

Biology 78
Molecular Mysteries
of Human Biology
Dartmouth College, Winter, 2024



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 Chevruei

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 w24 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 & Pratt, Berg, Tymoczko & Stryer, or Garrett & Grisham) may provide important background information.
2. **Course Readings:** 17 research manuscripts that are required course reading are posted on web site. Additional background information (also required) and helpful reviews (optional) for each topic also posted.

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

Date	Topic	Prob Set Posted	Prob Set Due
Watch by Friday, Jan 5	Video: The Hidden Epidemic: Heart Disease in America		
Wed, Jan 3	Atherosclerosis: The Loch Ness Monster and John Hunter's Ossified Arteries		
Fri, Jan 5	Plasma Lipoproteins: The Legacies of Michel-Eugène Chevreul and Mona Lisa		
Mon, Jan 8	Readings: Schöenheimer Effect Explained: Cholesterol Regulates Itself		
Wed, Jan 10	Readings: Lowering LDL: Targeting PCSK9 and LPL	#1	
Fri, Jan 12	Otto Warburg and the Mysterians: Metabolism in Cancer Cells		
Mon, Jan 15	MLK Day: NO CLASS		#1
Wed, Jan 17	Readings: An Alternative View of the Warburg Effect: Role of the NADH Shuttle		
Thurs, Jan 18, X-hour	Readings: Metabolite-Driven Antitumor Immunity by an Oncometabolite	#2	
Fri, Jan 19	Cachexia: Agostino Levanzi, the Irish Republican Army and Steve Jobs		
Mon, Jan 22	Readings: Reversing Cancer Cachexia via Inhibition of GFRAL/RET Signaling		#2
Wed, Jan 24	Readings: Activin A as a Driver of Cancer Cachexia	#3	
Fri, Jan 26	Bathsheba's Breast: Hendrickje Stoffels, Anne of Austria, Susan Sontag and Jill Ireland		
Mon, Jan 29	Readings: Fasting & Hormone Therapy Induce Breast Cancer Regression		#3
Wed, Jan 31	Readings: Fasting-mimicking Diets and Triple-Negative Breast Cancer	#4	
Thurs, Feb 1, X-hour	Dr. Laura Salama: A Patient with Breast Cancer		
Friday, Feb 2	Exercise: Sled Dogs, Toadfish, Frogs, Geese & Lance Armstrong		
Mon, Feb 5	Readings: Exercise & The Gut Microbiome: The Desire to Run		#4
Wed, Feb 7	Readings: An Exercise-Inducible Molecule That Suppresses Feeding & Obesity	#5	
Fri, Feb 9	Diabetes Mellitus: Paul Cezanne's Vision and Shirley Horn's Feet		
Mon, Feb 12	Readings: CaMKII, O-linked Glycosylation and Diabetic Cardiomyopathy		#5
Wed, Feb 14	Readings: Fatty Acid Uptake and Progression of Diabetic Nephropathy	#6	
Thurs, Feb 15, X-hour	Dr. Richard Comi: A Patient with Type 1 Diabetes Mellitus		
Watch on Thurs, Feb 15	Video: The Forgetting: A Portrait of Alzheimer's Disease		
Fri, Feb 16	Alois Alzheimer and Auguste D: Sailing Into Darkness		
Mon, Feb 19	Readings: Necroptosis in Human Alzheimer's Neurons: A Unique Model of Tauopathy		#6
Wed, Feb 21	Readings: TRIMming Away Tau Prevents Neurodegeneration	#7	
Thurs, Feb 22, Evening	Dinner/Movie: Iris: A Tale of Iris Murdoch & Discussion with Dr. Robert Santulli		
Fri, Feb 23	Aging: Luigi Cornaro & Ponce de Leon: Searching for the Fountain of Youth		
Mon, Feb 26	Readings: Is Taurine A Panacea to Slow Aging?		#7
Wed, Feb 28	Readings: Rejuvenation of the Aging Ovary by Spermidine	#8	
Fri, March 1	Readings: The Long and the Short of It: The Telomeres		
Mon, March 4	NO CLASS		#8

Biology 78 w24 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 Chevrueil, 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. Following the final presentation within each topic, a to-be-graded problem set based on topics raised by one/both of the papers and/or the accompanying lecture will be posted. *These assignments will be due as indicated on the course schedule and can be completed in an open-book format with full consultation with any source of information (save for generative AI), including others in the class (see below for details).*

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 three 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 and to complete all assignments on time unless the reasons for the lateness/absence have been discussed with Professor Witters in advance. In general, the only possible excuses for lateness/absence will be illness or unavoidable conflicts (e.g. job or med/grad school interview; being off-campus for a college-related activity). In each of these, however, PRIOR approval from him will be required.

- A 1% deduction per hour in grade will be assigned for any assignment that is late.
- Again, students are expected to communicate with Professor Witters in advance about any possible deviation from submission of assignments on time.

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).

- (40% of grade; 20 points for each set submitted; 40 points total). Eight (8) problem assignments, each worth 20 points, will be distributed during the term. Each student must complete two (2) of these (one in each half of the course), automatically excluding the two problems on the topics of their assigned papers AND excluding four others of their choosing (2 in each half of the course, these declared in advance of problem set posting). Each problem will relate to an aspect of the assigned reading and/or its accompanying lecture; answers are limited to two typewritten pages. In the last offering of this course, grades ranged 15-19.5 points on each problem set (mean: 18.5). *The distribution and due dates are indicated on the course schedule, on the student presentation assignments spreadsheet & on the Canvas course calendar.*

- **(40% of grade; 20 points per paper; 40 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 18-20 points per paper (mean: 19). More details below.**
- **(20% of grade; 20 points).** Engagement of and participation in class discussions and analysis of reading through thoughtful questions and comment & in group work on the problem sets will be an important part of the grading. Participation 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, use of & listing of collaborators on problem sets and use of Slack on the course web site for thoughtful questions, comments or postings. **In the last offering of this course, grades ranged from 16-20 points.**
- **There are no midterms, final exam or paper in this course.**

Course Materials

The course readings are included as .pdfs on the web site (along with links to each), as well as pertinent review articles & editorial commentaries on the readings that may be of value in preparing paper presentations. External links to all the research manuscripts are included, which can be value in viewing in color and in examination of supplemental data.

A biochemistry text, either Berg, Tymoczko & Stryer, Biochemistry or Voet, Voet & Pratt, Biochemistry or Garrett & Grisham might be very valuable in the review of some of the material and preparation of presentations.

The course web site is on Canvas (<http://canvas.dartmouth.edu>) where readings, Powerpoint slides, lecture/presentation Panopto videos (see below), web links, Slack link and other materials will be maintained.

Technologic snafus aside, we will be doing Panopto videos of all class sessions. While I do NOT regard this as a substitute for class attendance, it might be helpful for several of you if you have an unavoidable absence from class or would simply like to review aspects of a lecture or discussion (you can start and stop me!). Historically, many students have found these useful as a course study adjunct.

Other Course Issues

Illness & Our Class: PLEASE DO NOT COME to class or office hours if you have respiratory symptoms or fever. Even if not COVID, I have a family member who is at high risk from pulmonary infections. All sessions are being recorded and, if necessary, we will use Zoom for class, including the student presentations or for office hours. **Please ask if you are uncertain about your health status.**

Office Hours/Slack Students are very much encouraged to utilize weekday office hours for discussion and questions and to work on their assigned presentations. I care about all of you & enjoy getting to know you all well and to work with you on course material, “life after Dartmouth”, things you are up to, etc. You can schedule individual “live” office hours in my office (122 LSC; map on Canvas site) using **Calendly** (see Canvas site for link). Students are also encouraged to utilize the **Slack** section of the Canvas site. By posting questions (and having public answers), everyone in the class benefits. Students can also use Slack to post interesting articles or web links to information they encounter during the course. Lastly, I will be arranging specific office hours (2 sessions) to help each group prepare their paper presentation.

X-hours/Class Schedule: We will use two of the X-hours for a visit from a physician to present a patient case. I will NOT be recording this session consistent with patient confidentiality. We will also use one X-hour for a paper presentation, as well (during MLK week). We will also have a special evening dinner to watch a movie together and hear a discussion led by a guest physician.

Commitments Toward Your Success in This Course

As course designer and instructor, I care about each of you & am committed to your successful achievement of your goals in this course and to your well-being. I also understand that you may encounter challenges during the term. Resources are available to help you. These may include:

- **Accessibility support.** Students requesting disability-related accommodations and services for Bio78 are encouraged to schedule a meeting with me as early in the term as possible. This conversation will help to establish how your accommodations will be implemented in this course and what role Student Accessibility Services (SAS) or its Testing Center may play in assisting. In order for accommodations to be authorized, students are required to register with SAS.

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 (<http://www.dartmouth.edu/~upperde/>), the Counseling Center (<http://www.dartmouth.edu/~chd/>), and the Student Wellness Center (<http://www.dartmouth.edu/~healthed/>). The student-led Dartmouth Mental Health Union and their Peer Support Program (and other programs) may additionally be helpful to you.

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.** The Sexual Respect Website (sexual-respect.dartmouth.edu) provides information on your rights and obligations with regard to sexual respect and resources that are available to all in our community. Please

keep in mind that if you report prohibited conduct 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 specific issues about adherence to the Honor Principle for your assigned papers and the problem sets follows:

- **Assigned paper presentations** (more details below) **For completion of this Biology 78 assignment, 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 (except students who have previously enrolled in Bio78), textbooks and the biomedical literature. INTERNET RESOURCES (as URLs) ARE NOT ACCEPTABLE AS THE 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). *Presentation Powerpoint slides must be passed onto Professor Witters for posting on the course web site after the presentation.*
- **Problem sets** (more details below) Eight (8) problem sets will be distributed, each on the final class day of each of the topics to be covered & due 5 days later. Students must complete and submit two (2) of these, one (1) in each half of the course (Topics 1-4 & 5-8) **Two (2) are automatically excluded for each student, namely the ones on the topic they are presenting on. Students should then choose four (4) others (2 from each half of the course) for exclusion, declared in advance of the distribution of the problem.**

Class students are **encouraged** to work together in discussing and researching these assignments, but everyone is expected to **INDEPENDENTLY PREPARE** their written answer. You **ARE** required to list the names of the students you worked with on the problem sets. However, students **MAY NOT** consult with the students who prepared presentations about those particular topics. The completed assignments by individuals who discuss the assignment may reflect ideas developed by them together, but **each student must phrase their assignment answer in their own words and acknowledge the "helpful discussions" with their collaborators in the bibliography.** Therefore **DO NOT** share the computer files of your written answers (in draft or final form)! **For completion of this Biology 78 assignment, students are free to consult other sources of information (save for generative AI (see following)), but ALL THESE SOURCES must be documented in a bibliography.** In general, the problem sets can be answered entirely based on information that has been communicated in class or our readings; outside references are not necessary (and, in some instances, could confuse).

Artificial intelligence (AI) language models, such as ChatGPT, and online assignment help tools, such as Chegg®, are examples of online learning support platforms; they cannot be used for Bio78 course assignments except as explicitly authorized by me. The following actions are prohibited in this course:

- Submitting all or any part of an assignment statement to an online learning support platform;
- Incorporating any part of an AI-generated response in an assignment or working with others who have used generative AI;
- Using AI to brainstorm, formulate arguments, or template ideas for assignments;
- Using AI to summarize or contextualize source materials;
- Submitting your own work for this class to an online learning support platform for iteration or improvement.

If you are in doubt as to whether you are using an online learning support platform appropriately in this course, I encourage you to discuss your situation with me.

Some Specifics Regarding the Paper Assignments/Presentations and Problem Sets

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. Students may then “swap” with others (within each half of the course) during Week 1. 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 (problem sets, class presentations), 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 many 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. **Twenty (20) course points are assigned to each presentation.** For simple completion of the assignment, 16 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.

3. **Powerpoint slides** are a useful way to illustrate key points, and these sets will be distributed to all class members via the web site after the presentation. Professor Witters will give each student group the main figures from the paper as .jpg files to aid them in their preparation. There are several guidelines regarding the use and preparation of PP slides in your presentation.
- Plan about 35-45 total slides** (i.e. ~1/minute of presentation).
 - PP slides are best used to display images and to “bullet” key points. Keep font size large and avoid putting too much text on one slide. Large figures with many panels should be “broken up” and presented in parts of clarity and readability. **AVOID** reading your slides to the class. **REHEARSE!!** Use your presentation to amplify your bullet points and to review an image, figure, graph or table. Highlighting (by animation, arrows, boxes, call-outs, etc) key points in the data helps draw focus. The best slides have a declarative title at the top that states succinctly what the slide is trying to illustrate (example: ‘PCSK9 Impact on the Expression of the LDL receptor’ is the title on a slide that has a graph containing these data). Adding questions to the slides (unanswered initially, but then answered by animation) for the class is a good way to initiate discussion. *A summary slide is always a good way to end (and to start)! “Roadmap” slides (aka “flow diagram”) are also useful to inform the class what the flow of information will be. BE CREATIVE!*
 - Many student groups will create their PP set as a Google document. **Rather than send a link to your PP set, please download after your presentation and send to Professor Witters for posting after your presentation.** This avoids the occasional problem with my access to the Google document.
 - All slide sets should contain one slide as your critique and one with your bibliography.
 - Each student group should e-mail their PP set (as a .pptx, not .pdf file) to Professor Witters after completion of the presentation for posting on the web site.

I really want to work with all students to help you in the construction of a high-quality presentation. This has generally involved two (2) meetings, one to go over any questions you have about your paper after your initial reading and for me to review a few presentation points AND a second meeting (often the day before a presentation) to preview your PP slides, so I can offer suggestions. Contact me at an early date to arrange these meetings.

Written Problem sets

Eight (8) problem sets requiring submission of a written answer will be distributed during the term. They will be posted on-line at the end of each course topic at 5 PM and are due by 8 AM on the dates indicated (see the course schedule indicating the distribution and due dates). An electronic version (as a .docx or .doc file; not .pdf) should be submitted through the Canvas web site at the deadline. Any deviation from the announced deadlines **MUST** be sought in advance. A 1% reduction in grade per hour late will be strictly enforced unless prior permission for late submission has been granted by communication with me.

Students must complete and submit TWO (2) of these. Two (2) are automatically excluded for each student, namely the ones on the topics they presented. Students must then choose TWO (2) others to complete (one from each half of the course). Those to be excluded should be made known to Professor Witters in advance of the distribution of the problem.

Students are encouraged to work together in discussing and researching these assignments, but everyone is expected to **INDEPENDENTLY PREPARE** their written answer. You will be required to **list the names of the students you worked with on the problem sets. However, students MAY NOT consult with the students who prepared a presentation on that particular topic (or previously enrolled in this class).** The completed assignments by two or more individuals who had discussed the assignment may reflect ideas developed by together, but each student must phrase their assignment in their own words and acknowledge the "helpful discussions" with their collaborators in the bibliography. Therefore **DO NOT share the computer files for your written answers (in draft or final form)!** Further, all need to assure that they are **NOT working with others who themselves have used generative AI.**

For completion of all Biology 78 problem sets, students are free to consult other sources of information (save for generative AI (see statement of course policy in prior section about Honor Principle), but **ALL THESE SOURCES** must be documented in a bibliography. Possible sources include classmates (see exception in above paragraph), other non-class students (if they have not previously enrolled in this class), textbooks and the biomedical literature. **INTERNET RESOURCES (as URLs) ARE NOT ACCEPTABLE AS THE SOLE SOURCES OF INFORMATION; STUDENTS ARE EXPECTED TO USE STANDARD TEXTBOOKS AND THE BIOMEDICAL LITERATURE** (You are free to use the Internet (e.g. PubMed), of course, to identify these primary sources, but must consult them directly). **In general, the problem sets can be answered entirely based on information that has been communicated in class and outside references are not necessary (and, in some instances, could confuse).**

The assignment (to be submitted through the Canvas site) is limited to 2 pages (as a .docx or .doc file in 12 font with your name on first page at top & with the **SAME MARGINS** as the problem itself), exclusive of a bibliography, which will constitute a 3rd page (and should also list the names of the other students you consulted with about the problem). Problem sets will be graded not only on the "correctness" of the answer, but the organization, the succinctness & clarity of the explanation and the perceived effort in creating a first-class scholarly document. Where appropriate, tables are a good way to display some answers. *I will also be grading these answers for the quality of the expository writing, including spelling, syntax, sentence structure, punctuation and organization.*

A sample problem set from a topic previously used in the course and its "answer" from one submission are available on the Canvas 'Syllabus' page for your perusal to see a possible general format of problems and your answer.