Tufts UNIVERSITY | Graduate School of Biomedical Sciences

Biology of Aging, NUTR 0247, GSBS xxxx

Spring 2021

Course Director/s:
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Course Information:
Credit/s: To be determined by the Registrar based on class contact hours
Grading Option (select: A-F or S/U): A-F
Required or Elective: Elective
Prerequisites: Graduate Biochemistry (BCHM-0223) or instructor permission is required. In addition, it is recommended that students have taken undergraduate-level classes in Cellular or Molecular Biology and Genetics.

Course Contact Hours, Meeting Schedule, and Location:
The course will meet for once a week for 3 hours, for a total of 13 weeks.
The date/time/location of the class will be determined (we have requested Tuesdays in the late afternoon/early evening).
If necessary due to COVID-19 restrictions, the class will take place within Canvas with synchronous discussion sessions via Zoom.

Brief Course Description*:

This course is an in-depth examination of current topics in aging research, with a focus on human aging. Topics to be discussed include theories of aging; physiological, cellular, and epigenetic changes that occur with aging; biochemical and energetic processes that affect healthspan and lifespan; and interventions that may affect the aging process. Approximately 20% of the course material will be lecture-based, while 80% will involve students presenting and critiquing papers selected from a curated list of current aging research literature. To stay current with research in the field, some of the primary research papers may vary from year to year.

Learning Objectives:

At the conclusion of the course students should be able to:
1. Describe and compare various theories of aging.
2. Explain how various cellular machineries and genetic programs function to maintain healthspan and analyze how their breakdown can promote aging, including compromises to neurological, cognitive, vision, and immune function.
3. Examine how nutrition, genetics, and the environment interface with the functions of protective machineries.
4. Evaluate empirical evidence related to new dietary and pharmaceutical approaches to prolong healthspan and lifespan. Analyze opportunities for interventions.
5. Discuss the experimental and conceptual strengths and weaknesses of papers from the primary aging literature.

Course Texts and Materials:
*Please note that course syllabus is subject to changes

There is no required text for this course. All necessary lecture slides and readings will be posted on the course Canvas site.

Assignments and Grading:
Assessment will be based on: (1) your ability to present research papers to the class, (2) your ability to critique these papers in the context of course material, and (3) your participation in the class discussions.
Your final grade will be determined by your performance in each of the following three roles. Because we expect that you will gain fluency in the field with each presentation, we will take improvement into account when determining the final grades.

I. Selecting and presenting a research paper (2-3 times during the semester) 40% of total grade

- Rationale for selection of paper
- Preparation for class presentation (including meeting with professor)
- Clarity and completeness of background information
- Summary of importance of the paper in the field of aging research
- Identification and presentation of important figures in the paper

II. Serving as a discussant (2-3 times during the semester) 30% of total grade

- Preparation for discussion (including meeting with professor)
- Evaluation of the methods, results, and authors' conclusions
- Identification of controversial issues in the paper
- Suggestion of new experiments/methodology to extend the research
- Ability to engage other students in the discussion

III. Attendance and participation in paper discussions (throughout the semester) 30% of total grade

- Attending all classes and arriving on-time, barring exceptional unforeseen circumstances (please inform the instructors if you know you will miss a class ahead of time)
- Evidence that you have come to class having read the paper
- Contributing to discussions at least once per class and participating in small group activities
- Actively listening to others and showing respect to your colleagues if your interpretations of the papers differ from theirs

Detailed instructions for the research paper presentations and critiques will be provided at the beginning of the semester.

A passing grade in the course is 'B-'or better. Course grades will be based on the scale below (subject to revision during the course):

A	> 93%	C	70-80%
A-	90 - 93%	D	60-70%
B+	87 - 90%	F	<60%
B	83 - 87%		
B-	80 - 83%		

Penalties for late or incomplete assignments:

We will work with students to ensure that they can attend class when presenting research papers or serving as discussants. Excessive unexcused absences will negatively impact the participation part of a student's grade.

Remediation Policy:

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Because all students will have an opportunity to present a paper and act as a discussant within the first month of the class, we will be able to make adjustments early in the semester for students who are having trouble.

Course and Assignment Schedule:

DATE	TOPIC OR CLASS TITLE	ASSIGNMENTS & ACTIVITIES	LECTURER(S)
1-26	Introduction to Aging Theories	Introductory readings	McVey
2-2	Molecular signatures of aging and longevity	Readings/paper discussion	McVey
2-9	Studying aging in model organisms	Readings/paper discussion	McVey
2-16	The mTOR pathway and rapamycin	Readings/paper discussion	McVey/Taylor
2-23	Redox regulation of aging, mitochondria, and antioxidants	Readings/paper discussion	Taylor
3-2	Environment and nutrition effects on aging	Readings/paper discussion	Taylor/McVey
3-9	Ubiquitin proteolytic pathways and autophagy	Readings/paper discussion	Taylor
3-16	Diseases of old age and protein quality control: diabetes, cardiovascular disease, eye diseases, cancer, glyoxalase	Readings/paper discussion	Taylor
3-30	Inflammation and changes in the immune system during aging	Readings/paper discussion	Taylor/other experts
4-6	Proteotoxicity and diseases of protein aggregation	Readings/paper discussion	Taylor
4-13	Proteotoxicity and neurodegenerative aging Parkinson's and Alzheimer's diseases	Readings/paper discussion	
4-20	Recent advances in anti-aging interventions: senolytics and epigenetic reprogramming	Readings/paper discussion	McVey
4-27	Team summaries: wrap-up and discussion of new directions in aging studies	Group presentations	Taylor/McVey

This schedule is subject to modifications at the discretion of the course director.

Important University Policies:

- ***Sexual Misconduct Policy:*** Tufts is committed to providing an education and work environment that is free from sexual misconduct. If you or someone you know has been harassed or assaulted, please contact Dan Volchok, the GSBS Sexual Misconduct Reporting Liaison, at 6-6767 or daniel.volchok@tufts.edu. He can help you find appropriate resources and discuss your options. Anonymous reporting is available through the Tufts anonymous Incident Report Form: (https://tuftsuniversity.ethicspointvp.com/custom/tuftsuniversity/oeo/form_data.asp). Students may also obtain free confidential counseling through Talk One2One at 1-800-756-3124. Campus police may be contacted at 6-6911.

- ***Americans with Disabilities Act Policy:*** Tufts University is committed to providing reasonable accommodations for qualified individuals with disabilities. If you are interested in seeking accommodations in courses or in a laboratory setting, please contact Dan Volchok, the GSBS Disability Officer, at 6-6767 or at daniel.volchok@tufts.edu.

- ***Tufts Information Stewardship Policy*** outlines the actions all members of the Tufts community are expected to follow when working with institutional data and systems (https://it.tufts.edu/ispol).

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- ***Academic Conduct:*** All students are responsible for compliance with all academic standards and policies, including plagiarism and academic integrity, as outlined in the Graduate School of Biomedical Sciences Student Handbook (https://gsbs.tufts.edu/studentLife/StudentHandbook).

Detailed Description of Course Topics, Assignment Schedule, and Learning Objectives for Each Class

Week 1
Date of Class: January 26

Course Topic(s): Hallmarks, theories, and models of aging

Learning Objectives:

- List the main hallmarks of aging.
- Describe the evolutionary, disposable soma, replicative senescence, neuroendocrine, oxidative damage, rate of living, and genome maintenance theories of aging.
- Give examples of antagonistic pleiotropy.
- Explain advantages and disadvantages of different ways of measuring aging.
- Analyze benefits and drawbacks of using various model systems to study aging.

Required Reading:

1. AFAR Guide to Theories of Aging
2. Lopez-Otin et al., 2013. The Hallmarks of Aging. Cell: 153, 1194-1217.

Week 2
Date of Class: February 2

Course Topic(s): Molecular signals of aging and longevity

Learning Objectives:

- Describe how various molecular markers are used to measure rates of aging
- Compare and contrast the predictive power of various aging clocks, including telomere length, proteome profiles, and DNA methylation

Required Reading:

1. Ma and Gladyshev, 2017. Molecular signatures of longevity: Insights from cross-species comparative studies. Semin Cell Dev Biol: 70, 190-203.

Possible Papers for Discussion:

1. Lehallier et al., 2019. Undulating changes in human plasma proteome profiles across the lifespan. Nat Med: 12, 1843-1850.
2. Lu et al., 2019. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging: 11, 303-327.

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Week 3
Date of Class: February 9

Course Topic(s): Aging in model systems

Learning Objectives:
- Describe the seminal discoveries about the genetics of aging made in *C. elegans*, Drosophila, and mice
- Analyze the evidence for and against the role of sirtuins in aging
- Evaluate the usefulness of studying aging in model systems for the understanding of normal aging in humans

Required Reading:
1. Tian et al., 2017. Molecular Mechanisms Determining Lifespan in Short- and Long-Lived Species. Trends Endocrinol Metab 10: 722-734.

Possible Papers for Discussion:
1. Kenyon *et al*., 1993. A C. Elegans Mutant That Lives Twice as Long as Wild Type. Nature: 366, 461-464. (this paper was one of the first to show that single gene mutations could extend lifespan)
2. Tissenbaum and Guarente, 2001. Increased Dosage of a sir-2 Gene Extends Lifespan in Caenorhabditis Elegans. Nature: 410, 227-230. (this paper established that SIR2 levels can regulate lifespan in a model metazoan)
3. Burnett *et al*., 2011. Absence of effects of Sir2 overexpression on lifespan in C. elegans and Drosophila. Nature: 477, 482–485. (this paper called into question earlier studies regarding the role of sirtuins in promoting longevity)
4. Hu et al., 2020. Vertebrate diapause preserves organisms long term through Polycomb complex members. Science: 367, 870-874.

Week 4
Date of Class: February 16

Course topic(s): The mTOR pathway and rapamycin

Learning Objectives:
- Diagram the mTOR pathway and identify outcomes and points of regulation
- Explain how rapamycin impacts both healthspan and lifespan in a number of organisms
- Evaluate the impact that rapamycin and other mTOR inhibitors have on molecular markers of aging

Required Reading:
1. Weichart, 2018. mTOR as regulator of lifespan, aging, and celluar senescence: a mini-review. Geronotology 64:127-134.

Possible Papers for Discussion:
1. Harrison et al., 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460: 392–395.
2. Castillo-Quan et al., 2019. A triple drug combination targeting components of the nutrient-sensing network maximizes longevity. Proc. Natl. Ac Sci 116: 20817-20819.

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3. Mannick et al., 2014. mTOR inhibition improves immune function in the elderly. Sci Translational Medicine 6: 268ra179.

Week 5
Date of Class: February 23

Course Topic(s): Mitochondria and antioxidant enzymes; the free radical theory of aging

- Explain how free radicals form and can affect cellular physiology
- Describe how antioxidant enzymes alleviate prevent oxidative damage
- Analyze evidence for and against the oxidative damage theory of aging
- Evaluate evidence that oxidative stress can be beneficial to healthspan and lifespan

Required Reading:

1. Liochev, 2013. Reactive Oxygen Species and the Free Radical Theory of Aging. Free Radic Biol Med: 60, 1-4.

Possible Papers for Discussion:

1. Yuan et al., 2020. Two conserved epigenetic regulators prevent healthy aging. Nature: 579, 118-122.
2. Desjardins et al., 2017. Antioxidants reveal an inverted U-shapred dose response relationship between reactive oxygen species levels and the rate of aging in *Caenorhabditis elegans*. Aging Cell: 16, 104-112.

Week 6
Date of Class: March 2

Course Topic(s): Environment and nutrition effects on aging; caloric and dietary restriction

Learning Objectives:

- Explain how various types of dietary restriction and caloric restriction impact lifespan and healthspan.
- Compare the effects of changing levels of various nutrients on lifespan using studies from the primary geroscience literature.

Required Reading:

1. Hwangbo, D.-S.; Lee, H.-Y.; Abozaid, L.S.; Min, K.-J. Mechanisms of Lifespan Regulation by Calorie Restriction and Intermittent Fasting in Model Organisms. Nutrients 2020, 12, 1194.
2. Lee, B.C., Kaya, A. and Gladyshev , V.N. (2016), Methionine restriction and life‐span control. Ann. N.Y. Acad. Sci., 1363: 116-124. doi:10.1111/nyas.12973

Possible papers for discussion:

1. Colman, R., Beasley, T., Kemnitz, J. et al. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun 5, 3557 (2014). https://doi.org/10.1038/ncomms4557

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2. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. (2019). Cell Metab. 30 (3):462-476.e6. doi: 10.1016/j.cmet.2019.07.016
3. Bárcena, C., Quirós, P.M., Durand S. et al. Methionine Restriction Extends Lifespan in Progeroid Mice and Alters Lipid and Bile Acid Metabolism, Cell Reports 24: 9, 2392-2403. (2018). https://doi.org/10.1016/j.celrep.2018.07.089

Week 7
Date of Class: March 9

Course Topic(s): Ubiquitin proteolytic pathways and autophagy

Learning Objectives:
- Describe how defective proteins are designated for destruction and removed from cells.
- Explain how autophagy promotes healthspan and lifespan.
- Analyze how changing mTOR signaling affects energy balance and levels of autophagy.

Required Reading:
1. Shang and Taylor, 2011. Ubiquitin-proteasome pathway and cellular responses to oxidative stress. Free Radic Biol Med: 51, 5-16.
2. Dudley et al., 2020. TORwards a Victory Over Aging. J Gerontol A Biol Sci Med Sci: 75, 1–3.

Potential Papers for Discussion:
1. Gottlieb et al., 2019. Acute unfolding of a single protein immediately stimulates recruitment of ubiquitin protein ligase E3C (UBE3C) to 26S proteasomes. J Biol Chem: 294,16511-16524.
2. Polh and Dikic, 2019. Cellular quality control by the ubiquitin-proteasome system and autophagy. Science: 366, 818-822.
3. Pride et al., 2015. Long-lived species have improved proteostasis compared to phylogenetically-related shorter-lived species. Biochemical and Biophysical Research Communications: 457, 669e675.
4. Vilchez, 2012. Rape RPN-6 determines C. elegans longevity under proteotoxic stress conditions. Nature: 489, 263-70.
5. Kumsta et al., 2019. The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in C. elegans by inducing autophagy. Nat Commun. 2019 Dec 11;10(1):5648. doi: 10.1038/s41467-019-13540-4.

Week 8
Date of Class: March 16

Course Topic(s): Diseases of old age and protein quality control: diabetes, cardiovascular disease, eye diseases, cancer, glyoxalase

Learning Objectives:
- Identify proximate causes of the major common diseases associated with aging
- Analyze common factors that impact disease progression in diabetes, cardiovascular disease, and other aging-related disorders

Required Reading:
1. Cheon et al., 2019. Autophagy, Cellular Aging and Age-related Human Diseases. Exp Neurobiol: 28, 643-657.

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Possible Papers for Discussion:

1. Brouwers et al., 2011. Overexpression of Glyoxalase-I Reduces Hyperglycemia induced Levels of Advanced Glycation End Products and Oxidative Stress in Diabetic Rats. Journal of Biol Chem: 286, 1374-1380.
2. Rowan et al., 2017. A gut-retina axis and low glycemia arrest of age-related macular degeneration. Proc Natl Acad Sci USA: 114, 4472-4481.
3. Scaffidi and Misteli, 2006. Lamin A-dependent nuclear defects in human aging. Science: 312, 1059-63.
4. Dahl et al., 2006. Distinct structural and mechanical properties of the nuclear lamina in Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A: 103, 10271-10276.

Week 9
Date of Class: March 30

Course Topic(s): Inflammation and changes in the immune system during aging

Learning Objectives:

- List and describe factors that promote chronic inflammation.
- Give examples of physiological responses that lead to "inflammaging"
- Describe how immune responses change during aging
- Analyze how inflammatory responses can lead to other phenotypes associated with aging
- Explain how chronic inflammation in the gut leads to diseases of aging and impacts lifespan.

Required Reading:

1. Müller L., Di Benedetto S., Pawelec G. (2019) The Immune System and Its Dysregulation with Aging. In: Harris J., Korolchuk V. (eds) Biochemistry and Cell Biology of Ageing: Part II Clinical Science. Subcellular Biochemistry, vol 91. Springer, Singapore

Possible Papers for Discussion:

1. Ostan et al., 2016. Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine. Clin Sci (Lond): 130, 1711-25.
2. Singh, R., Chandrashekharappa, S., Bodduluri, S.R. et al. Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway. Nat Commun 10: https://doi.org/10.1038/s41467-018-07859-7.
3. Bonnay et al., 2013. Gut immune tolerance in Drosophila. Proc Natl Acad Sci USA: 110, 2957-2962.

Week 10
Date of Class: April 6

Course Topic(s): Proteotoxicity and diseases of protein aggregation

Learning Objectives:

- Give examples of diseases of protein aggregation.
- Explain the mechanisms by which changes in the proteasome can lead to disease states.

Required Reading:

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1. Labbadia and Morimoto, 2015. The Biology of Proteostasis in Aging and Disease. Annual Review of Biochemistry: 84, 435-464.

Possible Papers for Discussion:

1. Santra et al., 2015. Proteostasis collapse is a driver of cell aging and death. PNAS: 116, 22173-78.
2. Blasiak et al., 2019. Interplay between Autophagy and the Ubiquitin-Proteasome System and Its Role in the Pathogenesis of Age-Related Macular Degeneration. Int J Mol Sci: 20(1), doi: 10.3390/ijms20010210.
3. Sui et al, 2019. Widespread remodeling of proteome solubility in response to different protein homeostasis stresses. PNAS: 117, 2422-2431
4. Leeman et al., 2018. Lysosome activation clears aggregates and enhances quiescent neural stem cell activation during aging. Science: 359, 1277-1283.
5. Jacquin et al., 2017. Pharmacological modulators of autophagy activate a parallel noncanonical pathway driving unconventional LC3 lipidation. Autophagy: 13, 854-867.

Week 11
Date of Class: April 13

Course Topic(s): Proteotoxicity and neurodegenerative aging Parkinson's and Alzheimer's diseases

Learning Objectives:

- Evaluate the proximal causes of disease progression in various neurodegenerative aging diseases.
- Interpret primary data in the context of various theories of neurodegeneration for Alzheimer's and Parkinson's diseases.

Required Reading:

1. Ganguly et al., 2017. Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. Drug Des Devel Ther. 2017;11:797-810.

Possible papers for discussion:

1. Djajadikerta et al., 2019. Autophagy Induction as a Therapeutic Strategy for Neurodegenerative Diseases. J Mol Biol: 19, 30745-4.
2. Kumari et al., 2020. Amyloid aggregates of the deubiquitinase OTUB1 are neurotoxic, suggesting that they contribute to the development of Parkinson's disease. Journal Biol Chem: doi: 10.1074/jbc.RA119.009546
3. Wang et al., 2018. C/EBPβ regulates delta-secretase expression and mediates pathogenesis in mouse models of Alzheimer's disease. Nat Commun: 9, 1784. https://doi.org/10.1038/s41467-018-04120-z.
4. Friedman et al., 2018. Diverse Brain Myeloid Expression Profiles Reveal Distinct Microglial Activation States and Aspects of Alzheimer's Disease Not Evident in Mouse Models.. Cell Rep: 16, 832-847.

Week 12
Date of Class: April 20

Course Topic(s): Anti-aging interventions: senolytics, epigenetic reprogramming

Learning Objectives:

- Describe how senolytics extend lifespan through modification of previously discussed aging mechanisms.
- Evaluate the evidence for epigenetic reprogramming as an effective anti-aging therapeutic.

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Required Reading:

1. Pereira et al., 2019. Approaches towards Longevity: Reprogramming, Senolysis, and Improved Mitotic Competence as Anti-Aging Therapies. Int J Mol Sci: 20, E938.

Possible Papers for Discussion:

1. Xu et al., 2018. Senolytics improve physical function and increase lifespan in old age. Nat Med: 24, 1246–1256.
2. Ocampo et al., 2016. In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. Cell: 167, 1719-1733.
3. Lu et al., 2019. Reversal of ageing- and injury-induced vision loss by Tet-dependent epigenetic reprogramming. bioRxiv preprint first posted online Jul. 31, 2019; doi: http://dx.doi.org/10.1101/710210.

Week 13
Date of Class: April 27

Course Topic(s): Team summaries: wrap-up and discussion of new directions in aging studies

Learning Objectives:

- Summarize knowledge gained from the class.
- Synthesize various models of aging and evaluate their strengths and weaknesses in the context of the literature discussed throughout the class.
- Propose new topics for future class semesters based on emerging trends in the literature.

Required Assignment:

- Students will work in teams of 3 to present their summaries and recommendations for future semesters.

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