2020 Classic Papers in Biology: Biochem 210
Instructors: Bruce Alberts & Danica Fujimori

Meeting Dates: May 13, 18, 19, 20, 21, 22, 26, 27, 28, 29
Time: 1:30p - 4:00 pm

In this course, you will learn about great experiments in the history of biology, through reading carefully some papers that have changed the course of our science. But this is not primarily a history course. Each classic paper (from areas that span molecular biology, genetics, biochemistry, and developmental biology) will be paired with an outstanding recent paper that either uses a related approach or explores a related problem. Through discussions led by a pair of scientists with very different backgrounds, ages and personalities*, you will learn how to read these papers, and how to design and carry out good experiments, and good controls. The course also aims to stimulate students to think innovatively in planning their thesis research.

* Bruce Alberts, raised in suburban Chicago, and Danica Fujimori, who grew up on a dairy farm in rural Serbia.

Danica and Bruce look forward to meeting all of you at the first session of their minicourse, which will be held on Zoom, from 1:30p to 4pm starting on May 13.

For the 10 sessions of the course, there will be 8 sets of readings to discuss, as May 28 and 29 will consist entirely of in-class presentations by students.

Class sessions via Zoom >>
(Password required: 467155)

The course materials for each session are available in Box >>
Note that specific questions with regard to each reading will be added for sessions 2 to 8. We also plan to email these to you a few days before each sesion's reading assignment.

May 13 Session #1
Koch, Flu, and COVID-19
Led by Bruce and Danica

HOW THE POWER OF SCIENCE INCREASES WITH TIME: THE REVOLUTION IN OUR UNDERSTANDING OF INFECTIOUS DISEASE

In session 1, we shall see how remarkably science has increased humanity's power to confront infectious diseases. We begin by reading a chapter about Robert Koch from The Microbe Hunters by Paul de Kruif. That popular book, published in 1926 and now available as a free PDF online, is mentioned by nearly every scientist in Bruce's generation as having inspired them to seek that career. We then read the paper that finally proved that the infectious agent that had caused the 1918 worldwide pandemic (then thought to be caused by the bacterium *Haemophilus influenzae*) was actually caused by the influenza virus, which was too small to be visualized before the invention of the electron microscope. Finally we shall read a just-published paper by a large consortium of scientists, centered at UCSF, harnessing the latest advances in molecular biology to discover host factors co-opted by the virus and suggest potential new drugs to treat COVID-19 (with a video plus an excerpt from the New York Times as your guide to the virus and its proteins).

Reading
(All documents are in shared Box folder)

- Koch, the Death Hunter. Chapter 4 in The Microbe Hunters, Paul de Kruif, 1926.

  SPECIFIC QUESTION:
  What are the advantages and disadvantages of de Kruif's writing style? Find at least one place in the text where his writing might be criticized.

- Smith, W., Andrewes, C.H.. and Laidlaw, P. P. (1933) A Virus Obtained from Influenza Patients. *Lancet* 8: 66-68. Reviewed by Morag C. Timbury.

  SPECIFIC QUESTIONS:
  Koch's famous 1890 criteria for judging whether a given bacteria is the cause of a given disease, known as **Koch's four postulates** are as follows:

  - The bacteria must be present in every case of the disease.
  - The bacteria must be isolated from the host with the disease and grown in pure culture.

- The specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host.
- The bacteria must be recoverable from the experimentally infected host.

1. Substituting “virus” for “bacteria”, how are these four criteria addressed, or not addressed, in the Smith et al paper?
2. Look at the data in Figures 1 and 2 . How would we present the data for these experiments differently today?

- David E. Gordon, ……..Marco Vignuzzi, Adolfo García- Sastre, Kevan M. Shokat, Brian K. Shoichet, Nevan J. Krogan. (2020) A SARS-CoV-2 Protein Interaction Map Reveals Host Targets for Drug-Repurposing. *Nature* Accelerated article preview.

  SPECIFIC QUESTIONS:
  1. Viral genomes are very small, making virus heavily reliant on the host for its replication and propagation. What can host factors teach us about viral biology?
  2. Describe the workflow for identification of host factors and potential drugs.
  3. Most antiviral agents used in the clinic (e.g., the HIV drug Truvada) inhibit viral proteins. This study investigates another approach – targeting of host factors. What are potential advantages and disadvantages of targeting host factors?

  General background for Gordon et al:

  - Video: Overview of COVID-19’s properties, structure and activity, from Columbia University 5min. (2020)
  - Bad News Wrapped in Protein, by J. Corum and C. Zimmer, New York Times (2020). A pdf is in the shared Box Folder.

May 18 Session #2 Mendel and Genetic vs. Epigenetic Inheritance
Led by Danica

THE IMPORTANCE OF QUANTITATION AND CONTROLS: THE INHERITANCE OF TRAITS

In session 2, three readings are assigned. We will learn how Gregor Mendel founded the modern field of genetics. We will discuss the qualities that made it possible for Mendel to analyze plant crosses the way he did, and what inspired him to think about pea shapes and colors in the first place. We will also discuss a contrasting situation, in which traits can be inherited in a non-Mendelian epigenetic fashion.

We are assigning Mendel's actual paper. It's truly awesome. We are also assigning part (12 pages) of a great textbook chapter that helps to explain it. We will also talk about Mendel himself, and the history of it all.

As an introduction to Mendel, we suggest that you start by reading the excerpt from John A. Moore's textbook. In class, we will focus on the first 27 pages of Mendel's 1865 paper, which elegantly explain his now-famous research with peas. Although a monk by profession, Mendel had studied combinatorics – and it shows. Brilliant at strategy, note how carefully he designed his experiments.

Reading:

- Gregor Mendel: *Experiments in Plant Hybridization* (1865) English translation by William Bateson (http://www.mendelweb.org/Mendel.html)
- Cubas, P, C Vincent, and E Coen (1999) An epigenetic mutation responsible for natural variation in floral symmetry. Nature: 401-157-161.
- 12-page excerpt from John A. Moore textbook, Heredity and Development (1972) Full book available at http://www.nap.edu/catalog.php?record_id=13199

SOME QUESTIONS

1. Note that Mendel made several very imaginative, ad hoc assumptions that skillfully guided his work following his first set of experimental results. What were they, and why would they seem much less weird in 1900 when others independently reached similar conclusions?
2. How would we write Mendel's 9 categories of genotypes on p.16 today?
3. Some would say that his experiments that start on page 20 are awe-inspiring. Why?

We now know that not all inheritance is genetic. Thus, we will read and discuss a 1999 paper showing that a "mutant" plant described by Linnaeus in 1749 is actually a case of trans-generational epigenetic inheritance. Many more examples are now known, both in plants and animals. Might some environmental signals be able to affect the next generation in useful ways through such epigenetic mechanisms?

SOME QUESTIONS

1. What is a peloric plant?
2. What were the researchers expecting to find as the cause of Linnaeus's "mutant"?
3. How did they prove that the DNA methylation they observed causes the Lcyc gene to turn off?

May 19 Session #3 DNA and Watson-Crick
Led by Bruce

THE IMPORTANCE OF FOCUS IN SCIENCE: A PASSION FOR AN IMPORTANT MYSTERY

The assignment for this session is to read two brief papers that revolutionized our understanding of cell biology, plus two reviews of the history written for two anniversaries of the discovery by prominent, involved scientists -- Max Perutz and Francis Crick.

We suggest that you read the Max Perutz article first to get a sense of general DNA history, and then the two brief papers, published a month apart, that created a new field called molecular biology. Perutz won a Nobel Prize for protein structure determination by X-ray diffraction (haemoglobin,1962); he was also a scholar who wrote many thoughtful essays.

Reading:

- Max Perutz (1993) Before the double helix. Gene 135: 9-13.

SPECIFIC QUESTION:
Try to imagine a time, less than 100 years ago, when bacteria were “believed not to exhibit genetics”. What might this mean, and how did it inhibit progress?

- James Watson and Francis Crick (1953) Molecular Structure of Nucleic Acids. Nature 171: 737-738.

- James Watson and Francis Crick (1953) Genetical Implications of the Structure of Deoxyribonucleic Acid. Nature 171: 964-967.

SPECIFIC QUESTION:
What is an alternate tautomeric form of G? (Hint, it can readily pair with T). Note that the base pairs shown in paper 2 fail to designate double bonds.

We now know that cells commit more machinery to DNA repair than to DNA replication, and that the double helix solves the mystery of stable information storage in the face of the inevitable thermal decay of molecules. Is there any hint of this conceptual breakthrough in these two papers?

- Francis Crick (1974) The double helix: A personal view. Nature 248: 766-769.

SPECIFIC QUESTION:

Note Crick's strange comment near the end that "Jim was always clumsy with his hands. One had only to see him peel an orange …". Does anyone know what motivated this strange distraction?

May 20 Session #4 From Kornberg to Kowalczykowski
Led by Bruce

WHY STUDIES WITH PURIFIED PROTEINS ARE ESSENTIAL FOR UNDERSTANDING: RECONSTITUTED IN VITRO SYSTEMS

Why do we need biochemistry?

For this session 3 papers are assigned, each of which makes a related point.

We start by reading a brief history of the discovery of DNA polymerase, written as an introduction to a reprint of the classic paper for this session (Arthur Kornberg et al, 1956). The extension of that work would quickly earn Kornberg the Nobel Prize for Physiology or Medicine in 1959.

Reading:
● A. Kornberg et al: *The Early History of DNA Polymerase: A Commentary by Arthur Kornberg*. *Biochimica et Biophysica Acta* 1000 (1989) 53-56. Includes his original 1956 paper TO READ).

SPECIFIC QUESTIONS

1) In Table I of the 1956 paper, both fractions S and P are required. It would turn out that one of these 100-fold purified fractions of cell extract contained the enzyme DNA polymerase and that the other one contained the kinases needed to convert each of the A, T, C, and G deoxyribonucleotides to nucleoside triphosphates. How do you think this fact could be quickly discovered?

2) Kornberg was famous for his quote "don't waste clean thinking on dirty enzymes". How does this apply to the lack of a DNA polymerase requirement for all four of the A, G, T, and C nucleotides in Table II?

3) Note how even a very crude "activity assay" can empower a biochemist to purify the responsible factors in a complex mixture to homogeneity, which is what Kornberg's laboratory quickly did. In general, how is this done?

Several different laboratories (including Bruce's) would subsequently use the genetics that identified genes needed for DNA replication to purify and characterize the proteins that cooperate with DNA polymerase to guide its various activities. Tim Formosa was a UCSF graduate student (now a professor at University of Utah) who carried out the first biochemical experiments linking DNA synthesis to genetic recombination. As the link to recombination, he used a purified RecA-family member synthesized by bacteriophage T4 -- the T4 uvsX protein. Paper 2 is the main paper from his PhD thesis.

● T. Formosa and B. Alberts: *DNA Synthesis Dependent on Genetic Recombinations: Characterization of a Reaction Catalyzed by Purified Bacteriophage T4 Proteins* (1986). *Cell*, Vol. 47, 793-806.

SPECIFIC QUESTION

1) Note how the ability to manipulate the ingredients in a "reconstituted in vitro system" like this one generates important insights about a biological reaction that cannot be obtained in any other way. Explain why this is so by reference to the experiment in Figure 8; what was done and what finding did it generate?

Our final reading for this session asks: how does the RecA-type of protein, which is central to recombination reactions, enable its bound DNA single strand to scan double helices and quickly find a region of homologous DNA sequence, as required to prime the DNA synthesis in paper 2? By reading a paper from the Kowalczykowski lab at UC Davis, we will see how new single-molecule biochemistry technologies — utilizing purified proteins and DNA -- enable types of discoveries not otherwise possible.

● A.L. Forget and S.C. Kowalczykowski: *Single-molecule imaging of DNA pairing by RecA reveals a three-dimensional homology search* (2012) *Nature* 426, 423-427.

See the movie links just before the references at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288143/ The first movie (supplement 2) is especially useful for understanding the impressive method used, and we recommend watching it before getting too deep into the article. NOTE THAT THE MOVIE LINKS ON THE NATURE WEBSITE SEEM NOT TO WORK

SPECIFIC QUESTIONS

1) What is the broad take home lesson for protein-DNA interactions inside the cell? (It turns out to apply to much more than RecA).
2) With help from the movie, what does the kymograph in Figure 4 demonstrate?

May 21 Session #5 Sensing Oxygen - Semenza, Ratcliffe and Kaelin
Led by Danica

REGULATION OF ENZYME CATALYSIS BY THE AVAILABILITY OF A CO-SUBSTRATE ACROSS THE PHYSIOLOGICAL REGIME

Most organisms on Earth require oxygen for survival, as oxygen consumption is essential to maintain viability and function of trillions of cells in our own bodies. Yet as recently as 30 years ago, little was known about how metazoans sense and adapt to changes in oxygen availability. Starting with early 1990s and approaching the problem from different angles - in one case with a goal of elucidating regulation of erythropoietin expression and in another motivated by a mysterious familial cancer syndrome- three scientists from diverse backgrounds have uncovered the pathway by which metazoans sense and adapt to changes in oxygen availability. For their discovery of a central oxygen-sensing pathway, Kaelin, Ratcliffe and Semenza were awarded the Lasker Award in Basic Medical Research in 2016, and the Nobel Prize in Physiology and Medicine in 2019.

For this class, we will read the Nobel Prize announcement as an introduction to oxygen sensing. We will then read two publications that were critical in piecing together a critical oxygen sensing mechanism. Semenza'a 1995 publication describes purification of hypoxia-inducible factor 1 (HIF-1), a key transcription factor in oxygen sensing, and a 2001 publication by Ratcliffe's team describes the molecular basis for the oxygen dependency in HIF regulation. Our modern read is a 2019 publication by teams of Kaelin and Koivunen on oxygen-dependent regulation of chromatin modifications.

Reading:
- 2019 Nobel Prize in Physiology or Medicine announcement: https://www.nobelprize.org/uploads/2019/10/press-medicine2019.pdf
- G.L. Wang, G.L. Semenza *et al. Hypoxia-Inducible Factor 1 is a Basic-Helix-Loop-Helix-PAS Heterodimer Regulated by Cellular O_2 Tensions* (1995) *PNAS* 92: 5510-14.

SPECIFIC QUESTION

Describe how the Semenza lab determined the sequences of the HIF-1a and HIF-1b genes, and how they investigated the oxygen dependence of the HIF1 subunits.

- P. Jaakkola, P.H. Maxwell, C.W. Pugh, P.J. Ratcliffe *et al. Targeting of HIF-a to the von Hippel-Lindau Ubiquitylation Complex by O2-Regulated Prolyl Hydroxylation* (2001) *Science* 292: 468-472.

SPECIFIC QUESTION

In 2001, Ratcliffe's team described an enzyme, prolyl hydroxylase, that hydroxylates a proline residue in HIF1a to enable its degradation by the von Hippel-Lindau protein (pVHL), a ubiquitin ligase. How did they investigate the interaction between HIF1a and pVHL (Fig 1, D and E) and what are key aspects of their excellent biochemistry detective work that led to the identification of the activity that promotes this interaction, and the enzyme responsible for it (Fig 2, Fig 3 and Fig 5)?

- A.A. Chakroborty, P. Koivunen, W.G. Kaelin Jr. *et al. Histone Demethylase KDM6A Directly Senses Oxygen to Control Chromatin and Cell Fate* (2019) *Science* 363: 1217-1222.

SPECIFIC QUESTION

Recent work by the Koivunen and Kaelin labs shows that HIF is not the only oxygen sensor. The histone demethylases, a family of chromatin-acting enzymes, are direct oxygen sensors that control gene expression programs.

The gist of their finding is in Figure 1. What are the findings that they present, and why is it so important that they measure the Michalis constant for oxygen for their newly found oxygen sensor?

May 22 Session #6 Gurdon and Yamanaka
Led by Bruce

THE CRITICAL IMPORTANCE OF STRATEGY IN SCIENCE: CELL REPROGRAMMING AS AN EXAMPLE

It is very unusual for a Nobel Prize to be awarded for work spanning 44 years. For session 3, three readings are assigned plus a video.

The first quick reading is the brief citation prepared by the Nobel Committee for the 2012 Prize in Physiology or Medicine, awarded to John Gurdon and Shinya Yamanaka.

The main assignment is to read —and be prepared to discuss in detail — the two papers cited by the Nobel Committee in awarding this Prize "for the discovery that mature cells can be reprogrammed to become pluripotent", one published in 1962 and the other in 2006.

In addition, it is important that you watch 14 minutes of a charmingly frank talk given by Dr. Yamanaka when he received the 2009 Lasker Award. This talk is available at http://www.youtube.com/watch?v=DQNoyDwCPzM. Only minutes 19 to 33 are assigned, as being especially relevant for anyone planning a career in research; we shall discuss them in class.

Reading:

- Gurdon and Yamanaka by Nobel Committee: The Nobel Prize in Physiology or Medicine (2012) (www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html)

- J.B. Gurdon: *The Developmental Capacity of Nuclei taken from Intestinal Epithelium Cells of Feeding Tadpoles* (1962) J. Embryol. Exp. Morph. 10: 622-640.

SPECIFIC QUESTIONS.

1). In Table 1, only 10 of 726 transfers of intestinal epithelium nuclei (1.5 %) produced normal tadpoles. What were Gurdon's strategies that enabled him to eventually conclude that 24 percent of the intestinal nuclei can actually do so?

2). What was done in the experiments whose results are plotted in Figures 1 and 2?

- K. Takahashi and S. Yamanaka: *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors* (2006) *Cell* 126:663-676.

SPECIFIC QUESTIONS

1) Yamanaka began by developing a unique assay that allowed him to select rare cells with stem cell-like properties after retroviral transduction of fibroblasts with mixtures of genes. What was this assay?

2) Explain Figures 2A, 2B, and 2C. Was this the obvious way to do the gene search experiments?

Video:

- Dr. Yamanaka's 2009 Lasker Award Talk: http://www.youtube.com/watch?v=DQNoyDwCPzM

SPECIFIC QUESTION: What general lesson might you gain from the way that he designed his research strategy?

May 26 Session #7 Thalidomide and the Power of Chemical Biology
Led by Danica

FROM BIRTH DEFECTS TO A NEW MODALITY IN DRUG DISCOVERY: SMALL MOLECULE-INDUCED PROTEIN DEGRADATION

In 1950s, the drug thalidomide was a popular treatment for pregnancy-associated morning sickness. In 1961, obstetricians William McBride in Australia and Widukind Lenz in Germany began to notice cases of a rare birth defect involving absence, or abnormalities of limbs whose mothers used thalidomide. We will read the short expression-of-concern Letters to the Editor of Lancet written by these two obstetricians and their geneticist collaborators. The cause of the thalidomide-induced developmental abnormalities remained a mystery until2010, when the Handa Lab at the Tokyo Institute of Technology identified a primary target of thalidomide teratogenicity. The Handa laboratory's beautiful target identification paper will be the primary focus of this session. Finally, in a review from a biotech company Celgene, we will read how the basic science discoveries on the mechanisms of oxygen sensing (Session 5) and the thalidomide mode of action have heralded an entirely new field in drug discovery, that of targeted protein degradation.

Reading:

- WG McBride: Thalidomide and Congenital Abnormalities (1961). The Lancet, Letter to the Editor, December 16, 1961: 1358.
- W Lenz, PA Pfeiffer, W Kosenow, DJ Hayman: Thalidomide and Congenital Abnormalities (1962). The Lancet, Letter to the Editor, January 6, 1962: 45.
- T Ito, H Handa et al. Identification of a Primary Target of Thalidomide Teratogenicity (2010). Science 327, 1345-1350.
- PP Chamberlain and LG Hamann. Development of Targeted Protein Degradation Therapeutics (2019) Nat Chem Biol 15, 937-944.

SPECIFIC QUESTIONS:

1. In 2010, Ito et al identified cereblon as a primary target of thalidomide teratogenicity. Describe the workflow that allowed authors to identify cereblon as the relevant interacting partner (Figure 1, Ito et al Science 2010).
2. What is the function of cereblon and how is it modulated by thalidomide (Figures 2 and 3, Ito)?
3. In Figures 4 and 5, authors describe use of a zebrafish model to investigate role of cereblon in thalidomide teratogenicity. What did they learn from these experiments?
4. Authors conclude that “thalidomide exerts teratogenic effects, at least in part, by binding to CRBN and inhibiting the associated ubiquitin ligase activity”. Today we know that the story is a bit different, and that thalidomide acts as a “molecular glue” to recruit a transcription factor important for development to cereblon, leading to its ubiquitination

and degradation. These observations of targeted degradation by a small molecule led to an entirely new field of targeted protein degradation. Skim through the Nat Chem Biol perspective by Chemberlain and Hamann and let's talk more about potential and limitations of this approach in class.

May 27 Session #8 Darwin

Led by Bruce

DARWIN AND SCIENTIFIC STANDARDS

As the focus of our final reading assignment, we read most of two chapters from the first edition of Darwin's Origin of the Species, 1859. We also assign Bruce's Congressional Testimony that deals with scientific standards. Danica and Bruce hope that our focus on scientific standards in this class discussion (plus the other aspects of quality science emphasized in previous sessions) will help you to make good decisions during your own scientific careers.

Darwin was a model scientist in many ways, and we have highlighted in yellow on the pdf some of the aspects of his science that are worth discussing. In reading those 49 pages (the last bit of Chapter 11 plus a section of Chapter 12 are not assigned – see below), outline his major arguments and be prepared to discuss them. In addition, note Darwin's emphasis on testing what could be wrong with his own ideas, and how he treats his "competitor," Alfred Russel Wallace.

With reference to Bruce's Congressional testimony, we have also attached two papers designed to help us discuss why certain types of modern biomedical science seem to have gone astray.

Please only SCAN these two modern papers — we do NOT expect you to read them carefully. We may discuss a few selected figures.

Reading:

- Darwin: Origin of Species (1859). Two chapters on Geographical Distributions. Chapter 11 through p. 372; Chapter 12 through p. 399; then the summary for both chapters that begins at bottom of p. 406.

SPECIFIC QUESTIONS

Chapter 11

1. At the start of chapter 11, Darwin presents 3 “great facts”. What is the essence of each, and what is the prevailing theory for the origin of species that Darwin challenges by presenting them?
2. What experiments does Darwin carry out with seeds, and why did he do them?
3. How does Darwin explain the puzzling similarity between the plants and animals found near the top of mountain peaks in Europe and North America?

Chapter 12

1. Why are duck and bird feet so important to Darwin?
2. Note how Darwin never hides the possible arguments against his views, often structuring his text around them. In this connection, there is a remarkable sentence at the bottom of page 399 that ends in “.. and will, I do not doubt, be some day explained.” That puzzle that Darwin admits that he can not explain was eventually explained, although only a hundred years later – how?

- Alberts Congressional Testimony on “Scientific Integrity and Transparency” (2013). https://brucealberts.ucsf.edu/publications/Testimony.pdf
- C. Scholl et al. *Synthetic Lethal Interaction between Oncogenic KRAS Dependency and STK33 Suppression in Human Cancer Cells* (2009) *Cell* 137, 821–834.
- C. Babij et al: *STK33 Kinase Activity is Nonessential in KRAS-Dependent Cancer Cells* (2011) *Cancer Res* 71:5818-5826.

SPECIFIC QUESTIONS

1. Imagine yourself as a grad student who joins in this work, as part of the large team of 18 that -- by the time you join the lab -- is collecting additional data to support its already formed conclusion. How would you be likely to interpret your own results that failed to get the expected answers?
2. The 2009 paper, whose senior authors are leaders in their fields, has been cited more than 400 times and never retracted. Is that OK?

May 28 Session #9 and May 29 Session #10 Student Presentations

Led by Bruce and Danica

Plan a 15-minute presentation. Each presentation will be followed by ~10 minutes of discussion. Students may present individually, or team up with no more than one of their classmates. If your presentation is a joint effort, then both students should take a turn speaking. You can include as many as 6 simple powerpoint slides.

1) Present an important puzzle/mystery in biology that if you were "thinking like Koch, Mendel, or Yamanaka" you would like to solve through research. BE AMBITIOUS.

We seek specific problems, not a broad general one that cannot be reasonably addressed in four years of research. One of the favorites from prior years was a proposal to use modern technologies to decipher how it is possible for a single cell (paramecium) to exhibit adaptive learning. **A few other examples are listed at the end of this email.**

Be sure to address these questions:

A. Why do you think this problem is important? What difference might it make if you solve it?
B. Why do you like this puzzle? Without real passion for a challenge, you are unlikely to succeed.
C. Exactly what you would focus on? Strategy is everything in science.
D. Has your plan been inspired or informed by one or more of the readings from this course; if so, which one(s)?

2) Outline a general strategy for attacking the problem.

Be sure to address:

A. What new methods/approaches you . need to develop first, if any?
B. Why you think your approach might be feasible.
C. Roughly how much time (months/years?) would you need to invest in this strategy before you would know if it is worthwhile? (That is, how much time should it take to approximate a cost-benefit analysis?).

A FEW EXAMPLES TO ILLUSTRATE THE RANGE OF PAST STUDENT PROPOSALS:

Genome organization when the nucleus is mechanically distorted.

Exploring dynamic transcriptome regulation in the octopus.

Modulating immune tolerance during pregnancy.

Is the claustrum critical for consciousness?

Mapping drug-drug interactions using machine learning.