Center for BioMolecular Modeling
SMART TEAMS
2013-2014

ADVANCING HEALTH THROUGH RESEARCH AND DISCOVERY
CTSI

SEPA SCIENCE EDUCATION PARTNERSHIP AWARD
Supported by the National Institutes of Health

The SMART Team (Students Modeling A Research Topic) Program is supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number 8UL1TR000055. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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

Center for BioMolecular Modeling
SMART TEAMS
2013-2014

SMART Team Presentations

Session 1: 9:00 - 11:30am
Session 2: 12:30 - 3:00pm

Medical College of Wisconsin
Saturday, March 29th

http://cbm.msoe.edu/stupro/smart/local/index.html

Center for BioMolecular Modeling

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Lance Presser, Ph.D. & Sanjib Bhattacharyya, Ph.D.
Robert Peoples, Ph.D.
William Jackson, Ph.D.
Dave Nelson, Ph.D.
James R. Kincaid, Ph.D. & Piotr J. Mak, Ph.D.

SMART Team Teachers

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Dan Goetz, Fran Grant & Lisa Neeb
Donna LaFlamme
Melissa Kirby
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Kathy Stelling
Brian Coffey
Karen O'Donnell
Mary Anne Haasch
Louise Thompson
Karen Tiffany
Emily Harrington
Kevin Paprocki & Tyler Reed
Robbyn Tuinstra, Ph.D.
Keith Klestinski & Carl Kaiser
Christine Petzold
Joseph Kinscher

Order of Presentations

Order of Presentations









"Good Vibrations" Differential Hydrogen Bonding in Human CYP17A1 Determines Hydroxylation versus Lyase Chemistry

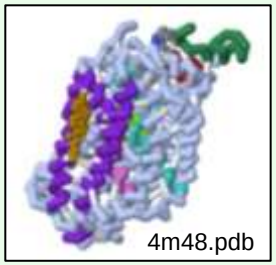
Valders High School

Authors: R. Ansorge, A. Brandl, R. Bushman, E. Evans, T. Evenson, A. Riederer and I. Schmidt
Teacher: Joseph Kinscher
School: Valders High School, Valders, Wisconsin
Mentors: James R. Kincaid, Ph.D. & Piotr J. Mak, Ph.D., Department of Chemistry, Marquette University

Inhibiting Cytochrome P45017 (CYP17A1) could prevent androgen synthesis and treat prostate, breast, and other hormone responsive cancers. Cholesterol is the precursor of all steroid hormones including testosterone and estrogen. CYP17A1, an enzyme bound to the membrane of adrenal cells, plays a critical role in the biosynthesis of steroid hormones. This enzyme determines whether corticoids, which control metabolism, or androgens such as testosterone, will form. CYP17A1 catalyzes the hydroxylation of its substrates pregnenolone (PREG) and progesterone (PROG) to form 17-OH pregnenolone (17-OH PREG) and 17-OH progesterone (17-OH PROG), respectively. Most interestingly, it can further process the 17-OH PREG by catalyzing the cleavage of the carbon 17, 20 bond as a next step, which is the first committed step in androgen biosynthesis. While the enzyme can similarly transform the 17-OH PROG, it does so with much lower efficiency, and it is this difference which has attracted the interest of researchers. Attention has been focused on a key amino acid, asparagine 202 (N202), whose amide fragment can provide differential H-bonding interactions with these two substrates. The technique of resonance Raman spectroscopy can provide structural insight into the mechanisms that direct the reaction along a given pathway. Improved structural resolution at the active site of CYP17A1, may help lead scientists to better anticancer drug development. The Valders SMART (Student Modeling A Research Topic) Team used 3D printing technology to model the protein CYP17A1.

Dopamine Reuptake Inhibition as the Means of Antidepressent Mechanism of Function

Madison West High School

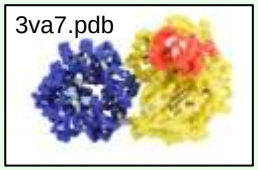


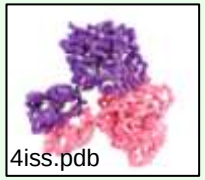
Authors: H. Deng, T. Luo and S. Vorperian
Teacher: Christine Petzold
School: Madison West High School, Madison, Wisconsin
Mentor: Dave Nelson, Ph.D., Department of Biomolecular Chemistry, University of Wisconsin – Madison

Maintaining the equilibrium of neurotransmitters (NT) at neural synapses is essential for normal brain functioning. Lack of regulation of NT levels is associated with disorders including depression, Parkinson's disease, ADHD, and epilepsy. The dopamine transporter (DAT) is the primary removal mechanism of the NT, dopamine, from the synaptic cleft. The regulation of NT reuptake is critical for preventing chemical imbalance and the inhibition of reuptake has become the primary target for antidepressants. The *Drosophila melanogaster* DAT was crystallized in complex with a tricyclic antidepressant (TCA) and found induced in an outward-open conformation towards the synaptic cleft. Three factors contribute to inhibiting the inward-facing conformation required for DAT activity: the antidepressant nortriptyline bound at the substrate-binding site blocks important helix movement, a cholesterol molecule stabilizes the outward conformation, and lastly the C-terminus caps the cytoplasmic gate. The Madison West SMART (Students Modeling a Research Topic) modeled the DAT structure using 3D printing technology. The structure of TCA-bound DAT provides new knowledge of eukaryotic transporters and enables a better understanding of the critical factors and conformational changes associated with NT transport inhibition to allow for targeted drug research.

The Great Escape: How Urea Amidolyase Allows a Pathogenic Fungus to Excape the Immune System

Greenfield High School

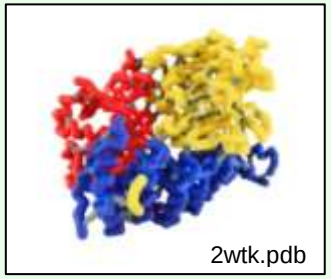




Authors: D. Alphin**,** A. Braatz, K. Cavins**,** F. Deleon-Camacho, S. Emkay, H. Flees, A. Franitza, A. Gerwig, E. Groth, L. Gangland, A. Idell, L. Klug, V. Nakhla, Z. Osberg, P. Paniagua and J. Wallner
Teachers: Julie Fangmann & Drew Rochon
School: Greenfield High School, Greenfield, Wisconsin
Mentor: Martin St. Maurice, Ph.D., Marquette University, Department of Biological Sciences

According to Rice University, 70% of people are affected by the infectious fungus *Candida albicans*. The immune system uses T and B cells to stop pathogens. People with suppressed immune systems, such as children with transplants, AIDS or cancer patients, lack functional T and B cells, so they rely on macrophages to destroy *Candida*. *Candida* can kill and exit macrophages due to an enzyme: urea amidolyase (UAL). While in the macrophage, *Candida* goes through a morphological switch from a sphere to a structure with hyphae due to an environment change. UAL converts urea to ammonia and CO_2, creating an environment for hyphae to form, bursting the macrophage. The Greenfield SMART (Students Modeling A Research Topic) Team used 3D printing technology to model the four domains of UAL. The biotin carboxylase (BC) domain uses energy from ATP cleavage to attach CO_2 to the swinging arm portion, or biotin carboxyl carrier protein (BCCP) domain. The BCCP domain swings across UAL, attaching CO_2 to urea forming allophanate in the carboxyl transferase (CT) domain. Allophanate moves to the allophanate hydrolase (AH) domain, which hydrolyzes the allophanate into CO_2 and ammonia. Increases in CO_2 and ammonia cause hyphae to form, destroying macrophages and allowing *Candida* to spread. Since humans lack UAL, researchers could block UAL's active sites to prevent *Candida's* macrophage-killing shape change, thus preventing systemic candidiasis without damaging human cells.

Growths in Your Colon Aren't Fun, Get Yourself Some LKB1! The Role of LKB1 in Cancerous Growth

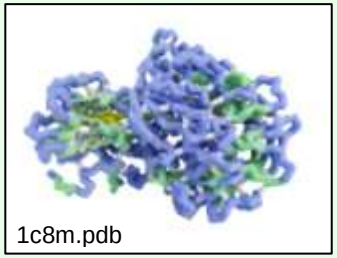


Grafton High School

Authors: S. Haider, B. Konon, A. Mosin, D. Potter, Y. Sueoka and H. Weber
Teachers: Dan Goetz, Fran Grant & Lisa Neeb
School: Grafton High School, Grafton, Wisconsin
Mentor: Stephanie Cossette, Ph.D., Department of Developmental Vascular Biology, Medical College of Wisconsin

The National Cancer Institute alone spends $4.9 billion every year on cancer research. Liver Kinase B1 (LKB1) stands out as one important protein that regulates cell metabolism, cell division, and therefore, cancerous growth. LKB1 is a key regulator of cell metabolism and cell division acting as a tumor suppressor by turning on other proteins that suppress tumor growth. Human mutations in LKB1 cause the disease Peutz-Jeghers syndrome, resulting in benign tumor-like growth called polyps in the intestine and a 50% chance of developing cancer by the age of 50. When cell energy, ATP, is low LKB1 will be activated. Active LKB1 regulates the activity of adenosine monophosphate-activated protein kinase (AMPK). LKB1 directly activates AMPK by adding a phosphate group to Thr-172. AMPK activity increases the production of ATP by activating glycolysis and fatty acid oxidation. AMPK can also decrease the amount of energy needed by the cell by inhibiting protein synthesis and cell growth. Both of these processes play a role in cancer development. Drugs like metformin, a successful diabetic drug, are thought to activate LKB1 by phosphorylating Thr-336, which in turn causes LKB1 to activate AMPK to cease cancerous growth by shutting down anabolic pathways. The Grafton SMART (Students Modeling a Research Topic) Team modeled LKB1 using 3D printing technology.

Standing in the Way of the Common Cold Pleconaril – Is it the "Key" to Keeping Rhinovirus Locked Out of Cells?



Marquette University High School

Authors: J. Fuller, D. Kim, R. Sung, E. Arnold, A. Borden, L. Ortega, R. Johnson, H. Albornoz-Williams, C. Gummin, A. Martinez, N. Boldt, D. Ogunkunle, P. Ahn, B. Kasten, Q. Furumo, N. Yorke, J. McBride, I. Mullooly, M. Tripi and D. Hutt
Teachers: Keith Klestinski & Carl Kaiser
School: Marquette University High School, Milwaukee, Wisconsin
Mentor: William Jackson, Ph.D., Microbiology and Molecular Genetics, Medical College of Wisconsin

According to World Health Organization statistics, the common cold is the most prevalent known disease of humans. The majority of colds are caused by the human rhinovirus--an enterovirus genetically similar to dangerous viruses like polio and hepatitis A. Rhinovirus infection can lead to 72-hour periods of morbidity, including symptoms like sore throat, runny nose, and muscle weakness, often causing people to miss school or work. Rhinovirus is inert until infection occurs causing the immune system to combat the virus. Rhinovirus transmission is usually *via* aerosolized respiratory droplets or contact with contaminated surfaces. Once in the body, the virus binds to the cell surface, allowing it to enter cells. Cells use the Intercellular Adhesion Molecule 1 (ICAM-1) signaling protein to latch on to each other, but viruses bind to ICAM-1 using a site on the virus surface known as the "canyon." Since there are over 150 rhinovirus serotypes, it is impossible to put every serotype in one vaccine. Instead, scientists are developing new drugs, such as pleconaril, that bind to the canyon and prevent the virus from attaching to the host cell. This prevents the virus from replicating thus eliminating the spread of the virus and the symptoms caused by it. The Marquette University High School SMART Team modeled a portion of the human rhinovirus capsid bound to pleconaril using 3D printing technology.

Modeling the Alcohol Binding Site of the NMDA Receptor Using the GluA2-receptor Structure

Brookfield Academy

Authors: M. Ali, S. Gundamraj, T. Kaur, S. Morris, S. Puri, R. Singh, V. Singh, L. Smith-Feinburg and L. Wang
Teacher: Robbyn Tuinstra, Ph.D.
School: Brookfield Academy, Brookfield, Wisconsin
Mentor: Robert Peoples, Ph.D., Department of Biomedical Sciences, Marquette University

According to the National Institute of Alcohol Abuse and Alcoholism, about 18 million people have an alcohol abuse disorder. Alcohol binds to the N-Methyl-D-aspartate Receptor (NMDA) receptor, inhibiting cognition, short-term memory formation, motor coordination, and overall regular CNS function. The Brookfield Academy SMART (Students Modeling A Research Topic) Team used 3D printing technology to model the alcohol binding site on the NMDA receptor. This receptor is an ion channel in CNS neurons. Binding of the neurotransmitter, glutamate, allows the passage of calcium and sodium ions through the channel, thus controlling multiple intracellular signaling pathways. Alcohol inhibits the gating of the receptor, preventing the flow of ions, leading to the symptoms of intoxication. The NMDA receptor is a heterotetramer, containing two GluN1 and two GluN2A subunits. Alcohol binds to the transmembrane domain of the receptor, interacting with the amino acids Gly638, Phe639, Phe639, Leu819, and Met818 (of subunit GluN1) and Met 823, Phe636, Leu824 and Phe637 (on GluN2A). Site-directed mutagenesis studies have identified the importance of these residues. Mutations in the same position on different subunits can drastically modulate the inhibition of the receptor by alcohol. Further understanding of the NMDA receptor mechanisms could lead to treatment for long-term alcohol abuse.

The Human RhD Protein and Hemolytic Disease of the Newborn

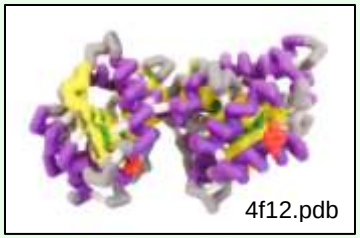
Saint Dominic School

Authors: J. Austin, G. Gundrum, G. Hilbert, C. Hildebrand, B. Hughes, S. Jaskolski, M. Kahler, W. Klingsporn, D. Lagore, K. MacDonald, T. Mark, J. Minessale, S. O'Brien, M. Peterman, S. Reinbold, A. Rusnak, L. Scott, R. Storts, M. Vuckovich, M. Weisse, N. Wilke and C. Wormington
Teacher: Donna LaFlamme
School: Saint Dominic School, Brookfield, Wisconsin
Mentor: Matthew Karafin, M.D., Associate Clinical Investigator, Blood Center of Wisconsin, Assistant Professor of Pathology, Medical College of Wisconsin

Hemolytic disease of the newborn (HDN) occurs during pregnancy when the red blood cells of an RhD positive (RhD+) baby comes in contact with the immune system of an RhD negative (RhD-) mother. The mother's immune system identifies the RhD protein on the baby's erythrocytes as foreign, and produces anti-D antibodies, which cross the placenta causing destruction of the baby's red cells. Resulting symptoms range from mild jaundice and anemia to perinatal death. The RhD protein belongs to an ancient family of ammonia channels and is found on RhD+ erythrocytes, but is missing from RhD- red cells. The St. Dominic S.M.A.R.T. Team has modeled RhD using 3-D printing technology. Our model highlights RhD's twelve transmembrane helices and the sidechains of its nonfunctional ammonia channel. Extracellular loops 3, 4, and 6 carry clusters of D antigen epitopes while loops 1, 2, and 5 do not play a major role in RhD antigenicity due to their sequence identity with RhCE. The RHD gene arose from gene duplication of the RHCE gene and has 93.8% homology. Along with RhAG (Rh associated glycoprotein) both RhD and RhCE are part of the trimeric Rh complex on erythrocytes, essential to the cell's structural integrity. HDN research led to the discovery of RhD and to the highly complex Rh blood group system whose major antigens are D, C/c, and E/e. Hemolytic disease of the newborn is now preventable by injecting RhD- mothers with anti-D immunoglobin to prevent them from developing active immunity to their babies RhD+ erythrocytes.

$GABA_B$ $Thera_P$

Kettle Moraine High School

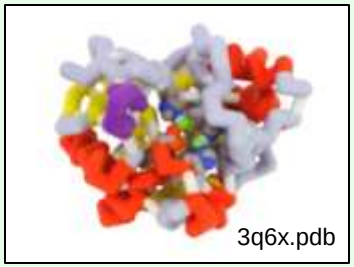


Authors: J. Doenier, J. Grewe, M. Griesbach, M. Gokuli, E. Hinds, L. Kim, M. King, A. Schwarzkopf and A. Smith
Teacher: Melissa Kirby
School: Kettle Moraine High School, Wales, Wisconsin
Mentor: Michelle Mynleiff, Ph.D., Deparment of Biological Sciences, Marquette University

In the mammalian central nervous system, gamma-aminobutyric acid (GABA) is the primary inhibitory signaling molecule. One receptor for this molecule, $GABA_B$, has been linked to feelings of calmness, as well as mental disorders such as alcoholism and depression. Pharmaceutical compounds that bind the $GABA_B$ receptor are currently used to treat muscle spasticity and various types of addiction. However, excessive activation of this receptor can hinder muscle function. Activation of the metabotropic $GABA_B$ receptor by GABA influences neuronal activity by coupling with G proteins to activate a signaling cascade that leads to downstream effects including the modulation of various ion channels. The $GABA_B$ receptor is a dimer composed of two different subunits (GBR1 and GBR2), each with 7 helices within the membrane and an extracellular domain that binds GABA. Only the GBR1 subunit directly binds the GABA molecule and other ligands with a similar structure. However, recent studies have shown that GBR2 can affect the efficiency of GABA binding to GBR1. In addition, the GBR2 subunit activates the G protein after GABA binds, leading to various downstream effects. One well known effect is the opening of potassium channels, hyperpolarizing the cell, preventing action potentials from firing, and ultimately stopping neurotransmitter release. Using 3D printing technology, the Kettle Moraine SMART (Students Modeling A Research Topic) Team has modeled the $GABA_B$ receptor to study its structure to determine therapeutic possibilities. $GABA_B$ receptors' widespread importance in the nervous system may lead to new uses in the neurological and medical fields.

The Emergence of a Superbug: NDM-1 and Its Role in Carbapenem Resistance

Milwaukee Academy of Science



Authors: L. Barns, C. Bester, C. Burrows, B. Daubon, D. Davis, N. Hall, J. Jackson, J. Jones, T. Jones, J. Kendrick, V. McCotry, N. Payne, R. Taylor, Q. Tyra, E. Walls and D. Washington
Teachers: Kevin Paprocki & Tyler Reed
School: Milwaukee Academy of Science, Milwaukee, Wisconsin
Mentors: Lance Presser, Ph.D. & Sanjib Bhattacharyya, Ph.D., City of Milwaukee Health Department Laboratory

Imagine going to the doctor to be treated for a normally treatable infection only to find that no effective treatments exist because all conventional antibiotics are ineffective. In some regions of the world, antibiotic prescription isn't regulated and overuse has lead to antibiotic resistance. Carbapenems are a class of antibiotics that inhibit bacterial cell wall synthesis and are often used as a last resort treatment for bacterial infections. New Delhi metallo-ß-lactamase-1 (NDM-1) is an enzyme that occurs in several types of bacteria and conveys resistance against carbapenems. The Milwaukee Academy of Science SMART Team (Students Modeling A Research Topic) modeled the NDM-1 protein using 3D modeling technology. NDM-1 is a single-chain polypeptide consisting of 270 amino acids found in the bacterial periplasmic space. The NDM-1 active site consists of two loops (L10 and the highly flexible L3) and two zinc ions. These zinc ions are held in place by three histidine amino acids (H120, H122, H189) on L3 and a triplet of amino acids on L10. The zinc ions bind to and sever the ß-lactam ring on carbapenems, inhibiting its antibiotic properties. It's the flexibility of L3 that gives NDM-1 the ability to hydrolyze the full spectrum of carbapenems. Researchers are concerned because the gene for NDM-1 is located on a plasmid that's frequently passed via horizontal gene transfer among various species of bacteria. An understanding of NDM-1's structure and function may prevent an outbreak of bacteria equipped with the NDM-1 enzyme.

Exoenzyme U and Ubiquitin: A Fatal Attraction

Saint Joan Antida High School

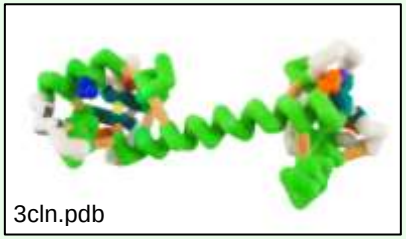

4akx.pdb

Authors: O. Adewale, A. Ali, J. Allen, V. Ammons, J. Gonzalez, A. Ray, I. Roberts and T. Woods
Teacher: Emily Harrington
School: Saint Joan Antida High School, Milwaukee, Wisconsin
Mentor: Dara M. Frank, Ph.D., Microbiology and Molecular Genetics, Medical College of Wisconsin

Exoenzyme U is the most toxic and destructive effector of the pathogen *Pseudomonas aeruginosa*, an omnipresent, strategic pathogen found in soil. Exoenzyme U (ExoU) is a strong phospholipase, a catalytic enzyme that targets the cleavage of phospholipids, which is activated inside mammalian cells by ubiquitin. ExoU is inactive in *P. aeruginosa* as prokaryotic cells do not have ubiquitin, a regulatory protein used in post-translational modification vital for processes in cells. The function of ExoU is to destroy immune cells, which allows the bacterium to replicate in vivo without being attacked by the immune system. ExoU injects toxins into a host cell that serve to destroy the cell's membrane. In this way, ExoU acts similarly to venom. Scientists have discovered that when ExoU interacts with ubiquitin, it is activated. Research has highlighted the C-terminal four-helix bundle of ExoU, principally located between residues 600 and 683, because it is a probable binding site between ExoU and ubiquitin. It is also known that Tyr-619 and Arg-661 (located near the end of the C-terminal) play a role in the binding and activation of ExoU. Arg-661 may also function as a substrate interaction or in binding. ExoU is problematic in people who use artificial breathing machines and have weak immune systems. The Saint Joan Antida SMART (Students Modeling a Research Topic) Team modeled the ubiquitin binding domain of ExoU using 3D printing technology.

CaM You Remember?

West Bend High Schools

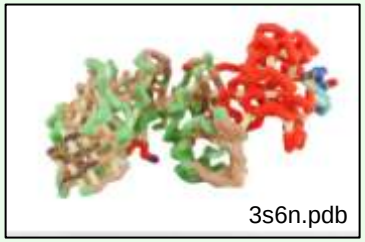

3cln.pdb

Authors: S. Boggs, L. Dommisse, R. Fisher, C. Kannenburg, S. Kassin, B. Laufer, J. Myers, T. Olwig, D. Sanfelippo and K. Vachuska
Teacher: Judy Birschbach
School: West Bend High Schools, West Bend, Wisconsin
Mentors: Audra Kramer, Ph.D. Candidate & Nashaat Gerges, Ph.D., Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin

According to the Alzheimer's Association, more than 5 million Americans are living with Alzheimer's. One in three seniors dies with this disease or another type of dementia. The potential to eliminate this painful disease lies within calmodulin, an intra-cellular receptor protein that is found throughout the body but functions in the brain to affect learning and memory. Calmodulin (CaM) plays a role in cell growth, proliferation and movement of electrons within the electron-transport chain. It enters from the post-synaptic side of the spine of a dendrite within the brain and automatically binds to calcium causing a conformational changing of the calmodulin itself. Calcium binds to the EF hand motif (a conserved helix–loop-helix sequence) found in calmodulin. The action of the calcium binding induces a conformational change to calmodulin, which forms a calmodulin-complex. An enzyme, CaM Kinase 2 binds to and activates the calmodulin-complex. Activation causes an influx in the amount of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), which increases the amount of calcium entering the cell. Researchers believe that an increase in calcium absorbed directly impacts the durability and stability of the brain. The West Bend SMART (Students Modeling A Research Topic) Team modeled CaM using 3D printing technology. Further calmodulin studies could prove to be the key to developing therapeutic treatments for mental illness, as well as finding ways to increase mental function.

Correct Splicing: The Desolation of SMA Interactions Between Gemin-2 and SMN

Hartford Union High School


3s6n.pdb

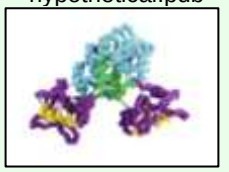
Authors: M. Daley, K. Erickson, J. Griesmer, M. Heimermann, B. Lewandowski, J. Loosen, O. Hoffman and G. Rigden
Teacher: Mark Arnholt
School: Hartford Union High School, Hartford, Wisconsin
Mentor: Mark McNally, Ph.D., Microbiology and Molecular Genetics, Medical College of Wisconsin

Spinal muscular atrophy (SMA) is a genetic disorder usually leading to death before age two. This is caused by the degeneration of motor neurons in the spine and affects one in six thousand babies yearly (Families of SMA, 2013). It is unknown why a point mutation or deletion of the SMN1 gene, which produces survival motor neuron (SMN) protein, causes this degeneration. The SMN complex, found in the cytoplasm, is made of SMN and smaller units called Gemin proteins. In a normally functioning system, the SMN1 gene codes for SMN proteins that are part of the SMN complex that forms small nuclear ribonucleoproteins (snRNPs) from SM proteins and sRNA. The SMN protein binds to Gemin-2 which holds five of the seven SM proteins, the smaller units in snRNPs, in place until the target snRNA sequence is located. The final SM proteins are added when the N-terminus of Gemin-2 is moved. The snRNPs have many functions in cells, and five of them are involved in RNA splicing. The knowledge that is available on normal interactions of SMN and Gemin-2 allow modeling of these proteins to be completed through 3D printing by the Hartford Union SMART (Students Modeling a Research Topic) Team. In children with SMA, the SMN protein cannot to bind to Gemin-2 because Asp44 is replaced by valine, causing a break in the ionic bond holding the helices together. While this situation still produces normally operating snRNPs, there are too few to correctly splice the pre-mRNA, leading to SMA.

Getting "Rit-R" Iron in the Cell: The Role of RitR in Reducing Iron Transport into *Streptococcus pneumonia*

Cedarburg High School


hypothetical.pdb



Authors: B. Allbee, N. Anderson, D. Blank, J. Bolgert, A. Bothe, N. Britt, A. Butt, S. Dyke, E. Geiser, T. Hammer, E. Janecek, I. Kalmer J. Lawniczak, M. Lesiecki, J. Levy, M. Marshall, N. Meaux, M. Ruzicka, J. Temmer, K. Tiffany, B. Vandenberg, J. Wankowski and E. Zeitlow
Teacher: Karen Tiffany
School: Cedarburg High School, Cedarburg, Wisconsin
Mentor: Nicholas Silvaggi, Ph.D., Chemistry and Biochemistry Department, University of Wisconsin-Milwaukee

According to the World Health Organization, pneumonia is the leading cause of death in children worldwide, and infection of lung tissue by *Streptococcus pneumonia* causes the bulk of bacterial pneumonia cases in children. The atypical response regulator, RitR (Repressor of iron transport Regulator), helps *S. pneumoniae* survive in the hostile oxidizing conditions in the lungs. RitR has two domains, a DNA-binding domain (DBD) and an aspartate-less receiver domain (REC). In its "inactive" form, these domains are docked (*i.e.*, close together) and the DBD is unable to bind DNA. In its "active" form, the domains are undocked; the DBD is freed from the REC. The "active" form dimerizes and can bind to DNA to turn off the iron transport genes. To study the changes that occur when RitR is activated, the Cedarburg High School SMART (Students Modeling A Research Topic) Team used 3D printing technology to model inactive RitR and a hypothetical active RitR dimer. RitR helps the bacterium survive in the oxygen-rich environment in lungs by stopping iron transport into the bacterial cell. If iron is transported into the cell, oxygen forms reactive oxygen species that damage and kill cells. *S. pneumonia* cells without RitR are unable to infect lung tissue, so RitR is a potential target for drug design.

Now You See It: The Role of Ocular Albinishm 1 in Foveal Development

Brookfield Central High School

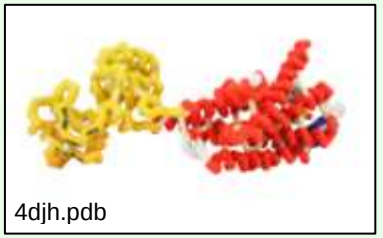

oa1.pdb

Authors: E. Afreen, D. Ajjampore, M. Czechowski, A. El-Meanawy, A. Fung, K. Gopal, J. Hubler, T. Iqbal, T. Jella, R. Karanam, E. Kim, R. Komandur, H. Mogallapalli, A. Morgan, E. Nesler, R. Sachdev, H. Shereen, N. Sood and A. Zheng
Teacher: Louise Thompson
School: Brookfield Central, Brookfield, Wisconsin
Mentor: Joseph Carroll, Ph.D., Department of Ophthalmology, Medical College of Wisconsin

One in every 60,000 children is born with ocular albinism type 1. Ocular albinism is a genetic disease in which pigmentation is lost in the eye, in the retinal pigment epithelium (RPE) located just below the photoreceptors in the retina. This reduced pigmentation affects the development of the fovea (an area of the retina responsible for 99% of vision) and leads to poor visual acuity (the capacity to see fine detail). The mutation causing ocular albinism occurs in the gene *Oa1*, which encodes a G-protein coupled receptor called Ocular albinism type 1 (OA1). OA1 is found in RPE cells, which normally absorb scattered light with melanin, allowing the eye to generate a high-contrast image. While its exact function is unknown, OA1 is known to be central to melanin biosynthesis and foveal development in the retina. Under normal conditions, the highly-selective ligand L-DOPA binds to OA1, which triggers tyrosinase to increase melanin synthesis. Simultaneously, tyrosinase also triggers L-DOPA to further bind with OA1, which activates a positive feedback loop. However, in many cases of albinism, this pathway is disrupted and tyrosinase is not fully efficient. To counter this, scientists are researching the possibility of bypassing the enzyme and flooding the cells with L-DOPA. Further understanding of OA1 and its function could lead to more effective treatments for albinism. The Brookfield Central High School SMART (Students Modeling A Research Topic) Team created a physical model of OA1 using 3-D modeling printing technology to better understand its structure-function relationship.

"I Wanna New Drug" Manipulating Kappa Opioid Receptor Ligands to Induce a Pain Relieving Response

Divine Savior Holy Angels High School


4djh.pdb

Authors: C. Assana, C. Feller, M. Fogel, A. Frelka, S. Gottfried, R. Jaber, M. Keyes, M. Koehler, K. Kujawa, N. Lautz, S. Olson, J. Pena, L. Ries, L. Schauer, C. Scherrer and C. Strandberg
Teacher: Stacey Strandberg
School: Divine Savior Holy Angels, Milwaukee, Wisconsin
Mentor: Christopher Cunningham, Ph.D., Concordia University Wisconsin School of Pharmacy

Dangerous painkillers may cause serious problems for those who fall into drugs' addictive trap, such as former NFL quarterback Brett Favre. The addictiveness of painkillers such as OxyContin and Vicodin is largely attributed to the response they trigger in proteins such as mu opioid receptors (MORs). This receptor activates cellular signaling pathways responsible for dulling pain; however, the protein also has the ability to stimulate cellular signaling pathways that makes MOP-based painkillers rewarding. An alternate target that alleviates pain but does not produce reward is the kappa opioid receptor (KOP). Unfortunately, many KOP agonists also activate intracellular signaling pathways that produce hallucinogenic effects. To investigate the changes that occur when KOP binds to different ligands, the Divine Savior Holy Angels SMART (Students Modeling A Research Topic) Team has used 3D printing technology to model the active site of the KOP with the neoclerodane diterpene, salvinorin A, to see how the induced fit changes the signal transduction pathways in a neuron of post-synaptic cells. KOP acts as a target for agonists, which are chemicals that bind to a receptor of a cell to trigger a response that activates chemical signaling pathways in cells. Manipulating receptor proteins such as the KOP to inhibit pain pathways without the addictive effect of MOP-targeting painkillers would represent a significant breakthrough in chronic pain management. Computer-aided drug design is being used to streamline the development of KOP ligands that activate this receptor in ways that result in less hallucinogenic effects.

NO S-nitrosylation, NO Memorization

Whitefish Bay High School

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Teachers: Katie Brown & Paula Krukar
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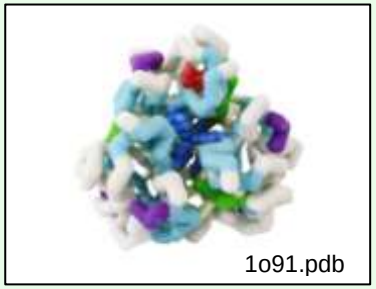
Nitrogen and oxygen are two components of the air we breathe. Bonded together as nitric oxide, they are an important signaling molecule that is involved in numerous physiological processes including the protein S-nitrosylation. The human body cannot function without this effective process, but if the regulation of this process breaks down, it can lead to common diseases such as Parkinson's and Alzheimer's. Irregular nitroslyase and denitrolayse activities may be involved in these diseases, so they are important therapeutic targets. This important process also allows blood vessels to expand, so they can transport more blood and retain more oxygen. The key component, nitric oxide (NO), attaches to glutathione to give the S-nitrosoglutathione molecule (GSNO). The NO from the GSNO then travels to a specific cysteine in a protein, which can affect the properties of that protein. Using 3D printing technology, the Whitefish Bay SMART (Students Modeling A Research Topic) Team is aiding its mentors as they research to figure out why the NO attaches to one cysteine specifically and what exactly this process does. Dr. Timerghazin and Mr. Khomyakov hypothesize that a positive amino acid, such as arginine, catalyzes the NO transfer and causes it to jump to the specific cysteine. Discovering what S-nitrolysation's physiological role as well as why one cysteine is chosen over others could lead to developments in our understanding of certain diseases that are linked to the erratic regulations of S-nitrolysation in the human body.

A Vertebral Variation Mystery: The Case for Missing Collagen-8A1

Wauwatosa West High School



Authors: P. Bonner, Z. Hassan, A. Ho, A. Lau, J. Mody, A. Rowley, Z. Stack, K. Thao and A. Zielonka
Teacher: Mary Anne Haasch
School: Wauwatosa West High School, Wauwatosa, Wisconsin
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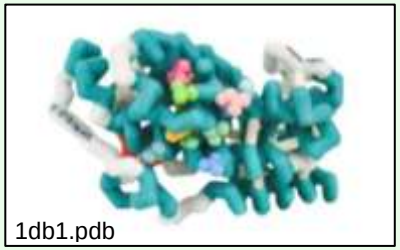
Scoliosis affects 6 to 9 million people in the United States, and collagen-8a1 may contribute to the disease's development. Collagen-8a1, a structural protein, is found throughout the body, generally serving as a connection at the base of endothelial cells, which line blood vessels and are critical to immune response and growth regulation. The molecule plays a role in angiogenesis, the development of new blood vessels, and smooth muscle cell migration. Collagen-8a1 is a highly conserved protein, meaning there are few variations of the amino acid sequence in different organisms. The only crystallized part of the molecule is a wide conical shape at the end of the uncrystallized rope-like structure. A trimer made of chains A, B, and C, collagen8a1 is held together by hydrogen bonds among sidechains such as Tyr660 and Tyr738 and water molecules in the central shaft. A single-point mutation at Tyr660 on the C chain of the molecule results in a mutant called gulliver in zebrafish, causing a distortion of the notochord. Thus, preliminary research in zebrafish suggests a new role for collagen-8a1 in bone formation during development of vertebrae. Research is currently in progress to understand how the absence or mutation of the molecule results in spinal malformations in zebrafish and if this is true for other organisms, including humans. This research could result in further knowledge as to whether dysfunctional collagen-8a1 results in spinal deficiencies. The Wauwatosa SMART (Students Modeling A Research Topic) Team modeled collagen-8a1 using 3D printing technology.

Vitamin D Receptor: An Underrated Hero

Wisconsin Virtual Learning

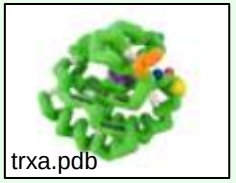


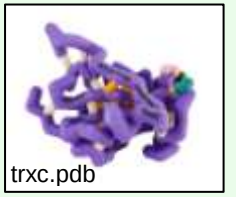
Authors: J. Amro, N. Amro, C. Gad, E. Merkel, C. Minter, S. Stuebs and H. Van Gorden
Teacher: Karen O'Donnell
School: Wisconsin Virtual Learning, Fredonia, Wisconsin
Mentors: Allie Reeme, Ph.D. Candidate & Richard Robinson, Ph.D., Microbiology and Molecular Genetics, Medical College of Wisconsin

For over a century, vitamin D (vit. D) has been used as therapy for the bacteria *Mycobacterium tuberculosis (Mtb)* due to its effects on the immune system. Interest has risen for vit. D's ability to modulate immune responses by signaling through the vitamin D receptor (VDR). Vit. D is obtained through dietary sources, like seafood, or exposure to sun's UVB rays. Vit. D in its active form can passively diffuse into multiple cell types, such as lymphocytes, while the VDR, a transcription factor for vit. D regulated genes, can regulate the effects of the hormone in these cells. Vit. D has been shown to modulate the immune response during Mtb infection by controlling production of cytokines and antimicrobial peptides and its interactions with the VDR is critical for these effects. In order to recognize VDR's role during the immune response to Mtb, the Wisconsin Virtual learning SMART Team (Students Modeling A Research Topic) is using 3D printing technology to model the structure, primarily highlighting amino acids Arg274 and His305 which are required for ligand binding to the VDR. Scientists, recognizing vit. D's positive role during an immune response, will continue to investigate vit. D as a therapeutic agent to treat this significant plight.

Second Verse, Same as the First Structures of Thioredoxin Proteins TrxA and TrxC from *Mycobacterium tuberculosis*

Messmer High School





Authors: I. Osademe, M. Cobb, J. Gonzalez Cruz, A. Richmond, J. Rios Llamosa, B. Rios Llamosa, A. Junior and A. Camacho
Teacher: Carol Johnson
School: Messmer High School, Milwaukee, Wisconsin
Mentor: Terrence Neumann, Ph.D., Concordia University Wisconsin School of Pharmacy

According to the World Health Organization, 8.6 million people became ill and 1.3 million died in 2012 from tuberculosis (TB). Thioredoxin A (TrxA) is a binding protein in the bacterium, *Mycobacterium tuberculosis*, the causative agent for TB. TB is prevalent in countries where infectious diseases have a high incidence due to weakened immune systems. TB mainly affects the lungs, but can also affect the lymphatic, circulatory, and central nervous systems. When a host organism is infected, the *Mycobacteria* in the lungs multiply often resulting in pneumonia, chest pain, and prolonged coughing. In response to this infection, host macrophages, a part of the natural immune system, engulf the *Mycobacteria* and attempt to destroy it by oxidizing bacterial proteins. To protect itself against this attack, the bacterial thioreductase system, consisting of the redox protein thioredoxin reductase (TrxR) and the thioredoxin proteins TrxA, TrxB, and TrxC, gives electrons back to the oxidized proteins. As this system works to maintain cellular redox homeostasis, finding ways to stop it might provide a new method for treating people with TB. TrxA whose function is unknown and TrxC, whose function has been well studied, have similar structures, thus it can be hypothesized that their functions are similar. Comparing binding sites between the proteins could provide insight if TrxA reacts with TrxR similarly to TrxC. By modeling TrxA and TrxC with 3D printing technology, the Messmer SMART (Students Modeling A Research Topic) Team can compare the structures of the two thioredoxins, which may lead to new strategies for curing or preventing TB.

MscL:
The Magic Behind theTouch

Laconia High School

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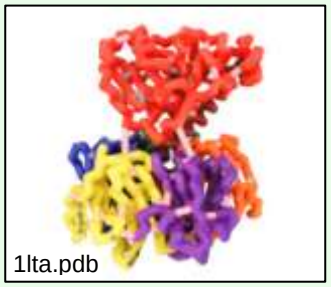
Teacher: Jodie Garb
School: Laconia High School, Rosendale, Wisconsin
Mentors: Andy Weyer, Ph.D. Candidate & Katherine Zappia, Ph.D. Candidate, Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin

The Institute of Medicine estimates $635 billion dollars are spent annually on people with chronic pain conditions. One debilitating symptom of these conditions is hypersensitivity to touch, where daily activities can be painful. Few therapeutics to ameliorate mechanical hypersensitivity exist because the mammalian ion channels that sense touch are poorly understood. The mechanosensitive channel of large conductance (MscL) is an ion channel in *Mycobacterium tuberculosis* which allows bacteria to respond to mechanical stimuli by electrochemical response, regulating membrane ion flow. Research shows structural changes in MscL causes the protein to open, allowing ions into the cell. Key amino acids include hydrophobic residues I14 and V21, creating a constriction at the cytoplasmic surface. R98, K99, K100, E102 and E104 are possibly a ligand binding site, potentially participating in the ion conduction pathway. Residues at the N-terminus of MscL, K3, F5, E7 and F8, may play a role in sensing membrane stretch. The Laconia SMART (Students Modeling A Research Topic) Team used 3D printing technology to model MscL. Understanding the structure-function relationships of the MscL channel protein may lead to better comprehension of how human mechanosensitive ion channels, like the Transient Receptor Potential Ankyrin 1, work and lead to a cure for hypersensitivity to touch.

Cholera Catastrophe

Audubon High School



Authors: N. Loeffler, Z. Zurheide, C. De Leon and E. Tovar
Teacher: Brian Coffey
School: Audubon Technology and Communication Center, Milwaukee, Wisconsin
Mentor: Joseph Barbieri, Ph.D., Microbiology and Molecular Genetics, Medical College of Wisconsin

According to the Centers for Disease Control, there are 3-5 million reported cases and 100,000 deaths each year from a diarrheal illness known as cholera. Cholera is caused by an infection of the intestine with the bacterium *Vibrio cholerae*. The toxin causes rapid and deadly dehydration and electrolyte imbalance in the infected person. Cholera is common in undeveloped countries, but has caused epidemics in all parts of the world. The bacterium spreads through the intake of contaminated food and water and is extremely unlikely to be spread directly from person to person. *Vibrio cholerae* produces a toxin that is heterodimeric, consisting of A and B subunits. The B subunit consists of five identical protein chains. These five chains are what binds to the surface of the cell and allows the catalytic part of the molecule to enter the cell. Once inside the cell, the catalytic A subunit seeks out the G protein, and attacks. With the G protein now corrupt, the cell becomes confused and sends mass amounts of sodium and water out of the cell. This action causes the flooding of the intestine and ultimately the diarrhea that can lead to deadly dehydration. Although this illness can be fatal, it is surprisingly easily cured. A person can be treated simply by getting rehydrated with clean uncontaminated water to replace the lost electrolytes. Currently there are two oral *Cholera* vaccines available, but they are only temporary protection. Researchers are working to find more efficient and permanent solutions, but currently the best way to combat cholera is good hygiene.

It's a Wonderful Metabo(life): The Story of Estrogen Sulfotransferase

Saint Thomas More High School

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Teacher: Kathy Stelling
School: Saint Thomas More High School, Milwaukee, Wisconsin
Mentors: Joseph McGraw, Ph.D., Pharm. D., & Cameron Patterson, Pharm. D. Candidate, Concordia University Wisconsin School of Pharmacy

Hypoplastic left heart syndrome is a disorder of the fetal heart in which the ventricles and aorta are formed improperly. As a result, infants with this condition will die shortly after birth unless they receive immediate surgery. According to the World Health Organization, this syndrome affects about 1 in every 4,000 babies born each year. Further research by Dr. Joseph McGraw and Dr. Andrew Pelech has linked this condition to brominated flame retardants, or BFRs. BFRs are a class of chemicals that have bromine atoms attached to them in a specific sequence. Estrogen sulfotransferase (EST) is a metabolic enzyme that metabolizes various fatty acids, neurotransmitters, and hormones. The Saint Thomas More SMART (Students Modeling A Research Topic) Team modeled EST using 3D printing technology to further investigate the structure-function relationship. One function of EST is to attach a sulfate group to thyroid hormone, thyroxin, in a developing fetus. This process changes the thyroid hormone from a non-polar to a polar substance. The polar form of thyroxine may be absorbed into the fetus and later metabolized back to the thyroid hormone for use in fetal organ development. BFRs can closely mimic thyroxin, which causes EST to attach sulfate groups to BFRs rather than thyroxin itself. However, BFRs do not function in the same way as thyroxin, and adversely sulfation in thyroid hormone metabloism. Further research may result in effective prevention or treatment of fetal developmental disorders such as hypoplastic left heart syndrome.

Myoglobin: O_2 or Not O_2 . . . That is the Question.

Brown Deer High School

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Teacher: David Sampe
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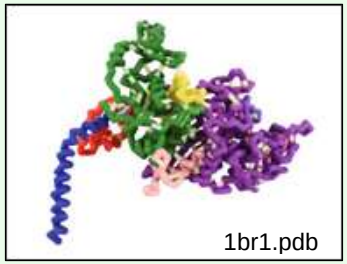
Mentors: Hannah Wagie, Ph.D. Candidate & Peter Geissinger, Ph.D., Chemistry and Biochemistry Department, University of Wisconsin-Milwaukee

Free divers can't hold their breath as long as whales, but they train their bodies to maximize their oxygen (O_2) storing potential using the protein myoglobin. Myoglobin's structure has been known for decades, but researchers are still trying to determine just how myoglobin functions. Found in muscle tissue, myoglobin stores O_2, a molecule needed to produce chemical energy. Toxic ligands, such as carbon monoxide (CO) and cyanide, also bind to myoglobin. When CO binds to a free heme group, the heme's binding affinity for CO is 20,000 times that for O2. When heme is surrounded by myoglobin, that binding affinity ratio drops to only 25. The decrease was thought to be due to steric interactions which prevented CO from occupying the same space as His64. Recent evidence suggests that electrostatic interactions and hydrogen bonds play a more important role. The O_2 is stabilized as opposed to the CO being pushed out. Several amino acids (His64, Val68, Phe43, Phe46, and Leu29,) seem to stabilize the ligand. With 3D printing technology, the Brown Deer SMART (Students Modeling a Research Topic) Team, funded by a grant from NIH-CTSA, created a model of myoglobin. If researchers can fully understand ligand discrimination by heme proteins, not only will divers be able to hold their breath longer, but we may be able to cure diseases like anemia where there is a lack of O_2 in the blood.

Myosin: Mighty Morphing Movement Molecule

Cudahy High School

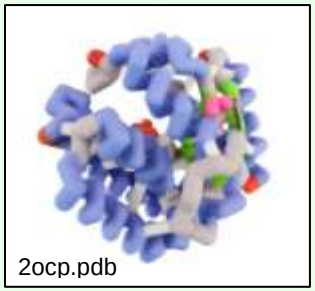


Authors: G. Ademi, S. Munoz, R. Dombrowski, S. Brzezinski, K. Tolbert, K. McDonald, P. Broekel, C. Schoemann and J. Hauk
Teachers: Dan Koslakiewicz & Dean Billo
School: Cudahy High School, Cudahy, Wisconsin
Mentor: Thomas Eddinger, Ph.D., Department of Biological Sciences, Marquette University

Muscle contraction is caused by the contractile protein myosin, which exists in various isoforms in different muscle types such as smooth, cardiac, and skeletal. Current data suggests smooth muscle myosin is in a non-functional conformation until light chain 20, which is associated with the myosin head, is phosphorylated. This allows either head to freely bind to actin, a protein also involved in contraction. The contractile process is initiated when ATP is hydrolyzed in the ATP binding region. The release of the products from ATP hydrolysis causes the “lever arm” portion of each myosin head to bend relative to the “motor domain,” pulling the actin fibers closer together, shortening the muscle cells for movement. If the contractile process is disrupted, bodily function is impaired. These key areas were modeled by the Cudahy SMART (Students Modeling A Research Topic) Team using 3D printing technology. Aortic coarctation, a developmental problem, involves a constriction of proximal aorta which increases blood pressure by narrowing the aorta, changing vascular smooth muscle in this region of vessel. While surgery can correct this anatomical constriction and prolong life, there remain long-term consequences that reduce life span. Drug treatments for a specific smooth muscle problem can be complicated by also altering function of other smooth muscles, causing undesired side effects such as incontinence. The question researchers face is targeting of a drug to a specific smooth muscle. Further understanding of smooth muscle function and regulation helps to better treat, prevent, and/or cure this and other smooth muscle diseases.

Deleterious Deoxyguanosine Kinase (dGK) Double Destruction

Westosha Central High School



Authors: J. Alberth, N. Bielski, D. Clements, J. Holloway, E. Kirsch, M. Kirsch, B. Lawrence, J. Mellor, M. Murphy, A. Papendick, S. Quist, A. J. Reeves, Z. Wermeling and J. Williams
Teacher: Jonathan Kao
School: Westosha Central High School, Salem, Wisconsin
Mentor: Jason Kowalski, Ph.D., Department of Biological Sciences, University of Wisconsin-Parkside and Department of Physics and Chemistry, Milwaukee School of Engineering

Mitochondrial Deficiency Syndrome (MDS) is characterized by a deficient amount of mitochondrial DNA (mtDNA). Without sufficient copies of mtDNA, the mitochondria cannot manufacture an adequate amount of ATP, leading to failure of energy expensive tissues such as the brain, skeletal muscle, and liver, ultimately causing death in early infancy. Deoxyguanosine kinase (dGK), an enzymatic protein, plays a role in regulating the replication of mtDNA by attaching a phosphate to a sugar/nitrogen-base nucleoside at the active site, amino acids Glu70 and Arg142. Once phosphorylated, the assembly of mtDNA proceeds. Mutations in dGK prevent the phosphorylation of mtDNA and lead to a decrease in mitochondrial function. Two point mutations have been shown to have a deleterious impact on dGK: the R142K mutation is 0.2% active when compared to the wild type, and the E227K mutation is 5.5% active when compared to the wild type. The 3D model designed by the Westosha Central SMART (Students Modeling A Research Topic) Team displays the active site, two specific mutations and additional mutations reported in MDS patients. Screening for MDS is difficult because the condition can be caused by a wide variety of dysfunctional proteins. One such protein is dGK; therefore identifying its structure can hasten an accurate diagnosis.