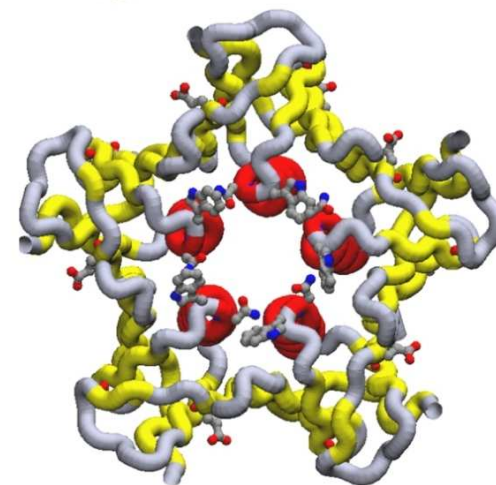


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The Center for BioMolecular Modeling would also like to thank Discovery World for hosting the SMART Team Final Presentations.

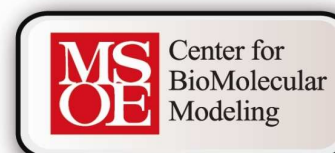
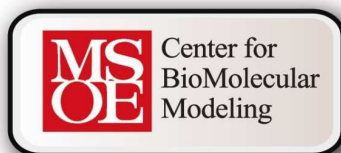


Shiga Toxin
1R4P.pdb

Binding To A Receptor In You!

March 17, 2007

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**Special Thanks for the Time and Effort of
SMART Teachers SMART Mentors**

- | | |
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Madison West High School

How Penicillin and Streptomycin Kill Bacteria



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Mentor: David Nelson, Ph.D., University of Wisconsin-Madison, Madison, WI

Prior to World War II, a bacterial infection would most likely lead to death. Especially crucial during the war, drugs were needed to combat infections that killed numerous wounded soldiers. Through an accidental discovery by Alexander Fleming in 1928, penicillin dramatically decreased the number of bacterial related deaths and amputations. Penicillin is an effective antibiotic that targets proteins (e.g. Penicillin Binding Protein 4--PBP4) responsible for cross-linking the components of the bacterial cell wall peptidoglycan layer. By targeting these bacterial specific proteins, penicillin weakens the cell wall of a dividing bacterium, thereby leading to the bacteria's subsequent death without harming the patient. However, it is not effective against all types of bacterial infections because it can only target certain types of bacteria (i.e. Gram-positive bacteria which lack the lipopolysaccharide layers that surround and protect Gram-negative bacteria). *Mycobacterium tuberculosis*, the causative agent of tuberculosis (an airborne disease which left untreated can lead to death and was indeed a major cause of death in the United States prior to 1943) is an example of a bacterial species that is immune to the effects of penicillin. Streptomycin was the first antibiotic (discovered in October 1943 by Selman Abraham Waksman and Albert Schatz) found to combat tuberculosis. Isolated from the soil organism *Streptomyces griseus*, this antibiotic binds tightly to bacterial 16S ribosomal RNA (rRNA), causing a conformational change within the A-site of the ribosome, creating a higher affinity between the A-site and "incorrect" tRNAs (the A-site is generally restrictive and has a low affinity for incorrect tRNAs). This makes protein translation "error-prone" and therefore protein synthesis is inhibited in the target bacterium. This process does not affect human ribosomes which do not have the 16S rRNA and the specificity of streptomycin to this ribosomal subunit makes it an ideal treatment. We are using rapid prototyping to model the interaction between penicillin and PBP4 as well as streptomycin and the 16S rRNA in order to better understand the general mechanisms of bacterial infection and the variety of antibiotic treatments available as well as antibiotic resistance.

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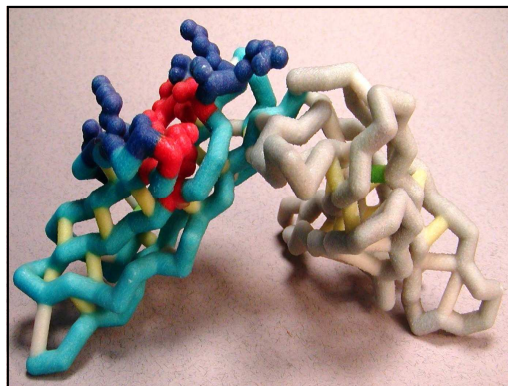
Dear Teachers, Students, Mentors and Honored Guests,

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 the family members who encourage their loved ones to excel in all 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 what you have this year. You have all worked very hard and we at the Center for BioMolecular Modeling would like to say Thank You!

CENTER FOR BIOMOLECULAR MODELING

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Tim Herman, Ph.D.	CBM Director

Glycoprotein VI: Thrombosis and Collagen Reaction



Authors: Colleen Anson, Matt Cain, Sam Ehrenreich, Otto Kletzien, Rachel Mayer, Mark Robitaille, Melanie Signer, Zhexi Wang, and Logan Vander Wyst

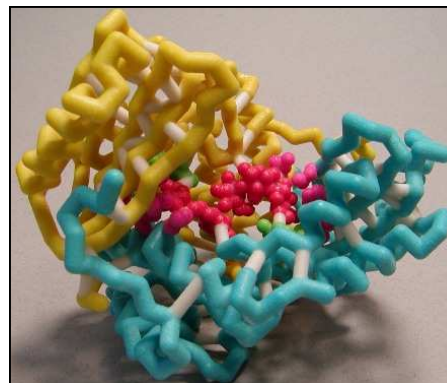
Teacher: Amy Reinholtz

School: Sheboygan North High School, Sheboygan, WI

Mentor: Debra Newman, Ph.D., Blood Center of Wisconsin, Milwaukee, WI

Platelets normally circulate in the bloodstream in an inactive state. When a blood vessel is damaged and proteins in the extracellular matrix surrounding the blood vessel are exposed, platelets become activated, stick to one another to form a thrombus, and close up the wound. One of the major components of the extracellular matrix is collagen. Glycoprotein VI (GPVI) is a protein that plays a major role in allowing platelets to bind to and become activated by collagen. GPVI is embedded in the membrane of platelets; the extracellular region of GPVI is the section that binds to collagen, whereas the intracellular region is active in sending a signal to the inside of the platelet that enables the platelet to become activated. Activation of platelets by collagen can be beneficial during wound healing but, if platelets are activated and form a thrombus on the inside of a blood vessel, a heart attack or a stroke can result. An example of situation associated with clinical thrombosis complications is the use of coronary angioplasty to open up blocked blood vessels. Patients undergoing coronary angioplasty may have damaged artery walls with exposed collagen, which can cause excessive formation of thrombi that block the blood vessel up again. Researchers in the laboratory of Dr. Debra Newman at BloodCenter of Wisconsin have discovered that individuals who have GPVI deficient platelets exhibit only minor bleeding disorders. They are therefore interested in trying to develop a drug that would shed GPVI molecules from the platelet's surface so as to treat patients with clinical thrombosis complications, with the expectation that such a drug would not cause major bleeding disorders.

The Growing Problem of Antibiotic Resistance: How Kanamycin Nucleotidyl Transferase (KNTase) Inactivates the Antibiotic Kanamycin in Drug Resistant Bacteria



Authors: Roy Currie, Ben Evans, Natasha Holmes, Lauren Hughes, Nate Reiners

Teacher: Patti Soderberg, Ph.D.

School: Conserve School, Land O'Lakes, WI

Mentors: Agnes Kanikula, University of Wisconsin-Madison and Hans H. Liao, Ph.D., Biotechnology Development Center, Cargill Incorporated, MN

The discovery of antibiotics revolutionized medical care as these powerful drugs enabled physicians to combat bacterial infections. Antibiotics became widely available in the 1940s. Kanamycin belongs to a family of antibiotics known as aminoglycosides. Kanamycin normally kills bacteria by binding to one of the ribosomal subunits, subsequently blocking the ability to produce proteins. Unfortunately, the overuse and misuse of these miracle drugs over the ensuing years has caused an alarming increase in the number of bacterial species that are resistant to one or more of our arsenal of antibiotics. The genes for resistance are typically found on plasmids, which are small circular pieces of DNA that can be transferred from one bacterium to another. One such plasmid encodes for an enzyme called kanamycin nucleotidyltransferase (KNTase) that inactivates kanamycin enabling bacteria to become resistant to it. This plasmid is widely used in the production of genetically modified organisms. KNTase was originally isolated from *Staphylococcus aureus*, a species of bacteria that is a major cause of hospital-acquired infections. An understanding of the molecular structure of KNTase is important in order to provide a model for the development of new, more effective drugs. In addition, a KNTase mutant isolated from thermophilic bacteria exhibits thermostability. It appears that a single amino acid mutation enables the enzyme to be stable at higher temperatures, making KNTase a good molecule for investigating the cause of enzyme thermostability.

NADPH-Cytochrome P450 Oxidoreductase

Catalyzing the Metabolism of Various Compounds



Authors: Brittany Ladewig, Katy Johnson

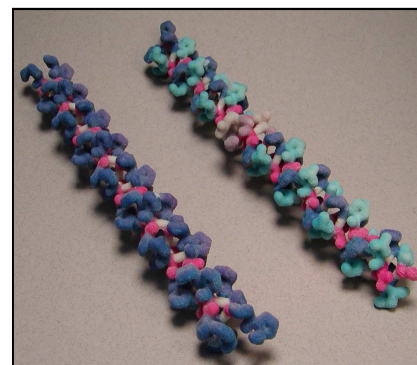
Teacher: MaryAnne Haasch

School: Wauwatosa East High School, Wauwatosa, WI

Mentor: Jung-Ja Kim, Ph.D., Medical College of Wisconsin, Milwaukee, WI

NADPH-cytochrome P450 oxidoreductase (CYPOR) is found in the endoplasmic reticulum in the cell. CYPOR's main function is to transfer electrons from NADPH to cytochromes P450, vital in the processes of all living things including the metabolism of drugs and steroid production in humans. CYPOR is a biomolecular machine. The enzyme opens up when it encounters NADPH, as if on a hinge; tryptophan-677 moves, allowing NADPH to enter and transfer two electrons to the CYPOR. These electrons are transferred, one at a time, to P450 via FAD and FMN. Scientists have verified several diseases due to deficiency of CYPOR. One of the more severe diseases is called Antley Bixler Syndrome (ABS), which affects the skeletal structure of the body, creating malformations, mostly to the head or facial region. In affected children or infants, abnormalities may include prominent foreheads, protruding eyes, and underdeveloped midfacial regions. Also, fusion of adjacent bones in the arm, long, thin digits, bowing thigh bones, or certain joints permanently flexed or extended are additional abnormalities caused by ABS. Other less severe cases of CYPOR deficiencies include steroid hormone deficiencies; ranging from cases to under-masculinization in males or virilization in females. Since CYPOR is a vital enzyme to our body and other living things, research is continuing to find other diseases that could be caused by malfunctions in the process. However, as mice embryos died before birth when the enzyme was absent, isolating this process in living organisms proves difficult. Also, because of CYPOR's function of detoxifying and breaking down drugs, it's important to know its effects on certain drugs to prevent any complications. Being such a vital part of every organism's system, the main question is how CYPORs transfer electrons using NADPH via FAD and FMN to the cytochrome p450. From answering this question, hopefully we can learn more about this complicated process.

Collagen: The Glue of Life



Authors: Shazia Ali, Jessica Hoffmann, Rituparna Medda, Katie Omernick

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School: Wauwatosa West High School, Wauwatosa, WI

Mentor: Françoise Van den Bergh, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Collagen, a structural protein, makes up 25% by mass of all proteins in our bodies. It is essentially the “glue” that holds our tissues together by providing strength and flexibility to our skin, cartilage, tendons, ligaments, and bones. So far, 28 types of collagen have been discovered. Our model demonstrates the basic structure of collagen: a left-handed helix made from a repeating sequence of three amino acids. These amino acids follow the pattern Glycine-X-Y, or in our model, specifically Glycine-Proline-Proline. To make the complete collagen molecule, three of these strands come together in the endoplasmic reticulum and are “zipped up” creating a trimer. Together, the polypeptides will form a right-handed helix. The individual strands are held together by hydrogen bonds between the Glycine. The Glycine is situated in the center of the helix because it is small and can be tightly packed together. When the production of collagen I is flawed, bones become easily fractured. This is called “brittle bone” disease or osteogenesis imperfecta. Dystrophic epidermolysis bullosa is caused by mutations in collagen VII. This disease causes fragility in the dermis, which then results in blister formations when skin is exposed to friction because there is no collagen to adhere the layers of skin together. Problems with collagen can also be caused by dietary factors, as in scurvy. When people do not eat enough vitamin C, collagen cannot be hydroxylated and loses its strength, causing gum disease and skin hemorrhaging. Collagen can also be affected in autoimmune diseases. One example involving the skin is bullous pemphigoid. In this disease the immune system “decides” that collagen XVII does not belong and an immune response develops against this protein leading to its destruction and the formation of blisters on the patient. You can see from these diseases the importance of the structural role of collagen. Without it, common tissues in our body could not be held together and activities most people take for granted become impossible. Collagen truly is the glue of life.

West Bend High School

Transcription Factor SPI

Zinc & Cadmium: Size Really Does Matter



Authors: Ryan Prinz, Jared Blommel, Brian Fossum, Paul Fossum, Michelle Geidel, Myranda Reimer, Emily Bruckert, Gib Flockert, Jen Donagen

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Mentor: Rajendra K. Kothinti, University of Wisconsin-Milwaukee, Milwaukee, WI

Cadmium is an environmental pollutant that can be responsible for failures in the human body. Humans are exposed to cadmium through the smoke of cigarettes; both first and second hand, contaminated water, and plants grown in contaminated soils. The accumulation of this toxic metal, cadmium, from our environment can interfere with a specific DNA transcription factor responsible for coding a protein, sodium-glucose transporter (SGLT1), which regulates the re-absorption of glucose into the blood. Sp1 was found to lose its binding capability with specific GC rich DNA (Petering et. al.). The protein that we are modeling is transcription factor IIIA, which has a comparable structure to SP1, the protein in study. The transcription factor which helps control the production of Finger 3 of transcription factor SP1 readily accepts a cadmium ion in place of the normal zinc ion due to their identical charges. The cadmium ion is significantly larger than the zinc, so the structure of the protein is altered to accommodate the size difference. Both the tertiary and quaternary structures are affected by this shift. Some pertinent amino acids that are altered are his21, his25, cys8, lys15, met18, and cys5. The helix's shift is especially notable because it causes the transcription factor to incorrectly bind to the DNA; thus, mRNA is not correctly transcribed and the glucose-regulating protein is not produced. The lack of this protein results in numerous health concerns, namely glucosuria (loss of glucose in the blood) and kidney failure. Our task is to show the specific differences caused by the binding of cadmium to transcription factor SP1. This research may help to expand knowledge of the specific health effects of toxic cadmium.

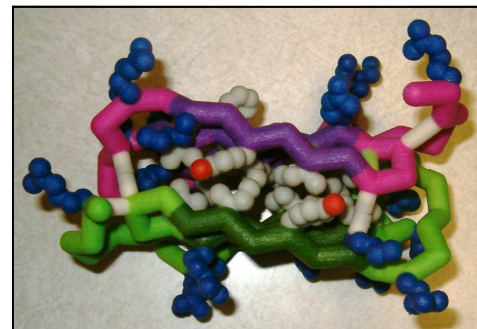
Tabatabai NM, Blumenthal SS, Petering DH. *Toxicology*. 2005 Feb 28;207(3):369-82.

Krepkiy D, Forsterling FH, Petering DH. *Toxicology*. 2004 Jul;17(7):863-70.

Grafton High School

The Tale of Two Structures: Lymphotactin 10 (Ltn 10)

and 40 (Ltn 40)



Authors: Renee Buchholz, Kyrstin Mueller, Dustin Studelska, Lindsay Zadra

Teacher: Fran Grant

School: Grafton High School, Grafton, WI

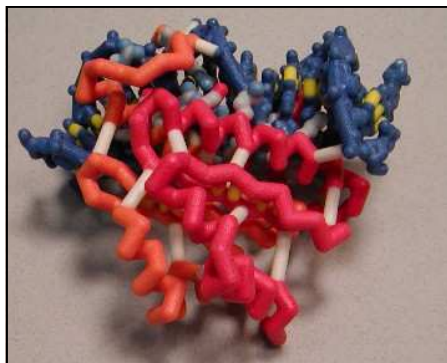
Mentor: Robbyn Tuinstra, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Chemokines, like Lymphotactin (Ltn), are small proteins that direct lymphocytes to sites of injury or infection, aiding in the healing process. Chemokines bind sugars on the surface of epithelial cells that line the vascular and lymphatic systems, allowing chemokines to “catch” circulating lymphocytes. The interaction of chemokines with lymphocytes is mediated by the activation of cell surface receptors, signaling immune cell migration. HIV targets a chemokine receptor to infect and replicate within the T-cells. Alternatively, diseases such as Crohn's disease and rheumatoid arthritis may result from a dysregulation of chemokine production and lymphocyte migration. In chronic inflammatory conditions such as these, there is an inappropriate or uncontrolled T-cell infiltration driven by Ltn. Unlike other chemokines, Ltn exists under physiological solution conditions in two distinct, yet equally populated structures. The conversion between these structures is freely reversible, but can be stabilized by changes in solution conditions. At 10°C and high salt concentration, Ltn is a monomer (Ltn10) exhibiting the conserved chemokine fold of a 3-stranded β -sheet and an α -helix. At 40°C, without salt, Ltn adopts a 4-stranded β -sheet structure (Ltn40). Two Ltn10 proteins turn themselves inside out and bind together to form one Ltn40 protein. While the Ltn10 structure appears to activate the Ltn receptor on immune cells, Ltn40 is believed to contain the sugar binding site. The long term objective of the research is to determine the mechanism of Ltn rearrangement and the biological significance of each structural species.

Marquette University High School

Serum Response Factor (SRF):

They Key to Making or Breaking a Heart



Authors: Wesley Borden, Daniel Brodzik, Patrick Carter, Brian Digiacinto, John Geary, Thomas Niswonger, Joseph Radke, Matthew Shields, and Caleb Vogt

Teacher: Keith Klestinski

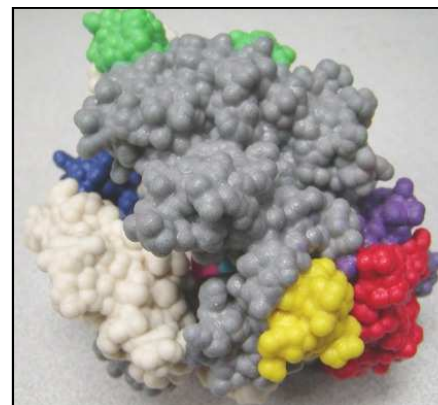
School: Marquette University High School, Milwaukee, WI

Mentor: Ravi Misra, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Serum Response Factor (SRF) is a protein transcription factor. Transcription factors use the information on DNA to regulate RNA production that ultimately encodes for proteins the body needs. SRF promotes the formation and growth of cardiac muscle cells. SRF functions as a "dimer" composed of two identical subunits. The SRF dimer works as a complex in cooperation with other associated factors to help control gene expression. The number and type of SRF-associated factors determines which genes are expressed, where they are expressed, and when they are expressed. SRF and the other factors bind a DNA sequence known as the Serum Response Element (SRE). The SRE region is known for its characteristic nucleotide sequence and is found in the promoters of SRF responsive genes in many different species. One way SRF is important for heart formation and function is based on its ability to regulate genes essential for the differentiation and growth of cardiac muscle cells. In mouse embryos, SRF is absolutely required for proper cardiac development. Research shows that embryos deprived of SRF die from underdeveloped hearts. Overexpression of SRF can result in cardiac hypertrophy (enlarged heart syndrome). Better understanding of SRF function holds the potential to develop therapies designed to repair human heart damage.

St. Dominic High School

RNA Polymerase II



Authors: Sam Andreski, Julie Armstrong, Greg Cigich, Andrew Cobb, Kevin Drees, Mark Engel, Matt Geisinger, Joe Heckes, Patrick Jordan, Ryan Kohl, Kevin Koprowski, Michael Moakley, Rachael Reit, Tara Robey, Andrew Ruka, Michael Russell, Lauren Schmidt, Tyler Sherman, Paige Siehr

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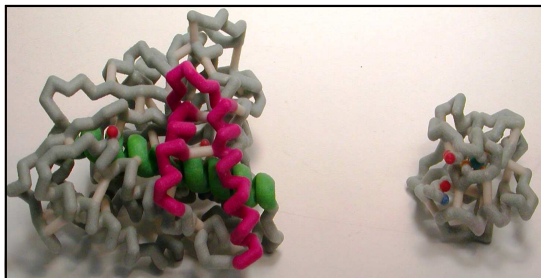
Mentor: Vaughn Jackson, Ph.D., Medical College of Wisconsin, Milwaukee, WI

RNA Polymerase II (Pol II), a major up-keeper of our cells, is found in the nucleus of all eukaryotic cells and is one of the most important enzymes in our body. Pol II has twelve protein subunits, which also makes it one of the largest molecules. Its function is to surround the DNA, unwind it, separate it into two strands, and use the DNA template strand to create a messenger RNA (mRNA) copy of a gene. These mRNA copies of genes are needed by the cell to make proteins to keep the cell healthy. The mRNAs are the templates used by ribosomes to link amino acids into long chains in the correct order to form all the different proteins in our bodies. In fact, RNA Pol II is so essential to life that when the poison, alpha-amanitin, from the Death Cap mushroom attaches to RNA Pol II, death occurs within 10 days. The alpha-amanitin goes into the funnel portion of Pol II and inserts under the bridge helix. The poison is thought to limit the movement of the bridge helix and prevent a ratcheting movement that translocates the DNA template. When working properly, RNA Pol II can make RNA copies of DNA at speeds of 1000 to 1500 bases per minute. The alpha-amanitin slows this speed to 2 or 3 bases per minute. At this slow speed, RNA Polymerase II cannot do its job of making messenger RNA copies of our genes. Without mRNA molecules, the ribosomes cannot make the thousands of different proteins needed for life.

Kettle Moraine High School

It's Positive to be Negative:

Electron Transfer and Cytochrome P450 Cam



Authors: Disa Drachenberg, Nicole Fischer, Andy Flick, Madelyn Homuth, Tom Lankiewicz, Matt Larson, Melanie Mayes, Kimi Struck, Kaitlin Swanson

Teachers: Peter Nielsen, Karen DeBoer, and Steve Plum

School: Kettle Moraine High School, Wales, WI

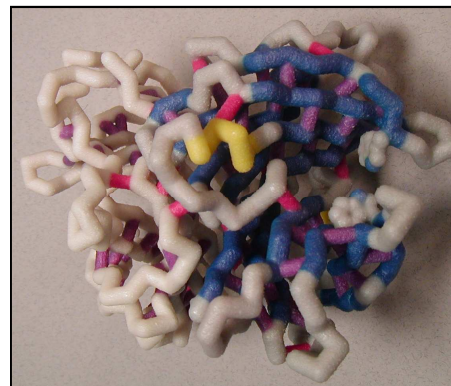
Mentor: Daniel Sem, Ph.D., Marquette University, Milwaukee, WI

Cytochromes P450 perform many functions, predominantly creating steroid-like hormones and metabolizing various organic compounds, vitamins, xenobiotics, pharmaceuticals, and carcinogens. They are present in most prokaryotic and eukaryotic cells. In humans, many cytochromes P450 are found in the adrenal cortex, but are primarily in the liver, where they metabolize ninety percent of all pharmaceuticals. P450cam is one of the few P450s that have been widely studied. This particular P450 hydroxylates camphor molecules and through electron transfer, lowers the activation energy, creating an energetically favorable circumstance for camphor metabolism. P450cam requires an allosteric regulator and electron source, putidaredoxin, to activate this process. Allosteric regulators can act like a key to either lock or unlock a molecule, thereby disabling or enabling metabolism. Putidaredoxin (PDX) interacts with P450cam at three specific points. At two of these points, ionic bonds form to connect the two molecules, and at the third point, an amino acid on the PDX buries itself inside P450cam, which pushes against a specific helix in the P450, termed the I-helix, on the P450cam, forcing the helix to straighten. When the I-helix straightens, another pair of helices, referred to as the F-G helices, move, and camphor molecules that are bound to the outside of the P450cam can gain access to the heme group, because the F/G-helices open like a trap door. Metabolism can begin once the PDX transfers electrons from its two-Iron/two-Sulfur ferredoxin cluster to the Iron in P450cam's heme group, thereby reducing it in preparation for catalysis. There are two likely electron pathways in this redox reaction. By studying P450cam as a model, general knowledge of the electron transfer mechanism and the pathways for heme reduction can be gained.

Edgewood Middle School

A Probable Treatment for Alzheimer's Disease:

Somewhere Between Confusion and Clarity, The Transthyretin Protein



Authors: Rebecca Cray, Walter Grosenheider, Sami Huntoon, Taylor Johnson, Corrie Lee, Eric Madsen, Claire McLaughlin, Mariah Popp, Jake Power, Kathleen Ralph, Sam Rothrock, Neil Sekhon, Emily Sharata

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Mentor: Jeff Johnson, Ph.D., University of Wisconsin- Madison, Madison, WI

The amyloid beta protein and transthyretin are two proteins of interest to scientists trying to understand how Alzheimer's disease develops. The disease results from the accumulation of a specific fragment of the amyloid beta protein, referred to as the A-beta protein. When this small piece of protein is cut from the amyloid precursor protein, the smaller piece is referred to as A-beta protein. The A-beta peptide protein forms plaques by aggregating together, causing neurons in the brain to die, resulting in Alzheimer's disease. Transthyretin, however, is the "good protein" and prevents the A-beta protein from killing those neurons. Though researchers do not specifically know how the transthyretin does this, it is hypothesized that the transthyretin binds with the A-beta so that it cannot interact with the neurons. In a healthy cell, transthyretin proteins are thought to be transport proteins the thyroid hormones. Though the A-beta protein is always being made in healthy cells, its regular function is not known. This has been an area of interest, because only some people get Alzheimer's disease. Researchers believe this may be due to different amounts of defense mechanisms, such as transthyretin, in each person's brain. Studies have shown that mice that have been genetically engineered to have higher levels of the A-beta protein also have more transthyretin, therefore preventing Alzheimer's disease. This increase in transthyretin, unfortunately, only happens in mice, and has not been seen in humans living with Alzheimer's disease. Because mice have dramatically increased transthyretin proteins, which block the A-beta toxicity, researchers are trying to find ways of increasing that protein in humans.

Brown Deer High School

The Beta Bunch: A-Beta of Amyloid Precursor Protein



Authors: Jason Baughman, Elaine Brushafer, Katie Easton, Andrew Faught, Sara Faught, Ben Jaberg, Adam Majusiak, Catie Pfeifer, Amy Ramirez, Karleisa Rogacheski

Teachers: Gina Vogt

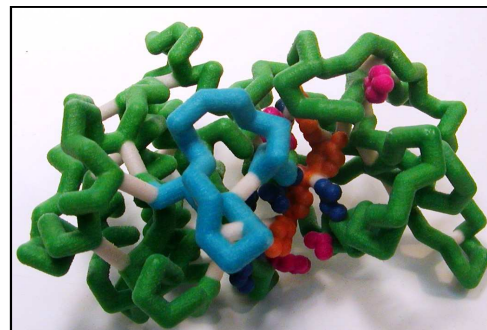
School: Brown Deer High School, Brown Deer, WI

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

The A-beta section of APP forms aggregates in the brain that are related to Alzheimer's disease. The year 2006 marks the 100th anniversary of the identification of Alzheimer's disease, an ailment affecting an estimated 4.5 million Americans, including, it is thought, approximately half of the population aged 85 and older. The ailment typically begins after age 60, and the risk of developing Alzheimer's disease increases with age since the disease is progressive in nature. A slow moving debilitating affliction, Alzheimer's disease causes mild forgetfulness in its early stages, but as the disease advances, Alzheimer's disease destroys nerve cells, disrupting connections between the cells in areas of the brain vital to memory. In addition, it chemically weakens their ability to send messages, which can impair thinking and memory. The subject of our study is the A-beta portion of the amyloid-beta precursor protein (APP), identified in the protein data bank as 1Z0Q; it may contain a potential link to the enigmatic nature of Alzheimer's disease. APP resides within the cell membrane and the A-beta portion is formed when APP is cleaved by the beta and gamma secretases, leaving a 42 amino acid peptide. After the protein is cut by these secretases sticky surfaces are exposed on the A-beta peptide. In the brain, the A-beta peptide aggregates in extracellular plaques. Presence of these plaques is associated with Alzheimer's disease; however, it is unknown whether the aggregates are a cause or an effect of the disease. Efforts to stop the progression of the disease target secretase identification and the resulting effect of selective drugs on these secretases as well as the aggregation of the A-beta peptide.

Bradford High School

Gleevec: Rational Drug Design for Cancer



Authors: Jonathan Jara-Almonte, David Jensen, Vincent LaRosa, Peter McGrain, Jessica Sherman

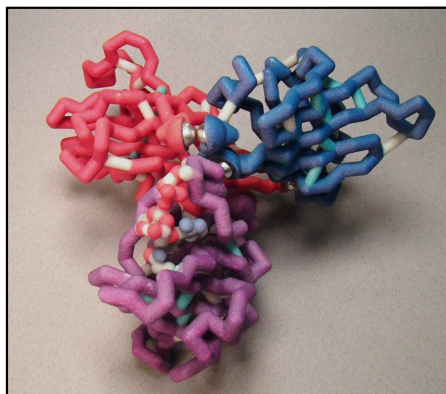
Teacher: Jean Lee

School: Bradford High School, Kenosha, WI

Mentor: Robert Deschenes, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Chronic myelogenous leukemia (CML) results from a translocation between chromosomes 22 and 9. The translocation results in an abnormal fusion between the BCR and the c-ABL tyrosine kinase gene which leads to uncontrolled cell division. The structure of the Abl kinase provides an understanding of kinase activation and a strategy for the design of inhibitors. The key to activation of c-Abl is the region of the protein called the activation loop. Phosphorylation alters the position of this loop such that when the kinase is active, the loop is fully extended in an open position. An aspartic acid residue (Asp-381 in Abl) within a conserved Asp-Phe-Gly (DFG) motif at the NH₂-terminal base of the loop is positioned to interact with the magnesium ion that coordinates the phosphate groups of ATP. The remainder of the loop provides an area for substrate binding. This continuously binds with ATP and leads to constitutive activation of the kinase. The drug Gleevec is designed base on the 3D structure to inhibit c-Abl. When Gleevec binds with the protein, the NH₂ terminal rotates drastically compared to the active conformation, so that Phe-382 points towards the ATP binding site. The rest of the loop mimics a substrate binding to the enzyme, thereby blocking the enzyme active site for ATP and preventing tyrosine phosphorylation. Gleevec is an effective treatment for patients with CML. However, mutated forms of c-Abl have emerged that are resistant to Gleevec. By studying the structure of the drug-resistant variants, scientist hope to create alternative forms of Gleevec that can be used in Gleevec resistant cases.

The N-Terminal Carbohydrate Recognition Site of the Cation-independent Mannose 6-Phosphate Receptor : The Internal Bouncer



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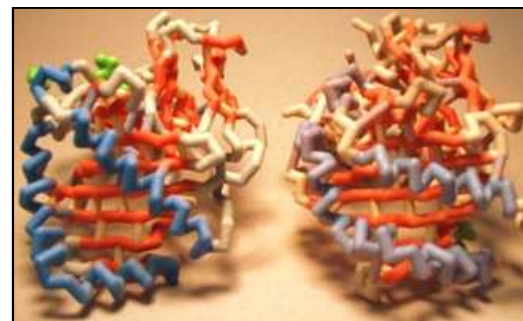
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In order for the human body to function properly, lysosomes are necessary. Lysosomes are found in virtually every cell in the body, and they rid cells of metabolic waste through the process of hydrolysis. Important assistants to the formation of lysosome are mannose 6-phosphate receptors, which guides the hydrolytic enzymes, to the lysosomes. These hydrolytic enzymes are tagged with a phosphorylated carbohydrate, mannose 6-phosphate, which allows for the recognition by the mannose 6-phosphate receptors. The hydrolytic enzymes are responsible for breaking down the metabolic waste within the lysosomes and are therefore essential to be taken into the lysosome. Without the mannose 6-phosphate tag, the receptors cannot recognize the enzymes, thus denying the delivery of the enzymes into lysosomes. The receptor has three sites to which the mannose 6-phosphate binds. The 300-kDa receptor plays a vital role in trafficking newly synthesized mannose 6-phosphate containing acid hydrolases to the lysosomes. It is not yet understood how the three sites are able to interact with one another. Though rare, lysosomes can malfunction, causing a toxic buildup, which damages and eventually kills the cell. In this case, Lysosomal Storage Disorder (LSD) results. There are over 40 Lysosomal Storage Disorders, the most common being Tay-Sachs Disease. Tay-Sachs, a degenerative disease, occurs when lysosomes fail to rid the brain of lipid waste material. Most cases are diagnosed in infancy, and death occurs by the seventh birthday. There are no known cures for the Lysosomal Storage Disorders. However, enzyme replacement therapy is available for the treatment of four of the Lysosomal Storage Disorders. This expensive therapy is performed to alleviate symptoms and the pain caused by the LSD.

Sound the Alarm! How the Immune System Responds



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When antigens invade the body, we need a way to protect ourselves. One of the defenses that we have in place is envelope antigens into the cell via endocytosis and break the antigen into pieces. These antigen pieces are presented on Class II Major Histocompatibility Complexes (MHC II), which are molecules present specifically in the human body in order to identify invaders. MHC II molecules are sometimes referred to human leukocyte antigen, or HLA molecules. Receptors located on T-cells recognize MHC II molecules and will mount an immune response against the antigen peptide piece which has been presented on the MHC II. The proteins which “cradle” the fragments during presentation are known as HLA-DR. The T-cell receptor binds to the antigen located in the HLA-DR and determines if the substance is harmful to the body. When the HLA-DR proteins are initially formed, they cradle a placebo antigen fragment, called CLIP. This fragment is essential for maintaining the structure of the HLA-DR protein in the absence of an antigenic peptide fragment. After an antigen has been endocytosed and broken into pieces, CLIP must be replaced by the best fitting fragment of antigen. HLA-DM is responsible for removing CLIP from HLA-DR and replacing it with a piece of the antigen. Additionally, HLA-DM also attempts to put in the best fitting peptide piece in order to produce the most stable complex to generate a long-lasting immune response. In facilitating the speed in which the removal and replacement of CLIP occurs, HLA-DM acts as a catalyst. With Andrea Ferrante and Dr. Gorski, our SMART Team has been researching exactly how HLA-DM and HLA-DR interact to produce the catalytic effect. By building models of certain parts of HLA-DM and HLA-DR, the researchers should find clues as to how their structures interact.