Classic Papers in Biology
Instructors: Bruce Alberts & Cynthia Kenyon

Time: 1:00 - 4:00 pm

Room: GH, S-204

Meeting Dates: May 12th thru 14th, 19th thru 23rd, and 30th

In this course, you will learn about some 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 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, personalities, and styles, * 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, featured in staid magazines like Chemical and Engineering News; and Cynthia Kenyon, featured in trendy magazines like Vogue.

May 12 Session #1 Watson and Crick
Led by Bruce and Cynthia

PASSION FOR AN IMPORTANT MYSTERY

Cynthia and Bruce look forward to meeting all of you at the first session of their mini course, which will be held in room S204 from 1 to 4pm on Monday May 12. The assignment for this first session is to read the two papers that are attached, plus an entire book: A recent annotated and illustrated version of The Double Helix by James Watson, originally published in 1968.

For the 9 sessions of the course, there will be 8 sets of readings to discuss, as May 30 will consist entirely of in-class presentations by students.

Reading:

- Watson and Crick: *Molecular Structure of Nucleic Acids* (1953) *Nature* 171: 737-738.
- Watson and Crick: *Genetical Implications of the Structure of Deoxyribonucleic Acid* (1953) *Nature* 171: 964-967.
- James Watson: The Annotated and Illustrated Double Helix (2013) Edited by Alexander Gann and Jan Witkowski. Simon and Schuster; NY.

May 13 Session #2 Mendel and Brunet
Led by Cynthia

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 a great book chapter that helps to explain it. (We will discuss this book chapter in class too.) We will also talk about Mendel himself, and the history of it all.

We now know that not all inheritance is genetic. Thus, we will read and discuss a recent paper showing that life extension can be inherited in a transgenerational, epigenetic fashion.

Reading:

- Gregor Mendel: *Experiments in Plant Hybridization* (1865) English translation by William Bateson (http://www.mendelweb.org/Mendel.html)
- E.L. Greer, A. Brunet et al: *Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans* (2011) *Nature* 479: 365-371.
- Excerpt from John A. Moore textbook, Heredity and Development (1972) Full book available at http://www.nap.edu/catalog.php?record_id=13199

May 14 Session #3 Gurdon and Yamanaka
Led by Bruce

CELL REPROGRAMMING

It is very unusual for a Nobel Prize to be awarded for work spanning 44 years. For session 3 on Wednesday May 14, 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.

Finally, we invite you to watch at least part 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. Minutes 19 to 33 are especially relevant for those planning a career in research, and we shall discuss them in class.

Reading:

- J.B. Gurdon: *The Developmental Capacity of Nuclei taken from Intestinal Epithelium Cells of Feeding Tadpoles* (1962) J. Embryol. Exp. Morph. 10: 622-640.
- K. Takahashi and S.: *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors* (2006) *Cell* 126:663-676.
- Gurdon and Yamanaka by Nobel Committee: The Nobel Prize in Physiology or Medicine (2012) (www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html)

Video:

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

May 19 Session #4 Prusiner and McKnight
Led by Bruce

PRIONS AND PRECIPITATES: THE IMPORTANCE OF ORIGINALITY IN SCIENCE

Initially a huge surprise, we now know that a specific type of protein aggregate called an *amyloid* can cause transmissible disease (Nobel Prize, 1997). Add to that a very recent surprise: "reversible amyloids" also exist, and they play central roles in cells.

For our session on Monday, May 19, two papers are assigned for careful reading. The first is a 1982 article in *Science* by Stan Prusiner reporting his discovery at UCSF that a pure protein can be infectious. This article (in which he coined the name "prion") was extremely controversial, with leading experts strongly attacking him as well as his conclusion.

We now know that the phenomenon first discovered by Prusiner -- a protein-propagated conformational change that creates amyloid fibers — is exploited by cells for useful purposes. The second assigned paper is from the laboratory of Steve McKnight in Dallas; published in 2012, it reports a breakthrough that may be equally significant for our future understanding of cells.

Reading:

- S.B. Prusiner: *Novel Proteinaceous Infectious Particles Cause Scrapie* (1982) *Science* 216:136-144.
- M. Kato, S.L. McKnight et al.: *Cell Free Formation of RNA Granules: Low Complexity Sequence Domains Form Dynamic Fibers with Hyrogels* (2012) *Cell* 149: 753-767.

May 20 Session #5 Scoville and Fire
Led by Cynthia

WAS IT JUST LUCK? IS IT EVER?

Many great discoveries come about serendipitously, but all require thought and attention. (Many scientists stumble across the truth. Most pick themselves up and keep on going without noticing…). In this session, we will discuss two serendipitous discoveries: the discovery that one specific part of the brain is crucial for long-term memory, and the discovery of RNAi.

Reading:

- W.B. Scoville and B. Milner: *Loss of Recent Memory after Bilateral Hippocampal Lesions* (1957), *J Neurol Neurosurg Psychiatry* Feb;20(1):11-21.
- A. Fire, C.C. Mello et al: *Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans* (1998). *Nature*. Feb 19;391(6669):806-11.

May 21 Session #6 From Kornberg to Kowalczykowski
Led by Bruce

IN VITRO SYSTEMS RECONSTITUTED FROM PURIFIED PROTEINS: WHY ESSENTIAL FOR UNDERSTANDING?

Why do we need biochemistry?

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

1) 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. Note how even a very crude "activity assay" can empower a biochemist to purify the responsible factors to homogeneity, which is what Kornberg's laboratory quickly did.

2). Several different laboratories (including mine) 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 who carried out the first biochemical experiments linking DNA synthesis to genetic recombination, employing a purified RecA family member synthesized by bacteriophage T4 -- the T4 uvsX protein. Paper 2 is the main paper from his PhD thesis. Note how the ability to manipulate a "reconstituted in vitro system" like this one generates important insights about a biological reaction that cannot be otherwise obtained.

3). How does a RecA-type of protein 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 recent paper from the Kowalczykowski lab at UC Davis, we will see how new single-molecule technologies — utilizing purified proteins and DNA -- enable types of discoveries not otherwise possible.

Reading:

- A. Kornberg et al: *The Early History of DNA Polymerase: A Commentary by Arthur Kornberg*. *Biochimica et Biophysica Acta* 1000 (1989) 53-56. (Originally 1956)
- 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.
- 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.

May 22 Session #7 Coleman and Friedman
Led by Cynthia

THE POWER OF SIMPLE EXPERIMENTS

In this session, we will read a classic paper by Douglas Coleman that set the stage for the molecular analysis of obesity, later pioneered by Jeff Friedman. We will read three papers: the Coleman paper, an early seminal paper by Friedman, and a recent review article. We will discuss the simple elegance and significance of Coleman's work, its molecular basis (from Friedman's work) and also the fascinating phenomena of hunger and obesity. For this special topic, we will provide snacks.

Objective Lesson:
Many great discoveries require disparate, sometimes deceptively simple experimental approaches. This is an example in which genetics, surgery, and molecular biology were all crucial and opened up an unexpected new field: a regulatory system for appetite.

Reading:

- D.L.Coleman: *Effects of Parabiosis of Obese with Diabetes and Normal Mice* (1973). *Diabetologia* 9, 294-298.
- C. Vaisse, J.M. Friedman et al: *Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice (1996)*. *Nature Genetics* 14, 95-97.
- J.M. Friedman: Rockefeller University Commemorative Lecture: *Leptin and the Regulation of Body Weight* (2011). *Keio J Med* 60(1): 1－9.

May 23 Session #8 Darwin
Led by Bruce and Cynthia

DARWIN AND SCIENTIFIC STANDARDS

Our assignment for Friday May 23 is to carefully read two chapters from the first edition of Darwin's Origin of the Species, 1859; plus Bruce's Congressional Testimony that deals with scientific standards. Cynthia and Bruce hope that our focus on scientific standards on in this class discussion (plus the other aspects of quality science emphasized in previous sessions) will help you to make good decisions in designing 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 65 pages, 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 papers — we do NOT expect you to read them carefully. We may discuss a few selected figures.

Reading:

- Darwin: Origin of Species (1859) Chapter 11 (Geographical Distribution) and Chapter 12 (Geographical Distributions Continued).
- Alberts Congressional Testimony on “Scientific Integrity and Transparency” (2013). (https://science.house.gov/hearing/subcommittee-research-scientific-integrity-transparency)
- 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.

May 30 Session #9 Student Presentations
Led by Bruce and Cynthia

Plan a 10-minute presentation. (Each presentation will be followed by ~10 minutes of discussion.) If your presentation is a group effort, then each member of the group should take a turn speaking.

1) Present an important problem/mystery in biology that, if you were “thinking like Darwin, Mendel, or Watson/Crick" you would like to solve through research.

We seek specific problems, not a general one such as “how did photosynthesis evolve?” One of our favorites from last year was a proposal to use modern technologies to decipher how it is possible for a single cell (paramecium) to exhibit adaptive learning.

Be sure to address these questions:
A) Why do you think this problem is important?
B) Why do you like this puzzle?
C) Exactly what you would focus on?

2) Outline a general strategy for attacking the problem.

Be sure to address:
A) Why you think your approach might be feasible.
B) What new methods/approaches you would need to develop first, if any.
C. 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 to approximate a cost benefit analysis).
D. Might you have to endure the scorn/skepticism of your colleagues while you are testing your idea, as Prusiner did?

YOUR PRIVATE CRITIQUE OF THE PRESENTATIONS OF OTHERS
(This is for Cynthia and Bruce to see only; we will use what you write to help us improve our own teaching).

Immediately following each presentation, we will provide you with 3 minutes to write a very brief evaluation of that presentation. We expect only a few sentences for both A and B below:

A) Rate the potential importance of the problem, giving it a grade from 5 (high) to 1 (low). State your rationale for rating it this way.
B) Rate the strategy, giving it a grade from 5 (high) to 1 (low). State your rationale for rating it this way.

   At the very end, we will provide time for you to revise each of these, if desired, based on all of the presentations you have heard.

YOUR SUGGESTIONS FOR NEXT YEAR

Which two “papers” that we read did you learn the most from?

Which two “papers” that we read might be replaced by something more valuable to you?

Many thanks for participating in this course!