

ARTICLE

Teaching Neuroimmunology to Undergraduate Students: Resource for Full Course or Modular Implementation

Junryo Watanabe

Biology Department, SUNY Oneonta, Oneonta, NY 13820.

This paper describes a course I designed to teach neuroimmunology to undergraduate students. In this course I incorporated many active learning strategies to help make it a student-centered class, where they developed communication skills, while reading and analyzing primary literature articles. As the field of neuroimmunology is relatively new, most textbooks in the field approached the subject from the perspective of neurology and autoimmune diseases. Therefore, I used reading, analysis, and student-led presentation of primary papers in the classroom to not only develop critical thinking and application of the scientific

method, but also oral communication skills. Other activities such as writing *New York Times*-style articles and literature review papers were employed to develop written communications skills. The goal of this article is to provide a reference tool for instructors trained in neuroscience to deploy an entire course on neuroimmunology or select a module or a single paper to incorporate into their existing course to offer students a taste for neuroimmunology.

Key words: neuroimmunology; primary literature; critical thinking; oral and written communication

As instructors of undergraduate science courses, we are often confronted with the opposing forces of teaching for breadth versus depth of content. When surveyed, life science faculty (Coil et al., 2010) and members of Faculty for Undergraduate Neuroscience (Kerchner et al., 2012) ranked critical and integrative thinking as the most important core competency for undergraduate science courses, and it ranked higher than basic neuroscience knowledge in the survey by Kerchner and colleagues (2012). The CREATE (consider, read, elucidate hypotheses, analyze and interpret data, and think of the next experiment) method is one way to develop students' critical thinking and scientific process skills in the classroom (Hartman et al., 2017). As described by Sally Hoskins and colleagues, the CREATE method increases the gain of students' ability to read and analyze primary scientific literature while also increasing their interest in research and researchers (Hoskins et al., 2007; Hoskins, 2008). The ability to apply the scientific process is one of the core competencies identified in Vision and Change in Undergraduate Biology Education: A Call to Action (American Academy for the Advancement of Science, 2011).

The ability to communicate effectively is another core competency identified in Vision and Change (AAAS, 2011). Not only should students practice written, visual, and oral communication skills as part of undergraduate biology education, they should also develop skills to communicate their ideas to people in other disciplines. By communicating scientific concepts to peers and people outside their discipline, it helps student comprehension and integration of other disciplines. Not surprisingly, both written and oral communication skills ranked high in importance of life science process skills (Coil et al., 2010).

In this paper, I describe a neuroimmunology course for undergraduate neuroscience majors. This course was based on analyses of primary-literature articles with emphasis on developing oral and written communication skills. As the field of neuroimmunology is relatively new, our

understanding is evolving at a rapid pace. By employing some of the fundamental pedagogical techniques of the CREATE method, the students not only analyzed primary papers that are defining the field, but they also witnessed the evolution of the field in real time. The dogma in the field of neuroscience for almost a century was that the central nervous system (CNS) is immune privileged – that is to say, the CNS is free from immune surveillance, because cells of the immune system do not cross the blood-brain barrier. Seminal experiments where tissues were transplanted in the brain and did not elicit immune-mediated tissue rejection led to this dogma (Shirai, 1921; Medawar, 1948). It is now clear there is an intricate relationship between the nervous and the immune systems, and in this course the students explored some key primary literature papers that are elucidating this relationship.

This article provides the class design and the list of primary literature papers with brief explanation of their relevance to the field of neuroimmunology. An instructor teaching this course should have a neuroscience background and a basic knowledge of immunology which can be obtained using the textbook described in this article. Alternatively, this course can be team-taught with an immunologist. Even though an entire semester-long neuroimmunology course is described, an instructor can adopt just a single module or paper described in this article into their existing neuroscience or immunology course. In the following sections, student learning outcomes (SLOs), course design, and teaching materials (such as the textbook, primary literature papers, and grading rubrics) are described and included. Additional primary and review papers are also included to aid potential instructors with supplementary background materials.

CLASS DESIGN

The student learning outcomes (SLOs) for this course were the following: 1) learn the fundamentals of how the immune

system works, 2) understand the bidirectional crosstalk between the immune and the nervous systems, through critically reading, analyzing, and evaluating primary literature, and 3) develop oral presentation skills to peers and written communication techniques of a scientific body of work to both scientific and non-scientific audiences.

To help achieve the learning outcomes, the course included six modules or focus areas:

1. The Immune System
2. Immune Molecules In The Nervous System, and Vice Versa
3. Immune System and Injury to the Nervous System
4. Diseases with Neurological Symptoms
5. Autoimmune Diseases
6. Stress and the Immune System

The textbook and papers used for each module are described in detail in the next section.

The prerequisite courses for this class were introductory cell and molecular biology and introductory neuroscience. As such, most of the students taking this class were third-year neuroscience majors. We did not offer an immunology course, but if such a course were to be added as a prerequisite, it might make this course inaccessible to many, leading to enrollment issues. The first module was designed to achieve the first SLO, to learn the fundamentals of the immune system. I delivered lectures on the topic of immunology. I employed two teaching strategies to maximize student learning and retention of the information in a short amount of time. The first was the use of KWL forms. Before each lecture, the students filled out and turned in the K and W columns of a KWL (what I know, what I want to know, what I have learned) chart (Ogle, 1986). This encouraged the reading of the appropriate chapter before class. It also informed me of particularly hard concepts to pay more attention to in lecture. After the lecture, the students filled out the L column of the chart and turned it in. For the second teaching strategy, I used concept mapping (Novak and Musonda, 1991). After each lecture, the students drew a concept map of the immune system, adding new content as it was introduced. By the end of the three-week lecture series, they drew the entire concept map of the immune system (Figure 1). I found the concept maps extremely helpful for students in organizing and keeping track of otherwise complicated interactions in the immune system. A picture of the completed concept map generated at the review session for the quiz on immunology was uploaded onto the class LMS site so that it was readily available as a resource to the students.

The primary literature papers were presented in the style of a journal club. Each student had the opportunity to present twice during the semester: once as a group of two or three students, and once individually. Before each journal club, the non-presenting students filled out a discussion comment. This helped encourage preparedness for the journal clubs to ensure lively discussions.

Only one paper was presented in the 50-minute class. After each journal club, the presenters received anonymous feedback from their peers and a graded feedback from

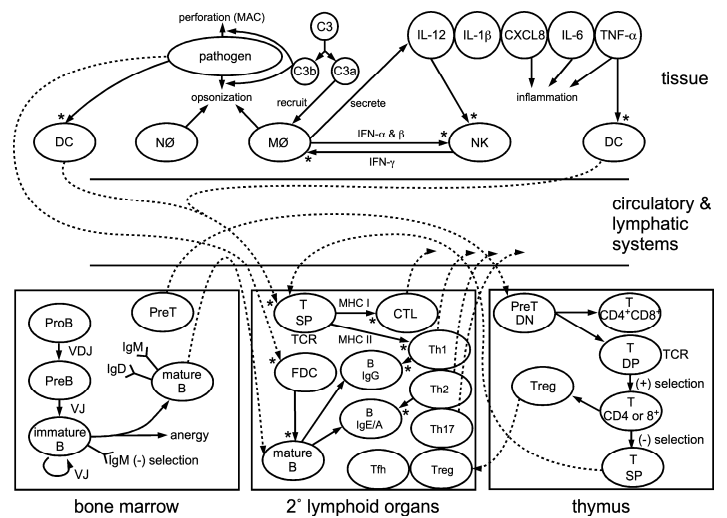


Figure 1. Concept map of the immune system. The students started the concept map of the immune system after the first lecture during class, and after each lecture they added more information. This was drawn on the whiteboard during the review session at the end of module 1 and represents the culmination of all the concepts learned. Solid lines with arrow heads represent development of cells or effect of molecules. Dotted lines with arrow heads represent movement of cells. Asterisks represent activation. (DC = dendritic cells, NØ = neutrophils, MØ = macrophages, NK = natural killer cells, C3 = complement component 3, MAC = membrane attack complex, B = B cells, T = T cells, FDC = follicular dendritic cells, SP = single positive, DP = double positive, CTL = cytotoxic T lymphocyte, TCR = T cell receptor, MHC = major histocompatibility complex).

myself on their presentation. The feedback rubrics are in Appendix 1. I presented the first journal club presentation to serve as a model for the students. I would often stop and comment on the actual technique of presentations to highlight key aspects of a good presentation. I stressed the importance of providing a clear framework or background information for the paper being presented (see syllabus in Appendix 2). The presentations developed oral communication skills as well as the skills to facilitate discussion in a class of about 24 students and to work collaboratively in groups.

To promote written communication skills, the students had two writing assignments. One was a *New York Times*-style article where they wrote about a primary literature article to an audience of non-scientists. Links to sample articles to be read and emulated were provided in the syllabus (Appendix 2). After they received the first draft with comments from me, they were required to ask three people (a non-biology science major student, a biology major student, and a non-student) to read and provide feedback on the legibility and the "level of science" of their article. They typed up the feedback summary, incorporated any feedback from the three readers, and edited their final draft accordingly to address any comments from the readers. The second written assignment was a literature review paper to promote scientific writing as well as to synthesize the current state of the field of neuroimmunology. Blinded peer-review was incorporated as part of the draft process to simulate the review process for submissions to scientific

journals. The literature review was heavily scaffolded to help break down the otherwise daunting task into smaller deliverables. Other details on the course materials, such as grading rubrics on the writing assignment, oral presentation evaluation forms, and course grade components, see the Appendices.

TEACHING MATERIALS

Module 1: The Immune System

Typically, an introductory neuroscience course is a second-year course after the students take the introductory biology sequence. Thus, from the perspective of prerequisite courses, there is a significant “entry barrier” for a neuroimmunology course. Further, if an immunology course is added as a prerequisite, it would further increase the entry barrier to the point where enrollment may become an issue. In addition, many undergraduate biology departments do not teach immunology as a standalone course. For these reasons, the first three weeks of the course were dedicated to teaching students the basics of the immune system. I found that Sompayrac’s *How the Immune System Works* (ISBN 978-1119542124) is an appropriate textbook for the purposes of this course (Sompayrac, 2019). It is short (168 pages) and easy to read as the writing style is like the author is having a casual conversation with the reader. This module focuses on students understanding the key terminology and concepts about the immune system.

Module 2: Immune Molecules in the Nervous System, and Vice Versa

This module was centered around the notion of the separation of the central nervous and the immune systems. The blood-brain barrier (BBB) describes the blood vessels of the CNS that are tightly regulated such that molecules in the serum do not simply “leak” across. The BBB allows for molecules used in the CNS to have different functions in the immune system and conversely molecules of the immune system can be used in the CNS in a novel way. In this module, we explored papers that demonstrate some unique roles of CNS and immune molecules.

MHC (Major Histocompatibility Complex)

MHC proteins are expressed on the cell surface essential in the adaptive immune system. They display antigens from either outside or inside the cell and signal to activate immune cells (such as T cells) or communicate the viral infection-state of the cell.

The paper from Carla Shatz’s lab demonstrated that MHC proteins expressed in the lateral geniculate nucleus (LGN) at the presynaptic terminals allow for proper synaptic refinement of retinal inputs (Datwani et al., 2009). Shatz is known for elucidating the role of electrical activity in the retinal ganglion cells in synaptic refinement in the LGN. In a seminal paper, they discovered that tetrodotoxin (TTX) not only prevented synaptic refinement during the critical period of plasticity but also decreased mRNA levels for MHC proteins (Huh et al., 2000). In the more recent paper, the authors reported retinal inputs to LGN in mice lacking MHC proteins failed to refine completely. Knockout of the MHC receptors also gave the same phenotype. Although this

paper was not the first to describe the presence of MHC molecules being expressed in the CNS, it did demonstrate the role of MHC molecules in synapse refinement. The quantification of synapse refinement was the same used in other papers in this module providing an excellent foundation for further course readings. Instructors who want more background on MHC proteins in synaptic refinement should read the review paper written by Shatz (Shatz, 2009).

An alternate paper that was not used, but is equally interesting, is from Rona Giffard’s lab. It demonstrated the role of MHC proteins and their receptors (PirB) in stroke (Adelson et al., 2012). Stroke elevated the neuronal expression of these molecules, and they found that knocking out the ligands or receptors protected the neurons from cell death after stroke.

Complement

Complement proteins are innate immune system molecules that enhance or complement the abilities of antibodies and phagocytic cells to clear pathogens.

The seminal paper from Ben Barres’ lab demonstrated the colocalization of complement proteins C1q and C3 with pre- and postsynaptic markers in the developing LGN (Stevens et al., 2007). Barres was known for helping to bring glial cells to the forefront of neuroscience. While profiling the gene of purified astrocytes, complement proteins were discovered. It was the first time that complement proteins were shown to be secreted by glial cells in the CNS. Complement-KO mice demonstrated failure of retinal input refinement, the same synapses described in the paper from Shatz describing the role of MHC in synapse refinement. A later paper by Beth Stevens showed that microglia are involved in synapse elimination and refinement (Schafer et al., 2012). A review paper co-authored by Stevens is a comprehensive reference for instructors interested in the topic of complement in the CNS (Tenner et al., 2018).

Dscam (Down Syndrome Cell Adhesion Molecule)

Dscam proteins are members of the immunoglobulin (Ig) superfamily of cell adhesion molecules (CAMs). Dscam was first identified in the Down syndrome (DS) critical region. When Dscam is overexpressed in the developing fetal brain it results in Down syndrome. The alternative splicing of *D. melanogaster* Dscam generates over 38,000 isoforms. Since invertebrate organisms only have the humoral (cell-based) immune system, it was postulated that the receptor diversity acts in the similar way the hypervariable regions of antibody of vertebrate adaptive immune system to give the immune cells the ability to recognize many different pathogens.

Dietmar Schmucker was the first to isolate *Drosophila* Dscam in a biochemical screen, and it was postulated the molecular diversity may play a role in specificity of neuronal connectivity (Schmucker et al., 2000). The later paper from Schmucker’s lab demonstrated that Dscam proteins are involved in cell contact-mediated axon guidance during development (Chen et al., 2006). When the authors genetically reduced the diversity of alleles, sensory neurons had altered branches and targets in the adult brain. This

important paper was the first to describe Dscam proteins functioning as axon guidance molecules. For instructors who want more background for Dscam, the review from the same lab should prove helpful (Schmucker and Chen, 2009).

GABA (Gamma-Aminobutyric Acid)

GABA is the primary inhibitory neuronal transmitter of mammalian CNS. Larry Steinman is known for his work on autoimmune diseases, especially Multiple Sclerosis (MS). This paper from his lab demonstrated that macrophages expressed functional GABA receptors and recorded inhibitory postsynaptic potentials (IPSPs) from macrophages with focal application of GABA (Bhat et al., 2010). In addition, they showed that by activating GABA receptors, the antigen presenting cells (APCs) were suppressed reducing inflammation and T cell activation. They went on to demonstrate that by activating GABA receptors on immune cells, they were able to ameliorate experimental autoimmune encephalomyelitis (EAE), an animal disease model for MS. Others had demonstrated the presence of GABA receptor subunits on immune cells (Alam et al., 2006) as well as suppression of immune function via GABA (Tian et al., 2004), but this paper was the first to show actual GABA-mediated IPSPs in immune cells.

Acetylcholine (ACh)

ACh is a neurotransmitter that functions in both the CNS and the peripheral nervous system (PNS). In the PNS, ACh has many targets within the sympathetic and parasympathetic nervous systems. The vagus nerve consists of about 20% efferent and 80% afferent nerves and is a major component of the parasympathetic nervous system. The vagus nerve provides the bidirectional communication between the CNS and the gastrointestinal tract that is termed the gut-brain axis (GBA) and facilitates fascinating interactions between the gut microbiome and emotion, but that was outside the scope of this class. The release of ACh in regulating heart-rate (Loewi, 1924) and release of adrenaline is well characterized, but its effect on the immune system is not.

The paper from Kevin Tracey's lab demonstrated that vagal efferent nerve, which uses ACh as the principal neurotransmitter, modulates inflammatory responses (Borovikova et al., 2000). They showed that macrophages reduce the secretion of cytokines such as TNF- α in response to ACh *in vitro*. When they electrically stimulated the vagus nerve *in vivo*, they were able to attenuate TNF- α release in response to endotoxin injection in rats. A later paper from the same lab demonstrated that a particular subunit of the ACh receptor is essential for mediating the anti-inflammatory response (Wang et al., 2003). A review paper by Reardon and colleagues provides an extensive overview of the neuroimmune communication, including the cholinergic system via the vagus nerve (Reardon et al., 2018).

TNF- α (Tumor Necrosis Factor Alpha)

TNF- α is a proinflammatory cytokine that was cloned in the 1970s. Macrophages are the major producers of TNF- α and acts on many different cells through the transmembrane

receptors TNFR1 and TNFR2. Dysregulation of TNF- α production is linked to autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease (Crohn's).

The effect of TNF- α has been studied since the 1990s in the context of its neurotoxic effects seen observed in human immunodeficiency virus (HIV) infection of the CNS (Gelbard et al., 1993). The seminal paper from Robert Malenka, who is known for his work on synaptic plasticity, showed evidence that TNF- α released by astrocytes increased the synaptic strength (Beattie et al., 2002). It was demonstrated that AMPARs (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors) were trafficked and inserted into the postsynaptic membrane such that the AMPAR/NMDAR (N-methyl-D-aspartate receptor) ratio increased. Conversely, when they blocked TNFR1, the AMPAR/NMDAR ratio decreased suggesting that AMPARs were removed. This paper was the first to demonstrate the TNF- α released by glial cells modulated synaptic strength. A review paper by Beattie and colleagues presents a good overview of the role AMPARs play in cell death (Beattie et al., 2010).

Module 3: Immune System and Injury to the Nervous System

This module explored the changes in the interaction between the nervous and the immune systems during injury to the nervous system. As mentioned earlier in the description for Module 2, the BBB keeps the interactions to a minimum, but injuries to the nervous system can lead to dramatic changes in the BBB properties. We explored various insults to the nervous system and the resulting effects of immune system entry into the nervous system.

Inflammation and Neurogenesis

There are cells that reside in the CNS that can produce proinflammatory cytokines, namely microglia and astrocytes. Both of these cells reside in a resting state during normal nervous system functions but can get activated to produce cytokines. The ability of astrocytes to become activated is interesting in its own as astrocytes derive from the ectoderm. On the other hand, microglia are hematopoietic cells of mesodermal origin that get "trapped" behind the BBB as the CNS vasculature develops and matures. Thus, microglia share many of the same cell markers as macrophages and, perhaps not too surprisingly, are able to be classically activated to secrete proinflammatory cytokines.

The paper from Theo Palmer's lab demonstrated that LPS- (lipopolysaccharide, endotoxin derived from gram negative bacteria) and radiation-induced activation of microglia resulted in the reduction of new neuron survival but did not affect the rate of proliferation of new cells in the hippocampus (Monje et al., 2003). The detrimental effects of radiotherapy on learning and memory were well known, but the cause was not (Monje and Palmer, 2003). This and another paper published about the same time (Ek Dahl et al., 2003) were the first to describe the detrimental effects of inflammatory cytokines on neurogenesis. A more recent paper investigated the role of activated microglia on

neurogenesis during early postnatal development (Shigemoto-Mogami et al., 2014). In contrast to the paper from Palmer and colleagues, they found that activated microglia enhanced neurogenesis. Together, these papers illustrate whether inflammatory cytokines are “good” or “bad” is not absolute, but rather highly depends on the developmental stages and local environment. A recent review provides an overview of radiation-induced inflammation and neuronal dysfunction (Pazzaglia et al., 2020).

Spinal Cord Injury

The topic of spinal cord injury and the following topic of injury to the PNS go hand in hand. Without medical intervention, injury to the spinal cord is permanent while PNS does regenerate quite robustly. The differences in the regenerative capacities are not innate: if you transplant a CNS neuron into the PNS, it will regenerate after axonal injury, and conversely, if you transplant a PNS neuron into the CNS and injure it, it will not regenerate (David and Aguayo, 1981; Vidal-Sanz et al., 1987). It is the local environment that make CNS neurons unable to regenerate. In both CNS and PNS injuries, the vasculature breaks down allowing cells and molecules of the immune system to enter the site of injury. In the CNS, the BBB only breaks down immediately adjacent to the site of injury, while in the PNS, the BNB (blood-nerve barrier) breaks down along the entire length of the nerve distally from the site of injury.

The paper by Phillip Popovich and colleagues identified two distinct activation states for macrophages entering the site of spinal cord injury (Kigerl et al., 2009). The M1 macrophages are classically activated macrophages that secrete proinflammatory cytokines and are neurotoxic and prevents axonal regeneration in the neurons. The M2 macrophages are alternatively activated macrophages that secrete anti-inflammatory cytokines that aide in the repair and regeneration of the neurons. The M1 macrophages dominate the site of injury in the CNS, and the presence of M2 macrophages is transient and short-lived. This paper was the first to demonstrate macrophage heterogeneity in spinal cord injury. A review on the topic of immune response to spinal cord injury and potential targets for therapy provides essential context for M1 and M2 macrophages (Brennan and Popovich, 2018).

PNS Injury

Unlike injuries to the CNS, PNS has the ability to repair and regenerate after injury. One key difference is the breakdown of the BNB along the entire distal length of the injured nerve allowing cells of the immune system to have access to the entire damaged nerve. Myelin has glycoproteins that are inhibitory for axonal growth, presumably to prevent axonal sprouting under normal conditions. But that means myelin must be cleared from injured nerves in order for axons to regrow. In the CNS, myelin debris remains in the white matter for years after the injury in both humans and primates (Gilliat and Hjorth, 1972; Chaudhry et al., 1992). In the PNS, however, nerve injury results in rapid myelin and axonal debris clearance making the environment permissive for axon growth and regeneration.

The paper from Ben Barres' lab, known for their work on neuron-glia interactions, demonstrated that rapid clearance of myelin debris is critical for robust axon regeneration (Vargas et al., 2010). They showed that antibodies recruit macrophage entry into the site to initiate clearance of myelin debris; without antibodies the debris clearance was delayed, and axons showed impaired regeneration. This report was the first instance where beneficial autoantibodies (antibodies that recognize degenerating tissue) through recruitment of macrophages actively promoted wound healing. Until this work, autoantibodies were always viewed negatively as hallmarks of autoimmune diseases. A review paper by Reyneveld and colleagues provides extensive detail on self-binding antibodies (Reyneveld et al., 2020).

Module 4: Diseases with Neurological Symptoms

In this module, we explored non-nervous system diseases that exhibit neurological symptoms. HIV is interesting in the context of this class as it is a virus that infects the cells of the immune system. To provide some background about HIV, I spent one class talking about the biology of HIV, HIV immunity, and the potential for stem cell treatment (Hütter et al., 2009).

HIV-Associated Dementia

HIV invades the CNS early in the infection and causes cognitive deficits such as HIV-associated dementia (HAD). The mechanism of HIV entry into the CNS is thought to occur via infected monocytes that transmigrate and become periventricular macrophages, a specialized type of leukocytes thought to perform immune surveillance of the CNS. The antiretroviral therapy (HAART) dramatically increases the lifespan of HIV-positive individuals, but the drugs do not cross the BBB, so the virus causes damage to the CNS (called NeuroAIDS) partly through infecting and activating microglia. The resulting damage to the CNS causes a downward spiral of the BBB becoming leaky allowing further migration of HIV infected cells into the CNS.

The paper from Shalom Avraham's lab demonstrated that cannabinoids can prevent HIV coat protein Gp120-mediated damage to the BBB (Lu et al., 2008). It has been shown by other labs that HIV infection alters BBB structure and function (Sweeney et al., 2018). They showed that cannabinoid agonist activation of CB1 receptors prevented BBB degradation and inhibited transmigration of monocytes. This observation was the first report of cannabinoids protecting the BBB from HIV-mediated cognitive impairment. Indeed, a recent study showed that cannabis exposure linked people living with HIV with lower neurocognitive impairment (Watson et al., 2020).

Malaria

Malaria is caused by *Plasmodium* parasites that invade red blood cells. During the later stages of the disease the parasites do not enter the CNS, but rather it triggers a proinflammatory response to clear the parasites from red blood cells. Unfortunately, the same inflammatory response leads to degradation of BBB function such that it may result in brain hemorrhages. A review paper by Rénia and colleagues explains in depth the relationship between BBB

and cerebral malaria (Rénia et al., 2012).

The paper from Maya Saleh's lab demonstrated that caspase-12 dampens and thus inhibits the immune response to malaria parasites (Labbe et al., 2010). In a landmark paper, Saleh was the first to describe the targeted deletion of caspase-12 conferring protection against sepsis (Saleh et al., 2006). Caspase-12 is a member of a family of protease enzyme that mediates pyroptosis, a highly inflammatory form of programmed cell death. A single-nucleotide polymorphism (T125C) exists in humans for caspase-12 and interestingly it is restricted to regions of the world where malaria exists. The thymidine at position 125 introduces a premature stop codon, while the cytosine results in a production of the full-length protein (Scott and Saleh, 2007). It turns out that the truncated caspase-12 originated in Africa about 100,000 years ago, and due to resistance to sepsis, it has reached near fixation. They showed that caspase-12 limits the elimination of *Plasmodium* parasites by binding and inactivating NF- κ B that produces IFN- γ , an inflammatory cytokine. Unfortunately, increased IFN- γ production leads to insults to the BBB and results in cerebral malaria. This instance was the first report of linking the caspase-12 T125C single-nucleotide polymorphism (SNP) to malaria. This paper is also good for teaching positive selection in genetics. While the truncated form of caspase-12 has all been fixed due to its sepsis resistance, the T125C SNP, the full-length caspase-12, still persists in regions where malaria exists, presumably it confers resistance to cerebral malaria that causes severe damage to the nervous system.

Module 5: Autoimmune Diseases

Autoimmune disease is a condition where the immune system attacks the host or self-tissue. For this course, this module was designed to explore the classic autoimmune diseases of the nervous system. This module started with MS, a classical autoimmune disease of the CNS. The rest of the topics dealt with neurological conditions that may have some autoimmune component. The papers in this module were exploratory, where students can decide for themselves if some cases of these conditions are indeed autoimmune diseases.

Multiple Sclerosis (MS) and Epstein-Barr Virus (EBV)

MS is a chronic inflammatory disease where the immune system attacks the myelin of the CNS. The loss of myelin may result in loss of balance, muscle control, vision, and other functions due to loss of action potential conduction. In MS, T cells cross the BBB and enter the CNS where they release inflammatory cytokines and damage the myelin and oligodendrocytes, which are glial cells that make myelin in the CNS. B cells get recruited and activated resulting in the production of antibodies against myelin. The cause of MS is yet unknown.

Bernhard Hemmer has been working on elucidating the viral origins of MS. The paper from his lab showed that antibodies purified from cerebral spinal fluid of MS patients showed higher reactivity to EBV proteins than controls (Cepok et al., 2005). Further, they showed increased T cell activation from MS patients to cells expressing the two

epitopes of the EBV protein. This was first evidence of EBV protein reactivity in MS patient CSF antibodies. They found EBV reactivity in CSF of MS patients using an unbiased screen of 37,000 proteins. These findings are in line with epidemiological studies where 1) almost all MS patients are seropositive for EBV titers (antibodies detected in serum), and 2) MS patients more frequently have a history of mononucleosis, a disease caused by EBV. These results suggest a molecular mimicry cause for MS: the patients experience an infection by the EBV, resulting in antibodies produced that cross-reacts with myelin thus triggering an immune attack against myelin. A recent paper by Hemmer and colleagues reported that in a large cohort study of early MS patients, 100% of 901 patients were seropositive for the EBV, further strengthening the link between EBV and MS (Abrahamyan et al., 2020).

Narcolepsy

Narcolepsy is a chronic disorder that affects the regulation of sleep-wake cycle. Symptoms include overwhelming daytime sleepiness and sudden involuntary attacks of sleep. The disorder is caused by the loss of approximately 70,000 hypocretin (Hcrt) cells in the hypothalamus. Hcrt, also known as orexins, is a neuropeptide and was discovered along with their receptors in 1998 (Sakurai et al., 1998). The disorder has been tightly linked to the human leukocyte antigen (HLA) allele DQB1*602: over 95% of people with narcolepsy carry this particular HLA subtype. HLA system is a group of proteins encoded by the MHC gene complex in humans, and they are responsible for regulation of the immune system. The immune system uses HLA to recognize self-tissue versus foreign cells. Due to the tight linkage to a particular HLA allele, narcolepsy is largely considered an autoimmune disease.

I used two papers from Emmanuel Mignot's lab for this topic. Mignot is an authority on sleep, especially on the disorder of sleep, narcolepsy. They showed that there was almost a complete lack of Hcrt mRNA in the hypothalamus of postmortem brains from human narcoleptic patients. This was the first instance of linking lack of Hcrt to narcolepsy in humans. Previous linkage was performed in narcoleptic dogs (Lin et al., 1999) and knockout mice (Chemelli et al., 1999). This first paper established the biology of narcolepsy, and the second paper reported cases of narcolepsy following H1N1 flu vaccination between 2009 and 2010 (Dauvilliers et al., 2010). First cases of narcolepsy in vaccinated children and adolescents were reported in Sweden, but additional cases were reported in Finland, France, England, Ireland, and Quebec Province of Canada. The vaccines used a specific adjuvant, AS03, and was produced by GalaxoSmithKline and marketed as Pandemrix. This specific vaccine against H1N1 resulted in 6.6-fold increase in risk among vaccinated children and adolescents. Among those who developed narcolepsy after vaccination, the DQB1*602 haplotype had the highest risk. It was thought that the AS03 adjuvant used to stimulate the immune system somehow triggered an autoimmune response in individuals who were already predisposed to narcolepsy. Together these papers lead to lively discussions on the safety of vaccines.

Autism Spectrum Disorders (ASD)

ASD is a developmental disorder characterized by difficulty in communication and social interactions as well as obsessive interests and repetitive behaviors.

Daniel Geshwind is known for his work on neurogenetic approaches to understanding autism (Wamsley and Geschwind, 2020). The paper from his lab reported enrichment of astrocytic and microglial genes in postmortem autism brains using RNA-seq and genome-wide association study (GWAS) data set (Voineagu et al., 2011). This unbiased approach confirmed earlier report of increased inflammatory cytokines in CSF of people with ASD (Vargas et al., 2005). These papers merely hinted at microglial activation and possible immune component to ASD. In a recent paper, however, the role of microglia in ASD has been brought to the forefront (Xu et al., 2020). Prior to this work, a single polymorphism in the *EIF4E* gene was identified in ASD that leads to overexpression of eIF4E in mice which display autism behaviors (Gkogkas et al., 2013; Santini et al., 2013). The authors of the recent paper showed that when they overexpressed eIF4E in only microglia, only the male mice displayed autism-like behavior with microglia adopting an activated phenotype with reduced phagocytic activity leading to higher synaptic density and excitation-to-inhibition ratio, a phenotype seen in human ASD brains. Moreover, ASD in humans predominantly affect males.

Schizophrenia

Schizophrenia is a mental health disorder involving the breakdown of relation between thought, emotion, and behavior that manifests as disorganized speech or behavior, social withdrawal, and delusions. The cause is not known but various genetic and environmental factors increase the risk for schizophrenia. For example, identical twins have 50% concordance for schizophrenia (Cardno and Gottesman, 2000). Also, schizophrenia patients are more likely to be born in the winter or spring (Brown, 2011).

The papers from Javier Gonzalez-Maeso's lab demonstrated mice born to mothers either stressed (Holloway et al., 2013) or infected with the H1N1 influenza virus (Moreno et al., 2011) displayed schizophrenic behavior with increased serotonin 5-HT_{2A} and decreased metabotropic glutamate receptor mGlu₂ receptor expression in the prefrontal cortex. The altered expression of these receptors is consistent with that seen in postmortem brains from people with schizophrenia. 5-HT_{2A} receptors are necessary for the action of psychoactive drugs such as LSD and PCP. In the paper where they administered the H1N1 virus to the pregnant mice, the antibodies but not the virus was detected in the embryos. These results suggest that increased inflammatory cytokines in the mother, either through influenza viral infection or increased stress, triggers neurodevelopmental alterations in the embryos that result in schizophrenia. Further, these results are consistent with the observation that schizophrenia patients are more likely to be born in the winter or spring when flu virus is more prevalent. A review paper by Cordeiro and colleagues covers many types of maternal infections and possible alterations of fetal brain development (Cordeiro et al., 2015).

Epilepsy

Epilepsy is a disorder in which neuronal firing becomes abnormal causing seizures. Typically, neuronal activity is asynchronous, but during seizures, excitatory glutamatergic neurons become hyperexcitable resulting in runaway excitation. Seizures can be focal and limited to a certain region, but tonic-clonic seizures (previously called grand mal seizures) are the result of spread of uncontrolled excitation throughout the cortex. Seizures can result from too little inhibition, too much excitation, or both.

The seminal paper from James McNamara's lab demonstrated that antibodies against glutamate receptor 3 (GluR3) has significant role in Rasmussen's encephalitis characterized by severe, intractable seizures (Rogers et al., 1994). When rabbits were vaccinated with GluR3, they developed seizures. What makes this paper unique by today's standards is that they performed human trials. They collected serum from four patients with diagnosed Rasmussen's encephalitis and found antibodies for GluR3 in three out four patient samples. This led to the hypothesis that removing GluR3 antibodies might alleviate the epileptic symptoms. They performed plasma exchange (PEX) on a patient to remove GluR3 antibodies from the serum. Seizure frequency decreased by 80% and cognition, speech, and motor skills improved correlating with diminished GluR3 antibody titer. But with time, as the antibody titer increased, so did the seizure frequency and other phenotypes.

Sydenham's Chorea (SC)

SC is part of a group of disorders collectively known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). SC is characterized by rapid, jerky, irregular, and involuntary movements and was so named for the Greek word for dance. SC mostly affects children and young adolescents.

W. Ian Lipkin is known for his work in infectious diseases and their neurological impact. It was reported in an earlier paper that when mice were injected with streptococcal bacterial particles, they displayed a variety of motor and neuropsychiatric symptoms including chorea and tics. The more recent paper from the same lab showed that passive transfer of IgG antibodies directed against streptococcus M protein was necessary and sufficient to produce PANDAS symptoms in naïve mice (Yaddanapudi et al., 2010). When they used the anti-streptococcus M IgG to probe brain sections, the hippocampus and the periventricular regions bound that antibody the strongest. The target antigen in the brain for this antibody has yet to be determined, but it seems likely that this antibody is a product of molecular mimicry that triggered the autoimmune response.

Parkinson's Disease (PD)

PD is caused by the loss of dopaminergic neurons in the substantia nigra that results in symptoms such as tremor, bradykinesia, and loss of posture and balance. One of the hallmarks of PD is the accumulation of aggregated forms of α -synuclein.

David Standaert specializes in movement disorders, especially PD. The paper from his lab showed that α -synuclein induced neuroinflammation and

neurodegeneration caused MHCII expression by microglia that resulted in subsequent activation and presentation of α -synuclein antigen to T cells, cytokine release, and dopaminergic neuron degeneration (Harms et al., 2013). The MHCII-KO mice were protected against the microglia activation and loss of dopaminergic neurons. A recent paper demonstrated that microglia released exosomes containing α -synuclein was fully capable of producing protein aggregation in recipient neurons (Guo et al., 2020). This new report implicated microglia in actively “spreading” α -synuclein protein aggregations via exosomes. A thorough review on the role of the immune system in PD by Schonhoff and colleagues is a useful resource for instructors (Schonhoff et al., 2020).

Alzheimer’s Disease (AD)

AD is a progressive disease characterized by dementia that affects memory, thinking, and behavior. There are two main hypotheses on the cause of AD: amyloid and tau. Amyloid hypothesis postulates that amyloid beta ($A\beta$) is the primary influence driving AD pathogenesis and that neurofibrillary tangles (tau) are secondary. Tau hypothesis postulates that tau hyperphosphorylation and subsequent formation of neurofibrillary tangles are the primary drivers of AD.

The paper from Jochen Herms’ lab showed, using two-photon *in vivo* images, microglia migrating and accumulating around a neuron over the course of several days before the neuron disappearing in AD mice (Fuhrmann et al., 2010). In the CX₃CR1-KO mice, neuronal loss was completely rescued. CX₃CR1 is a chemokine receptor expressed in microglia that binds to CX₃CL1 that is expressed in neurons and presumably acts as a cell adhesion or chemoattraction molecule. These results are consistent with the observation that neurons cultured in $A\beta$ without microglia do not degenerate and only do so if microglia are present (Giulian et al., 1996). A review paper by Bartels and colleagues explores the current understanding of the role of microglia in PD and AD (Bartels et al., 2020).

Module 6: Stress and the Immune System

By the time we reached this module towards the end of the semester, students were experiencing the stresses of final exams. We explored the various effects of stress from the cellular level to behavior.

Effects of Stress at the Cellular Level

Stress activates the HPA axis and results in the release of glucocorticoids. Acute stress can be beneficial, such as gluconeogenesis in the liver, but also can suppress inflammation mediated by the immune system. Chronic stress and long-term suppression of the immune system has detrimental consequences.

The paper from Christopher Norbury’s lab demonstrated that glucocorticoids impair the ability of dendritic cells (DCs) to cross-present antigens on MHC I to activate cytotoxic or killer T cells (Hunzeker et al., 2011). The activated cytotoxic T cells kill cells presenting the same antigen on MHC I that are infected with an intracellular pathogen like viruses. Therefore, if DCs cannot activate cytotoxic T cells, virally infected cells will continue producing viral particles. This

perhaps is one of the reasons why students get the flu when they return home from school, because with the removal of stress, the immune system is finally relieved of suppression. For instructors who want information on the effect of stress on the immune system, a chapter written by Seiler and colleagues will be helpful (Seiler et al., 2020).

Effects of Stress on Neurogenesis

Chronic stress and dysregulation of glucocorticoids is associated with depression and impaired cognition. Neurons in the hippocampus express high levels of receptors for stress hormones, and glucocorticoids have been shown to inhibit adult neurogenesis (Mirescu and Gould, 2006). The hippocampus sends negative feedback to the HPA axis to dampen glucocorticoid release.

Heather Cameron is known for elucidating the effect of stress on neurogenesis. Cameron and colleagues demonstrated that adult neurogenesis is required for normal endocrine (HPA axis inhibition) and behavioral response to stress (Snyder et al., 2011). Mice lacking neurogenesis showed higher levels of glucocorticoids in response to stress and increased anxiety and depression-like behaviors. This suggests that adult neurogenesis in the hippocampus buffers stress by keeping glucocorticoid levels from getting too high and returning it quicker to baseline after stress. Exercise has been shown to promote adult neurogenesis in the hippocampus, and one of the benefits of exercise maybe the increased ability to buffer stress (Cooper et al., 2018). This paper elicited stimulating discussions about exercising especially during high-stress periods of life, such as finals week. A review paper provides an overview on the effect of stress of neurons (Cameron and Schoenfeld, 2018).

DISCUSSION

This paper provides resources to instructors with background in neuroscience to teach a semester-long neuroimmunology course to undergraduate students. The modular design of this course allows for individual modules or papers to be deployed into preexisting neuroscience or even immunology courses. If an immunologist is available in the department or a program, an alternative method of deploying this course is to team teach thereby reducing the necessity for the neuroscience instructor to learn and teach immunology. Alternatively, an immunology course can be added as a prerequisite. The neuroimmunology course as described in this paper reduced the necessary immunology background to three weeks of lecture within the course (as opposed to a prerequisite immunology course) with the goal to minimize the number of prerequisite courses and make it accessible to more students.

The ideal number of students for this type of course is between 20 and 30. As designed, the students present a primary literature paper twice during the semester, once as a group and another individually. If class size is small, the instructor can increase the presentation number to three, but going higher may put too much burden on the students. The presenters were asked to keep the target length of the presentations to 30 minutes and leave 20 minutes for discussions (see syllabus in Appendix 2). As designed, all students were expected to contribute to the discussion. If

the class size is large, it might pose a logistical challenge to get all the students to say something in the time allotted for the class. For large classes, removing this expectation might be desirable.

The use of primary papers as an alternative to textbooks provided the development of essential critical thinking and analysis skills that are highly ranked core competencies by life science faculty (Cash et al., 1994; Kerchner et al., 2012). Embedded in this course was development of oral and written communication skills, as described in the student learning outcomes. Writing a literature review is a daunting task for anyone, let alone for undergraduate students. But because the students were developing the skills to read, analyze, dissect, and synthesize information from primary papers, they were able to apply those competencies to writing a literature review.

This course was designed with specific student learning outcomes (SLOs): 1) learn the fundamentals of how the immune system works, 2) understand the bidirectional crosstalk between the immune and the nervous systems, through critically reading, analyzing, and evaluating primary literature, and 3) develop oral presentation skills to peers and written communication techniques of a scientific body of work to both scientific and non-scientific audiences. SLO 1 was assessed using a quiz at the end of the module. Both the concept map (Figure 1) and the quiz (Appendix 3) give the depth and breadth of immunology concepts students were able to master in three weeks. The mean grade for the quiz was 89 ± 22 percent (Table 1). Even though some students struggled in the quiz, as shown by the large standard deviation of the mean, it was impressive how quickly students were able to grasp the key immunology concepts (Figure 1). SLO 2 was assessed using the student writings of the *New York Times*-style article and the literature review. Both writing samples required students to read, analyze, and evaluate primary literature papers. The mean grade for the article was 93 ± 6 percent, while the mean grade for the literature review paper was 87 ± 21 percent (Table 1). The large standard deviation is mainly due to one student failing to turn in the final draft, thus receiving a zero for the literature review assignment. The prospect of writing a literature review paper for an undergraduate student can be a daunting task, so the assignment was sufficiently scaffolded throughout the semester to help approach it in small discrete segments (syllabus in Appendix 2). As the grades show, students did exceptionally well critically reading, analyzing, and evaluating primary literature papers, where some of the writing quality rivaled any literature review written by postdoctoral fellows. The *New York Times*-style articles and the literature reviews were also used to assess SLO 3 along with journal club presentations. The group and individual journal club presentation assessment resulted in mean grades of 94 ± 6 and 96 ± 6 percent, respectively. Grading rubrics for the artifacts as well as the quiz is included in the Appendices. Overall, these assessment scores suggest that students met and, in some cases, exceeded the expectations as outlined in SLOs for this course.

One potential limitation of this course is that students need to take an introductory cellular/molecular neuroscience

SLO	Assessed Artifact	Mean Grade (%)
SLO 1	Immunology Quiz	89 ± 22
SLO 2 & 3	<i>New York Times</i> -Style Article	93 ± 6
SLO 2 & 3	Literature Review	87 ± 21
SLO 3	Journal Club Presentation (Group)	94 ± 6
SLO 3	Journal Club Presentation (Individual)	96 ± 6

Table 1. Assessment of student learning outcomes (SLOs). SLO 1 - learn the fundamentals of how the immune system works. SLO 2 - understand the bidirectional crosstalk between the immune and the nervous systems, through critically reading, analyzing, and evaluating primary literature. SLO 3 - develop oral presentation skills to peers and written communication techniques of a scientific body of work to both science and non-science audience. The data shows mean \pm 1 standard deviation of assignment grades in percent ($n=26$). See Appendices for rubrics and sample quiz.

course as a prerequisite. For institutions that have a neuroscience program or department, this is not an issue, but for places that do not, the instructor will have to adapt this course. One way to adapt this course for biology students without a prerequisite neuroscience class is to provide relevant neuroscience background before each module. That would mean, however, reducing the number of papers and/or topics to be covered in a module. The other potential drawback or barrier to teaching the entire neuroimmunology course, is that the instructor would need to learn some immunology. As I mentioned the textbook used in Module 1 is an appropriate starting place to teach oneself immunology. For a more comprehensive textbook, *The Immune System* by Peter Parham is recommended (Parham, 2014). Although this paper describes the design and implementation of a semester-long neuroimmunology course, one does not need to implement this course in its entirety. The modular design of this course allows for an instructor to adopt a module or a single paper into their preexisting neuroscience course. By providing background and supplemental information on each paper, syllabus, quiz, and grading rubrics for oral and written assignments, it is my goal to have as many undergraduate neuroscience students get exposed to the field of neuroimmunology. Finally, this class can be adapted for the remote or virtual classroom. All of the lectures and written assignments can easily be transformed to an online format, but I think the challenge lies in the journal club presentations, especially the discussions, though that is not to say it cannot be done. One potential challenge that cannot be ignored is the digital divide which might pose an issue for some students in both preparing for (e.g., accessing online journals) and presenting journal club presentations.

REFERENCES

- American Association for the Advancement of Science (2011) Vision and change in undergraduate biology education: a call to action. Washington, DC.
- Abrahamyan S et al. (2020) Complete Epstein-Barr virus

- seropositivity in a large cohort of patients with early multiple sclerosis. *J Neurol Neurosurg Psychiatry* 91(7):681-686.
- Adelson JD, Barreto GE, Xu L, Kim T, Brott BK, Ouyang YB, Naserke T, Djuricic M, Xiong X, Shatz CJ, Giffard RG (2012) Neuroprotection from stroke in the absence of MHC1 or PirB. *Neuron* 73(6):1100-1107.
- Alam S, Laughton DL, Walding A, Wolstenholme AJ (2006) Human peripheral blood mononuclear cells express GABAA receptor subunits. *Mol Immunol* 43(9):1432-1442.
- Bartels T, De Schepper S, Hong S (2020) Microglia modulate neurodegeneration in Alzheimer's and Parkinson's diseases. *Science* 370(6512):66-69.
- Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, Von Zastrow M, Beattie MS, Malenka RC (2002) Control of synaptic strength by glial TNF α . *Science* 295(5563):2282-2285.
- Beattie MS, Ferguson AR, Bresnahan JC (2010) AMPA-receptor trafficking and injury-induced cell death. *Eur J Neurosci* 32(2):290-297.
- Bhat R, Axtell R, Mitra A, Miranda M, Lock C, Tsien RW, Steinman L (2010) Inhibitory role for GABA in autoimmune inflammation. *Proc Natl Acad Sci U S A* 107(6):2580-2585.
- Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405(6785):458-462.
- Brennan FH, Popovich PG (2018) Emerging targets for reprogramming the immune response to promote repair and recovery of function after spinal cord injury. *Curr Opin Neurol* 31(3):334-344.
- Brown AS (2011) The environment and susceptibility to schizophrenia. *Progress in Neurobiology* 93(1):23-58.
- Cameron HA, Schoenfeld TJ (2018) Behavioral and structural adaptations to stress. *Front Neuroendocrinol* 49:106-113.
- Cardno AG, Gottesman, II (2000) Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am J Med Genet* 97(1):12-17.
- Cash E, Minty A, Ferrara P, Caput D, Fradelizi D, Rott O (1994) Macrophage-inactivating IL-13 suppresses experimental autoimmune encephalomyelitis in rats. *J Immunol* 153(9):4258-4267.
- Cepok S, Zhou D, Srivastava R, Nessler S, Stei S, Büssov K, Sommer N, Hemmer B (2005) Identification of Epstein-Barr virus proteins as putative targets of the immune response in multiple sclerosis. *J Clin Invest* 115(5):1352-1360.
- Chaudhry V, Glass JD, Griffin JW (1992) Wallerian degeneration in peripheral nerve disease. *Neurol Clin* 10(3):613-627.
- Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M (1999) Narcolepsy in orexin knockout mice. *Cell* 98(4):437-451.
- Chen BE, Kondo M, Garnier A, Watson FL, Püettmann-Holgado R, Lamar DR, Schmucker D (2006) The molecular diversity of Dscam is functionally required for neuronal wiring specificity in *Drosophila*. *Cell* 125(3):607-620.
- Coil D, Wenderoth MP, Cunningham M, Dirks C (2010) Teaching the process of science: faculty perceptions and an effective methodology. *CBE Life Sci Educ* 9(4):524-535.
- Cooper CI, Moon HY, Van Praag H (2018) On the Run for Hippocampal Plasticity. *Cold Spring Harb Perspect Med* 8(4):a029736.
- Cordeiro CN, Tsimis M, Burd I (2015) Infections and Brain Development. *Obstetrical & Gynecological Survey* 70(10):644-655.
- Datwani A, McConnell MJ, Kanold PO, Micheva KD, Busse B, Shamloo M, Smith SJ, Shatz CJ (2009) Classical MHC1 molecules regulate retinogeniculate refinement and limit ocular dominance plasticity. *Neuron* 64(4):463-470.
- Dauvilliers Y, Montplaisir J, Cochen V, Desautels A, Einen M, Lin L, Kawashima M, Bayard S, Monaca C, Tiberge M, Filipini D, Tripathy A, Nguyen BH, Kotagal S, Mignot E (2010) Post-H1N1 narcolepsy-cataplexy. *Sleep* 33(11):1428-1430.
- David S, Aguayo AJ (1981) Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. *Science* 214(4523):931-933.
- Ekdahl CT, Claassen JH, Bonde S, Kokaia Z, Lindvall O (2003) Inflammation is detrimental for neurogenesis in adult brain. *Proceedings of the National Academy of Sciences* 100(23):13632-13637.
- Fuhrmann M, Bittner T, Jung CKE, Burgold S, Page RM, Mitteregger G, Haass C, Laferla FM, Kretschmar H, Herms J (2010) Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. *Nat Neurosci* 13(4):411-413.
- Gelbard HA, Dzenko KA, DiLoreto D, del Cerro C, del Cerro M, Epstein LG (1993) Neurotoxic Effects of Tumor Necrosis Factor Alpha in Primary Human Neuronal Cultures are Mediated by Activation of the Glutamate AMPA Receptor Subtype: Implications for AIDS Neuropathogenesis. *Dev Neurosci* 15(6):417-422.
- Gilliatt RW, Hjorth RJ (1972) Nerve conduction during Wallerian degeneration in the baboon. *J Neurol Neurosurg Psychiatry* 35(3):335-341.
- Giulian D, Haverkamp LJ, Yu JH, Karshin W, Tom D, Li J, Kirkpatrick J, Kuo YM, Roher AE (1996) Specific domains of β -amyloid from Alzheimer plaque elicit neuron killing in human microglia. *J Neurosci* 16(19):6021-6037.
- Gkogkas CG, Khoutorsky A, Ran I, Rampakakis E, Nevarko T, Weatherill DB, Vasuta C, Yee S, Truitt M, Dallaire P, Major F, Lasko P, Ruggero D, Nader K, Lacaille J-C, Sonenberg N (2013) Autism-related deficits via dysregulated eIF4E-dependent translational control. *Nature* 493(7432):371-377.
- Guo M, Wang J, Zhao Y, Feng Y, Han S, Dong Q, Cui M, Tieu K (2020) Microglial exosomes facilitate α -synuclein transmission in Parkinson's disease. *Brain* 143(5):1476-1497.
- Harms AS, Cao S, Rowse AL, Thome AD, Li X, Mangieri LR, Cron RQ, Shacka JJ, Raman C, Standaert DG (2013) MHCII is required for alpha-synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. *J Neurosci* 33(23):9592-9600.
- Hartman AK, Borchardt JN, Harris Bozer AL (2017) Making Primary Literature Come Alive in the Classroom. *J Undergrad Neurosci Educ* 15(2):R24-R28.
- Holloway T, Moreno JL, Umali A, Rayannavar V, Hodes GE, Russo SJ, Gonzalez-Maeso J (2013) Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: role of maternal immune system. *J Neurosci* 33(3):1088-1098.
- Hoskins SG (2008) Using a Paradigm Shift to Teach Neurobiology and the Nature of Science—a C.R.E.A.T.E.-based Approach. *J Undergrad Neurosci Educ* 6(2):A40-A52.
- Hoskins SG, Stevens LM, Nehm RH (2007) Selective use of the primary literature transforms the classroom into a virtual laboratory. *Genetics* 176(3):1381-1389.
- Huh GS, Boulanger LM, Du H, Riquelme PA, Brotz TM, Shatz CJ (2000) Functional Requirement for Class I MHC in CNS Development and Plasticity. *Science* 290(5499):2155-2159.
- Hunzeker JT, Eftman MD, Mellinger JC, Princiotta MF, Bonneau RH, Truckenmiller ME, Norbury CC (2011) A marked reduction in priming of cytotoxic CD8+ T cells mediated by stress-induced glucocorticoids involves multiple deficiencies in cross-presentation by dendritic cells. *J Immunol* 186(1):183-194.
- Hütter G, Nowak D, Mossner M, Ganepola S, Müßig A, Allers K, Schneider T, Hofmann J, Kücherer C, Blau O, Blau IW, Hofmann WK, Thiel E (2009) Long-term control of HIV by

- CCR5delta32/delta32 stem-cell transplantation. *N Engl J Med* 360(7):692-698.
- Kerchner M, Hardwick JC, Thornton JE (2012) Identifying and using 'core competencies' to help design and assess undergraduate neuroscience curricula. *J Undergrad Neurosci Educ* 11(1):A27-A37.
- Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG (2009) Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J Neurosci* 29(43):13435-13444.
- Labbe K, Miu J, Yeretssian G, Serghides L, Tam M, Finney CA, Erdman LK, Goulet ML, Kain KC, Stevenson MM, Saleh M (2010) Caspase-12 dampens the immune response to malaria independently of the inflammasome by targeting NF-kappaB signaling. *J Immunol* 185(9):5495-5502.
- Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, De Jong PJ, Nishino S, Mignot E (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 98(3):365-376.
- Loewi O (1924) Über humorale Übertragbarkeit der Herznervenwirkung. *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere* 204(1):629-640.
- Lu T-S, Avraham HK, Seng S, Tachado SD, Koziel H, Makriyannis A, Avraham S (2008) Cannabinoids inhibit HIV-1 gp120-mediated insults in brain microvascular endothelial cells. *J Immunol* 181(9):6406-6416.
- Medawar PB (1948) Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. *Br J Exp Pathol* 29(1):58-69.
- Mirescu C, Gould E (2006) Stress and adult neurogenesis. *Hippocampus* 16(3):233-238.
- Monje ML, Palmer T (2003) Radiation injury and neurogenesis. *Curr Opin Neurol* 16(2).
- Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302(5651):1760-1765.
- Moreno JL, Kurita M, Holloway T, Lopez J, Cadagan R, Martinez-Sobrido L, Garcia-Sastre A, Gonzalez-Maeso J (2011) Maternal influenza viral infection causes schizophrenia-like alterations of 5-HT2A and mGlu2 receptors in the adult offspring. *J Neurosci* 31(5):1863-1872.
- Novak JD, Musonda D (1991) A Twelve-Year Longitudinal Study of Science Concept Learning. *Am Educ Res J* 28(1):117-153.
- Ogle DM (1986) K-W-L: A Teaching Model That Develops Active Reading of Expository Text. *The Reading Teacher* 39(6):564-570.
- Parham P (2014) *The Immune System*. 4th Edition. New York, NY: W. W. Norton & Company.
- Pazzaglia S, Briganti G, Mancuso M, Saran A (2020) Neurocognitive Decline Following Radiotherapy: Mechanisms and Therapeutic Implications. *Cancers* 12(1):146.
- Reardon C, Murray K, Lomax AE (2018) Neuroimmune Communication in Health and Disease. *Physiol Rev* 98(4):2287-2316.
- Rénia L, Howland SW, Claser C, Gruner AC, Suwanarusk R, Teo T-H, Russell B, Ng LFP (2012) Cerebral malaria. *Virulence* 3(2):193-201.
- Reyneveld GI, Savelkoul HFJ, Parmentier HK (2020) Current Understanding of Natural Antibodies and Exploring the Possibilities of Modulation Using Veterinary Models. A Review. *Front Immunol* 11.
- Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, Hughes TE, Heinemann SF, McNamara JO (1994) Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. *Science* 265(5172):648-651.
- Sakurai T et al. (1998) Orexins and Orexin Receptors: A Family of Hypothalamic Neuropeptides and G Protein-Coupled Receptors that Regulate Feeding Behavior. *Cell* 92(4):573-585.
- Saleh M, Mathison JC, Wolinski MK, Bensinger SJ, Fitzgerald P, Droin N, Ulevitch RJ, Green DR, Nicholson DW (2006) Enhanced bacterial clearance and sepsis resistance in caspase-12-deficient mice. *Nature* 440(7087):1064-1068.
- Santini E, Huynh TN, Macaskill AF, Carter AG, Pierre P, Ruggero D, Kaphzan H, Klann E (2013) Exaggerated translation causes synaptic and behavioural aberrations associated with autism. *Nature* 493(7432):411-415.
- Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA, Stevens B (2012) Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 74(4):691-705.
- Schmucker D, Chen B (2009) Dscam and DSCAM: complex genes in simple animals, complex animals yet simple genes. *Genes Dev* 23(2):147-156.
- Schmucker D, Clemens JC, Shu H, Worby CA, Xiao J, Muda M, Dixon JE, Zipursky SL (2000) Drosophila Dscam is an axon guidance receptor exhibiting extraordinary molecular diversity. *Cell* 101(6):671-684.
- Schonhoff AM, Williams GP, Wallen ZD, Standaert DG, Harms AS (2020) Innate and adaptive immune responses in Parkinson's disease. *Prog Brain Res* 252:169-216.
- Scott AM, Saleh M (2007) The inflammatory caspases: guardians against infections and sepsis. *Cell Death Differ* 14(1):23-31.
- Seiler A, Fagundes CP, Christian LM (2020) The Impact of Everyday Stressors on the Immune System and Health. In: *Stress Challenges and Immunity in Space: From Mechanisms to Monitoring and Preventive Strategies* (Choukèr A, ed), pp 71-92. Cham: Springer International Publishing.
- Shatz CJ (2009) MHC Class I: An Unexpected Role in Neuronal Plasticity. *Neuron* 64(1):40-45.
- Shigemoto-Mogami Y, Hoshikawa K, Goldman JE, Sekino Y, Sato K (2014) Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. *J Neurosci* 34(6):2231-2243.
- Shirai Y (1921) On the transplantation of the rat sarcoma in adult heterogeneous animals. *Japan Med World* 114-15.
- Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA (2011) Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature* 476(7361):458-461.
- Sompayrac LM (2019) *How the Immune System Works*. 6th Edition. Hoboken, NJ: Wiley-Blackwell.
- Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, Micheva KD, Mehalow AK, Huberman AD, Stafford B, Sher A, Litke AM, Lambris JD, Smith SJ, John SW, Barres BA (2007) The classical complement cascade mediates CNS synapse elimination. *Cell* 131(6):1164-1178.
- Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol* 14(3):133-150.
- Tenner AJ, Stevens B, Woodruff TM (2018) New tricks for an ancient system: Physiological and pathological roles of complement in the CNS. *Mol Immunol* 1023-13.
- Tian J, Lu Y, Zhang H, Chau CH, Dang HN, Kaufman DL (2004) γ -aminobutyric acid inhibits T cell autoimmunity and the development of inflammatory responses in a mouse type 1 diabetes model. *J Immunol* 173(8):5298-5304.
- Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol* 57(1):67-81.
- Vargas ME, Watanabe J, Singh SJ, Robinson WH, Barres BA (2010) Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. *Proc Natl Acad Sci U S A* 107(26):11993-11998.

- Vidal-Sanz M, Bray GM, Villegas-Pérez MP, Thanos S, Aguayo AJ (1987) Axonal regeneration and synapse formation in the superior colliculus by retinal ganglion cells in the adult rat. *J Neurosci* 7(9):2894-2909.
- Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474(7351):380-384.
- Wamsley B, Geschwind DH (2020) Functional genomics links genetic origins to pathophysiology in neurodegenerative and neuropsychiatric disease. *Curr Opin Genet Dev* 65:117-125.
- Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, Al-Abed Y, Czura CJ, Tracey KJ (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 421(6921):384-388.
- Watson CW-M, Paolillo EW, Morgan EE, Umlauf A, Sundermann EE, Ellis RJ, Letendre S, Marcotte TD, Heaton RK, Grant I (2020) Cannabis exposure is associated with a lower likelihood of neurocognitive impairment in people living with HIV. *J Acquir Immune Defic Syndr* 83(1):56-64.
- Xu Z-X, Kim GH, Tan J-W, Riso AE, Sun Y, Xu EY, Liao G-Y, Xu H, Lee S-H, Do N-Y, Lee CH, Clipperton-Allen AE, Kwon S, Page DT, Lee KJ, Xu B (2020) Elevated protein synthesis in microglia causes autism-like synaptic and behavioral aberrations. *Nature Communications* 11(1).
- Yaddanapudi K, Hornig M, Serge R, De Miranda J, Baghban A, Villar G, Lipkin WI (2010) Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Mol Psychiatry* 15(7):712-726.

Received August 17, 2020; January 4, 2021

Address correspondence to: Dr. Junryo Watanabe, Biology Department, SUNY Oneonta, 108 Ravine Pkwy., Oneonta, NY 13820. Email: junryo.watanabe@oneonta.edu

Copyright © 2021 Faculty for Undergraduate Neuroscience

www.funjournal.org

APPENDIX 1: ORAL PRESENTATION/JOURNAL CLUB GRADING RUBRIC

Your presentation is numerically rated on a scale of 1 to 10 or 1 to 5 for each of the categories below, and constructive comments are also provided.

Ratings: 10 (or 5) = excellent; little or no room for improvement
8 (or 4) = good; effective performance, but could be improved
6 (or 3) = adequate; minimally acceptable, but needs considerable improvement
4 (or 2) = poor; not effective
2 (or 1) = unacceptable; essentially a waste of everyone's time

INTRODUCTION/BACKGROUND:

Did the speaker present the background material in a clear, concise fashion? _____/10

Comments:

Did the speaker generate interest in the topic? _____/10

Comments:

Did the speaker explicitly state the important question(s) in this field, and the hypothesis that the author is addressing?

Comments:

_____/10

ANALYSIS OF EXPERIMENTS:

Was the speaker knowledgeable about the experimental approach and techniques used in the studies?

Comments:

_____/10

Was the presentation of data prefaced with a brief explanation of why the experiment was done?

Comments:

_____/10

Did the audience leave the talk with a good understanding of the experiments discussed?

Comments:

_____/10

APPROACH:

Did the speaker clearly explain the approach that was used to address the hypothesis? Was a rationale for the approach stated? Were predictions stated? Were statistics that were used to evaluate expected results appropriate?

Comments:

_____/10

SUMMARY AND CONCLUSIONS:

Was there a clear and succinct summary of points made earlier?

Did the speaker mention potential pitfalls and have ways to address them?

Do you have a sense of the relevance of this work?

Comments:

_____/5

DISCUSSION:

Did the speaker and/or topic bring about a stimulating discussion?

Comments:

_____/5

Did the speaker handle questions well?

Comments:

_____/5

GENERAL:

Organization and content

- talk consisted of a logical development of information
- appropriate length and depth of material
- appropriate choices of areas to cover

_____/5

Comments:

PREPARATION:

- knowledge of the material and preparation of seminar
- speaker conformed to the time allotted

_____/5

Comments:

VISUAL AIDS:

- organized
- legibility from the back of the room?

_____/5

Comments:

Total: _____/100

Two (or more) things that the speaker did well:

Two (or more) things that the speaker should improve, and suggestions on how to do so:

APPENDIX 2: SYLLABUS

Textbooks:

1. (Required) How the Immune System Works. L. Sompayrac. Blackwell Publishing. 4th Edition (2013)
2. (Optional) The Immune System. P. Parham. Garland Science. 3rd Edition (2009). May come in handy in Med School if that is your path. Chock full o' details should you want to delve deeper.

Additional Materials:

Selections from other texts, reviews, and primary literature will be provided. Background research materials for group and individual presentations, *NY Times*-Style Article, and Literature Review Paper will be selected by you. (see below for details)

Course Description:

The course explores the role of immune molecules in neural development, and the bi-directional mechanisms by which the brain and immune system communicate with each other in health and during injury or infection. Topics include: innate immunity in brain development, inflammation in neurodegenerative diseases, central nervous system infections, autoimmune diseases, and the immune system in psychiatric disorders. Emphasis will be placed on critically reading and evaluating primary literature, experimental design, and scientific writing.

Course Objectives:

1. Learn the fundamentals of how the immune system works.
2. Understand the bi-directional crosstalk between the immune and the nervous systems through critically reading, analyzing, and evaluating primary literature.
3. Develop oral presentation skills to peers and written communication techniques of a scientific body of work to both scientific and non-scientific audiences.

Expectations:

My expectations of you are that you come prepared by reading the required textbook and/or the primary literature before the class at which it will be discussed. You should be prepared to actively discuss experiments or specific figures even though you may not be the main presenter(s) of a particular paper/topic. Since discussions on primary literature are a main focus of the class, active participation in each class is **required** by each individual.

That said, I want this class to be a place where we explore the rapidly emerging field of neuroimmunology. I want you to be curious and explorative. If you find additional neuroimmunology topics that are of interest to you, please let me know and I'll try to incorporate them into the class as time allows. Please don't hesitate to ask questions or have discussions with me. I'm here to help you be as excited about neuroimmunology as I am.

Lectures and Quiz:

In order for all of us to have a meaningful discussion-based learning on neuroimmunology, we all must learn the fundamentals of immunology. The first three weeks of class are going to be lecture-based. In order for you to get the most out of these lectures, you need to read the relevant chapters in the textbook before class. Please also fill out the KWL form for each lecture. KWL (what I know, what I want to know, what I have learned) form will help you organize your thoughts as well as prepare questions to ask during lecture. Before lecture you will fill out the K and W portions of the form, and after lecture (5 minutes) you will have a chance to fill in the L portion, as well as new W that might have arisen. You will turn in this KWL by 10am the next day via Blackboard, and these will count towards the quiz grade. Each KWL form will be worth one (1) point of the Quiz, with KWL and Quiz totaling 50 points. There will be a quiz at the end of the three weeks to test your general knowledge on immunology.

Discussion Comments:

After the fundamentals of immunology lectures, the class will transition to journal club style discussion. For each of those classes and related to each primary literature article, you are required to write a Discussion Comment in order to best prepare to participate in discussions. You must upload them to Blackboard by 7pm the night before the class in which the paper will be discussed. If it is submitted after 7pm but before the start of class, you will receive half credit. No credit will be given for Discussion Comments submitted after the start of class. You do NOT have to submit one if you are presenting that day. In your Discussion Comment, please answer ONE of the four questions:

- Why was this paper selected for this journal? In other words, what made this paper special?
- What was the main hypothesis being tested in this paper?
- What were the major techniques used to test this hypothesis?
- Were they successful and did they use the appropriate techniques? Controls?

Please keep this brief... four sentences should be more than sufficient. Also in the Discussion Comment, please include a question that you have about this article. It could be about a technique used in the paper to the interpretation of the results. We will be reading and discussing 26 papers in class. That means you have to submit 24 Discussion Comments, because you will present 2 of those papers (1 as a group and 1 alone). I will present papers no one elects to present.

Presentations:

You will present a primary literature article twice during the semester: one article as a part of a group, and one article alone. Plan and practice each presentation, aiming for approximately 30 minutes to cover the paper and allowing about 20 minutes for discussion. Prepare thought-provoking questions to stimulate discussion. The papers have been selected by me, and they can be found in Blackboard.

You will present these articles in a “journal club” style. Journal clubs are a feature of nearly every graduate program in life science where a student or faculty member presents a journal article of interest. The presentation of scientific research is a highly structured endeavor with the following basic format:

- **Introduction:** What biological question is being addressed? What background information is absolutely necessary to understand this question? Is there a hypothesis, either explicitly stated or implicit? What were the major findings that were reported? (Note: for many types of talks, major findings would be reported later. The primary goal in presenting science is clarity, and it really helps to give away the “punch line” early!)
- **Experiments:** Be able to explain the experimental approach taken, and the advantages and limitations of such an approach. What was the question the authors were trying to answer? What types of data were collected, and what are their conclusions? “Walk” the audience through each experiment, methodically explaining and summarizing each experiment as you proceed through this section. (Note: the presentation and evaluation of the data are the most important components of a scientific presentation. Take the time to fully understand the data and to clearly present this section of the talk. You frequently will need to seek out additional sources to understand the techniques.)
- **Conclusions:** What were the authors’ conclusions? Are such conclusions valid? Are there other plausible explanations for the data? What would be the logical next-step experiments? How significant is this work in defining our view of the field? Are there opposing/conflicting ideas/data from others in the field? How do they or you as a presenter address/resolve this? Is there an alternate explanation or interpretation of the results? Are there weaknesses or pitfalls in the article? (Note: this is your chance to be both critical and creative. Have fun with it!)

The thought flow of the presentation should be “hourglass shaped.” You should start with broad ideas to help place this primary literature in context, focus down into the nitty-gritty details of the paper, and then end broadly by touching on issues such as future directions, contribution to the knowledge of the field, potential therapeutic applications, etc. It’s okay if you don’t understand a figure or a result... this is a discussion-based presentation and that is why we are doing this. You will be evaluated by me on your clarity, understanding, completeness, presentation style, and preparative work as well as your ability to lead and facilitate a discussion. Visual aids are very useful, and I highly recommend PowerPoint/Keynote-type presentations. Here are a few tips for PowerPoint/Keynote presentations:

- In these presentations, we want to focus on the science, not glitzy presentation. Using a white or blue background goes very far in achieving simplicity. Use black background when the slide only contains a photograph, especially a fluorescent micrograph.
- Minimize text! Most slides should just have a single figure or table (or sometimes just one panel of a multi-part figure). Don’t put the figure legend on the slide. Add your own labels if it’s not clear what’s what. Don’t crowd the figure and distract the audience from the data by listing conclusions on the data slide — use a separate slide for conclusions. Keep all-text slides to an absolute minimum! If you do use text — most likely for the background and conclusions — use short phrases with bullets, not whole sentences or paragraphs.
- Don’t use animations or effects unless they serve a purpose.

Resources for giving presentations:

- Pechenik, J. 2001. “Preparing oral presentations.” Ch. 13 in *A Short Guide to Writing About Biology*, 5th ed., Addison-Wesley-Longman, New York.
- “Gratuitous advice on giving a talk” – tips for an effective PowerPoint presentation. www.swarthmore.edu/NatSci/cpurin1/powerpointadvice.htm

In week 3, you will choose a presentation partner as well as an article to present as a group and another to present by yourself. We will choose papers in the style of “fantasy draft.” You will draw a number out of a hat to determine the “draft” order. The first one up will choose their paper/topic of choice to present. You can choose whichever paper/topic you want, as long as it is still available. Depending on the total number of students in the class, anywhere between the first 8 or 10 papers/topics will be reserved for group presentations. The later papers/topics will be for individual presentations.

Please note that papers/topics are date specific. Please check your calendars for potential “killer weeks.” Also, I highly recommend that you read the abstracts of all papers before “draft day” so that you get an idea which papers/topics you really want to present and have ranked preferences of the paper/topic/days you like to present.

NY Times-Style Article:

The ability to effectively communicate to laypeople is a skill that all scientists (or aspiring scientists) should have. In order to gain experience doing this, you will write a *New York Times*-Style Science Article about any topic (pre-approved by me) in neuroimmunology. The topic can be the same as your group/individual presentation. Please turn in your list of two topic choices by the end of week 3. You will focus on one primary paper on that topic and write a summary directed to a lay audience incorporating other background and general ideas on the topic. Here are some *NY Times* science articles that you may use as a guide to the style and content:

- “Baboon study shows benefits for nice guys, who finish 2nd” by James Gorman
(<https://www.nytimes.com/2011/07/15/science/15baboon.html>)
- “Cancer’s secrets come into sharper focus” by George Johnson
(<https://www.nytimes.com/2011/08/16/health/16cancer.html>)

Maximum length of this Article is 1500 words. Please turn in your first draft by the end of week 5. The first draft will be peer reviewed by two other students in the class. That means you will peer review two other classmates’ Articles. Please turn in your edits/comments of your peers’ articles by the end of week 7. You will then ask two people (one who has taken Introductory Biology but not in Introductory Neuroscience, and one who hasn’t taken any Biology classes) to evaluate your updated Article. These people can be roommates, climbing buddies, family members, high school friends, or even people you meet in a coffee shop. The criteria are that you have them read the Article without any guidance and then ask them to explain to you what the main points were. You will be asked to write a maximum 300-word summary for each interaction that you had with a layperson, citing how much of the science was understood and what was changed in the Article as a result of the interaction. Please turn in the layperson interaction summary by the end of week 9. The final version of the *NY Times*-Style Article is due by the end of week 10.

Literature Review Paper:

You will select a specialized area of neuroimmunology on which you will write a maximum 5000-word review article. The topic can be the same as your group/individual Presentation and/or your *NY Times*-Style Article. You will turn in a topic by week 8. You will then turn in a reference list and an outline of your topic by week 10. This reference list should include at a minimum of six (6) articles (at least four (4) primary articles and two (2) review articles) but can include as many as 12 articles total. I highly recommend using reference software (e.g., RefWorks or EndNote). The first draft is due on week 12. The first draft will be peer reviewed by one (1) other student in the class. Again, that means you will peer review one (1) other classmate’s Review Paper. The peer reviews are due at the end of week 13. The final version of the Literature Review Paper will be due week 16. You are encouraged to look at example reviews in journals such as *Journal of Neuroscience*, *Neuron*, *Nature Neuroscience*, *Nature Immunology*, *Nature Medicine*, *Current Opinions in Neurology*, *Current Opinions in Neurobiology*, *Trends in Neuroscience*, *Journal of Immunology*, *Cell*, and many more.

***Any instance of academic dishonesty/plagiarism will result in zero points for the assignment and will be reported to the Dean of Students. ***

Peer Review Expectations:

When peer reviewing your fellow classmate’s writing (*NY Times*-Style Article or Literature Review Paper), here are some points to address:

- Grammar and punctuation – here you are being a copy editor.
- Style – does this writing follow the style of *NY Times* science article or a review article? (Different styles for different assignment)
- Story telling – is it easy to read? Does the story follow a logical thought process, or does it feel disorganized or jumping from point to point?
- Ideas – are the ideas presented clear and compelling? Did they choose the correct articles to site?
- Grading rubric – I will provide you with a grading rubric, for both the *NY Times*-Style Article and the Literature Review Paper, which will provide a useful framework for which to review your peers’ work.

All written assignments should be submitted to Blackboard by the specific due date.

Due Dates:	Assignments
Week 3	Presentation articles/dates selected <i>NY Times</i> Article topics submitted
Week 5	<i>NY Times</i> Article 1 st draft due
Week 7	<i>NY Times</i> Article peer review due
Week 8	Literature Review Paper topics submitted
Week 9	<i>NY Times</i> Article layperson interaction write-up due
Week 10	<i>NY Times</i> Article final version due

Week 10	Literature Review Paper outline and reference list due
Week 12	Literature Review Paper 1 st draft due
Week 13	Literature Review Paper peer review due
Week 16	Literature Review Paper final version due

Point Distributions:

Grades in this course are divided between your performance in class and on written work. Late written assignments will lose 10% per day late (including weekends). In addition, for each day a topic submission is late one point will be deducted. Missed presentations will ONLY be excused if you have a doctor's note or a family emergency. Under these excused circumstances, the missed presentation will not count either for or against your final grade. For group presentations, you are expected to share the work evenly. There are severe penalties for not doing so, and I ask you to let me know (confidentially of course) if your group is not dividing work evenly.

IN CLASS:	Points:
Class Participation	100
Presentation (group)	150
Presentation (individual)	150
Quiz/KWLs	50
WRITTEN:	Points:
Discussion Comments	50
<i>NY Times</i> Article Peer Review	50
<i>NY Times</i> Article Layperson Write-up	50
<i>NY Times</i> Article	150
Literature Review Peer Review	50
Literature Review	200
GRAND TOTAL	1000

Grades:

Your final grade in this course will be determined based on the number of points you get on the above assessments. If you earn the number of points below you will earn the grade below.

920-1000 = A	750-790 = C+
890-920 = A-	720-750 = C
860-890 = B+	690-720 = C-
820-860 = B	600-690 = D
790-820 = B-	Below 600 = F

APPENDIX 3: IMMUNOLOGY QUIZ

(10 points) Explain how the MHC I and MHC II antigen loading pathways are different. How do these differences account for the types of pathogens presented by MHC I vs. MHC II?

(11 points) Explain the concept of “enough, but not too much” TCR signaling as it relates to the two main phases of T cells development (positive and negative selection) in the thymus. Why are these selection processes important?

(11 points) Autoantibodies are characteristic of autoimmune diseases, such as systemic lupus erythematosus (SLE), type I diabetes, Graves’ disease, and many others. Describe three ways in which the immune system actively guards against the development of autoreactive B cells.

(11 points) Opsonization of pathogens by C3 (complement component 3) aids in the endocytosis by macrophages and dendritic cells. There are people who have deletions in the C3 genes such that there are no detectable levels of C3 in their blood. Would you expect these people to have a normal adaptive immune response? Why or why not?

(Extra credit: 3 points) You have a patient with autoimmune hemolytic anemia in which antibodies are produced against red blood cells. This disease is caused by autoreactive B cells that have undergone clonal expansion and have a single unique antigen specificity. You devise a treatment using monoclonal antibodies that would attack only a patient’s abnormal B cells. This monoclonal antibody recognizes immunoglobulin on the abnormal B cell that is specific for this patient. What would be the downside of using this therapy for a large number of patients? What are the benefits and disadvantages if the monoclonal antibodies attacked all the patient’s B cells, instead of just the abnormal autoimmune B cells?

**APPENDIX 4:
NEW YORK TIMES-STYLE ARTICLE GRADING RUBRIC**

(40 points) Introduction/Background

Did the article present the background material clearly and concisely?

Did the article generate interest and excitement in the topic and/or the paper being presented?

Did the article explicitly state how this paper is relevant to important question(s) in this field? In other words, did the article present how or why this paper is advancing the respective field?

Did the article state the hypothesis that the author of the paper is addressing?

(40 points) Analysis and Explanation of Experiments

Did the article explain, in lay terms, the experimental approach and/or techniques used in the study?

Was the rationale behind the key experiments and results stated clearly?

Did the article present the right amount of details of study? (i.e., not so much detail that it reads like a review)

(40 points) Summary and Conclusions

Was there a clear and succinct summary of the major findings of the study?

Did you get a sense of the relevance of this work?

Did you get a sense of the importance of this work?

Did you get a sense of why you should care about this work?

(30 points) Style

Did the article flow well? Was the "story" told well?

Was the quality of the writing (e.g., grammar, spelling, punctuation) strong?

Was there enough

Peer Review Instructions:

Please keep the above questions in mind while reviewing the draft article. This is the rubric I will be using to grade the final product. With that in mind evaluate how successfully the article addresses these specific questions. Throughout the article, make comments, suggestions, and edits to help strengthen the article.

APPENDIX 5: LITERATURE REVIEW GRADING RUBRIC

(30 points) Section: Introduction

Does the introduction clearly describe a problem in the literature?

Is there enough scientific background information provided for the reader to understand the general importance and significance of the work?

Does it include a statement of the main topic of the review?

Are limitations given about what the review will cover?

(70 points) Section: Body

Are trends and themes in the literature mentioned?

Does the author have a clear opinion about the literature?

Is their position defended well with specific examples from the literature?

Does the author address the continuity between previous and present research?

Are problems, controversies, gaps in the literature presented and explained in detail? Are they presented at the appropriate points?

Does the author address the strengths and weaknesses of the papers that they cover in the review? In detail? With specific examples?

Are there suggestions for improvement? Are the suggestions detailed?

Are details from the articles incorporated in a manner that effectively provides support/context for the author's point of view?

Is this section clearly and logically organized?

(30 points) Section: Conclusion

Does the author build a strong case for future studies? Do they state their approach?

Does the author have a hypothesis statement on what the next step in the research will be?

(40 points) General Writing Considerations

Is the paper carefully edited and proofread?

Are sentences clear?

Do paragraphs have topic sentences?

Are paragraphs unified, coherent and developed?

Are explanations or descriptions concise, avoiding redundancy and wordiness?

Are there transitions between sections?

Does the writing flow, in general? (i.e., are points or arguments developed logically?)

Are references cited throughout the paper? Is there a reference section at the end?

Were they appropriate to the points/arguments being made? Are they in an appropriate format?

(30 points) Quality

Sophistication

Originality of interpretation

Effort put into the project