraged to report it to the Title IX Coordinator in the Office of Equal Opportunity and Affirmative Action, 135 Park Building, 801-581-8365, or the Office of the Dean of Students, 270 Union Building, 801-581-7066. For support and confidential consultation, contact the Center for Student Wellness, 426 SSB, 801-581-7776. To report to the police, contact the Department of Public Safety, 801-585-2677(COPS).