

## 7.342. G-Protein Coupled Receptors: Vision and Disease

### Week 1 Introduction

*Feb 8*

Introduction of instructor and students.  
Overview and aims of the course.  
How to read scientific papers and search the literature using PubMed.

GPCRs mediate the actions of an enormous variety of signals from peptides, hormones, lipids, neurotransmitters, as well as from light and other sensory stimuli. Mutations in GPCRs result in several health problems, such as allergies, depression, pain, obesity, hypertension and various central nervous system disorders. GPCRs are the most common targets of therapeutic drugs and have been a major focus of drug discovery in the pharmaceutical industry.

A short movie about GPCR signal transduction will be shown.

### Week 2 The Magnificent Seven

*Feb 15 G-Protein Coupled Receptors and rhodopsin*

GPCRs share a similar structural architecture consisting of an N-terminal extracellular domain, a bundle of seven membrane  $\alpha$ -helices connected by intracellular and extracellular loops, and a cytoplasmic tail. Many aspects of GPCR structure, signaling, and regulation are conserved. The rhodopsin gene was the first GPCR gene cloned, and rhodopsin also the first GPCR to be crystallized. Rhodopsin serves as a model for GPCRs.

We will discuss the structure of rhodopsin obtained using x-ray crystallography and electron cryomicroscopy.

### Week 3 How do we see?

*Feb 22 Visual Cascade Part I - Activation of rhodopsin by light*

George Wald and his group pioneered our understanding of the molecules responsible for the first steps of vision. For this work Wald received a Nobel Prize in Physiology or Medicine (1967). He determined that the protein rhodopsin in the rod cells consists of two molecular parts: a colorless polypeptide, opsin and a chromophore, retinal (the aldehyde of vitamin A).

It is the rhodopsin in the retina, which is about 0.25 mm thick at the back of the eye, that absorbs the light that enters our eye. Upon absorbing light, the retinal molecule that is

embedded inside the rhodopsin protein undergoes photoexcitation, resulting in a conformational change in rhodopsin. We will discuss how conformational changes in rhodopsin are recorded using absorption spectroscopy and electron paramagnetic resonance (EPR).

**Week 4**      **I have seen the light**  
**March 1**      **Visual Cascade Part II - Rhodopsin and G protein (transducin) interaction**

The light-activated rhodopsin, metarhodopsin II, binds to transducin, a heterotrimeric G protein. This protein complex binds to phosphodiesterase, located in the inner membrane of the cell. Phosphodiesterase activation reduces levels of cGMP and causes ion channel closure and reduced cellular levels of sodium ions. This in turn causes an imbalance of charge across the cell membrane that finally causes a current to be transmitted down the optic nerve to the brain. The brain interprets this and other light-induced signals, resulting in vision.

In this class, we will discuss the experimental techniques used to study the interaction between rhodopsin and transducin.

**Week 5**      **Visit to an Atomic Force Microscopy Facility (16-352)**  
**March 8**

We will visit an Atomic Force Microscopy laboratory in the Department of Bioengineering at MIT. We will see how AFM is used for imaging biological tissues. You also will learn the uses of AFM. We will discuss how rows of rhodopsin dimers were identified in the mouse retina using AFM in our next week's class.

**Week 6**      **The ants go marching two by two!**  
**March 15**      **Rhodopsin dimerization**

The classical idea of GPCR signal transduction is that GPCRs function as monomeric entities. However, recent studies show that several GPCRs form and function as dimers or oligomers. In addition to homodimers, heterodimers between members of the GPCR family, both closely and distantly related, have been reported. These recent GPCR oligomerization studies challenge the traditional GPCR signal transduction pathway. The existence of GPCR dimers may have important implications for the development and screening of new drugs.

Rhodopsin has also been shown to exist as dimers in the native disc membrane of rods by atomic force microscopy and transmission electron microscopy. Today we will discuss how rows of rhodopsin dimers in the mouse retina were identified.

**Week 7      Rhodopsin mutations, retinal degeneration and night blindness**

***March 22***

Mutations in rhodopsin lead to retinitis pigmentosa (RP) and congenital night blindness. RP is an inherited retinal degeneration and is characterized by night blindness and a gradual loss of rods and cones, ultimately leading to blindness. RP is an incurable disease and affects about one million people worldwide. This debilitating condition can be caused by any of over 120 mutations in the rhodopsin gene. Congenital night blindness is caused by overactivations of rhodopsin and the G protein transducin.

**Week 8**      **Field trip to the Novartis Institutes for BioMedical Research**  
*April 5*      <http://nibr.novartis.com/>

**Week 9**      **Drug addiction - Dopamine receptors and activation mechanism**  
*April 12*

Dopamine (DA) is a small-molecule neurotransmitter involved in the control of both motor and emotional behavior and associated with the pleasure system of the brain. Dysfunction of DA neurotransmission in the brain has been implicated in Parkinson's disease, drug addiction, and schizophrenia.

DA mediates its biological actions *via* at least five distinct dopamine receptors, all GPCRs. In this class, we will watch a movie about the dopaminergic pathway. We will discuss the activation mechanism of dopamine receptors and the role of dopamine receptors in drug addiction. We will also discuss experimental techniques used to dissect the dopamine receptor dimer interface and how heterodimerization of two types of dopamine receptors activate a novel pathway.

**Week 10**      **Allergies - Histamine receptors**  
*April 19*

The antihistamines we take for allergies - Allegra, Claritin and Benedryl - block histamine receptors. These histamine receptors are all GPCRs.

Histamine (2-[4-imidazolyl] ethylamine) is a biogenic amine involved in local immune responses, gastric acid secretion and neurotransmission. Histamine is synthesized by decarboxylation of the amino acid histidine by L-histidine decarboxylase. Sir Henry Dale and his group first isolated histamine from the mold *Claviceps purpurea*, a parasitic fungus, about 100 years ago (1910). Histamine has an active role in allergies and anaphylaxis. Four types of histamine receptors, H1, H2, H3 and H4, mediate the effects of histamine.

In this class, we will discuss how a small chemical compound, histamine, causes allergies and how antihistamines block histamine receptors and prevent allergies.

**Week 11**      **How do mutations in chemokine receptors inhibit CCR5-mediated**  
*April 26*      **HIV infection?**

Human chemokine receptor 5 (CCR5) functions as a co-receptor for HIV-1 infection. CCR5 belongs to the GPCR family. Often, mutations in GPCRs lead to health problems

in humans. By contrast, in the case of chemokine receptors (CCRs), a mutation in CCR5 (CCR5-delta32) protects against HIV-1 infection.

In this class, we will discuss how CCR5 mutation protects against HIV-1 infection and the experimental techniques used to study the heterodimer formation of CCR5.

**Week 12**      **Sense of smell**  
*May 3*        *Olfactory receptors*

How do we detect and remember many many different types of odors? Our sense of smell is mediated by GPCRs located on the olfactory receptor cells, which occupy a small area in the upper part of the nasal epithelium and detect the inhaled odorant molecules. In 1991, Linda Buck and Richard Axel discovered a large gene family comprising about 1000 genes, which encode olfactory receptors. They received the Nobel Prize in Physiology or Medicine for this work in 2004.

In this class, we will discuss how olfactory receptors were discovered and what experimental techniques were used. We also will discuss how different odorants have different binding affinities to olfactory receptors.

**Week 13**      **Sense of taste**  
*May 10*        *Taste receptors*

The pleasure of food is linked with taste. Our sense of taste is capable of recognizing five primary taste sensations: sweet, bitter, sour, salty, and umami (the taste of the amino acid, glutamate, as tasted in the seasoning monosodium glutamate, or MSG). These tastes are detected by GPCRs in the taste cells. Senses of taste and smell are related. Together with smell, taste regulates a wide range of behaviors.

In this class, we will discuss how we can perceive sweet taste and the experimental techniques used to identify sweet taste receptors. We also will discuss the receptor for caffeine.

**Week 14**      **Oral presentations**  
*May 17*        **General Discussion and Future Perspectives**