

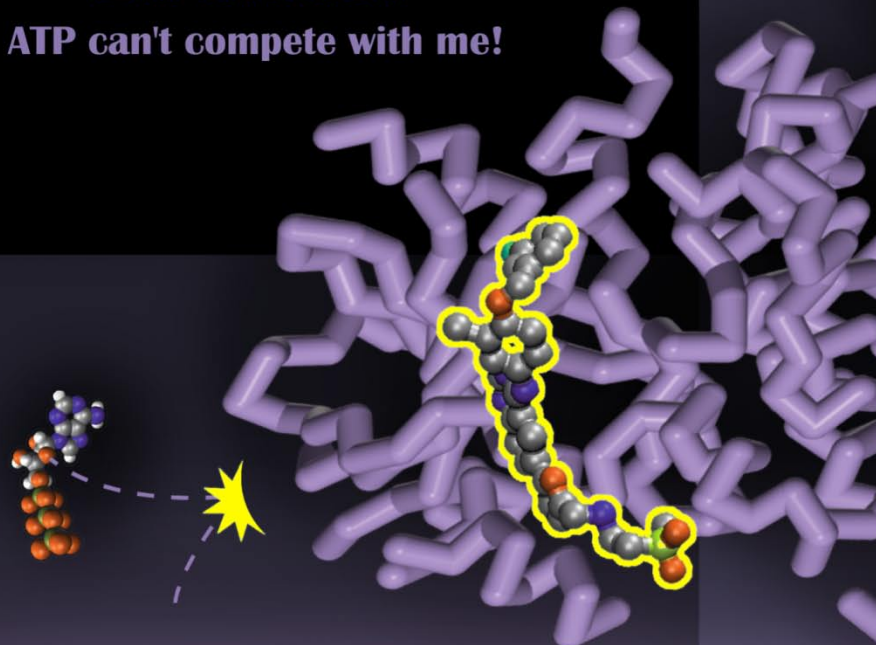


The Center for BioMolecular Modeling would like to acknowledge and thank the Science Education Partnership Award (SEPA; Grant #R25RR022749), a program sponsored by the National Institutes of Health (NIH) – National Center for Research Resources (NCRR), for their support in funding the SMART Team program.

The Center for BioMolecular Modeling would also like to thank the Medical College of Wisconsin for hosting the SMART Team Poster Session and Final Presentations.



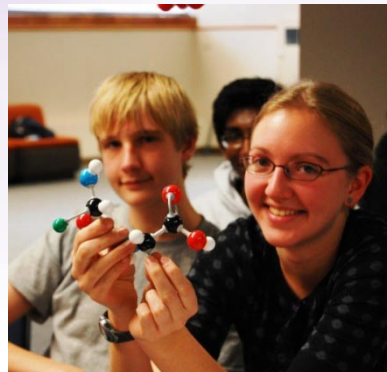
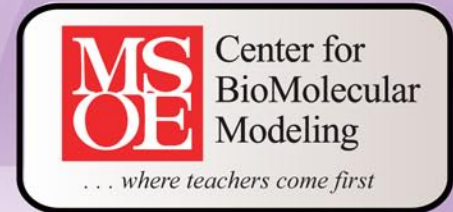
**LAPATINIB:**  
ATP can't compete with me!



**SMART TEAMS**  
2008-09  
**FINAL PRESENTATIONS**

March 14, 2009

Medical College of Wisconsin  
[www.rpc.msoe.edu/cbm/smartteams](http://www.rpc.msoe.edu/cbm/smartteams)



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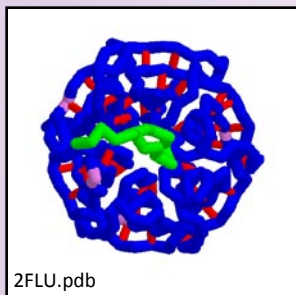
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# The Effect of Nrf-2 in Parkinson's Disease

Edgewood Campus School



**Authors:** Emma Johnson, Cassidy McDonald, Katie Wall, Kira Dohrn-Jones, Marcy Prince, Zoe Havlena and Sara Murphy.

**Teacher:** Dan Toomey

**School:** Edgewood Campus School, Madison, WI

**Mentor:** Jeffrey Johnson, Ph.D., University of Wisconsin – Madison

Neurodegenerative diseases affect one's memory and the brain, specifically the substantia nigra, a part of the brain that regulates movement. Parkinson's disease, a neurodegenerative disease that affects nearly 1.5 million Americans, with about 60,000 new cases yearly, is a possibly disabling and fatal disease that many scientists have been investigating. Symptoms of this disease include belated movement and tremors. Recently, Jeffrey Johnson and his lab at the University of Wisconsin-Madison have released results from a study regarding Parkinson's disease. These results indicate that adding extra copies of a gene, Nrf-2, completely neutralizes the disease state in chemically treated mice. Mice are exposed to a chemical, MPTP, to induce Parkinson's disease. MPTP is contaminant found in synthetic heroin that caused young drug addicts to look like they were in the late stages of Parkinson's. MPTP normally attacks the dopamine neurons in the substantia nigra, the part of the brain that controls movement. The presence of extra Nrf-2 leads to the production of several protective antioxidant proteins that neutralize the toxicity of Nrf-2. Astrocytes make Nrf-2, which then attaches itself to DNA, starting the activity of hundreds of genes that can protect the neurons from oxidation, a combination of chemical reactions that can injure or kill cells, by releasing certain chemicals called reactive oxygen species. Clinical trials for this information are at least two years into the future; however, if the manipulation of Nrf-2 is effective in the treatment of Parkinson's disease, then it can effectively lengthen the lives of those 1.5 million people affected by Parkinson's disease

**Dear Teachers, Students, Mentors, and Honored Guests,**

Thank you for supporting the SMART Team program. We would not be able to continue to host this program without the teachers who donate their time, the students who commit themselves to the program, the mentors who work diligently with their teams, the administration who support their faculty, and family members who encourage their loved ones to excel in all that they pursue. We would not be here without all of you. A SMART Team is composed of several different members; it takes a team effort to accomplish all that you have this year. You have all worked very hard and we at the Center for BioMolecular Modeling would like to say thank you and congratulations to you all!

## Center for BioMolecular Modeling

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## Carbonic Anhydrase:

### Breathe in, Breathe Out

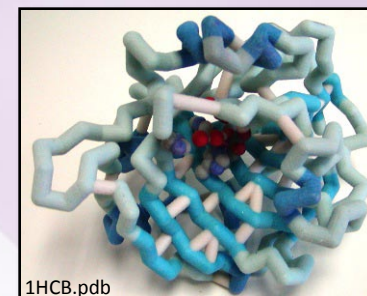
#### Wauwatosa West High School

**Authors:** Matt Berggruen, Ali Hassan, Jimmy Kralj, Kayla Lemmon, Emily Myers and Mariah Rogers

**Teacher:** Mary Anne Haasch

**School:** Wauwatosa West High School, Wauwatosa, WI

**Mentor:** Dale Noel, Ph.D., Marquette University



All animals breathe in oxygen and breathe out carbon dioxide (CO<sub>2</sub>). Carbonic anhydrase, which is found within red blood cells, catalyzes a reaction converting CO<sub>2</sub> and water into carbonic acid, which dissociates into protons, and bicarbonate ions. Said to be “near perfection”, carbonic anhydrase is able to catalyze at a rate of 10<sup>6</sup> reactions per second. We modeled the alpha form, found in humans.

The enzyme contains a pocket of amino acids His94, His96, and His119 that hold a zinc ion. When a CO<sub>2</sub> enters the active site of the enzyme, it gains an OH<sup>-</sup> that was bonded to the zinc, forming carbonic acid that is then released. In order to replenish the OH<sup>-</sup>, water dissociates. The OH<sup>-</sup> binds to the zinc and the H<sup>+</sup> is released. The reaction can now repeat itself.

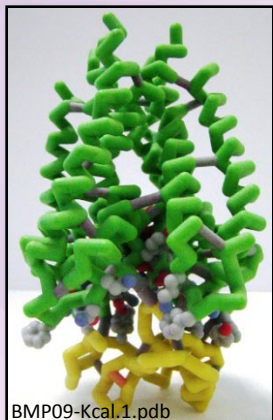
In the lungs, carbonic anhydrase reverses the reaction, turning the carbonic acid back into CO<sub>2</sub> to be exhaled. This process also maintains blood pH by controlling the amount of bicarbonate ions and protons dissolved in the blood.

Malfunctions in carbonic anhydrase’s regulation can cause glaucoma, the second leading cause of blindness. This disorder can be treated with inhibitors of the enzyme that prevent over-secretion of fluid that presses on the optic nerve. Carbonic anhydrase inhibitors are also used to treat ulcers, neurological disorders, and osteoporosis.

## Toxic!

### The role of scorpion toxin and BK channels in the Tobacco Hawkmoth

#### Brookfield High School



**Authors:** Zach Gerner, Emily Gerner, Que Kim, Josh Speagle, Sai Vangala and Darshan Shankar.

**Teacher:** Louise Thompson

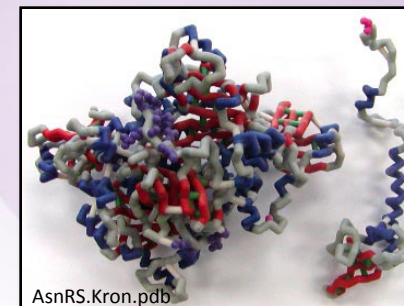
**School:** Brookfield Central High School, Brookfield, WI

**Mentor:** Jane Witten, Ph.D., University of Wisconsin-Milwaukee

A partnership between the Brookfield Central High School students participating in the MSOE SMART Team (Students Modeling a Research Topic) program and a researcher enabled the team to explore the structure and function of a potassium channel bound to a toxin and to build a 3D physical model of the protein. In the larvae of the Tobacco Hawkmoth, the Tobacco Hornworm, the muscle under study is a posture muscle that has a slow recovery (repolarization) rate, and is classified as “slow-twitch”. Metamorphosis transforms this muscle into a flight muscle requiring a fast repolarization rate, becoming a “fast-twitch” muscle. The repolarization rate of these muscle cells is directly linked to the muscle’s rate of contraction. An explosive increase in the number of the  $\text{Ca}^{2+}$ -gated  $\text{K}^+$  channels (BK) in these muscles corresponds to these metamorphic changes. The Chinese scorpion toxin Bmp09, from *Buthus martensi* Karsch, will be used to identify the BK channel as responsible for the change from posture to flight muscle. This toxin binds specifically to the BK channel, preventing the channel from removing  $\text{K}^+$  from the cell, slowing repolarization. Binding the toxin to flight muscle, repolarization rates can be studied to determine if the BK channel is involved in the transformation from posture to flight muscle.

### Get “Hooked” On *Brugia malayi* Asparaginyl tRNA Synthetase

#### Brown Deer High School



**Authors:** Amanda Arnold, Charles Bach, Sam Bach, Andy Faught, Sadie Haeflinger, Alex Her, Kristin Lillie, Trevor Martin, Kristi Noll, Kate Peak, Collin Rice, Pat Rice, Kaitlyn Rogacheski, Amanda Schulman, Aaron Suggs and Samantha Weber

**Teacher:** Gina Vogt

**School:** Brown Deer High School, Brown Deer, WI

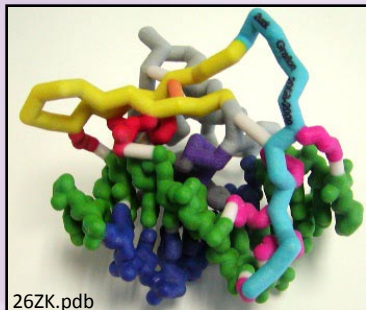
**Mentor:** Michael A. Kron, M.D., M.S., Medical College of Wisconsin

A partnership between the Brown Deer High School students participating in the MSOE SMART Team (Students Modeling A Research Topic) program and a scientist enabled the team to explore asparaginyl-tRNA synthetase (AsnRS), a potential drug target to treat lymphatic filariasis, and to build a 3D physical model of the protein. Lymphatic filariasis results from mosquitoes transferring the nematode, *Brugia malayi*, to host lymph nodes, leading to swelling of affected limbs. AsnRS hooks asparagine to tRNA, used during protein synthesis. AsnRS is a member of the aminoacyl tRNA synthetase (AARS) family, a set of structurally heterogeneous enzymes, specific for each amino acid. AARS are potential drug targets as they are essential for survival and are structurally different between species. AARS also functions as an immunosuppressant, blocking interleukin 8 receptors in humans. Current research for treatment targets parasitic AARS. If multiple functions could be mapped to the same region of the protein, a single drug could target these functions. Inhibition of the tRNA-aminoacylation function of AsnRS would prevent protein synthesis, thus causing death of the parasite. Preventing AsnRS from blocking interleukin 8 receptors, would act as an immunostimulant in humans. Further research on this family of enzymes could provide alternative therapies to treating parasitic diseases.

## When Good Guys Go Bad

### FoxO3a Mediating Apoptosis in HIV-Positive T-Cells

Grafton High School



**Authors:** Dan Burghardt, Lexi Chopp, Ashley Emery, Kaleigh Kozak, Jenna Ostrowski, Adam Schaezner and Lindsay Wendtlandt

**Teacher:** Fran Grant

**School:** Grafton High School, Grafton, WI

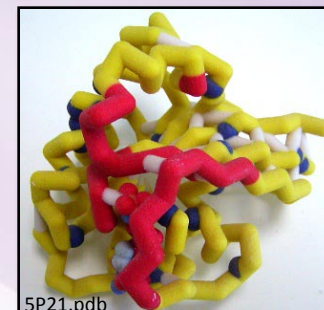
**Mentor:** Sarah Kohler, Ph.D., Medical College of Wisconsin

Within every cell, DNA provides instructions needed to sustain life. DNA is used to make proteins which perform countless cellular functions. One example of a protein is FoxO3a, a transcription factor involved in regulating cell metabolism and apoptosis (cell death), among other processes. To perform these functions, FoxO3a binds to compacted chromatin and opens the DNA for access by other transcription factors and the transcriptional machinery. Because it can perform these functions, FoxO3a is known as a “pioneer” transcription factor. The H3 helix of FoxO3a recognizes its cognate binding sequence within the DNA (GTAAACA). Once bound, the N and C termini wrap around the DNA, causing the DNA to unwind, while the two wings help to secure FoxO3a to the DNA.

Understanding the connection between FoxO3a and cell function enables researchers to explore potential therapies. For example, researchers are examining the potential role that FoxO3a may play in treating patients with HIV. FoxO3a has been suggested to regulate apoptotic genes in T cells, which are a vital part to the immune system. In healthy humans, T cells protect the body by killing abnormal or virus-infected cells. When a person contracts HIV, their T cells are attacked, and their immune defense is compromised. Inhibiting FoxO3a may prevent the upregulation of the apoptotic pathway in T cells, thereby increasing the lifespan of the T cell slightly. Researchers hypothesize that inhibition of the apoptotic pathway may maintain the efficiency of the immune system for a short period of time and hopefully slow the progression of HIV.

## Good Vibrations?

Kettle Moraine High School



**Authors:** Greg Dams, Disa Drachenberg, Mike Goelz, Allie Greene, Bronson Jastrow, Kris Krause, Jake Laux, Nick Merritt, Nate Murray, Kara Reese and Bradley Wilson

**Teachers:** Kelly Beck and Stephen Plum

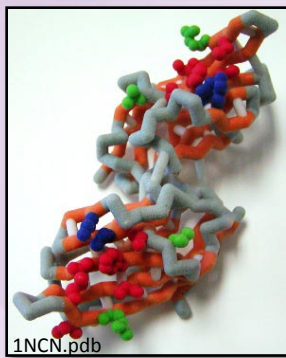
**School:** Kettle Moraine High School, Wales, WI

**Mentor:** Evgenii Kovirgin, Ph.D., Medical College of Wisconsin

Cancer is manifested by uncontrolled cell growth, which occurs due to mutations in signaling proteins. Ras GTPase (Ras) is one of the most important signaling proteins that help regulate cell growth and division. Mutations in Ras leading to its permanent activation and uncontrolled cell growth are responsible for nearly 30% of human cancers. When functioning normally, Ras binds guanosine triphosphate (GTP), and adopts active signaling conformation. When activated, Ras interacts with other proteins and activates them resulting in cell growth and cell division (proliferation). When GTP is hydrolyzed and turned into guanosine diphosphate (GDP), Ras adopts its non-signaling conformation and can no longer bind other proteins and activate them (signaling was 'turned off'). However, if Ras has a specific oncogenic mutation, it cannot hydrolyze GTP and instead permanently signals for cell growth, causing cancer. One of the keys to figuring out how Ras causes cancer might be to better understand how the protein changes its conformation while performing its signaling function. Structural and dynamic studies of Ras using NMR techniques suggest that the protein, when active and bound to GTP, has two majorly different conformations it can take. Understanding how the protein changes conformation and interacts with other proteins could shed light on how it signals for cell growth. This information could further cancer treatments and potentially lead to a cure for cancers caused by Ras mutations.

## The Role of B7-2 in the Regulation of T cell Activation in Multiple Sclerosis

### Messmer High School



**Authors:** Carolina Herrera, Lillian A. Rios and Edna Blackma

**Teacher:** Carol L. Johnson

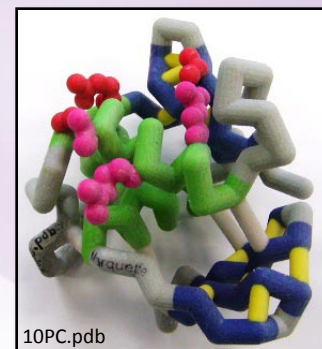
**School:** Messmer High School, Milwaukee, WI

**Mentor:** Bonnie N. Dittel, Ph.D. and Ashley Conrad, Ph.D., Blood Research Institute, BloodCenter of Wisconsin

Multiple Sclerosis (MS) is a disease of the central nervous system that affects individuals 20 – 40 years old. MS is thought to be an autoimmune disease in which T cells attack and destroy the myelin sheath surrounding neurons. Demyelinated neurons have a reduced capacity to transmit electrical impulses, causing symptoms from loss of muscle control to memory loss. One protein thought to play a role in MS is B7-2, a member of a family of proteins that regulate T cell functions expressed by antigen presenting cells (APC). Generation of an immune response by T cells requires two signals: binding of the T-cell receptor to the antigen/MHC complex on APC and binding of B7-1 to CD28 on the T cells. B7-2 is thought to be involved in suppression of the T cell response through binding to CTLA-4. Research using the mouse model of MS, EAE, demonstrated that injection of B7-2 specific antibodies resulted in a more severe disease course. These data suggest that B7-2 plays a role in negative regulation of the immune response during EAE, possibly by binding CTLA-4. To investigate how B7-2 interacts with CTLA-4, we developed a physical model of B7-2 based on its crystal structure (1ncn.pdb) using 3D printing technology that highlights the protein's  $\beta$  sheet structure and amino acids thought to be important in CTLA-4 binding. This model was built as a part of the SMART team program at Milwaukee School of Engineering.

## OmpR: Outer Membrane Protein Gene Regulator Regulating *Xenorhabdus nematophila*'s "Appetite for Destruction"

### Marquette University High School



**Authors:** Mohammed Ayesh, John Basich, Wesley Borden, Alexander Brook, John Day, Mahmoud Elewa, Grant Flesner, Patrick Jordan, Lucas Kuriga, Hector Lopez, Ben Maier, David Moldenhauer, Joseph Radke, Caleb Vogt, Brandon Wolff and Zeeshan Yacooob

**Teachers:** Keith Klestinski and David Vogt

**School:** Marquette University High School, Milwaukee, WI

**Mentor:** Steve Forst, Ph.D., University of Wisconsin – Milwaukee

A partnership between Marquette University High School students participating in the MSOE SMART Team (Students Modeling A Research Topic) program and a researcher enabled the team to explore structure and function, and to build a physical model using 3D printing technology, of OmpR. OmpR is a transcription factor necessary for the nutrition gathering strategy of the bacterium *Xenorhabdus nematophila*. Bacteria absorb food through membrane pores, which change in size to optimize food intake and to protect themselves from toxins.

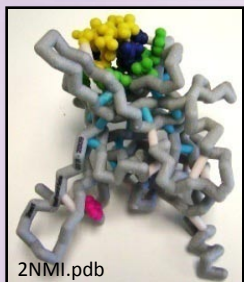
*X. nematophila* has sensor proteins in the outer membrane. When food touches an outer membrane receptor (EnvZ), the receptor transfers phosphate to OmpR forming OmpR-P, which can bind to DNA. When nutrients are abundant, OmpR-P binds to OmpC, a gene promoting formation of a small pore, allowing food yet limiting influx of toxins. When food is scarce, OmpR-P binds OmpF, a gene promoting formation of a large pore, allowing more food intake and growth of a flagellum enabling movement to a nutrient rich location.

The OmpR gene is also responsible for production of antibiotic compounds that combat a broad range of microorganisms. *X. nematophila* often forms a mutualistic relationship with nematodes. The bacterium-nematode pair seek to inhabit and eventually kill certain insects, benefiting from the nutrients provided by the insect's corpse.

## Botulinum Neurotoxin B:

### The Biochemical Blade

Nathan Hale High School



**Authors:** Rebecca Ruechel, Nicholas Dolan, Nicholas Goldner, Samuel Hall, Brenna Hanley, Katelyn Milos and Ajay Sreekanth

**Teachers:** Susan Getzel and Anne Xiong

**School:** Nathan Hale High School, West Allis, WI

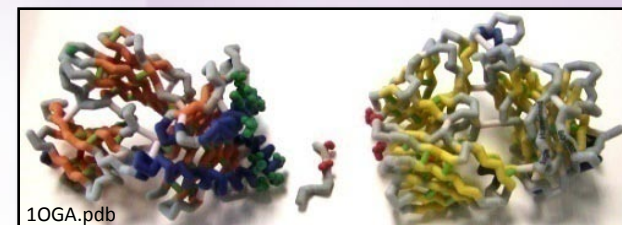
**Mentor:** Joseph T. Barbieri, Ph.D., Medical College of Wisconsin

Botulinum neurotoxins (BoNTs) are highly toxic proteins that cause the fatal neuroparalytic illness called botulism. BoNTs are produced by the anaerobic bacteria *Clostridium botulinum*. Although most prominently contracted from contaminated food, botulism can also be contracted from the soil, through the air, or from an open wound. BoNTs are **AB** toxins composed of three domains. The first domain, the **A** domain of BoNT, is the catalytic component, a Zinc-dependent protease. The second and third domain, or the translocation and receptor-binding domain respectively, comprise the **B** domain of the toxin, the binding component. Botulinum neurotoxin serotype B (BoNT/B) is a specific type of neurotoxin that binds to the neurons. The membrane of a neuron depolarizes which then stimulates the transport of calcium ions into the neuron. Proteins on the transmitter vesicle bind the calcium and the vesicles are then transported to the plasma membrane by SNARE proteins to release the neurotransmitter acetylcholine. BoNT/B enters the lumen of the neurotransmitter vesicle and binds to the luminal loop of synaptotagmin, causing the loop to change from a coil to an alpha helix. This represents the high affinity binding of BoNT/B to neurons. Inside the neuron, the A domain of the toxin is translocated across the vesicle membrane by the translocation domain in a pH-dependent mechanism and cleaves the vesicle associated membrane protein (VAMP). This prevents neurotransmitter vesicles from fusing to the plasma membrane and inhibits further release of acetylcholine. Since acetylcholine is important in movement and memory, a lack of acetylcholine causes the nervous system to slow down and causes flaccid paralysis of the muscles, otherwise known as botulism.

## “You Look Familiar...”

### How the Immune System Specifically Targets and Kills Infected Cells

Homestead High School



**Authors:** Sophia Dantoin, Dhruv Metha, Yelena Ostrerov, Sahitya Raja, Nikhil Ramnarayan and Rahul Subramanian

**Teacher:** Christine Schultz

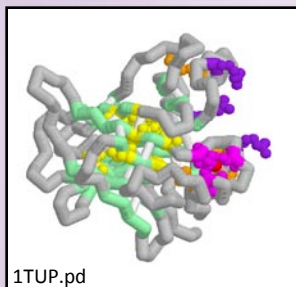
**School:** Homestead High School, Mequon, WI

**Mentor:** Andrea Ferrante, M.D., Blood Research Institute, BloodCenter of Wisconsin

The Acquired Immune System offers highly specific protection from infection by viruses, bacteria and other microbes by recognizing the pathogen, triggering an immune response resulting in pathogen elimination, and establishing immunological memory for future recognition. It relies on two types of responses: cell-mediated and humoral. Humoral responses are mediated by B-lymphocytes that produce antibodies, which bind to specific antigens on the pathogen, labeling it for destruction. Cell-mediated responses involve T-lymphocytes, which play regulatory and/or killing functions. In particular, cytotoxic T-lymphocytes (CTL) identify and kill infected cells by examining pieces of proteins (antigens) on the cell membrane as illustrated by the CTL response to the influenza virus. Upon infection, viral antigens from the cytoplasm are transported to the cell membrane and presented on the outside of the cell by class I HLA proteins as a viral antigen-class I HLA protein complex. Each CTL scans the peptide/HLA complex repertoire with its receptor (TCR), and upon binding with a cognate complex, destroys the infected cell. In the present model, an influenza-derived peptide (MP (58-66)) is complexed with HLA-A2, and binds to the TCR Vb17Va10.2. The portion of this TCR that interacts with the peptide-HLA-A2 complex has an arginine-serine-serine sequence which gives reason to the specificity of recognition. The structural modeling of this interaction aids in the understanding of TCR bonding at the molecular level, thereby allowing for the prediction of TCR binding to closely related peptides. This could explain how the immune system responds specifically to new pathogens after involution of T cell production.

# Preventing Cancer: p53 Tumor Suppressor Protein

Madison West High School



**Authors:** Dianna Amasino, Axel Glaubitz, Yang He, Susan Huang, Joy Li, Junyao Song and Connie Wang

**Teacher:** Basudeb Bhattacharyya, University of Wisconsin, Madison

**School:** Madison West High School, Madison, WI

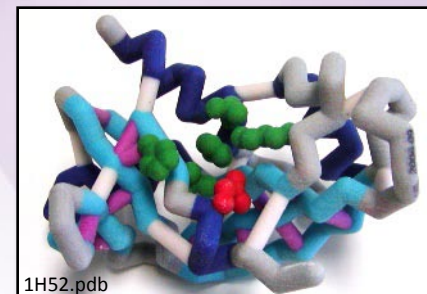
**Mentor:** Dave Nelson, Ph.D., University of Wisconsin – Madison

Each year, nearly 40% of cancer patients die of the disease in the U.S., and more than 50% of human tumors contain a mutation or deletion of the *TP53* gene. Tumor protein 53, also known as p53, is a transcription factor coded by *TP53*, and possesses many anti-cancer mechanisms, such as initiating apoptosis and inhibiting angiogenesis. Usually p53 is inactive, bound to protein HDM2, which promotes its degradation. Once activated by cancer-causing agents (such as UV radiation or oncogenes), p53 is released by HMD2 and binds with DNA, inducing the expression of the *CDKN1A* gene, which encodes for protein p21. These proteins then interact with a cell division-stimulating protein (cdk2) to arrest cell division. Therefore, under normal conditions, p53 is able to regulate the cell cycle to prevent cancer through this process. However, mutant p53 cannot bind to DNA, and thus cannot trigger the production of p21, resulting in uncontrolled cell division and, ultimately, tumors. If one has only one functional copy of *TP53*, it will most likely lead to Li-Fraumeni Syndrome, which entails tumor development in early adulthood. Also, pathogens, such as the Human Papillomavirus (HPV), can produce proteins that inactivate p53. In addition, p53 itself induces HDM2 in a negative feedback loop; mutant p53, however, don't often do so, and therefore accumulate within the cell, disrupting normal p53 levels. Increasing the amount of p53, however, does not hold therapeutic potential, since it causes premature aging; restoring the function of the protein may serve as a feasible treatment instead. Through a more thorough understanding of the function of p53, we hope to formulate better treatments for cancer patients.

# The Blister Battle:

The Application of Angiogenin in the Treatment of Bullous Pemphigoid

St. Joan Antida High School



**Authors:** Ava Al-Awami, Essraa Amer, Maritza Campos, Meghan Krause, Claire Marshall, Corie Marshall, Kayla Mazul, Ana Schuessler, Jade Taylor and Kristen Wagner

**Teacher:** Linda Krause

**School:** St. Joan Antida High School, Milwaukee, WI

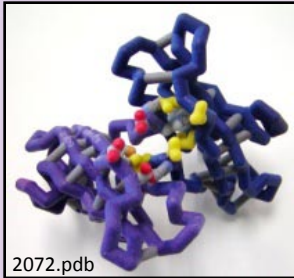
**Mentor:** Françoise Van den Bergh, Ph.D. and Nathan Duncan, Medical College of Wisconsin

Bullous pemphigoid (BP) is an autoimmune disease which primarily affects the elderly and is characterized by large, fluid-filled blisters on the surface of the skin. BP currently has only a general, invasive cure. In BP, the body's immune system produces antibodies to attack collagen XVII, also called BP180, in the skin's basement membrane. When inflammation cells flock to the distressed membrane, painful blisters result. Traditional treatments for severe cases of BP include immunosuppressant drugs, which suppress the patient's immune system while treating the blisters, increasing the risk of development of certain cancers and infections. Research centering on angiogenin, a naturally occurring member of the ribonuclease superfamily, has led scientists to believe that a cure for BP may be found in the coupling of angiogenin with a specific region of BP180.

Research suggests that if angiogenin is fused to NC16A, a domain of BP180 and the target of the body's B-cells, the angiogenin and NC16A complex would be absorbed by the B-cell as it attacks BP180. Angiogenin, normally playing a crucial role in the formation of new blood vessels, becomes toxic once directly introduced to a cell. The angiogenin, acting as a toxin inside the B-cell, would use its depolymerization mechanism to destroy the B-cell's RNA. With the B-cell unable to make protein due to the loss of its RNA, apoptosis [cell death] would occur. Any angiogenin-NC16A complex remaining after the apoptosis would neither elicit a negative immune response nor produce any toxic side effects as angiogenin is naturally present in the body. Relief may thus be provided for BP sufferers.

# Modeling the Cell Adhesion Molecule E-Cadherin

## Brookfield Academy



**Authors:** Anshu Aggarwal, ZeeShan Chattha, Amanda Doyle, Stuart Hunter, Natalie Profio, Sheil Shukla and Joey Steven

**Teacher:** Robbyn Tuinstra, Ph.D.

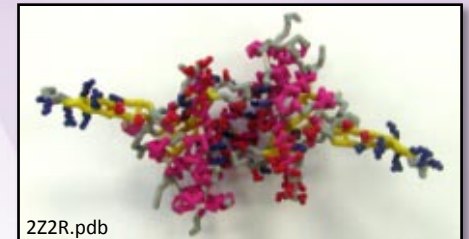
**School:** Brookfield Academy, Brookfield, WI

**Mentor:** Mary Holtz, Ph.D., Medical College of Wisconsin

E-cadherin is a transmembrane protein essential for cell adhesion in organ and tissue development and integrity. Cadherins form plasma membrane structures called adherens junctions. Adherens junctions provide direct connections between adjacent cells and are crucial to maintaining epithelial membranes and blood vessel integrity. Adhesion of neighboring cells via E-cadherin occurs through a salt bridge interaction between the N-terminal Aspartate-1 of an E-cadherin protein on one cell and a Glutamate-89 of the opposing E-cadherin protein from the adjacent cell. Additional contacts are provided by hydrophobic and hydrogen-bonding between residues Trp2, Asp90, and Met92 located at the binding interface. E-cadherin is a classical  $\text{Ca}^{2+}$ -dependent cadherin and loss of function may contribute to developmental abnormalities and cancer progression. Balance between maintenance and remodeling of cell adhesion junctions is required for normal embryonic development. For example, in the development of the embryonic heart, E-cadherin proteins facilitate connections between adjacent epithelial cells of proepicardial tissue. The proepicardium is an embryonic structure from which the coronary vasculature is formed. Cells of the proepicardium must migrate over the surface of the developing heart and then differentiate into the endothelial and smooth muscle cells of the mature coronary vasculature. In contrast, cancer progression and tumor growth involve metastasis and new blood vessel formation, two processes that rely on dissolution of normal cell-cell contacts. Understanding the mechanisms of formation and dissolution of adherens junctions provides important insight into cardiac development and may provide direction for new cancer therapies.

# Nucleosome Assembly Protein 1

## St. Dominic Middle School



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**Teacher:** Donna LaFlamme

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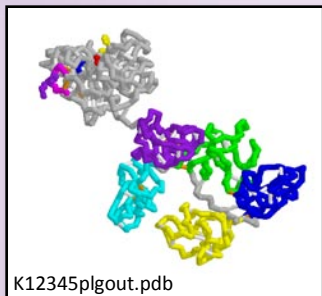
**Mentor:** Vaughn Jackson, Ph.D., Medical College of Wisconsin

The two meters of DNA in every human cell must be tightly packaged in order to fit in the nucleus and to protect the genetic information. NAP1 (Nucleosome Assembly Protein 1) is a histone chaperone that helps assemble and disassemble the nucleosomes used to package this DNA. A nucleosome consists of a core of eight positively charged proteins called histones around which are wrapped 147 base pairs of DNA. The eight histones are actually four heterodimers; there are two H2A/H2B dimers and two H3/H4 dimers. The histones' positive charges are attracted to the DNA's negative charge; this attraction causes the DNA to form left-handed super coils around the histones. The experiment shown on our poster demonstrates that, *in vitro*, NAP1 can assemble nucleosomes on DNA without the help of other chaperones. Histone chaperones like NAP1 are essential in cells because without them the first step in protein synthesis, transcription – the process of making RNA copies of the genes encoded in DNA – cannot occur because RNA polymerase needs to access the DNA strands. This would not be possible if the DNA remained super coiled around nucleosomes. Nucleosomes must also disassemble for replication – the process of copying DNA by DNA polymerase – to occur. Replication is important in cell division because the DNA must be copied and distributed to the two daughter cells. NAP 1 is so vital to these cellular processes that evolution has conserved it in organisms from one-celled yeast to humans with trillions of cells.

## Plasminogen:

### The Clot Buster

#### Cedarburg High School



**Authors:** Daniel Greinke, Jessica Knap, Michelle Sella, Elissa Hornick, Kelsey Jeletz, Kirsten Loberg and Sara Panighetti

**Teacher:** Karen Tiffany

**School:** Cedarburg High School, Cedarburg, WI

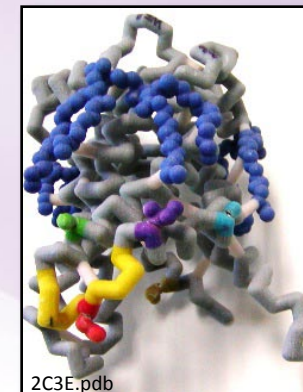
**Mentor:** Richard Bohnsack, Ph.D., Linda Olson, Ph.D., Nancy Dahms, Ph.D., Medical College of Wisconsin

Coagulation and fibrinolysis comprise a complex system involving many proteins designed to form fibrin clots when needed to repair a blood vessel and dissolve these clots when no longer needed. One key fibrolytic protein, plasmin, circulates in the blood as plasminogen, an inactive protein made of several domains. Five domains are kringle domains that help plasmin bind to lysine residues in fibrin, while the catalytic domain exhibits protease activity that fragments the fibrin network. Plasminogen is incorporated within the fibrin network as a clot forms, but the catalytic domain is only able to break down fibrin when plasminogen has been activated and converted to plasmin. One substance known to convert plasminogen into plasmin, tissue plasminogen activator (tPA), is a serine protease that cleaves the peptide bond between Arg561 and Val562 in plasminogen. The endothelial cells of damaged blood vessels slowly release tPA that activates the plasminogen embedded within a fibrin clot. Because increased plasmin levels help dissolve clots, tPA is given clinically to treat conditions caused by blood clots, like heart attack and stroke. To further understand the structural implications of activation, a 3D physical model of plasminogen has been designed and built by the Cedarburg High School SMART (Students Modeling a Research Topic) Team using 3D printing technology.

## Fueling Up:

### Transporting ADP and ATP Across the Mitochondrial Membrane

#### Whitefish Bay High School



**Authors:** Zachary Kaplan, Ian Gee, Sami Luber, Tess Nottoli, Youngjoon Choi, Xavier Durawa, Shirley Hu, Tim Murray, Ana Novak, Eric Schwartz and Minh-Tam Trinh

**Teachers:** Marisa Roberts and Judy Weiss

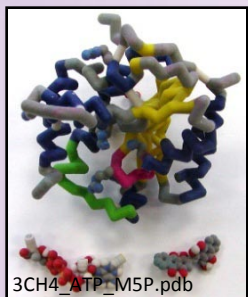
**Mentor:** Rosemary Stuart, Ph.D., Marquette University

Cells store energy by transforming ADP into ATP in mitochondria. Across the outer mitochondrial membrane, ADP and ATP readily diffuse through the protein porin. Across the inner mitochondrial membrane, the Bovine Mitochondrial ADP-ATP carrier, an anti-port, transports ADP in and ATP out. When this protein malfunctions, the resulting inefficient distribution of ATP can cause certain neuromuscular disorders. One disorder, characterized by drooping eyelids and the inability to move the eyes, results from a mutation in the C1 portion of the carrier protein. Cells make multiple types of these carrier proteins, which compensate if one form of the protein is defective. In cells where the disease occurs, there is usually one dominant type of carrier protein, reducing the ability of the other types to compensate. However, the transport function of the carrier protein still has the capacity to transport ADP and ATP despite the mutation. Therefore, it is unclear why the mutation causes problems. The C1 mutation may interfere with the ADP-ATP carrier protein's ability to interact with its partner proteins such as TIM23, a voltage-gated channel, or the cytochrome  $bc_1$ -cytochrome oxidase enzymes, an  $H^+$  pumping complex. Further research on the interaction of the carrier protein with neighboring proteins may provide insight into cures for such neuromuscular disorders.

## Drug Discovery and Development:

### The Senna Plant and Phosphomevalonate Kinase Inhibition

Valders High School



**Authors:** Corrine Brandl, Andrea Herrmann, Katarena Hubbartt, Nicole Maala, Alexandria Meidl and Hallie Reznichak

**Teacher:** Joseph Kinscher

**School:** Valders High School, Valders, WI

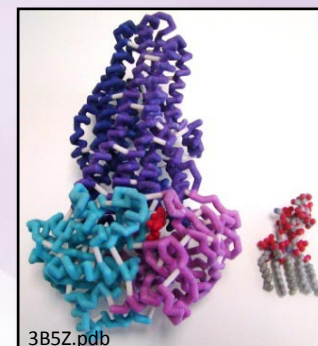
**Mentor:** Daniel S. Sem, Ph.D., Marquette University

In 2008, the leading cause of death in the United States was heart disease. Familial hypercholesterolemia (genetically high blood cholesterol levels) is a major factor responsible for this unfortunate statistic. Phosphomevalonate kinase (PMK) is a cytoplasmic enzyme predominantly found in the liver that is involved in the process to synthesize cholesterol. Two ligands bind to PMK: mevalonate 5-phosphate and ATP. Using the  $\gamma$ -phosphate from ATP, PMK converts mevalonate 5-phosphate (M5P) to mevalonate 5-diphosphate, which is a precursor to cholesterol. ATP binds to the catalytic “Walker A” loop of the kinase, which results in a conformational change. Once bound, M5P causes the domains to move together, around certain hinge residues, so that the two ligands are positioned to react, creating mevalonate 5-diphosphate. The negatively charged phosphates present in both M5P and ATP make this process difficult as the molecules repel one another due to the negative charges on each; therefore, neutralization of the ligands is necessary for catalysis by means of positively charged residues in or near the “Walker A” loop (Arginine 18, 19 and 110, and Lysine 17, 19 and 22). Understanding how PMK catalyzes this reaction could lead to alternative therapies to statin drugs for the control of hypercholesterolemia. Statin drugs may have negative side-effects, like kidney damage; inhibiting PMK would be an option for patients intolerant of statins. Heart disease caused by hypercholesterolemia continues to be a major concern in the U.S. Manipulation (by means of phosphomevalonate kinase) of the rate-limiting pathway by which cholesterol is synthesized may lead to a treatment for this genetic condition.

## Flippin' Lipids:

### Transport of Lipid A by MsbA, a Lipid Flippase

Bradford High School



**Authors:** John DeVroy, Kevin Patel, Ronak Patel, Fred Seewald, Beth Stebbins, April Szfranski, Jazzmyne Washington and Mike Weber

**Teacher:** Jean Lee

**School:** Bradford High School, Kenosha, WI

**Mentor:** Candice Klug, Ph.D., Medical College of Wisconsin

MsbA is a member of the ABC transporter class of proteins, one of the largest found in nature. ABC transporters move solutes across the cell membrane. MsbA consists of two transmembrane domains and two nucleotide binding domains. The transmembrane domains consist of 6  $\alpha$  helices embedded in the phospholipid bilayer. The nucleotide binding domains are found in the cytosol and are the site of ATP hydrolysis, which provides the energy for the protein to function.

MsbA is a lipid flippase, which means it transports lipid A produced in the cytosol to the outer leaflet of the outer cell membrane, flipping it so the hydrophilic end faces out. Lipid A is essential to the outer cell membrane of Gram-negative bacteria. If MsbA does not function properly, lipid A can kill the bacteria by accumulating in the intracellular layer of phospholipids. This is important to researchers, as MsbA has homology to human multi-drug resistance proteins. Finding a way to render MsbA inactive could lead to antibiotics that kill bacteria, such as Salmonella, which have traditionally been hard to treat. This is of much concern in today's society, as bacteria outbreaks in food seem to be happening more and more often.

# $\alpha_{IIb}\beta_3$ : The Key to Platelet Aggregation (and Clotting)

Wauwatosa East High School



**Authors** David Covell, Nate Deisinger, Brian Hoettels, Nate Kolpin, Henry Mittelstadt, Molly Rasper and Lucia Roegner

**Teachers:** Phil Kroner, Ph.D. and Terry Teske

**School:** Wauwatosa East High School, Wauwatosa, WI

**Mentor:** Gilbert White, M.D., Blood Research Institute, BloodCenter of Wisconsin

Blood coagulation, or the clotting of blood, is a vital process in the body wherein a damaged area of a blood vessel is blocked by platelets and fibrin to stop bleeding until it can be repaired.

This process involves proteins known as integrins, a kind of integral membrane protein, which mediate cell-cell and cell-surface interactions. Integrin  $\alpha_{IIb}\beta_3$ , comprised of two glycoprotein subunits and acting as a transmembrane protein, rests on and in the surface of platelets and plays a crucial role in the clotting process by acting as a receptor for proteins that mediate the interaction of one platelet to another.

When a blood vessel is damaged, proteins under the endothelial layer of the blood vessel are exposed at the site of injury. Other receptors cause platelets to bind to the site of damage. This initial binding causes the platelets to become activated, which causes the release of many substances supportive of the clotting process, and also results in the activation of  $\alpha_{IIb}\beta_3$ . It is vital that the activation of  $\alpha_{IIb}\beta_3$  is controlled, as an overly large amount of activated  $\alpha_{IIb}\beta_3$  would cause excess clotting. During activation, the structure of  $\alpha_{IIb}\beta_3$  changes dramatically, converting from a bent, inactive conformation, into a comparatively 'straight' protein. These changes occur in the integrin because a salt bridge between the intracellular domains of  $\alpha_{IIb}$  and  $\beta_3$  is broken. As a result of this conformational change, amino acids are exposed which form the binding site to several plasma proteins which adhere to the damaged blood vessel, including fibrinogen, von Willebrand Factor, fibronectin, and vitronectin. The binding of fibrinogen cross-links the platelets and results in platelet aggregation at the site of damage. Despite intensive study, the changes leading to the activation of  $\alpha_{IIb}\beta_3$  functions are still being clarified. However, because blood clotting plays a role in cardiovascular diseases, scientists are working hard to fully understand the structure and function of  $\alpha_{IIb}\beta_3$  and its role in platelet aggregation.

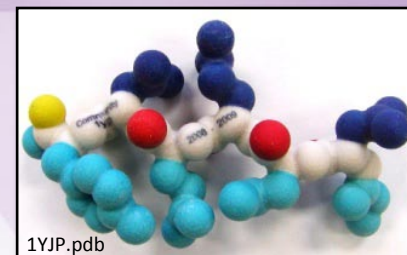
# Who's Afraid of the Big, Bad, Misfolded Protein?

Community SMART Team

**Authors:** Moses Mispion, Meghan Murphy, Christine Pollnow, Joel Pollen and Maia Stack

**Teachers:** David Stack, Ph.D.

**Mentor:** Anita Manogaran, Ph.D., University of Illinois at Chicago



Fatal prion diseases, such as Creutzfeldt-Jakob disease in humans, are associated with the conversion of the normally folded mammalian PrP protein to a misfolded prion form that aggregates. Understanding how prions behave has been greatly facilitated by the study of prions in *Saccharomyces cerevisiae*, or baker's yeast. In yeast, the translation release factor, Sup35, misfolds to form the  $[PSI^+]$  prion. Although the Sup35 protein has a significantly different primary sequence from PrP, its prion form behaves similarly to human prions. The N-terminus of Sup35 is Q/N-rich and responsible for prion formation. Determining the structure of this region has proven difficult since the N-terminus forms aggregates instead of the ordered crystals required for structural studies. However, a small seven amino acid sequence (GNNQQNY) from Sup35's N-terminus was crystallized by Nelson et al. (2005). We have constructed a 3D physical model of GNNQQNY as part of the MSOE SMART Teams program using 3D printing technology. GNNQQNY's structure suggests that multiple prion molecules assemble into strong fibrous aggregates through tightly structured interlocking parallel beta sheets called a cross- $\beta$  spine. The structure of GNNQQNY suggests a potential model of how human prions assemble, which could potentially help in developing therapies that prevent aggregation.

## Don't Forget It: Thrombin Related Alzheimer's Disease

### Lincoln High School



**Authors:** Eric Auchter, Vanessa Heck, Danielle Niquette, Jenna Schuh, Kira Schultz, Jen Stenson and Brandon Vance

**Teacher:** Ann Hansen

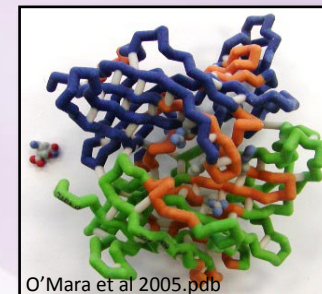
**School:** Lincoln High School, Manitowoc, WI

**Mentor:** Sally Twining, Ph.D., and Malathi Narayan, Medical College of Wisconsin

Alzheimer's disease is an incurable and terminal neurodegenerative disorder and is the most common form of dementia. There are 5.2 million people in the United States living with Alzheimer's and it is projected that 10 million baby boomers will eventually develop the disease. One of the three major competing hypotheses explaining Alzheimer's disease involves thrombin, a serine protease involved in blood coagulation. Normally present inside the brain's neurons, thrombin cleaves tau, a microtubule protein. In the brains of Alzheimer's patients, thrombin is also present outside the brain cells, where it binds and cleaves PAR-1, a protease activated receptor embedded in the cell membrane. The interaction between thrombin and PAR-1 exposes a peptide sequence that initiates a series of reactions which activate kinase enzymes that add phosphate groups to tau. Intracellular thrombin is then unable to cleave the phosphorylated tau and the neuron microtubules become clumped, losing their ability to function. As Alzheimer's disease advances, microtubule clumping becomes more prominent throughout the brain, explaining the progression of symptoms from confusion and memory loss to eventual death. Scientists are interested in studying the binding of thrombin to PAR-1 because this interaction is a possible therapeutic target for developing treatments for Alzheimer's and other neurodegenerative disorders.

## GABA<sub>A</sub> Receptor's Role in Keeping the Brain Calm

### Pius XI High School



**Authors:** Steven Brzezinski, James Carian, Katie Eszes, Bilal Garner, Brittany Givens, Jenna Motz, Bernie Mulvey, Richa Rathore, Joseph Schwemmer, Kathryn Sulik, Stefan Thompson, Jordan Zawacki and Sydney Zettler

**Teachers:** Julie Fangmann and Mimi Verhoeven

**School:** Pius XI High School, Milwaukee, WI

**Mentor:** David Wagner, Ph.D., Marquette University

Numerous neurological pathologies, such as anxiety disorders, epilepsy, and insomnia, are due to neurons in the brain malfunctioning by being overactive. Like a stop sign directing traffic, the activation of gamma-amino butyric acid (GABA<sub>A</sub>) receptors reduces neural activity preventing neurons from firing excessively. When GABA binds to the GABA<sub>A</sub> receptor, negative chloride ions flow into the neuron. This inhibits neural activity because neurons need a net positive charge inside them to send messages. GABA<sub>A</sub> receptors are targets for depressants, including alcohol, benzodiazepines (such as Ambien™, Valium™, and Xanax™), and general anesthetics. These drugs bind to the GABA<sub>A</sub> receptor to increase inhibition of neural activity. The specific GABA binding site(s) on the GABA<sub>A</sub> receptor are unknown. Current research focuses on altering amino acids potentially involved in binding GABA. If one of these amino acids in the binding site is altered, GABA will unbind faster from this mutated GABA<sub>A</sub> receptor than it does from the wild type (normal) receptor. Finding the specific amino acids involved in binding GABA could lead to breakthroughs in GABA<sub>A</sub> receptor-related pathologies and allow for better design of new drugs.