Cannabis, commonly known as marijuana, is a product of *Cannabis sativa* plant, and the active constituents from this plant are called cannabinoids. Marijuana has been known to humans for thousands of years both in its medicinal and recreational form. The cannabis plant has more than 480 chemicals. In mid-1960s, scientists discovered 9·-tetrahydrocannabinol (THC) as the major psychoactive principle in marijuana. Today, over 60 active cannabinoids have been identified in marijuana. In addition to THC, cannabidiol (CBD) is another major constituent of cannabis that has been shown to be non-psychotropic. Despite early identification of THC, it was not until mid-1980s that the researchers identified the receptors through which cannabinoids act. In addition, it was discovered that cells in the brain and immune system also produces small amounts of cannabinoids called endocannabinoids. The identification of cannabinoid receptors and their endogenous ligands has led to significant growth in research aimed at understanding how cannabinoids regulate various physiological functions. The cannabinoid receptors include CB1, predominantly expressed in the brain and spinal cord, and CB2, primarily found on the cells of the immune system. Marijuana has been used for recreational and medicinal purposes for thousands of years. However, due to its psychotropic effects and potential for addiction, its production and use has been controlled in the United States and other countries. Scientific research has shown that marijuana, when smoked, can pose adverse effects on the lungs as well as other functions such as cardiovascular and neurocognitive. However, medicinal uses of marijuana have also been widely noted. Thus, THC in its purified form has been approved by the FDA for medicinal use such as to treat anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy. Cannabinoids have been shown to lower the intraocular pressure (IOP) and thus have been suggested for their potential use to treat glaucoma. Immune system consists of a complex network of cells and the mediators that they produce, called cytokines. The main function of the immune system is to fight against infections and cancer. However,
when the immune system goes haywire, it can trigger allergies and autoimmune diseases. Recent studies have shown that chronic inflammation can also trigger a wide range of diseases including obesity, neurodegenerative diseases, cancer, and cardiovascular diseases. Interestingly, immune cells express cannabinoid receptors and produce endocannabinoids. Recent research has suggested that cannabinoids can suppress immune response through multiple pathways. Cannabinoids can suppress T cells that cause inflammation such as Th1 cells and Th17 cells while promoting anti-inflammatory T cells such as Th2 cells and Tregs. Together, such effects suppress inflammation. Cannabinoids have also been shown to trigger a unique type of immune cells called Myeloid-derived Suppressor cells (MDSC), which are potent immunosuppressive cells. THC and other cannabinoids are also potent inhibitors of cytokines. In addition, cannabinoids can trigger apoptosis (programmed cell death) in T cells and dendritic cells, thereby suppressing inflammation. Interestingly, malignancies of the immune system including lymphomas, myelomas, leukemias and the like, also express cannabinoid receptors. Thus, experimental data has shown that cannabinoids are very effective in killing cancer cells and curing the host of the disease. Because CB2 receptors are primarily expressed only on immune cells, there is growing potential to use CB2-select agonists as anti-inflammatory agents. Such drugs will not have psychotropic activity seen with THC. It is noteworthy that cannabidiol which is found in marijuana, is non-psychoactive, and is also immunosuppressive. Marijuana rich in cannabidiol has been reported to have beneficial effects in preventing seizures. Thus, cannabidiol has recently been granted orphan drug status for the treatment of children with Dravet syndrome, which is a severe disorder of drug-resistant epilepsy. It is also possible to develop drugs that can increase the levels of endocannabinoids in the body, which may also serve as novel drug targets. In summary, marijuana cannabinoids have opened new avenues to pursue research aimed at treatment of inflammatory and autoimmune diseases. There are over 80 autoimmune diseases for which currently there is no cure. These also include diseases of the eye such as uveitis and a wide spectrum of orbital inflammatory diseases. Because chronic inflammation is the underlying cause of a majority of clinical disorders, the cannabinoid system of receptors and ligands provide a novel platform to advance research aimed promoting health and preventing disease.
The Impact of Marijuana Use on Brain Structure and Function

Staci Gruber, PhD

This presentation will focus on the impact of marijuana on brain structure and function with a particular emphasis on those who begin smoking early (prior to age 16) as compared to those who begin marijuana use later (after age 16). Dr. Staci Gruber will:

- Introduce current attitudes and perceptions regarding marijuana (MJ) use and how this has affected national trend data in the United States, specifically among emerging adults
  - MJ use remains the most widely used recreational and illegal drug in the US
  - Risk and harm related to MJ use is at an all-time low; as perceived risk and harm of MJ decreases, individuals are initiating MJ use more frequently and at younger ages

- Review of adolescent brain development and the potential impact of MJ on the developing brain during a critical period of neuromaturation.
  - Given the specific vulnerabilities associated with adolescence, particular emphasis will be placed on differences between those who begin smoking MJ prior to the age of 16 (early onset) relative to both individuals who begin smoking after the age of 16 (late onset) and healthy, non-MJ smoking controls

- Discuss recent studies of MJ use and the brain, including data from studies utilizing neurocognitive and multimodal neuroimaging techniques (e.g. fMRI, DTI, etc.)
  - MJ smokers show impairments on measures of frontal/executive function and altered brain activation, specifically on tasks assessing inhibitory control
  - Changes in white matter microstructure have also been observed; these have been shown to be related to age of onset as well as reported levels of impulsivity

- Conclusions
  - The need for early identification, intervention and education regarding recreational MJ use among our nation’s youth will be addressed
The Cannabinoids and Ophthalmology

Allan Flach, MD, PharmD

Professor of Ophthalmology

University of California San Francisco

I. Historical Introduction: A brief review of the history of marijuana and its therapeutic use will help explain why interest in marijuana and its components have continued to the present.

II. Pharmacology and Toxicology:
   a. Ocular: Review of ocular pharmacologic effects will permit the anticipation of potential therapeutic uses and complicating toxicities.
   b. Cardiovascular: Discussion of potential cardiovascular pharmacologic effects will reveal dangers that may counteract beneficial ocular effects.
   c. Central Nervous System: CNS effects complicate therapeutic use of the cannabinoids in ophthalmology as will be discussed.

III. Clinical Use in Ophthalmology: Interest in using cannabinoids for the treatment of the glaucomas has been present for many years. Potential advantages and problems will be considered.

IV. Compassionate Access Program: Some patients with end-stage glaucoma refractive to medical and surgical treatments in California were convinced they were being deprived from a potentially vision saving treatment and were, therefore, risking police arrest to gain access to marijuana. The Compassionate Access Program they participated within will be reviewed. An emphasis will be placed upon requirements for admission, method of follow-up, observed results and conclusions following cessation of the Program.

V. Commercial Products: Attempts to prepare topically effective cannabinoids for the treatment of glaucoma will be discussed.
VI. **Future Use in Ophthalmology**: The potential ophthalmic use of marijuana or one of its 480 ingredients will be discussed.