

Biology 78
Molecular Mysteries
of Human Biology
Dartmouth College, Winter, 2025



JW Waterhouse, *The Crystal Ball*, 1902

It will always be impossible to make science agree with the eternally changing imagination.

Madame de Champ, granddaughter of Michel-Eugène Chevreul

We learn as much from sorrow as from joy, as much from illness as from health, from handicap as from advantage---and indeed perhaps more. Not out of fullness has the human soul always reached its highest, but often out of deprivation.

Pearl Buck, '*The Child Who Never Grew*',

Biology 78 w25 Molecular Mysteries of Human Biology

Lectures: Monday, Wednesday & Friday, 9L (8:50-9:55 AM) **X-hour:** Thursday, (9:05-9:55 AM)

Text/Reading:

1. **Recommended text:** Any biochemistry text (e.g. Voet & Voet 4th, 5th or 6th editions) may provide important background information.
2. **Course Readings:** 17 research manuscripts that are required course reading are posted on web site. Additional complementary & background information (also required) and helpful reviews (optional, but useful for presentations & paper previews) for each topic also posted.

Course Web Site: <http://canvas.dartmouth.edu>

Date	Topic
Watch by Monday, Jan 6	Video: The Hidden Epidemic: Heart Disease in America
Mon, Jan 6	Atherosclerosis: The Loch Ness Monster and John Hunter's Ossified Arteries
Wed, Jan 8	Plasma Lipoproteins: The Legacies of Michel-Eugène Chevrueil and Mona Lisa
Thurs, Jan 9 X-hour	X-HOUR: Dr. Sarah Tsiras (DC '99): A Patient with Coronary Artery Disease
Fri, Jan 10	Readings: Schöenheimer Explained? Regulation of Hepatic Cholesterol Synthesis
Mon, Jan 13	NO CLASS
Wed, Jan 15	Readings: Lowering LDL: Targeting PCSK9 and ANGPTL-3
Thurs, Jan 16 X-hour	NO X-HOUR
Friday, Jan 17	Otto Warburg and the Mysterians: Metabolism in Cancer Cells
Mon, Jan 20	NO CLASS: MLK DAY
Wed, Jan 22	Readings: Metabolite-Driven Antitumor Immunity by an Oncometabolite
Thurs, Jan 23 X-hour	Readings: An Alternative View of the Warburg Effect: Role of the NADH Shuttle
Fri, Jan 24	Cachexia: Agostino Levanzin, the Irish Republican Army and Steve Jobs
Mon, Jan 27	Readings: Activin A as a Driver of Cancer Cachexia
Wed, Jan 29	Readings: Reversing Cancer Cachexia via Inhibition of GFRAL/RET Signaling
Thurs, Jan 30 X-hour	NO X-HOUR
Fri, Jan 31	Bathsheba's Breast: Hendrickje Stoffels, Anne of Austria, Susan Sontag and Jill Ireland
Monday, Feb 3	Readings: Fasting-mimicking Diets and Triple-Negative Breast Cancer
Wed, Feb 5	Readings: Fasting & Hormone Therapy Induce Breast Cancer Regression
Thurs, Feb 6. X hour	NO X-HOUR
Fri, Feb 7	Exercise: Sled Dogs, Toadfish, Frogs, Geese & Lance Armstrong
Mon, Feb 10	Readings: An Exercise-Inducible Molecule That Suppresses Feeding & Obesity
Wed, Feb 12	Readings: Exercise & The Gut Microbiome: The Desire to Run
Thurs, Feb 13, X-hour	NO X-HOUR
Fri, Feb 14	Diabetes Mellitus: Paul Cezanne's Vision and Shirley Horn's Feet
Mon, Feb 17	Readings: CaMKII and Diabetic Cardiomyopathy
Wed, Feb 19	Readings: Fatty Acids and Progression of Diabetic Nephropathy
Thurs, Feb 20, X-hour	X-HOUR: Dr. Richard Comi: A Patient with Type 1 Diabetes Mellitus
Watch by Friday, Feb 21	Video: The Forgetting: A Portrait of Alzheimer's Disease
Fri, Feb 21	Alois Alzheimer and Auguste D: Sailing Into Darkness
Mon, Feb 24	Readings: ApoE4 Homozygosity vs ApoEChristchurch: An Alzheimer's Risk Spectrum
Wed, Feb 26	Readings: ApoE4/E4 and Microglial Lipid Droplets/Neurotoxicity
Thurs Feb 27 X-hour	NO X-HOUR
Thurs, Feb 27, Evening	Dinner/Movie: Iris: A Tale of Iris Murdoch & Discussion with Dr. Robert Santulli
Fri, Feb 28	Aging: Luigi Cornaro & Ponce de Leon: Searching for the Fountain of Youth
Mon, March 3	Readings: Is Taurine A Panacea to Slow Aging?
Wed, March 5	Readings: Inflammation & Longevity: Blocking IL-11 Increases Lifespan
Thurs, March 6 X-hour	NO X-HOUR
Fri, March 7	Readings: Rejuvenation of the Aging Ovary by Spermidine

Biology 78 w25 Course Format & Expectations

Course Goals and Format

Knowledge of molecular mechanisms allows new approaches to understanding human biology and disease. This course will explore the normal and abnormal biology of several human conditions relying on biochemistry, molecular genetics, and physiology as tools of inquiry. Examples will be drawn from the histories of Mona Lisa, Michel-Eugène Chevreul, Otto Warburg, Steve Jobs, Hendrickje Stöffels, Bobby Sands, Paul Cézanne, Lance Armstrong, Auguste D and Luigi Cornaro, among others.

The eight class topics are organized in blocks of approximately one week, the introduction of which will begin with a lecture (or two) by Professor Witters who will discuss an area of normal or abnormal human biology to be investigated. He will include information on the relevant physiology/pathophysiology and basic biochemical & molecular background to set the context for further discussions. In the following two classes, the assigned reading will be discussed. Students (in groups of 2) will be assigned to TWO papers for the term (see below for details) and will analyse, critique and present the paper to which they are assigned. **For each of these classes, ALL students will be expected to have read the background & research papers AND to participate in the discussion.** Some “editorial comments” or review papers included on the course web site are also valuable in setting the context and will provide supplementary information to assist students in their preparation of their paper presentations & others in their reading of assigned papers. **Papers not assigned to student groups will be presented by Professor Witters with the same expectations for student participation.**

Throughout the course, it will be important to put a human face/context to the biochemical/molecular events we are studying, illustrating the “life” experience where biology is normal or abnormal. We will hope to achieve this aim in several ways. The **background reading** can be a very important complement to the molecular details. In two class meetings, we will have a **guest physician** discussing a patient dealing with one of the topics under discussion. We will also preview two of the course blocks with **out-of-class viewing of videos** that will help introduce or amplify some of these points & will have a special evening **dinner/movie** to explore the humanistic aspects of one of the topics.

Expectations and Grading

Expectations for and grading of students consists of several elements. **Students are expected to attend class, to have done the reading, to fully participate in course discussions and be prepared to answer questions about the readings when presented.** It is possible to accumulate 100 points in the course in 3 ways anticipating the median grade to be A-/A (based on prior offerings of this course).

- **(80% of grade; 40 points per paper; 80 points total).** **Presentation in class of 2 assigned papers** (see below for assignment details). Each student (in groups of 2) will be expected to prepare a scholarly oral presentation of **TWO papers (one in each half of the course)**, providing background on the topic, an exposition and review of the data and the methodology of the papers under review and a critique of the paper’s findings and conclusions. Each presentation should be accompanied by a PP set, including a bibliography. **In the last offering of this course, grades ranged from 32-40 points per paper. More details below.**
- **(20% of grade; 20 points).** **Engagement of and participation in class discussions and analysis of reading through thoughtful questions and comment** will be an important part of the grading. **Participation in class is the key word, not whether the student is “right or wrong”.** Indeed, clarifying questions are participation! Evidence that student has read/prepared for each paper presentation will also be sought. **Other “evidence” of participation** will include the use of office hours and use of /presence on Slack for thoughtful questions, reflections/comments or postings. **In the last offering of this course, grades ranged from 16-20 points.**
- **There are no problem sets, midterms, final exam or paper in this year’s course.**

Services (SAS) or its Testing Center may play in assisting. In order for accommodations to be authorized, students are required to register with SAS.

For SAS access: Use this link or phone number: Where to Start

(<https://students.dartmouth.edu/student-accessibility/students/where-start/apply-services>); 603-646-9900) and request an accommodation email be sent to me in advance of the need for an accommodation. If students have questions about whether they are eligible for accommodations, they should contact the SAS office. All inquiries and discussions will remain confidential. It is **very important that we then continue to communicate** over the term to assure that your needs are being met. Receiving accommodations **does NOT** relieve you of the responsibility of communicating with me about any deviations from course requirements **BEFORE** the fact.

- **Mental health and wellbeing support.** The academic & social environments at Dartmouth are challenging, our terms are intensive, and classes are not the only demanding part of your life. There are a number of resources available to you on campus to support your wellness, including: your undergraduate dean (<https://students.dartmouth.edu/undergraduate-deans/>) Counseling Center (<https://students.dartmouth.edu/health-service/counseling/about/counseling-center-staff-0>), and the Student Wellness Center (<https://students.dartmouth.edu/wellness-center>). The student-led Dartmouth Mental Health Union and their Peer Support Program (and other programs) may additionally be helpful to you. The Commitment to Care web site is a comprehensive gathering of many important services.

Find phone numbers for emergency mental health support, information on how to make a counseling appointment, and links to mental health and wellness resources across the institution at

<https://home.dartmouth.edu/mental-health-resources>

- **Financial support.** Some courses may require purchases of course materials, though this is likely not the case for Bio 78. If help needed, consult with your dean, review Financial Aid Policies and Resources, and keep me informed.
- **Support around issues of sex or gender-based harassment, sexual assault, and their after-effects.** Title IX Office's "Get Help Now" web site (<https://sexual-respect.dartmouth.edu/get-help-emergency-0>) provides information on how to receive help quickly. Please keep in mind that if you report prohibited conduct to me as detailed in the Sex and Gender-based Misconduct policy, I am obliged to share your concern with the Title IX Coordinator.

Please make me aware of anything that will hinder your success in & enjoyment of this course.

I will help and I will put you in touch with others who can help even more.

The earlier I am aware of issues, the more I can do to assist you.

Preparation of Assignments and the Dartmouth Academic Honor Principle: The Dartmouth College Student Handbook states: "Fundamental to the principle of independent learning are the requirements of honesty and integrity in the performance of academic assignments, both in the classroom and outside. Dartmouth operates on the principle of academic honor, without proctoring of examinations. Students who submit work which is not their own or who commit other acts of academic dishonesty forfeit the opportunity to continue at Dartmouth." Students are responsible for the information concerning plagiarism and proper citation found at:

<https://students.dartmouth.edu/community-standards/>

<https://writing.dartmouth.edu/support/sources-and-citations>

Some Specifics Regarding the Paper Assignments/Presentations

Paper Presentation Assignments

Students have been "pre-assigned" to 2 papers (one in each half of the course) with a partner using a random list generator. **This assignment will be updated during the 1st week as the course enrollment stabilizes.** Students may then "swap" with others (within each half of the course) by the beginning of the 2nd week (January 13, noon deadline). After that, assignments are final unless unforeseen circumstances emerge. I will be presenting the first two papers in Week 2; thus, student presentations will begin in Week 3.

Each student group of two is to prepare a scholarly 40-45 min (~20+ min per student) presentation using Powerpoint that includes a bibliography of any additional readings beyond that provided in class. This time leaves ~20 minutes for additional discussion/questions. For completion of all Biology 78 assignments, students are free to consult other sources of information, but ALL THESE SOURCES must be documented in a bibliography. Possible sources include classmates, other non-class students, Professor Witters/other faculty, textbooks and the biomedical literature. INTERNET RESOURCES (as URLs) ARE NOT ACCEPTABLE AS SOLE SOURCES OF INFORMATION; STUDENTS ARE EXPECTED TO USE STANDARD TEXTBOOKS AND THE BIOMEDICAL LITERATURE (You are free to use the Internet, of course, to identify these primary sources, but must consult them directly). *All presentation Powerpoint slides must be passed onto Professor Witters for posting on the course web site after the presentation.*

The presentation should include the following **FOUR** elements:

1. A **brief background** on the biology and clinical issues of the relevant topic addressed by the paper
2. **Presentation of the important data** displayed in the paper (it is not necessary to present ALL the data; attention should be paid to the data which supports the major experimental conclusions). *Indeed, your ability to identify which are the key data is part of your grade!* When presenting the data, the figure from the text should be shown where applicable and the experimental technique(s) used to generate the data briefly explained. The data presentation should include any critique about the techniques used or conclusions drawn about any of the data sets. **Each student group will be given all the figures from the body of the paper (as .jpg files) to assist in their preparation. Supplemental data to some of the papers can be linked to from the Canvas site. In general, the supplemental data should NOT be a major part of your analysis (give the sheer density of many of these supplements).** However, you certainly can use these data if you think they are particularly important. Note also some supplements have **valuable summary figures** (as do the review articles and the editorial comments accompanying some of the paper postings).
3. A **summary and critique** (the latter to be elicited first from the class) of the major conclusions of the paper and the ramifications of the study in terms of future research.
4. **Engagement of the rest of the class through provocative or interesting questions.** This is a crucial (and "graded") element of the presentation. The questions should be analytical and thought-provoking, not just regurgitative of what everyone has read or can see (i.e. not "softball"). Asking classmates to interpret data, to provide alternative explanations for conclusions, to critique the information presented and to synthesize different pieces of data are all examples of the kinds of engagement that should be elicited.

Other important points about presentations:

1. The **time limit** of ~40-45 minutes allows sufficient time for Q&A and discussion, so rehearsal of the presentations is **STRONGLY ENCOURAGED.**
2. Students will be **informed of their grade** shortly after the class presentations. **Forty (40) course points are assigned to each presentation.** For simple completion of the assignment, 32 points would be the expected (but not guaranteed) grade; more (or fewer) points will be awarded depending on the quality of the presentation and the effort of the presenters to engage the rest of the class.

Readings for Biology 78

Readings are indicated by inclusive dates we will be covering each subject area in class. EVERYONE is expected to have done the reading. Background reading on the human context and/or physiology/pathophysiology AND the molecular/biochemically-oriented research papers to be presented in class are REQUIRED. Optional, but helpful, review articles for each topic are included in this list, including some that are valuable editorial comments on the research papers (with a summary figure). All readings are available on the Canvas site. External links are also provided on the Canvas site for each of the papers. *In addition, there may be additional supplemental on-line material for many of the research papers (e.g. supplemental figures, videos, some tables) other than those included on our web site; students should directly link to the paper to access this information.*

January 6-January 15: Atherosclerosis

The Loch Ness Monster and John Hunter's Ossified Arteries

Plasma Lipoproteins: The Legacies of Michel-Eugène Chevrueil and Mona Lisa

Physiologic/Pathophysiologic/Historical Background:

Bryan, CS and Podolsky, SH (2019) Sir William Osler (1849-1919)-The uses of history and the singular beneficence of medicine, *New Eng J Med*, 381, 2194-2196

Kligfield, P (1980) John Hunter, angina pectoris and medical education, *Am J Cardiol*, 45, 367-369

Kligfield, P (1982) The early pathophysiologic understanding of angina pectoris, *Am J Cardiol* 50, 1433-1435

Libby, P (2021) The biology of atherosclerosis comes full circle: lessons for conquering cardiovascular disease, *Nature Reviews Cardiology*, 18, 683-684

Molecular Aspects:

Engelking LJ, Liang G, Hammer RE, Takaishi K, Kuriyama H, Evers BM, Li WP, Horton JD, Goldstein JL, Brown MS. (2005) Schöenheimer effect explained--feedback regulation of cholesterol synthesis in mice mediated by Insig proteins, *J Clin Invest*. 115, 2489-98

Complementary article Hu, X, Chen, F et al (2024) A gut-derived hormone regulates cholesterol metabolism, *Cell*, 187, 1585-1600 (look at visual abstract only)

Wang, J, Zhao, J, Yan, C et al (2022) Identification and evaluation of a lipid-lowering small compound in preclinical models and in a Phase 1 trial, *Cell Metab*, 34, 667-680.

OPTIONAL, BUT HELPFUL

Goldstein, JL and Brown, MS (2015) A century of cholesterol and coronaries: from plaques to genes, *Cell*, 161, 161-172

Libby, P (2021) The changing landscape of atherosclerosis, *Nature*, 592, 524-533

Björkegren, JLM and Lusis, AJ (2022) Atherosclerosis: recent developments, *Cell*, 185,1630-1644

Molecular Aspects:

Queiroz, AL et al (2022) Blocking ActRIIB and restoring appetite reverses cachexia and improves survival in mice with lung cancer, *Nature Comm*, 13:4633

Suriben, R et al (2020) Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice, *Nature Medicine*, 26, 1264-1270

Companion clinical paper: Groake, JD et al (2024) Ponegromab for the treatment of cancer cachexia, *New Engl J Med*, 10.1056/NEJMoa2409515

Companion audio interview: NEJM at ESMO — Ponegromab in Cancer

Cachexia E.J. Rubin, O.O. Yeku, and S. Morrissey (2024), 10.1056/NEJMe2411491

OPTIONAL, BUT HELPFUL

Rohm, M et al (2020) An antibody attack against body wasting in cancer, *Cell Metabolism*, 32, 331-333 (editorial comment on Suriben paper (figure included))

Talbert, EE & Guttridge, DC (2022) Emerging signaling mediators in the anorexia-cachexia syndrome of cancer, *Trends in Cancer*, 8, 397-403 (excellent short recent view)

Ferrer, M et al (2023) Cachexia: an system consequence of progressive, unresolved disease, *Cell*, 186, 1824-1845 (excellent comprehensive & recent review)

January 31-February 5: Bathsheba's Breast: Hendrickje Stoffels, Anne of Austria, Susan Sontag and Jill Ireland

Physiologic/Pathophysiologic/Historical Background:

Braithwaite PA, Shugg D (1983) Rembrandt's Bathsheba: the dark shadow of the left breast, *Ann R Coll Surg Engl*. 65(5):337-8.

Selected readings about Anne of Austria, Susan Sontag and Jill Ireland from *Bathsheba's Breast: Women, Cancer and History*, Olson, JS, Johns Hopkins University Press, 2002, pp. 14-26; 167-170; 245-249.

Molecular Aspects:

Salvadori, G et al (2021) Fasting-mimicking diet blocks triple-negative breast cancer and cancer stem cell escape, *Cell Metab*, 33, 2247-2259

Caffa, I et al (2020) Fasting-mimicking diet and hormone therapy induce breast cancer regression, *Nature*, 23, 620-624

OPTIONAL, BUT HELPFUL

Giaquinto, AN et al (2024) Breast cancer statistics, *CA Cancer J Clin*. 74, 477-495

Nolan, E et al (2023) Deciphering breast cancer: from biology to the clinic, *Cell*, 186, 1708-1728 (excellent comprehensive review)

February 14-20: Diabetes Mellitus: Paul Cezanne's Vision and Shirley Horn's Feet

Physiologic/Pathophysiologic/Historical Background:

Parker, DM and Mark, R (eds), *Reflections On A Life with Diabetes: a memoir in many voices, Section IV: Complications-Tales of Coping*, Virtualbookworm.com Publishing, 2004, pp. 207-233

Brownlee M (2005). Banting Lecture: The pathobiology of diabetic complications: a unifying mechanism, *Diabetes*. 54:1615-1625 (dated, but classic review with continued relevance)

Molecular Aspects:

Lebek, S, Chemello F et al (2023) Ablation of CaMKII δ oxidation by CRISPR-Cas9 base editing as a therapy for cardiac disease, *Science*, 239, 179-185

Companion editorial: Hegyl, B & Bers, DM (2023) New cardiac targets for empagliflozin: O-GlycNAcylation, CaMKII and calcium handling, *Am J Physiol Heart Circ Physiol*, 324, H338-H340. (brief review of useful clinical drug that alters O-glycosylation; useful figure)

Mori, Y et al (2021) KIM-1 mediates fatty acid uptake by the renal tubular cells to promote progressive diabetic kidney disease, *Cell Metabolism*, 33, 1042-1061

OPTIONAL, BUT HELPFUL

Erickson, JR (2014) Mechanisms of CaMKII activation in the heart, *Frontiers Pharmacology*, 5, 1-5 (helpful for background of paper #1 (figure included))

Huang, H et al (2021) Skimming the fat in diabetic kidney disease: KIM-1 and tubular fatty acid uptake, *Kidney Intl*, 100, 969-972 (editorial commentary on Mori paper)

Mohandes, S et al (2023) Molecular pathways that drive diabetic kidney disease, *J Clin Invest*, 133(4) e165654 (excellent recent comprehensive review on DKD)

Drucker, DJ (2024) Prevention of cardiorenal complications in people with type 2 diabetes and obesity, *Cell Metab*, 36, 338-353 (excellent recent review)

February 21-27: Alois Alzheimer and Auguste D: Sailing Into Darkness

Physiologic/Pathophysiologic/Historical Background:

Stelzmann, RA, Schnitzlein, N and Murtagh, RF (1995) An English translation of Alzheimer's 1907 Paper, "Über eine eigenartige Erkrankung der Hirnrinde", *Clin Anat*, 8, 429-431

Mauer, K, Volk, S and Gerbaldo, H (1997) Auguste D and Alzheimer's Disease, *Lancet*, 349, 1546-1549

Bayley, John (1999) *Elegy for Iris*, St. Martin's Press, New York, p. 253-260

Kaiser, J (2024) The burden of a gene, *Science*, 385, 1154-1157

- Madeo, F et al (2018) Spermidine in health and disease, *Science*, 359, 410 (**excellent comprehensive review with helpful figures of pathway, sources & health effects**)
- Guarente, L, Sinclair, DA and Kroemer, G (2024) Human trials exploring anti-aging medicine, *Cell Metab*, 36, 354-376 (**excellent comprehensive review**)
- López-Otin C et al (2023) Hallmarks of aging: an expanding universe, *Cell*, 186, 243-278 (**excellent comprehensive review with some useful figures**)
- Longo, VD & Anderson, R (2022) Nutrition, longevity and disease: From molecular mechanisms to interventions, *Cell*, 185, 1455-1470 (**excellent review of several diets**)
- Mihaylove MM et al (2023) When a calorie is not just a calorie; diet quality and timing as mediators of metabolism and healthy aging, *Cell Metab*, 35, 1114-1131 (**excellent review of several popular interventions**)
- Olahansky, SJ et al (2024) Implausibility of radical life extension in humans in the twenty-first century, *Nature Aging*, published online 10/7/24