

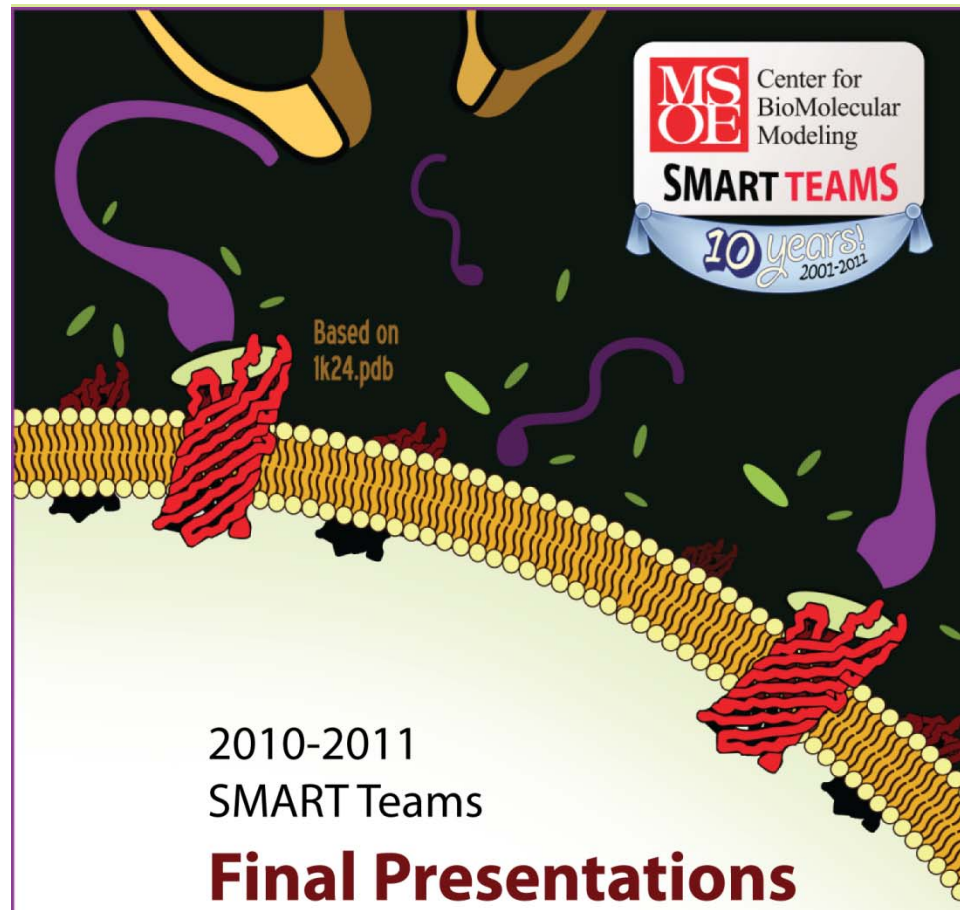


**National Center for
Research Resources**



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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.



2010-2011
SMART Teams

Final Presentations

Medical College of Wisconsin
March 19, 2011

Session 1: 9:00-11:00am
Session 2: 11:30am-1:15pm
Session 3: 1:30-3:15pm

<http://cbm.msoe.edu/stupro/smart/index.html>

SMART Teams are supported by grants from the NIH-NCRR-SEPA and the NIH CTSA Award to the Medical College of Wisconsin.

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 administrators who support their faculty, and the 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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Order of Presentations

Session 1 (9:00 – 11:00 AM)

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Cytoplasmic Dynein: It Walks the Walk St. Dominic School

Authors: Jesse Austin, Jenna Brockman, Hannah Brown, Ben Caballero, Ryan Chaffee, Luke Emery, Amanda Hodgson, Finola Hughes, Jackie Jarosz, Kevin Kohl, Connor Lagore, Chris Malliet, Kerri Jo Mark, Emily Ott, Drew Rusnak, Mitchell Sauer, Josh Schmirler, Graydon Schroeder, Katie Seim, Aaron Siehr, Joe Valentyn, Keegan von Estorff, Michael von Estorff and Evan Wetzel

Teacher: Donna LaFlamme

School: St. Dominic Middle School,
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Mentor: Jason Bader, Ph.D.,
Medical College of Wisconsin



Cytoplasmic dynein is a multi-subunit motor protein powered by ATP hydrolysis that “walks” along the microtubules (MTs) of a cell’s cytoskeleton carrying cargo that is too large to diffuse such as lysosomes, endosomes and parts of the Golgi complex. With the help of accessory proteins dynein can transport cell components as large as the nucleus. During mitosis dynein associates with the kinetochore of chromosomes and captures spindle MTs so that chromosomes can be positioned correctly. Because of this crucial role in cell division, lack of dynein is lethal for mammalian embryos and death occurs 5-7 days after fertilization. Cytoplasmic dynein assembles as a homodimeric complex consisting of a tail where cargo is attached and a force producing head known as the motor domain. The head consists of a motor domain composed of six AAA+ ATPase subunits arranged in a ring. In addition, the head contains two microtubule binding domains (MTBD’s) which are connected to the motor domain by coiled coil stalks. The MTBD, stalk, and motor domain form the “legs” of dynein that walk along microtubules. The stalks are composed of two anti-parallel alpha helices that can move relative to each other. Changes in conformation in the motor domain caused by ATP binding to the AAA+ ring are thought to be transmitted along the stalk to the MTBD causing it to be pulled off the microtubule while conformational changes in the six helices of the MTBD upon binding to the microtubule are thought to be transmitted back along the stalk to the motor domain readying it for ATP binding.

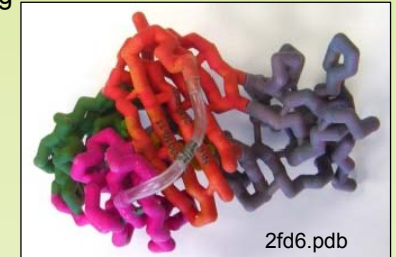
Urokinase Plasminogen Activator Receptor (uPAR) and Its Role in Metastasis Nathan Hale High School

Authors: Karmenleen Bajwa, Ashley Brost, Nick Gonzalez, Sukhwinder Kaur, Callan Loberg, Joelle Pietrzak, Rachel Pietrzak, Jamie Rypel, Samantha Toth and Kyle Tretow

Teachers: Susan Getzel and Anne Xiong

School: Nathan Hale High School,
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Medical College of Wisconsin



Cancer is spread by the plasminogen activation system which is also responsible for biological processes including clearance of fibrin clots, cell migration, and activation of growth factors. The key role is played by urokinase plasminogen activator receptor (uPAR) which is a tethered membrane protein receptor having three domains, one of which is critical in activating its substrate, the serine protease urokinase plasminogen activator (uPA). uPA activation begins when two of uPA’s domains (an N-terminal growth factor domain (GFD) and a kringle domain) interact with domain one of uPAR, creating a tight bond which converts uPA to its active form. The proteolytic cascade reaction continues when activated uPA converts inactive plasminogen to the active protease plasmin. Plasmin is a multi-use protease that can activate several matrix metalloproteinases, which along with plasmin, leads to digestion of extracellular matrix (ECM) and enhanced cellular migration. The binding of uPA to uPAR localizes these proteolytic cascades to the migrating edge of the cell, thereby clearing a path in the extracellular matrix that the cells can move through. Tumor cells often express high levels of uPA and uPAR, facilitating metastasis. uPA-uPAR expression can change a benign tumor into a malignant tumor. The activity of uPAR can be regulated by the proteolytic removal of its N-terminal D1 domain. When uPAR’s N-terminal D1 domain is disabled or removed it cannot bind to uPA, therefore the cancer cells lack the ability to metastasize. This prevention technique could lead to the cure for cancer.

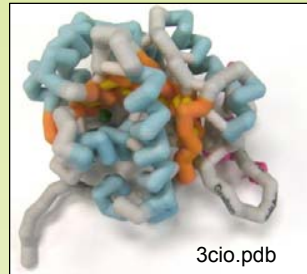
Rollin' Like a Tank The Critical Function of Wzc in Gliding Motility Grafton High School

Authors: Lisa Borden, Kelsi Chesney, Elizabeth Fahey, Alex Konop, Gabrielle Kosloske, Kaleigh Kozak, Michaela Liesenberg, Chris Rose, and Nick Scherzer

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Mentor: Ryan Rhodes, Ph.D.,
University of Wisconsin- Milwaukee



Cells of *Flavobacterium johnsoniae* move over surfaces using gliding motility. Gliding motility is widespread among the phylum *Bacteroidetes*, and several members cause disease in fish. In gliding motility, surface-exposed adhesins mediate attachment and movement of cells, and are propelled around the cell surface by motor proteins anchored in the periplasm. Evidence suggests that exopolysaccharides secreted by *F. johnsoniae* coat the substratum and provide a substrate for binding of the cell surface adhesins. Polysaccharide secretion across the outer membrane of Gram negative bacteria is facilitated by the pore-forming protein Wza and regulated by Wzc. The proteins involved in *F. johnsoniae* gliding motility are novel, and the structures have not been determined. Consequently, we modeled the tyrosine kinase domain of *E. coli* tyrosine kinase (Etk), a protein domain homologous to Wzc in *E. coli* and *F. johnsoniae*. In *E. coli*, Wzc protein forms a tetrameric oligomer, and reversible, two-step phosphorylation regulates polysaccharide secretion. In the first step, autophosphorylation of Tyr569 occurs through an intramolecular process resulting in the removal of Arg614 from the kinase active site. Unblocking the active site of Tyr569 activates the protein kinase activity of Wzc, allowing for the intermolecular phosphorylation of the tyrosine cluster on a neighboring Wzc protein. Interaction of the phosphorylated and dephosphorylated Wzc tetramer with Wza in *E. coli* results in the regulation of polysaccharide export, and researchers hypothesize that a similar mechanism controls polysaccharide secretion in *F. johnsoniae*. Elucidating the molecular mechanisms involved in gliding motility and cell adherence will advance understanding of disease pathogenesis and aid in vaccine development.

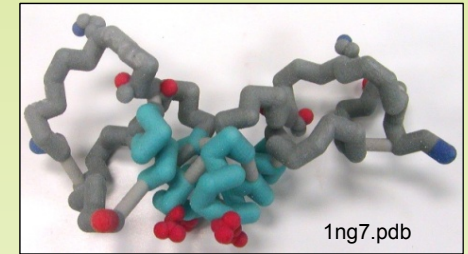
“Bad Roommate!” 3A: An Inhibitor of ER to Golgi Traffic Valders High School

Authors: Grace Ebert, Nicole Maala, Joe Nagel, Paige Neumeyer, Stacie Pearson, Gavin Schneider, Luke Schuh, Kayla Walsh, Emily Weyker and Alyssa Yindra

Teacher: Joe Kinscher

School: Valders High School,
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Mentor: William Jackson, Ph.D.,
Medical College of Wisconsin



Acute respiratory illnesses (colds), Hepatitis, Poliomyelitis, and livestock diseases are caused by members of the viral family *Picornaviridae*. The common cold is the most prevalent infectious disease in humans and results in major economic impact through loss of productivity and strain on healthcare systems. 3A is a membrane protein produced by these viruses that is necessary for forming viral replication complexes which could be targeted to combat these diseases. Normally, cells communicate with each other using the secretory pathway. Proteins from the endoplasmic reticulum (ER) enter the Golgi apparatus where they are processed and packaged into vesicles for secretion. When cells are infected by viruses, the cells produce cytokines and display viral peptides on major histocompatibility complex molecules to induce an immune response. Picornavirus 3A inhibits the host cell immune response by interrupting this communication pathway. 3A binds to Golgi-specific-brefeldin-factor 1, which inhibits protein transport. This is thought to inactivate secretion and promote the remodeling of the endoplasmic reticulum membranes into replication complexes for viral RNA synthesis. Studies have found that some 3A amino acids have been evolutionarily conserved and therefore important to 3A function. Knowing the significance of these amino acids could lead to an attenuated vaccine encoding a mutated form of 3A.

VDAC: Voltage Dependent Anion Channel

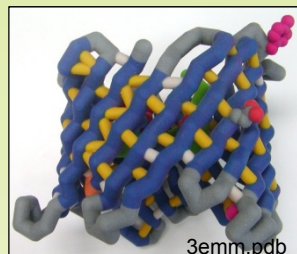
Marquette University High School

Authors: Patrick Jordan, Alexander Borden, John Fuller, Christian Gummin, Joe Puchner, Judson Bro, Kevin Bustos, Keegan English, Andrew Keuler, Qateeb Khan, Daniel Kim, Hasaan Munim, Ryan Sung and Nicholas Zausch

Teachers: Keith Klestinski, David Vogt and Mike Caballero

School: Marquette University High School, Milwaukee, WI

Mentors: Yifan Zhou and Wai-Meng Kwok, Ph.D., Medical College of Wisconsin



VDAC (Voltage Dependent Anion Channel) is a channel protein located on the outer mitochondrial membrane. It regulates mitochondria functions and cell respiration through the exchange of molecules between the cytoplasm and the organelle, such as ADP, ATP, anions, cations, and other small, hydrophilic molecules. VDAC has been implicated in cardiac ischemia-reperfusion injury as well as cancer cell survival. Yet, the precise functional roles of VDAC in cardiac injury and cancer have not been elucidated. Recent structural information of VDAC obtained at a high resolution provides essential clues to the molecular mechanism that governs this protein. Movement of the positive N-terminus voltage sensor into and out of the protein coupled with putative sites of phosphorylation facing both the cytoplasm and the intermembrane space give VDAC greater regulatory abilities. In fact, VDAC may regulate several cell survival and cell death signals, as it can potentially prevent the release of cytochrome C and, consequently, prevent apoptosis. If scientists learn more about the functions of this protein, it very well could represent a viable target for new therapeutics to treat ischemia-reperfusion injury in the heart and cancer. The Marquette University High School SMART Team (Students Modeling A Research Topic) created a physical model of VDAC using 3D printing technology.

Nek7: A Kinase with Self-Control

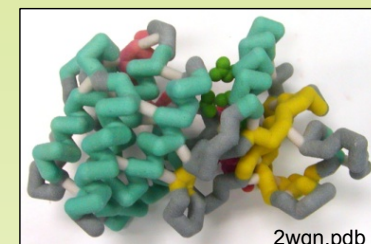
Wisconsin Virtual Learning

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Teacher: Trish Strohfeldt

School: Wisconsin Virtual Learning

Mentor: Kerstin M. Janisch, D.Sc., Medical College of Wisconsin



Blindness, polycystic kidney disease, cancer, and more can result from problems with the primary cilia of cells. Cilia are long, slender protuberances extending from the cell body. Although certain cells of human tissue (e.g. lung epithelium) have many motile cilia, most human cells typically possess one non-motile primary cilium. Primary cilia are responsible for receiving important signals for cells. They form from a basal body, which also doubles as a centromere during mitosis. The basal body forms the base of the cilia (where it connects to the cell body) and organizes the construction of the cilia from microtubules. Within retinae, specialized primary cilia connect the outer part of rod photoreceptor cells to the cell body. The length of these cilia is important in receiving the correct amount of light to allow proper vision. Nek7 is a kinase involved in mitosis and the formation and length of a primary cilium. As a kinase, Nek7 transfers a phosphate group from a high-energy ATP molecule to a protein (though the specific substrate of Nek7 is unknown). This essentially activates or deactivates the target protein. Normally, Nek7 has an auto-inhibitory tyrosine complex which blocks the active site until the conformation is altered and the protein is activated. When mutations alter this tyrosine complex, Nek7 remains active and can cause cells to multiply uncontrollably, leading to cancer. Abnormalities in Nek7 can also alter cilia length in retinae, negatively affecting and possibly eliminating vision. Further research on Nek7 could lead to new cancer and vision treatments.

Pax3-Fox01: Forbidden Transcription by Fusion Protein

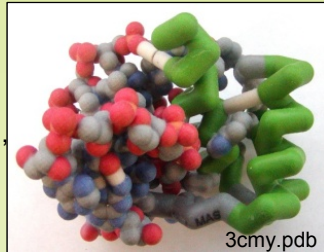
Milwaukee Academy of Science

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Mentor: Fengjie Liu and Sarah Kohler, Ph.D., Medical College of Wisconsin



Alveolar Rhabdomyosarcoma (aRMS) is a type of aggressive muscle cancer that is the number one most common non-cranial childhood cancer. For 90% of all rhabdomyosarcomas, the Pax3-Fox01 fusion protein is detected and implicated. A fusion protein results from a chromosomal translocation event in which a piece of one chromosome breaks off and attaches to another chromosome, generating a hybrid genetic code that is translated to create a new protein. In the case of aRMS, two transcription factors, Pax3 from the 2nd chromosome and Fox01 from the 13th chromosome, are fused together and generate the Pax3-Fox01, a new transcription factor which can initiate genes on strand of DNA to be read to make mRNA, which in turn is read to make protein. Pax3-Fox01 contains the DNA binding domain of Pax3, which is involved in the early human development of the eyes, ears, face, nerves, and muscles. This fusion protein also contains the Fox01 transactivation domain containing DNA remodeling abilities that help unravel chromatin for potential transcription. Together, the activities of these two proteins allow the fusion proteins to activate genes that should only be activated during early stages of human development. This leads to oncogenesis in aRMS. Pax3-Fox01 is capable of binding to Pax3 binding sites on several muscle genes' regulatory elements, including the enhancer of MyoD, the master regulator for muscle development. The Cirillo lab has demonstrated that Pax3-Fox01 can open compacted chromatin. Together, this data suggests that the Fox01 portion of the protein untangles chromatin, and the Pax3 portion recognizes and reads DNA both at Pax3 normal binding sites and at additional, non-Pax3 binding sites, leading to activation of embryonic genes and cancer genes in aRMS. If this hypothesis is true, this research on Pax3-Fox01 will elucidate a potential target for treatment of aRMS.

Sepsis Takes a Toll on Human Health: Understanding the Role of Toll-like Receptor 4

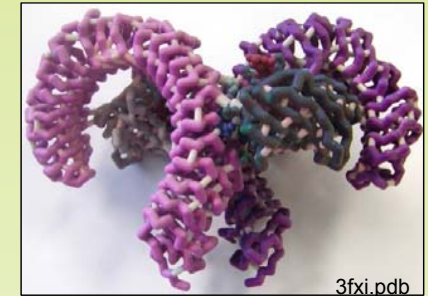
Laconia High School

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Teacher: Jodie Garb

School: Laconia High School, Rosendale, WI

Mentor: Ben Tourdot and Debra Newman, Ph.D., Blood Research Institute, Blood Center of Wisconsin



Sepsis, the tenth leading cause of death in the United States, is a whole-body inflammatory response to infection. Sepsis leads to septic shock, a condition with a 30-40% mortality rate caused by multiple organ failure and development of hypotension. Lack of understanding of the pathophysiology of sepsis limits successful treatment options. Gram-negative bacteria are a major cause of sepsis. The outer membrane of Gram-negative bacteria contains lipopolysaccharide (LPS). LPS is recognized by a receptor complex expressed by certain immune cells that includes the transmembrane glycoprotein, Toll-like receptor 4 (TLR4), and myeloid differentiation factor-2 (MD-2). Over-stimulation of immune cells by LPS through TLR4/MD-2 results in sepsis. TLR4-mediated activation of immune cells is also responsible for allergic contact dermatitis due to nickel, a common and less fatal condition than sepsis. The crystal structure of TLR4-MD-2-LPS has elucidated residues involved in LPS binding to TLR4/MD-2 and in TLR4 dimerization, which are essential events involved in immune cell activation and induction of sepsis. A better understanding of interactions between TLR4, LPS and MD-2 will help create better drugs to disrupt the interactions. The Laconia SMART (Students Modeling A Research Topic) Team used 3-D printing technology to model the TLR4 dimer in collaboration with MSOE.

Detecting B-Type Natriuretic Peptide to Better Diagnose Congestive Heart Failure

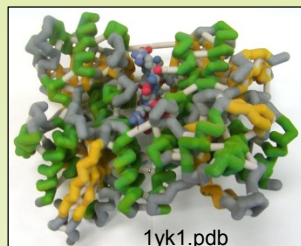
Greenfield High School

Authors: Tammy Tian, Jordan Tian, Panfua Thao, Robin Sandner, My Nguyen, Guetzie Maya, Elizabeth Konieczny, Amber Inman, Chi Huynh, Marlene Hagen, Hope Gueller, Nick Evers, Brayden Campagna, Tania Alvarez and Jodi Allison

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Mentor: Shama Mirza, Ph.D., Medical College of Wisconsin



There are about 400,000 new cases of Congestive Heart Failure (CHF) every year in the United States. CHF is a disease that interferes with the heart's ability to pump blood efficiently throughout the body. Major symptoms of CHF are fatigue, shortness of breath, nausea, sleeplessness, and swelling of the heart, lungs, and legs. One indicator of CHF is B-type Natriuretic Peptide (BNP), a hormone released due to stress on heart ventricles. A biologically active BNP molecule consisting of 32 amino acids (BNP-32) results from proteolytic cleavage of the precursor protein (originally 134 amino acids long). While CHF patients have a high concentration of BNP, this protein does not cause the disease. BNP-32 indirectly regulates sodium and water levels to reduce swelling. Natriuretic peptides, like BNP, do this by causing vasodilation and decreasing levels of certain chemicals that cause swelling. One of the receptors of BNP is Natriuretic Peptide Receptor-C (NPR-C), a clearance receptor found in the heart and other organs. When BNP binds to NPR-C, BNP is removed from the bloodstream and broken down, and swelling in that area reduces. Since CHF patients have a large amount of BNP, the receptors are unable to break down all of it and the swelling remains. Continual stress and swelling can be fatal. A way to measure the level of BNP *in vivo* could diagnose CHF before it becomes serious. Scientists are currently working on this through quantification of BNP using mass spectrometry-based technology.

A Molecular Weapon Against Viral Infection: The Puzzle of Protein Kinase R Structure Solved

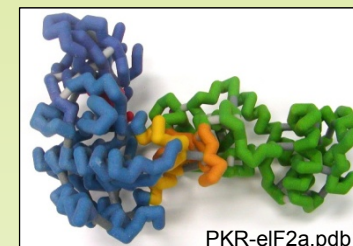
Brookfield Central High School

Authors: Justin Fu, Zach Gerner, Shariq Moore, Nickhil Nabar, Vickrum Nabar, John Scanlon, Josh Speagle, Sai Vangala and Nikil Prasad

Teacher: Louise Thompson

School: Brookfield Central High School, Brookfield, WI

Mentor: Madhusudan Dey, Ph.D., University of Wisconsin-Milwaukee



One common mechanism against viral infection is to inhibit cellular protein synthesis, thus preventing viral propagation. The protein kinase R (PKR) is one of several enzymes involved in cellular immunity against viral infection through the phosphorylation of translation factor eIF2 α . PKR is composed of two domains: two double stranded RNA binding domains (dsRNA) and a kinase domain (KD). The crystal structure of the PKR KD bound to its substrate eIF2 α revealed that each KD is composed of two lobes: an N-terminal lobe (N-lobe) and C-terminal lobe (C-lobe). The active site lies between these two lobes where the ATP is bound. The two N-lobes of each PKR KD interact to form a dimer whereas the C-lobe is bound to eIF2 α composed of an S1 domain and a helical domain. Upon viral infection, PKR senses the dsRNA inserted by the virus, and is dimerized and activated. The active PKR molecule then binds to eIF2 α . Upon binding, a conformational change in eIF2 α brings the helix insert containing Ser51 (phospho-acceptor residue) closer to the ATP. The γ phosphate of ATP is then transferred to the Ser51. The phosphorylated eIF2 α inhibits cellular protein synthesis in infected cells. Such fundamental insights into the mechanisms of substrate recognition and phosphorylation by PKR will help design a small molecule that will activate PKR more effectively leading to improved immunity against multiple viral infections. In addition, the general mechanism of PKR function may be applied to cancer therapy due to its role in controlling cell differentiation.

Rap1b: Stopping Blood Everywhere

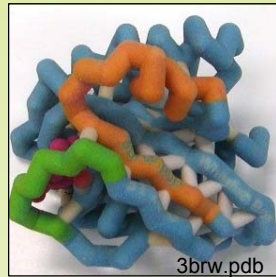
Whitefish Bay High School

Authors: Colleen Ackermann, Isaiah Kaplan, Lazura Krasteva, Shannon Mahony, Andrew Phillips, Zack Serebin and Alice Xia

Teachers: Paula Krukar and Michael Krack

School: Whitefish Bay High School, Whitefish Bay, WI

Mentor: Jackie Porath and Gil White, M.D., Blood Research Institute, Blood Center of Wisconsin



Blood clotting is crucial for maintaining homeostasis, or equilibrium of internal conditions. However, unintended consequences may result if blood is unable to clot or clots excessively. The protein Rap1b plays a key role in the process of regulating blood clotting, which is facilitated by platelets sending activation signals. When endothelial cells are damaged, matrix proteins are exposed; hence, activation signals are sent to Rap1b. In its inactive state, Rap1b is bound to GDP. Through the replacement of GDP with GTP, two switch regions on the now-activated Rap1b change shape. With the help of guanine nucleotide exchange factors (GEFs) and GAP proteins, Rap1b then binds to an effector protein, activating integrins, which control the attachment of cells to matrix proteins. In turn, the activated integrins located on the cell membrane of a platelet will allow platelets to stick together, forming a blood clot. Research has shown that if a mutation occurs at amino acid N17, the protein is permanently set to an inactive state. However, when amino acid G12 mutates into valine, Rap1b is constitutively active. An imbalance in the signaling cascade of blood clotting leads to health risks, such as strokes or bleeding disorders. Studying Rap1b brings us one step closer to understanding how the body regulates platelet activation and clotting.

Of Mice and MAGL (Monoacylglycerol Lipase)

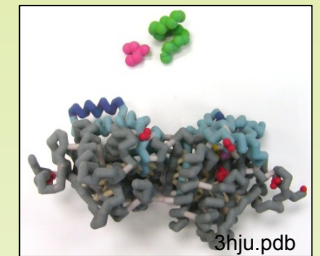
Brown Deer High School

Authors: Sophia Andera-Cato, Amanda Arnold, Samuel Bach, Aaron Blumberg, Taylor Bombinski, Maxwell Bord, Matthew Daniels, Ariel Feiertag, Mark Greaves, Danielle Gross, Alexander Her, Trevor Hogg, Erica Kennedy, Keirra Lewis, Trevor Martin, David McMurray, Evan Naber, Carlos Orozco, Nickolas Perez, Collin Rice, Alana Rodgers, Andreas Sauer, Jordan Schubert, Amanda Schulman, Colin Tubbs, Shavon Tucker and Taylor Wray

Teacher: Gina Vogt

School: Brown Deer High School, Brown Deer, WI

Mentor: Cecilia Hillard, Ph.D. and Lalita Shrestha, Medical College of Wisconsin



About 18.8 million American adults suffer depressive disorders that may occur with anxiety and substance abuse. Tetrahydrocannabinol (THC), a compound in marijuana, is a cannabinoid chemical that binds to and activates cannabinoid receptors (CB1) in the pre-synaptic cell membrane as part of neuron-to-neuron transmission in the endocannabinoid system (ECS). Glutamate in the pre-synaptic cell is released and binds to the post-synaptic cell triggering the synthesis and release of 2-arachidonoylglycerol (2-AG). 2-AG returns to the pre-synaptic cell binding to and activating CB1 receptors. THC mimics 2-AG action, and is used to study the ECS retrograde signaling system and its effect on appetite and mood. A protein from the pre-synaptic cell, monoacylglycerol lipase (MAGL), hydrolyzes 2-AG into arachidonic acid (AA) and glycerol controlling 2-AG levels. When MAGL is hyperactive, too much 2-AG degrades, which is hypothesized to contribute to depression and anxiety. Hypoactive MAGL activity creates an excess of 2-AG. It is hypothesized that this can contribute to obesity and addictive behaviors. The Brown Deer Students Modeling a Research Topic Team, in alliance with MSOE, built a MAGL model using a 3D printer. Study of MAGL crystal structure may provide the key to regulating MAGL's enzymatic activity leading to therapies that will prevent neurodegenerative disorders.

ExoU: A Poor Clinical Outcome

Kettle Moraine High School

Authors: Samantha Cinnick, Maggie Davies, Alexandra Greene, Anna Henckel, Grant Hoppel, Sridevi Prasad and Matt Wright

Teacher: Steven Plum

School: Kettle Moraine High School

Mentor: Jim Feix, Ph.D.,
Medical College of Wisconsin



Pseudomonas aeruginosa, the bacterium which is a major cause of pneumonia and other infections, is especially fatal to cystic fibrosis patients with an excessive build-up of mucous in the lungs. This in turn creates favorable conditions for the *P. aeruginosa* to invade and release the protein ExoU. ExoU, one of the key proteins in *P. aeruginosa*'s invasion process, is a phospholipase which breaks down lipids. If a cystic fibrosis sufferer acquires *P. aeruginosa*, the ExoU produced by the bacterium will digest the membranes in the lung cells, leading to poor clinical outcome. ExoU can be found on the surface of the *P. aeruginosa* bacterium and is transported into the host cell through the type III secretion system. Next, ExoU kills the host cell by destroying the integrity of the plasma membrane, cleaving the lipids in the membrane. If ExoU is defective or blocked, *P. aeruginosa* is completely unable to attack the host cell. Given that the structure of ExoU is mostly unknown, Patatin, a phospholipase similar to ExoU is being studied by scientists in order to develop a better understanding of the structure and function of ExoU. From this understanding, scientists may then be able to create drugs to lessen the severity of *P. aeruginosa* infection, thus increasing the chances of survival for infected cystic fibrosis patients.

Coming to a Location within You: Localization of Protein Kinase A and DPY-30

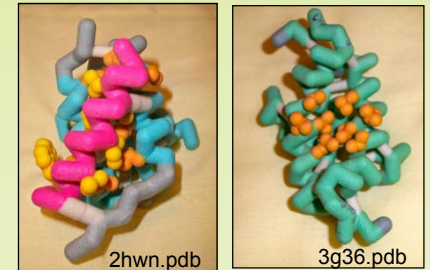
Cedarburg High School

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Signal transduction is an essential process in cells. One critical signaling molecule, protein kinase A (PKA), phosphorylates target proteins, thereby changing their conformations and modifying their functions. PKA is a component of multiple signaling pathways that regulate a variety of proteins. Since the broad substrate specificity of PKA can lead to phosphorylation of unintended proteins, PKA activity must be limited to specific times and places. A-kinase anchoring proteins (AKAPs) bind and help localize PKA to specific areas. The RIIa domain in PKA provides a shallow groove for an amphipathic helix of AKAP to bind via interactions of hydrophobic side chains. A similar binding motif is found in the DPY-30 domain, which suggests this domain may also play a localization role. The ability of AKAP to interact with PKA and regulate its activity is essential for the specificity of many cellular responses. The ability of a cell to localize proteins containing a DPY-30 domain may also be important for proper function. If localization is disrupted, serious problems like heart disease and cancer may result. To further understand the impact of structural interactions on localization, physical models of RIIa, DPY-30, and AKAP amphipathic helix have been designed and built by the Cedarburg High School SMART (Students Modeling a Research Topic) Team using 3D printing technology.

People Suffer Because of A Disulfide Bond The Role of Thioredoxin in Tuberculosis

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Tuberculosis, a disease caused by the bacterium, *Mycobacterium tuberculosis*, affects about one-third of the world's population, killing 2 million people each year. The bacteria reside in macrophages of the respiratory tract of infected individuals. Macrophages are a type of immune cell whose function is to engulf and kill foreign substances such as bacteria that invade the body. Macrophages do this by bleaching, or oxidizing, bacterial cell proteins, rendering the bacterial cell susceptible to cell death. To protect against these lethal oxidative attacks by macrophages, two bacterial cell proteins, Thioredoxin C (TrxC) and Thioredoxin Reductase (TrxR), function to reduce the oxidized proteins, thus stabilizing them and enabling the survival of the bacteria. To accomplish this protective reduction and maintain redox homeostasis in the bacterial cell, TrxC donates electrons to the oxidized bacterial cell proteins, becoming oxidized in the process. In order to continue to donate electrons to protect the cell, TrxC itself must now gain electrons (be reduced). TrxR is the protein that donates electrons to oxidized TrxC converting it back to the reduced form, continuing the redox cycle. NADPH then reduces the oxidized TrxR with its electrons stored in a tightly bound FAD. To accomplish this redox cycle, TrxC binds to TrxR through a disulfide bond, and is stabilized by a hydrophobic pocket on TrxC that fits into a crevice on TrxR. If this reaction can be prevented, the protective redox cycle of TrxC/TrxR could be stopped thus leading to cell death of the *Mycobacterium tuberculosis*, preventing many deaths.

Gluten For Punishment – The Role of HLA DQ2 in Celiac Disease

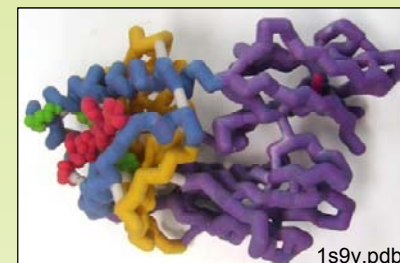
Cudahy High School

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Celiac disease is an inflammatory disease of the gastrointestinal tract. Many people are affected by this disease, but are undiagnosed. They dismiss the digestive and neurological symptoms as nothing more than malaise. Those who are diagnosed need a controlled, gluten-free diet to alleviate symptoms, since there is currently no medical treatment. The HLA-DQ2 allele is the second highest risk factor for celiac disease. HLA-DQ2 is a MHCII molecule, which presents antigens to a specific subset of T cells (T helper). An MHCII molecule is a protein exposed on the membrane of antigen presenting cells; these cells populate several body districts like small bowel mucosa. In a physiological setup, T cells are able to distinguish between “self” and “non-self” antigens, and they can be stimulated only upon recognition of “non-self” antigens bound to a “self” MHCII. Structurally, HLA-DQ2 has a binding groove, composed of two alpha helices and a beta sheet floor, where peptides from undigested gluten (gliadins) bind. The interaction of gliadins with this particular HLA allele relies specifically on the presence of Tyr-22, Leu-53, Arg-70 and Lys-71, leading to HLA-DQ2-gliadin complex formation. This complex may be recognized by T helper cells as “non-self,” with subsequent activation and initiation of an autoimmune response. The ensuing inflammation causes disruption of the structure and function of the small intestine. By learning about binding of gliadins to MHCII, scientists may find a drug that can block the binding groove from gliadins or modify the gliadins to prevent their interactions with HLA-DQ2.

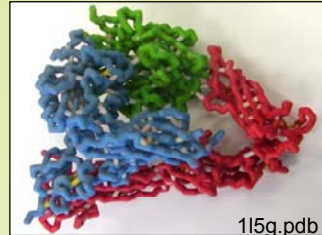
An Integrin with Integrity The Manipulated Interactions of $\alpha_v\beta_3$ Saint Joan Antida High School

Authors: Beanca Buie, Brianna Castanon, Neli Jasso, Alexis Lockett-Glover, Shiny Vang, Fatima Yacoob and Sukaina Yacoob

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In order for a cell to interact and adapt to its environment, the cell needs receptors to recognize and respond to external signals. These signals tell a cell to migrate, proliferate, or specialize. Without receptors, a cell would be unable to function within its environment. One group of receptors that enable a cell to interact with its environment are the integrins. There are several families of integrins, one of which is the β_3 family. Cyr61, a protein associated with breast cancer, wound healing, and vascular diseases such as atherosclerosis and restenosis, is an activation-dependent ligand of the β_3 integrin family. This group of adhesive receptors mediates cell-cell and cell-extracellular matrix interactions. One of the two family members is $\alpha_v\beta_3$, an integrin expressed on the surfaces of endothelial cells, smooth muscle cells, monocytes, platelets, and osteoclasts. Binding of Cyr61 to $\alpha_v\beta_3$ stimulates angiogenesis, the creation of blood vessels, and migration of tumor cells.

$\alpha_v\beta_3$ integrin commonly binds to the amino acid sequence RGD (arginine, glycine, and aspartic acid) on many extracellular molecules such as vitronectin and fibronectin, however, Cyr61 binds to $\alpha_v\beta_3$ via a unique sequence. When a ligand binds to $\alpha_v\beta_3$ integrin, a conformational change in $\alpha_v\beta_3$ initiates a signaling cascade that results in increased cell migration. Over-expression of $\alpha_v\beta_3$ can lead to life-threatening cancers such as breast cancer, melanoma, and colon cancer. Understanding and finding a way to restrict the expression and activation of $\alpha_v\beta_3$ integrin may lead to a new treatment of tumors with decreased side effects compared to conventional chemotherapy.

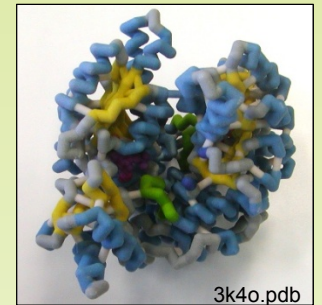
DOPA Decarboxylase: It's Dope! Using DOPA Decarboxylase to Understand the Production Effects of Dopamine and Serotonin Wauwatosa West High School

Authors: Jimmy Kralj, Jordan Llanas, Natalie Mullins, Leah Rogers, Jordan Voit and Jack Wongtam

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Dopamine and serotonin are neurotransmitters that affect a myriad of behaviors including basal locomotive activity and aggression in animals. The synthesis of both neurotransmitters involves the enzyme DOPA decarboxylase (DDC). In humans DDC will decarboxylate several different substrates; in flies, DDC is selective in that it decarboxylates only a few substrates. One of the main differences in the structure of fly DDC compared to mammalian DDC is the presence of a loop that may account for the substrate specificity of fly DDC. For the decarboxylation reaction to occur in flies, this loop must move out of the way. The DOPA can then access the active site, which contains PLP (pyridoxal-5'-phosphate) bound to the enzyme. At this site, DDC decarboxylates DOPA by breaking a carbon-carbon bond and releasing a carboxyl group. During this reaction an unstable negative charge is created. This charge is stabilized by PLP, allowing the reaction to proceed. In this way DDC is essential to the production of dopamine as well as serotonin. By studying the effects of serotonin and dopamine in flies, scientists can further investigate the biochemistry of basal locomotive activity and aggressive behavior.